TREATMENT OF TUMORS OF THE CHOROID PLEXUS EPITHELIUM

CPT-2000:
A pilot study evaluating the feasibility of an intercontinental phase III chemotherapy study for patients with choroid plexus tumors.

sixteenth Draft, October, 2000

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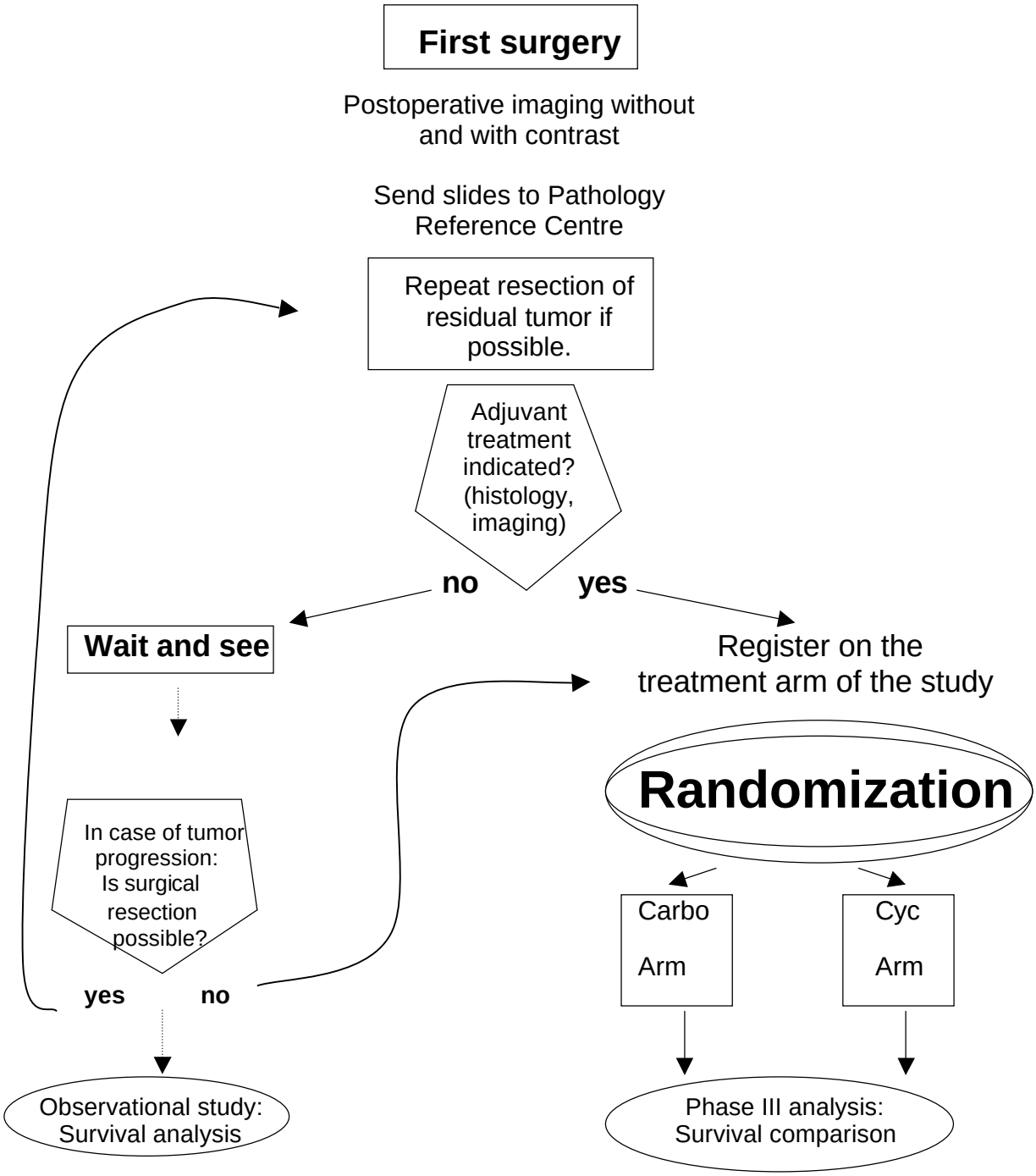

SUMMARY

Tumors of the choroid plexus epithelium are rare and account for only 0.5% of all tumors in adults and children. Several lines of evidence suggest that simian virus 40 (SV40) can cause these tumors. On histology, the WHO classification recognizes choroid plexus papilloma (CPP) as the relatively benign (Grade I), and choroid plexus carcinoma (CPC) as the malignant version (Grade III) of this entity. The differences between the two entities are not clear-cut. Intermediate histologies are often referred to as atypical or anaplastic choroid plexus papilloma and a development to increasing histological malignancy within an individual tumor has been documented. The best treatment remains unknown. No randomized treatment trials have been attempted yet. Maximal possible surgical resection is generally believed to be of prognostic value. The role of adjuvant treatment is less clear. There is some agreement for adding adjuvant treatment after incomplete resection of CPC, and for avoiding adjuvant treatment after gross total resection of CPP. Indicators for adjuvant treatment are unclear for the remaining groups of patients, as is the choice of treatment modality, and the order of modalities. Chemotherapy is uniformly given in multiagent protocols. No information is available about the value of single agents. A literature review further showed improved survival when irradiation is given in choroid plexus carcinoma and an overall response rate of 30-40% to multiagent chemotherapy.

This study will address the question, "which of the two agents, carboplatin or cyclophosphamide, is more effective in choroid plexus tumor treatment" in a randomized phase III approach. This study will also prospectively collect tumor specimens and clinical data to analyze the prognostic relevance of histological characteristics and SV40 expression. Data and samples are collected in an intercontinental setting. The study will start with a prephase of two years, which will evaluate the feasibility, especially the compliance to randomization, available patient numbers, and feasibility of intercontinental e-mail communication. During this prephase it is up to the participating cantres, if they want to contribute only to the registration part of the study or elso also to the randomized treatment.

Treatment begins with maximal surgical resection. All patients with choroid plexus carcinoma will receive adjuvant treatment. Patients with choroid plexus papilloma will be followed without adjuvant treatment and reoperated in case of recurrence. Those patients will be enrolled in the adjuvant treatment protocol, once evidence of tumor growth occurs and further surgical resection is impossible. The adjuvant treatment will be randomized between a carboplatin based protocol and a cyclophosphamide based protocol. Both arms will also include vincristine and VP16. The majority of patients are infants. They will not receive irradiation on this study. However, irradiation will be given in both treatment arms after the second block of chemotherapy, if the patient is older than three years of age. The total length of treatment will be 7 months.

Details of the adjuvant treatment are:

Carboplatin arm: One Chemotherapy block contains: VP16 100 mg/m^2 over 1 hour on days 1-5, carboplatin 350 mg/m^2 over 22 hours on day 2 and 3, vincristine 1.5 mg/m^2 on day 5. Six blocks are given in 4 weeks intervals (day1 to day1).

Cyclophosphamide arm: One Chemotherapy block contains: VP16 100 mg/m^2 over 1 hour on days 1-5, cyclophosphamide 1 g/m^2 over 1 hour on day 2 and 3, vincristine 1.5 mg/m^2 on day 5. Six blocks are given in 4 weeks intervals (day1 to day1).

Irradiation: The majority of patients will not receive irradiation. Patients over 3 years of age with CPC get craniospinal irradiation with 35 Gy and local boost up to a total of 54Gy. This will be given after the second block of chemotherapy in both treatment arms. Further details are described in the protocol.

German Summary: Zusammenfassung

Tumoren des Choroid Plexus Epithels sind selten und machen nur etwa 0.5% aller Gehirntumoren bei Kindern und Erwachsenen aus. Mehrere Hinweise deuten darauf hin, dass das Simian Virus 40 (SV40) diese Tumoren verursachen kann. Die Welt-Gesundheits-Organisation (WHO) klassifizierte die Tumoren histologisch in die relativ gutartigen Choroid Plexus Papillome (CPP), Grad I und die relative boesartigen Choroid Plexus Karzinome (CPC), Grad III. Die Unterscheidung zwischen diesen beiden Turmoren ist nicht immer eindeutig. Zwischenformen werden "anaplastische" oder "atypische" CPP genannt. Auch Faelle von Malignisierung wurden beschrieben. Die beste Behandlung ist unbekannt. Randomisierte Therapiestudien hat es bisher nicht gegeben. Generelle Uebereinstimung besteht, dass maximal moegliche chirurgische Resektion eine grosse prognostische Bedeutung hat. Die Rolle von adjuvanter Therapie ist weniger klar. Weitgehende Uebereinstimmung besteht, dass adjuvante Therapie notwendig ist, wenn ein CPC nicht vollstaendig entfernt werden konnte, und dass adjuvante Therapie nicht sinnvoll ist, wenn ein CPP komplett reseziert werden konnte. Keine Einigkeit besteht ueber die Behandlung der anderen Gruppen und die Auswahl der adjuvanten Therapie. Chemotherapie wird generell als Medikamenten–Kombination gegeben, Erfahrungen ueber die einzelnen Substanzen fehlen. Eine retrospektive Literaturanalyse zeigte, dass Patienten mit vollstaendig resezierten CPC eine besser Prognose hatten wenn sie Radiotherapie bekamen, und dass 30-40% der unvollstaendig resezierten CPC auf Chemotherapie ansprachen.

Die Studie wird als Phase III Fragestellung untersuchen, ob Cyclophosphamid oder Carboplatin effektiver in der Behandlung von Choroid-Plexus Tumoren ist. Darueberhinaus werden prospektiv Tumormaterialen und klinische Daten sammeln um die prognostische Relevanz der SV40 Expression ueberpruefen. Die Daten und Tumormaterialien werden interkontinental gesammelt. Die Studie beginnt mit einer Vor-Phase von zwei Jahren, in der die Machbarkeit der Hauptstudie getestet wird. Insbesondere wird die Durchfuehrung der randomisierten Therapie-Entscheidung, die Zahl der verfuegbaren Patienten und die Durchfuehrbarkeit der interkontinentalen Kommunikation getestet. Waehrend dieser Vorphase ist es den beteiligten Zentren freigestellt, ob sie nur an der Registrierung der Tumoren oder auch an der Randomisierung teilnehmen wollen.

Die Behandlung beginnt mit groesstmoeglicher chirurgischer Resektion. Alle Patienten mit Choroid Plexus Karzinom werden adjuvante Behandlung erhalten. Patienten mit Choroid Plexus Papillomen werden zunaechst beobachtet und erhalten nur adjuvante Therapie, wenn Tumorwachstum documentiert wird und weite chirurgische Resektion unmoeglich geworden ist. Die adjuvante Therapie wird zwischen zwei Behandlungsarmen randomisiert. Der eine Arm enthaelt Carboplatin, der andere Cyclophosphamid. Beide Behandlungsarme enthalten darueberhinaus Vincristine und VP16. Die Mehrheit der Patienten sind Saeuglinge. Diese Patienten werden keine Radiotherapie erhalten. Radiotherapie wird aber den Patienten in beiden Therapiearmen nach dem zweiten Block Chemotherapie gegeben, wenn die Patienten aelter als drei Jahre sind. Die Gesamtlaenge der Behanndlung ist 7 Monate.

Die Einzelheiten der adjuvanten Therapie sind: *Carboplatin Arm*: Ein Chemotherapieblock besteht aus: VP16 100 mg/m2 ueber 1 Stunde an den Tagen 1-5, Carboplatin 350 mg/m2 ueber 22 Stunden an den Tagen 2 und 3, Vincristin 1.5 mg/m2 am Tag 5. Sechs Bloecke werden im Abstand von 4 Wochen (Tag 1 bis Tag 1) gegeben.

Cyclophosphamid Arm: Ein Chemotherapieblock besteht aus: VP16 100 mg/m2 ueber 1 Stunde an den Tagen 1-5, Cyclophosphamid 1 g/m2 ueber 1 Stunde an den Tagen 2 und 3, Vincristin 1.5 mg/m2 am Tag 5. Sechs Bloecke werden im Abstand von 4 Wochen (Tag 1 bis Tag 1) gegeben.

Radiotherapie: Die Mehrzahl der Patienten erhalten keine Radiotherapie. Patienten ueber 3 Jahre mit CPC erhalten craniospinale Bestrahlung mit 35Gy und lokale Aufsaettignung auf 54Gy. Die Radiotherapie wird nach dem zweiten Chemotherapieblock in beiden Behandlungsarmen gegeben. *Weitere Einzelheiten sind dem Protokoll zu entnehmen.*

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BACKGROUND

Epidemiology

Tumors of the choroid plexus epithelium are rare. The most frequently cited number for the total frequency is 0.5% of all tumors in adults and children (Zulch 1957). It is based on extrapolated numbers of tumor collections in one single pathology centre. Population based databases can be used for further estimations. However, even then, estimates vary largely. The lowest number came from Spain: According to the data collected from the National Spanish Registry for Pediatric Tumors and made available to us by Dr. Aurora Navajas, during the period of 1980-1999 a total of 1955 tumors in children below 15 years of age were localized in the CNS. There were 22 cases of choroid plexus tumors (15 papillomas and 7 carcinomas). This is an incidence of only 1 per year in Spain with a population of 39 million people. The other end of the spectrum came from Italy. Here, a single city (Genova, 0.7 million people) had a higher total incidence than that of all of Spain (1.1 /year Garre at al 2000). The SEER registry, which covers approximately 10% of the USA has only 26 choroid plexus tumor patients registered between 1973 and 1996. This is again on the lower end of the spectrum from various sources. In addition, the age distribution of the SEER data is different than expected: Half of these patients are over 15 years, suggesting that the registration of very young patients is incomplete. In addition, only malignant versions are encoded. Another population based source is the Alberta registry. The total incidence of brain tumors can be estimated using this database: In 1996, 159 brain tumors were recorded in a population of 2,571,763 (Statistics Canada Annual Demographics Statistics, 1997, catalogue 91-213, Ottawa, 1998). In this population, 3 plexus papilloma patients were registered in a 10 year period (1983–1993). The total incidence for brain tumors in Alberta was 52.1/million inhabitants in that year. The world population is estimated at 6 billion people. Extrapolating the Alberta data gives a total incidence of 312,600 new brain tumors diagnosed per year worldwide. If 0.5% of those were choroid plexus tumors, 1,563 patients will develop choroid plexus tumors per year around the world, with 79 of those in the USA. Using the 0.2% (Alberta registry) figure in this calculation will result in 625 patients/year around the world, and with 32 of those in the USA. The true incidence will likely be higher than these numbers since rare tumors generally tend to be under diagnosed. This calculation is consistent with the estimation of Packer (1992) of 20 children with choroid plexus carcinoma per year in Northern America. About half of the tumors appear in the first year of life. **In summary**, an educated guess can assume 1500 choroid plexus tumor patients/year around the world, 90 of those in North America, of which 30 are children with choroid plexus carcinoma. This number is too small for a meaningful treatment study in North America. A study must therefore be conducted in a larger population.

Pathology

Choroid plexus tumors are defined as epithelial tumors arising from the choroid plexus of the cerebral ventricles. WHO classification (Kleihues 1993) classified the relatively benign choroid plexus papilloma (CPP) as grade I, and the relatively malignant choroid plexus carcinoma (CPC) as grade III. Choroid plexus papilloma are composed of a simple or pseudo stratified layer of cuboidal to columnar cells resting upon a basement membrane overlying papillary, vascularized, connective tissue cords. Cytological atypia, occasional mitoses, and a rare focus of necrosis may be present. An oncocytic variant is occasionally observed.

Choroid plexus carcinoma (Paulus 1990) is defined by histological evidence of anaplasia, e.g. increased mitotic activity, nuclear atypia, loss of papillary differentiation with transition of patternless cellular sheets and necrosis. It might be difficult to distinguish this tumor from metastatic carcinoma to the choroid plexus.

Atypical choroid plexus papilloma is a term not recognized by the WHO classification, but it is quite frequently used in the literature. “The distinction between choroid plexus papilloma

and choroid plexus carcinoma is not always clear cut, as some tumors show only one of a few histological features of malignancy, e.g. increasing mitotic activity. These tumors have been termed atypical choroid plexus papilloma, but clear diagnostic criteria have not been established" (Kleihues 1997). An increase in the degree of malignancy during the history of individual tumors has been described (Diengdoh 1993, Niikawa 1993).

The pattern of metastases confirms the gray area between the degrees of malignancy, because both the malignant (Peschgens 1995, Kang 1997, Bennedbaek 1990) and the benign version (Leys 1986, Domingues 1991, Enomoto 1991) of the tumor are known to metastasize. Metastatic pathways include most frequently but not exclusively the cerebral spinal fluid. These metastases were located in other parts of the brain (Allen 1992), the abdomen (Geerts 1996), the bone (Valladares 1980), and the lung (Sheridan 1994). Abdominal seeding has been described in patients with ventricular-peritoneal shunt (McCallum 1988) and one case of metastasis of tibia was published (Hayakawa 1979).

The tumors occur most frequently in the lateral ventricles, but all ventricles are possible, as well as primary multiple locations.

Etiology

Choroid plexus tumors are the model for viral induction of brain tumors. The simian virus 40 (SV40), which naturally infects Asian macaques, has been shown in several lines of evidence to induce choroid plexus tumors. The virus is capable of transforming human choroid cells in vitro (Shein 1962, Carruba 1983, Carruba 1984, Carruba 1985) and creates CPT in hamsters (Kirchstein 1962, Davis 1979) and mice (Brinster 1984, Small 1985, Reynolds 1988, Enjoji 1996). Transgenic mice harboring the SV40 large T antigen gene developed papillomas of the choroid plexus by 80 - 90 days (Cho 1989). Tumors in these mice develop focally, but when the T antigen is controlled by another virus, the proliferation is uniform (Chen 1992). Within the SV40 virus, the T-antigen is sufficient to induce the tumors, and the SV40 enhancer (72 base-pair repeat region) has a role in directing tumors to choroid plexus (Palmiter 1985). The T-antigen of the virus binds to tumor suppressor genes such as p53 (Palmiter 1985) and pRB (Chen 1992). Interestingly, dogs develop spontaneous plexus tumors (Kurtz 1971, Ribas 1989, Steiss 1990, Ohashi 1993). In human plexus chorioideus tumors, SV40 are frequently found (Tabuchi 1978, Bergsagel 1992, Lednicky 1995, Martini 1996). Involvement of the p53 tumor suppressor gene in patients is suggested by the occurrence of two cases of CPC (Garber 1990, Yuasa 1993), and two cases of CPP in families with Li-Fraumeni syndrome (Kleihues 1997) and one case with p53 inactivation demonstrated in tumor tissue (Vajtai 1995). This is quite strong evidence for SV40 induced tumorgenesis. The only higher level of evidence would be a controlled experiment with humans. This cannot be done, but in the 1970's the vaccine for poliomyelitis was contaminated with the SV40 virus. As an infection with SV40 is not pathogenic for humans, the contamination was not recognized clinically. If SV40 infection results in choroid plexus tumors, the frequency of those tumors should be higher in the population immunized during that time. The data, however, are inconclusive. It, therefore, still remains questionable if SV40 induces choroid plexus tumors in humans. It is a secondary objective of this study to determine the prognostic relevance of SV40 infections in plexus tumors.

Treatment of Choroid Plexus Tumors

Due to the low incidence of this tumor, randomized trials have not yet been attempted. Therefore, only low level evidence is available. The 10 year projected overall survival rate of the choroid plexus tumor patients registered in the SEER analysis 1973 – 1996 is 25%. An analysis of treatment modalities is not possible with these data. In preparation for this prospective study, a systematic literature review was conducted, creating a patient database from published cases. This database includes 541 choroid plexus tumors. Of those, 432 include information about follow up, which is necessary to calculate prognostic values. The only

categorical variant that had prognostic relevance in the univariate analysis was histology. Choroid plexus papilloma patients did better than choroid plexus carcinoma patients. Within the histological groups, surgery was a significant variable in both choroid plexus papilloma and choroid plexus carcinoma. This confirms the opinion of most publications in this field (Asai 1989, Packer 1992, Berger 1998) and is also not questioned in verbal discussions in international conferences. In the literature database, the next step was to stratify further according to the degree of surgical resection. This allowed analysis of the relevance of radiotherapy in the group of CPC patients with gross total resection, which is the most controversial subgroup. The literature database included 48 patients, half of whom had received radiation. The 5-year projected survival rate (Kaplan-Meier) for the irradiated patients was 68% (+/- 11% standard deviation), compared to 12% (+/-14% standard deviation) for those without irradiation (log-rank test: p=0.035, Wolff 1999). These data therefore suggest irradiation of patients with gross totally resected CPC. When the group was further stratified according to the variable age, the significant benefit of irradiation was lost for patients younger than 3 years of age but remained true for older patients. Response to chemotherapy was reported occasionally. The only single agent treatment, ever reported to our knowledge, to cause tumor response was VP16 (Packer 1992), which was given to a patient with relapsed CPC (table 1). All other reports used multiagent treatment (table1), not allowing determination of the influence of single agents. They sum up to a response rate of 36% in 22 reported patients. The five most frequently used drugs are: Cisplatin, vincristine, cyclophosphamide, carboplatin and etoposide. Of those, etoposide (VP16) was most frequently involved in protocols creating response. A stratified univariate analysis analyzing the benefit of chemotherapy on survival did not come out statistically significant. However, the multivariant (Cox regression model) analysis showed chemotherapy as a prognostic beneficial parameter ranking after histology and age at diagnosis. Unpublished reports showed response to chemotherapy also in choroid plexus papilloma (D. Ashley personal Communication).

In summary, The treatment of choroid plexus tumors should include maximal possible surgery. There is some evidence that irradiation and chemotherapy can be helpful, but the specific role of single agents remains unclear.

Conclusion for the Study-Protocol:

It is the aim of this study to start gaining specific information, upon which further studies can build. The available evidence suggests benefit of surgery for all patients and irradiation for patients over 3 years of age. Among the chemotherapeutic agents the best evidence was found for VP16, followed by vincristine, cyclophosphamide, and the platinum drugs. Among many interesting treatment questions, only one variable can be compared in the small number of patients available. An international discussion around this study, which occurred from 1998-2000 in various national and continental groups, showed that the comparison of cyclophosphamide with carboplatin is the best feasible question. Carboplatin was preferred over cisplatin because of the lower ototoxicity and the difficulties in testing hearing in infants. The study will result in the first reliable drug specific information. Multiagent treatment is viewed as standard care in many groups. Therefore the most frequently used drugs, VP16 and vincristine, are added to both arms of the protocol. This combination of DNA-binding drugs, with topoisomerase inhibitors and mitosis inhibitors is well based on theoretical/preclinical thinking and is generally used in almost all pediatric brain tumor protocols. Radiotherapy can presently not be randomized internationally. The majority of patients are young and the majority of physicians agree that they should not receive irradiation. For patients over three years of age, this study asks for irradiation, based upon the literature review conducted for this study (Wolff 1999). However, in case of disagreement with this approach, participation in the study only for patients under three years of age will be allowed for national groups. The other patients will be documented and followed in the documentation part of the study.

Table 1: RESPONSE TO MULTIAGENT CHEMOTHERAPY IN CHOROID PLEXUS CARCINOMA

	AUTHOR	***PUB. YEAR***	***AGE(YEAR)***	***LOCATION***	***CHEM-DRUG***	**RESPONSE**
	ARICO	1994	0.25	LAT.VEN	VCR-CCNU-PRC-MTX	SD
	ALLEN	1992	1.5	LAT.VEN	POG-BLEO VBL	CR
	ALLEN	1992	2.25	LAT.VEN	POG	CR
	ALLEN	1992	0.75	LAT.VEN	(VP-CDDP)(5FU-LEUCOVORIN)	SD
	GEERTS	1996	2.5	LAT.VEN	VCR-VP16-CARBOPLATIN-CYC	CR
	DUFFNER	1995	1	LAT.VEN.	VCR-CYC-VP16-CDDP	SD
	DUFFNER	1995	0.66	LAT.VEN	VCR-CYC-VP16-CDDP	SD
	DUFFNER	1995	1.83	LAT.VEN	VCR-CYC-VP16-CDDP	PR
	DUFFNER	1995	1.75	LAT.VEN	VCR-CYC-VP16-CDDP	PR
	PACKER	1992	2.75	PARANCHY	CDDP-VP16-5FU	NR
	PACKER	1992	2.16	PARANCHY	CDDP-VP16-THIOTEPA	NR
	PACKER	1992	2.58	LAT.VEN	CYC-VCR-CDDP	PD
	BERGER	1998	1.5	INFR.TENT.	BB SFOP	PD
	BERGER	1998	3.58	SUPR.TEN.	VP16-CARBO	PD
	BERGER	1998	1.5	SUPR.TEN.	BB SFOP	PD
	BERGER	1998	2	SUPR.TEN.	VP16, IFO, CARBO	CR
	BERGER	1998	1.91	SUPR.TEN.	BB SFOP	CR
	BERGER	1998	0.75	INFR.TEN.	BB SFOP	CR
	BERGER	1998	1.08	SUPR.TEN.	CARBO IFO	SD
	BERGER	1998	2.75	SUPR.TEN.	BB SFOP	SD
	BERGER	1998	4	SUPR.TEN.	BB SFOP	SD
	BERGER	1998	3	SUPR.TEN.	VP16-CARBO	SD

Abbreviations/agents

Bleo = bleomycin
CCNU = lomustine
CDDP = cisplatin
Carbo = carboplatin
Cyc = cyclophosphamide
MTX = methotrexate
PRC = procarbazine
IFO = ifosfamide
VP16 = etoposide
VBL = vinblastine
VCR = vincristine

Response in combination:

1 of 1 = 100%
0 of 1 = 0%
6 of 16 = 37%
4 of 11 = 36%
7 of 14 = 50%
0 of 1 = 0%
2 of 7 = 29%
1 of 2 = 50%
8 of 9 = 89%
0 of 1 = 0%
7 of 15 = 47%

BB SFOP = Carbo, PRC, VP16, CDDP, VCR, Cyc
POG = VCR, Cyc, CDDP, VP16
SD = stable disease
CR = complete response
PR = partial response
PD = progressive disease
NR = no response

This table contains one patient per line. Only patients, with residual disease prior to chemotherapy, and well documented response to multiagent chemotherapy are included.

GOAL AND OBJECTIVES

OVERALL GOAL

To improve choroid plexus tumor treatment through better understanding of the tumor biology and through increased knowledge about the benefit of specific treatment elements.

SPECIFIC OBJECTIVES

Prephase / Test phase

This study will have a two-year prephase, after which a decision will be made on whether or not the main phase will start. The prephase serves to evaluate the feasibility of a randomized study. During the prephase participating centres may decide to either contribute to the registration only or else to registration and randomization.

Primary Specific Objective:

To determine the number of patients accountable per year for randomization in a worldwide study.

Secondary Specific Objective:

To gather organizational experience on a worldwide randomized treatment trial for children and adults.

Main phase:

The main phase will start after the prephase. The predicted approximate duration is 5 years accrual and 5 years observation. This will be modified using the data created by the prephase.

Primary Specific Objective:

To compare the survival times after cyclophosphamide based treatment with the survival times after carboplatin based treatment in choroid plexus tumor patients.

Secondary Specific Objectives:

1. To compare the resectability of choroid plexus tumors after two blocks of cyclophosphamide based treatment with the resectability after two blocks of carboplatin based treatment
2. To compare response rates of incompletely resected choroid plexus tumors to two blocks of cyclophosphamide based treatment with the response rates after two blocks of carboplatin based treatment
3. To determine the prognostic relevance of histological atypia and SV40 in choroid plexus tumors.

ELIGIBILITY AND EXCLUSION CRITERIA

ELIGIBILITY criteria for first registration (SIOP approved data collection study):

1. Histological diagnosis of a choroid plexus tumor by a local pathologist/neuropathologist. This includes choroid plexus papilloma, atypical choroid plexus papilloma, anaplastic choroid plexus papilloma, malignant choroid plexus papilloma, and choroid plexus carcinoma. WHO brain tumor classification 1.5.1 and 1.5.2 (Kleihues 1993), ICDO classification M-9390/0, M-9390/3 (WHO 1990).
2. Slides have been sent to the pathology reference centre (by declaration of the sending centre).

EXCLUSION criteria from first registration

1. Patient or legal guardian does not consent to enrollment with electronic data processing or sending of tumor slides to the pathology reference centre.

ELIGIBILITY criteria for registration for randomization (Centre dependend voluntary second registration)

1. The first registration on the study was completed.
2. The reference centre has confirmed the receipt of slides sent.
3. The postoperative imaging has been done and the result is available.
4. The indication criteria (Table 2) are met.
5. The chemotherapy start criteria (Table 3) are met.
6. The agreement of patient or legal guardian has been documented according to the local guidelines.

Comment: *The histological diagnosis for the second registration is made by the local neuropathologist/pathologist. A confirmation of the histological diagnosis by the reference center is not a requirement for second registration. The service of the reference center at the time of diagnosis will be provided upon request by the local neuropathologist. Until funding for the reference center is in place, all other slides will be reviewed only once per year and findings will be used for the analysis of this study.*

Table 2: Indication Criteria for Newly Diagnosed* Tumors After Maximal Surgery

Histology (local neuropathologist)	Metastases	Residual Tumor	Adjuvant Treatment
Choroid Plexus Papilloma Grade I (no doubt)	No	regardless**	No
	Yes	regardless**	Yes *consider surgery* of metastases
Atypical or Anaplastic Choroid Plexus Papilloma (malignancy questionable)	No	No	No
	No	yes **	Yes
	yes	regardless**	Yes
Choroid Plexus Carcinoma	*regardless*	*regardless***	*Yes*

***In recurrent or progressive Choroid plexus tumors** adjuvant treatment is indicated. In addition, when there is clear evidence of tumor growth, even when the histological diagnosis is choroid plexus papilloma.

*** reconsider further surgery!*

M1 status (tumor cells in cerebrospinal fluid but no indication of metastasis on diagnostic imaging/MRI) has become increasingly rare with the improvements of diagnostic imaging. In early postoperative phase, surgical debris may mimic tumor cells. Therefore an initial pathological lumbar punction without correlate in diagnostic imaging, should be repeated at day 14 post surgery. Unquestionable M1 findings at this point in time classify the disease as metastatic. Questionable findings are to be discussed with the national representative, and if appropriate with the international study coordinator and the reference pathologist. The final decision on whether a disease will be classified as metastatic according to the terms of this protocol will made **by the national representatives,** who are able to read the reports and discuss the findings with the treating physicians in their own languages.

Table 3: Chemotherapy start criteria:

White blood cell count:	> 2000 / ul
platelet count:	> 85,000 / ul
serum creatinine:	in normal range
pregnancy test :	negative (only females in relevant age)
audiology:	hearing loss less than 30 dB at 3,000 Hz.

EXCLUSION criteria for randomization/second registration:

1. Previous irradiation or chemotherapy
2. Patient or legal guardian does not agree with treatment or randomization.
3. Clinical start criteria for the planned adjuvant treatment as outlined in treatment modification guidelines not met.
4. The protocol did not pass the local centre required approvals, such as the Ethics Committee or the scientific review.

Patients not eligible for randomization but eligible for first registration will be followed as a prospectively collected control group.

There is no age limit in this study. There is also no limitation given by membership or nationality of the treating physicians and institutions. Patients with recurring tumor after surgery are eligible, if they did not have irradiation or chemotherapy before.

Non-evidence-based types of treatment (so called “alternative treatment”), as well as antiangiogenic treatment, local gene therapy, and immunotherapy are not considered to be “chemotherapy” here, since they are unlikely to induce resistance to the treatment recommended in this protocol. These non-chemotherapeutic treatments do not exclude patients from the randomized part of the study.

SURGICAL GUIDELINES

Preoperatively, one might consider a tumor to be classified as choroid plexus tumor when a brain tumor is located in the ventricle, has very high contrast enhancement with only limited edema, when tumor markers for germ cell tumors aFP bCHG are negative and Carcinoembryonal antigen (CEA) is positive, and when the patient is a young child. Choroid plexus tumors are frequently highly vascularized and there is a considerable risk for massive bleeding during surgery (Pencalet 1998). If the clinical situation leaves sufficient time, an angiogram is highly recommended. The vascular supply to tumors in the lateral ventricles might be anterior choroidal (Goldberg 1974), posterior choroidal, or lateral striae vessels (Johnson 1989, Sanford 1994). Third ventricular tumors are frequently attached to the choroid of the tela chorioidea. Fourth ventricular tumors arise from part of the roof of the ventricle and may adhere to the anterior medullary velum. The blood supply is often derived from branches of the posterior inferior cerebellar artery (Gupta 1996). Preoperative embolization of the major tumor vessels should be considered. Planning the surgery in two subsequent approaches; first ligation of the major tumor vessels and one week later resecting the tumor should be considered. At the time of surgery, a ventricular drain is usually first put in place in order to reduce brain tension and allow sufficient brain retractions. Detailed outlines of surgical approaches are provided by Velasco-Siles (1982) and Gupta (1996). Intraoperative prevention of hemorrhage requires presurgical identification and early intraoperative control of the vascular pedicle, which is usually medial and inferior to the tumor with the venous drainage medial and posterior (Sanford 1994). The tumor mass of choroid plexus papilloma is often large and firm, not lending itself to displacement at operation, and choroid plexus carcinoma are even more difficult to mobilize because of its invasive nature and increased vascularity associated with peritumoral parasitized vascular supply (Sanford 1994). Postoperatively a ventricular drain may be left several days to measure intraventricular pressure and to determine whether shunting of the fluid is required (Gupta 1996).

The relevance of gross total resection is the best documented piece of information about choroid plexus tumor treatment. Therefore, all efforts should be undertaken to resect as much of the tumor as possible with acceptable risks for neurological sequela. Postoperatively, the best available radioimaging study should be done in the time period between 24 and 72 hours after surgery. This study should be done without and with contrast enhancement. In the case of residual tumor, second surgery should be considered prior to adjuvant treatment, independent of the degree of malignancy of a choroid plexus tumor.

Resection of metastases is recommended, when the histology of the primary tumor is choroid plexus papilloma.

Following the approach of Berger (1998), the situation of a non-resectable tumor might be changed by adjuvant treatment. Therefore, surgical resection after adjuvant treatment is encouraged. During the adjuvant treatment protocol, three reasonable timepoints for a delayed tumor resection are:

1. After the response evaluation to the first two blocks of chemotherapy (= week 8).
2. After completing adjuvant treatment (week 37 or 42)
3. At any timepoint when the tumor grows despite adjuvant treatment.

The surgeon should use the operative report and the appropriate forms to document the modalities employed during surgery. Copies of operative notes and appropriate forms are to be sent to the international study coordinator, who will forward them to the reference neurosurgeon for review.

PATHOLOGY GUIDELINES

(section revised by Dr David Ellison July 2000)

In this study, whether a patient will receive adjuvant therapy is based on the diagnosis of the local neuropathologist. The local laboratory will submit 2 x H&E stained histological sections, and 6 unstained sections on coated (e.g APES) slides (or 8 unstained slides) to the neuropathology reference centre for review at the end of the study and possible research purposes. The histology of the tumours will be examined systematically and particular features related to clinical variables. This will not influence the treatment decisions or the randomization. The reference centre however, is willing to provide support with the histological diagnosis, if asked by the local neuropathologist.

Local pathologists should adhere to the WHO classification (2000) when reporting these tumours. Standard H&E staining frequently allows differentiation between choroid plexus tumors and other brain tumors. Immunohistochemistry may add further information. Transthyretin (Megerian 1997), cytokeratin (Muthupei 1995), glucose transporter type 1 (Kurosaki 1995), collagen type VII (Paulus 1995), laminin (Furness 1990), E-cadherin (Figarella-Branger 1995) and Ezrin (Bohling 1996), have been reported as useful differentiating markers.

The differentiation between choroid plexus-carcinoma (CPC WHO grade lll) and choroid plexus-papilloma (CPP, WHO grade 1) can be difficult. CPCs show nuclear pleomorphism, a high nuclear:cytoplasmic ratio, loss of papillary architecture and foci of necrosis (Paulus 1990). Average labelling indices with MIB-1, a cell cycle marker, were 3.7% in CPP and 14% in CPC (Vajtai 1996).

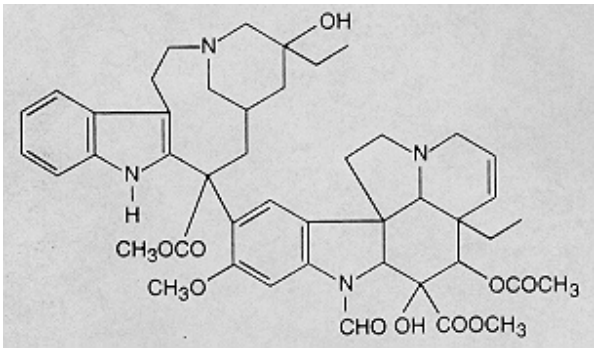
Diagnosis according to the WHO classification is preferred, however, the study does give guidelines, how to proceed, if diagnosis such as “atypical choroid plexus papilloma” or “anaplastic choroid plexus papilloma” cannot be avoided. The local neuropathologist is asked to provide a detailed report of the histology, including the immunophenotype, when submitting the slides to the reference centre. We would encourage the transmission of a fax of this report to the study coordinator, even when no English translation is available.

CHEMOTHERAPY

The value of chemotherapy in choroid plexus tumors is largely unknown. This study will compare cyclophosphamide with carboplatin. Chemotherapy is the one and only modality of adjuvant treatment for patients under 3 years of age. In patients older than 3 years of age, irradiation will be given after the second block followed by further chemotherapy. The same protocols are used in both age groups. The decision of which protocol-arm to be used is made by randomization. This is done by the International Study Office in Calgary.

Agents used in this study are:

Vincristine
Other names: VCR, Vencasar[R], Vincrex[R], Oncovin[R], Pericristine[R], Kyocristine[R], 22-Oxovincaleukovlastine Sulfate.



Chemistry: Plant derived agent, Vinca alkaloid, molecular weight 923.0, chemical formula $C_{46}H_{56}N_4O_{10}H2SO_4$, sensitive to light, should be stored at 2 to 8ºC. However, it is stable at room temperature for at least one month. Most frequently supplied as clear fluid in aqueous solution with solvents such as methyl-4-hydroxybenzoate, propyl-4-hydroxybenzoate, benzyl alcohol, sodium chloride, lactulose, and mannitol.

Pharmacology: After standard dose bolus injection, peak plasma concentrations of 0.4 μmol are reached. 48% of vincristine is protein bound. The drug is primarily metabolized by the liver and excreted in the stool, and, to a lesser extend, in urine. The initial half-life is less than 5 minutes, the mean-terminal half-life is one hour (Bender 1977).

Vincristine has been demonstrated to enter the central nervous system in sub-human primates rapidly after intravenous injection, and concentrations of above 1 nM have been maintained in cerebral spinal fluid for longer than 72 hours after intravenous bolus injection (El Dareer 1977). Spinal fluid concentrations in humans have been 20 to 30 folds lower than in concurrent plasma levels and did not exceed 1.1 nM in another study (Jackson1981). However, the concentration of vincristine is higher in CSF as compared to other vinca alkaloids. On the cellular level, vincristine binds to tubulin dimers, which are necessary for the activity of the spindle apparatus during mitosis. Resistance to vincristine may arise from the MDR1 (multiple drug resistance) mechanism with the membrane pump P170, which pumps several agents out of the cells. Resistance may also arise from mutations in tubulin.

The drug is the most frequently used chemotherapeutic agent in pediatric oncology. Seven of 15 CPC patients treated with VCR containing regimens responded (Table 1).

Dosing: 1.5 mg/m^2 intravenous bolus injection. Maximal dose: 2 mg. Vincristine may never be given intrathecally.

Schedule: The vincristine injection is given at the end of the chemotherapy block because the agent blocks the cell cycle, making tumor cells potentially less responsive to other agents when given prior to them.

Side Effects**:**

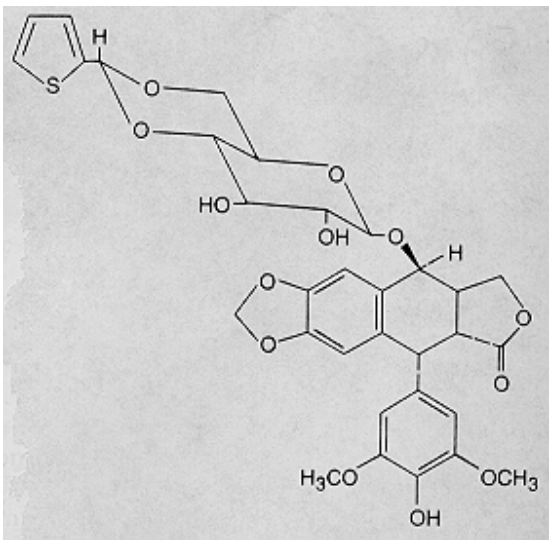
	Common Happens to 21-100 children out of 100	**Occasional** Happens to 5-20 children out of every 100	**Rare** Happens to <5 children out of 100
Immediate: Within 1-2 days of receiving drug	Local ulceration if extravasated	Jaw pain	
Prompt: Within 2-3 weeks, prior to the next course)	Hair loss	weakness, constipation	Paralytic ileus, ptosis, vocal cord paralysis, myelosuppression, CNS depression, inappropriate ADH, seizure
Delayed: Any time later during therapy, excluding the above conditions	Loss of deep tendon reflexes	Numbness, tingling and clumsiness	
Late: Any time after the completion of treatment			
**Unknown Frequency and Timing: ****Fetal and teratogenic toxicities			

(L) Toxicity may also occur later

**Fetal toxicities and teratogenic effects of vincristine (either alone or in combination with other antineoplastic agents) have been noted in humans. The toxicities include: chromosome abnormalities, malformation, pancytopenia, and low birth weight.

VP16

Other names: Etoposide, Vepeside, Chemical name - 4' -demethylepipodophyllotoxin 9-{4,6-0-(R), ethylidene-beta glucopyranoside}; 4' -demethylepipodophyllotoxin-beta-D-ethylidene glucoside.



Chemistry: Plant derived agent, epipodophyllotoxin, molecular weight 588.6, chemical formula $C_{29}H_{32}O_{13}$. Lipid soluble, supplied as solution with polyethylene glycol, polysulfate, benzyl alcohol, citric acid, ethyl alcohol. The pH of the clear yellow solution is 3 to 4. The unopened vials are stable for 2 years at room temperature. In further diluted form it is at least stable for 2 days at room temperature.

Pharmacology: 290mg/m^2 injections resulted in peak plasma concentrations of 29 mg/ml (Muggia 1971). A distribution half life time of 1.5 hours and a terminal half life time of 3-11 hours result in no accumulation after daily administration for 5 consecutive days. One third of the given dose is excreted with urine (Hande 1984). Bile secretion results in feces excretion of approximately 10% (Creaven 1982, Allen 1975). Renal excretion seems to be higher in children. 94% of the total drug is protein bound. Only 1 - 2% of the plasma level is reached in cerebral spinal fluid.

The mechanism of action of epipodophyllotoxins is believed to be topoisomerase II inhibition. These agents stabilize the enzyme DNA complex in a cleavable state (Van Maanen 1988). In addition, these agents may exert cytotoxic actions via free radicals that bind directly to DNA (Haim 1986, Sinha 1983).

Resistance against etoposide can be multiple drug resistance gene 1 (MDR1) related (Seeber 1982, Pommier 1986). Etoposide is the only drug reported to create response in a choroid plexus tumor, when given as a single agent (Packer 1992). It is one of the most frequently used agents in pediatric neuro-oncology, mostly as additive to a DNA alkylating agent. Eight of 9 CPC patients responded to VP16-containing drug combinations (Table 1).

Dose schedule: 100 mg/m^2 given over 1 hour as intravenous infusion on 5 consecutive days.

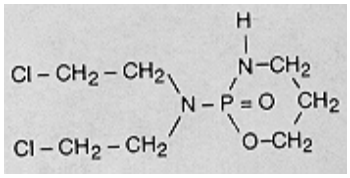
Side Effects:

	Common Happens to 21-100 children out of every 100	**Occasional** Happens to 5-20 children out of every 100	**Rare** Happens to <5 children out of every 100
Immediate: Within 1-2 days of receiving drug	Nausea, vomiting		Hypotension, anaphylaxis, skin rash
Prompt: Within 2-3 weeks, prior to next course	Myelosuppression	Alopecia (L), enhanced damage due to radiation, diarrhea	Peripheral neuropathy, stomatitis
Delayed: Anytime later during therapy, excluding the above conditions			
Late: Anytime after completion of therapy			Secondary malignancy

(L) Toxicity may also occur later

Cyclophosphamide

Other names: Endoxan, Cytoxan, Neosar, 2(bis(2-chloroethyl)-amino) tetrahydro-2H-1,3,2,oxazphosphorine 2-oxide monohydrate.



Chemistry: Chemical group of nitrogen mustard, molecular weight: 261.1, chemical structure: $C_7H_{15}O_2N_2PCl_2$. Drug is dissolved in sterile water and diluted with glucose, normal saline or Ringer solution. In this form, it is stable for 24 hours at room temperature.

Pharmacology: The drug is activated in liver by P450-dependent hydroxylation. Other metabolites such as acrolein participate in toxicity but not in the efficacy of cyclophosphamide. There is considerable inter-patient variation of metabolism and clearance of cyclophosphamide and its metabolites. In general, one quarter of the original drug appears in urine. On the tumor cell level, the agent works as an DNA alkylator. Mechanisms of resistance include cytosolic detoxification with sulfhydrate groups, increased repair or deceased apoptotic pathways. The drug is given with mesna, a sulfhydrate-containing drug excreted rapidly in urine. Mesna inactivates the toxicity of cyclophosphamide metabolites to urinary tract epithelium, preventing hemorrhagic cystitis. Cyclophosphamide is one of the most frequently used drugs in pediatric neuro-oncology, often given in combination with VP16. Seven of 14 CPC patients responded to drug combinations containing cyclophosphamide.

Dosage: 1 g/m^{2}given over two hours on two consecutive days.

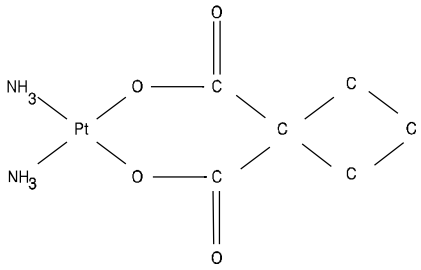
Side Effects:

	Common Happens to 21-100 children out of every 100	**Occasional** Happens to 5-20 children out of every 100	**Rare** Happens to < 5 children out of every 100
Immediate: Within 1-2 days of receiving drug	Anorexia (L), nausea (L), vomiting (L)	Metallic taste (L), inappropriate ADH[1]	Transient blurred vision[1], cardiac toxicity with arrhythmias[1], myocardial necrosis[2](L).
Prompt: Within 2-3 days of receiving drug	Myelosuppression (L), alopecia (L)	Hemorrhagic cystitis (L)	
Delayed: Anytime later during therapy, excluding the above conditions	Immunosuppression, gonadal dysfunction/sterility (L)		Pulmonary fibrosis[3](L)
Late: Anytime after completion of treatment			Secondary malignancy, bladder fibrosis
Unknown timing and frequency: **Fetal and teratogenic toxicities			

[1] Less common with lower doses.
[2] Only with very high doses.
[3] Risk increased in someone who has had chest irradiation.
(L) Toxicity may also occur later.

Carboplatin

Other names: Carboplatin, Carbo, Paraplatin, Cyclobutanedicarbonacid-cisdiamminplatinum, CBDCA, Carboplat, Ribocarbo, Paraplantin-AQ.



Chemistry: Inorganic platinum compound, molecular weight: 371.29, chemical structure $PtN_2H_{12}C_6O_4$. Very soluble in water. Poorly soluble in lipids. It is administered with mannitol.

Pharmacology: Transport in blood as inactive molecule with slowly increasing protein binding over hours. Accumulation in tumor tissue. Renal elimination mainly by glomerular filtration. Terminal plasma half-life time for intact carboplatin is only 2 to 6 hours.

On the tumor cell level, carboplatin penetrates the cellular membrane by an unknown mechanism. Intracellularly, the cyclobutane ring is split leaving the same hydrated activated platinum molecule as cisplatin. It binds with two sites to the DNA, most frequently to the N7 position of guanine. The most abundant binding is intrastrand cross link in two adjacent guanine/cytosine molecules. Less frequent are interstrand cross links. Mechanisms of resistance include reduced cellular accumulation by yet poorly described membrane mechanisms, increased intracellular sulfhydrate groups such as glutathione, increased excision repair and decreased apoptotic response pathways. Simultaneous administration with Mesna can inactivate platinum drugs.

Carboplatin is a very frequently used drug in treatment of solid tumors in both adult and pediatric oncology. It is often combined with VP16. Four of 11 patients found in the above mentioned literature analysis with CPC responded to combinations containing Carboplatin.

Dosage: 350 mgm^2 over 1 hour on two consecutive days (=700 mg/block)

Schedule: Carboplatin is given on day 2 and day 3 of the chemotherapeutic block, preceded and followed by two etoposide infusions. This way, the topoisomerase inhibition is effective, while platinum binds to DNA. Topoisomerase II dependent repair is inhibited while apoptotic pathways are initiated.

Carboplatin Side Effects:

	Common Happens to 21-100 children out of 100	**Occasional** Happens to 5-20 children out of every 100	**Rare** Happens to < 5 children out of every 100
Immediate: Within 1-2 days of receiving drug	Nausea (L), vomiting (L)		Metallic taste
Prompt: Within 2-3 weeks, prior to the next course	Myelosuppression[1]	Electrolyte disturbances (L)	Peripheral neuropathy, hepatotoxicity (L), renal toxicity (L), ototoxicity (L)
Delayed: Anytime later during therapy, excluding the above conditions			Hearing Loss
Late: Anytime after completion of treatment			Secondary leukemia

(L)Toxicity may also occur later.

Drug Combinations: These drugs are frequently combined in many chemotherapeutic protocols. The side effects of combinations represent the sum of the side effects of the individual agents. Additive toxicity occurs mainly in bone marrow toxicity (resulting in low counts).

RADIOTHERAPY

(Autor: R Kortman et.al 07.2000)

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Radiation therapy in choroid plexus carcinoma is a standard treatment. However, data concerning dose response relationship and necessary target volumes with respect to histological grade and extent of disease at diagnosis is largely unknown. A literature search suggested, that radiation is a significant prognostic factor in choroid plexus carcinoma (Wolff 1999). The guidelines of the protocol were therefore defined in analogy to the treatment of other malignant pediatric brain tumors such as medulloblastoma.

Radiation starts after the response evaluation after 2 blocks of chemotherapy. Radiation will be given only to patients that have completed their 3rd year of life (after the 3rd birthday). The recommended field depend on histology, completeness of surgery, response to chemotherapy, and metastases (MET):

Radiotherapy Table 1:

Histology	**Metastases**	**post-operative Tumor**	**Response to Chemo-**	**local dose: Tumor(+Met)**	**cranio spinal Dose** (Gy)
Choroid Plexus	No	No		no	no
Papilloma	No	Yes	regardless	yes	no
WHO Grade I	Yes	regardless	regardless	yes	no
(no doubt)					
Atypical or Anaplastic	No	No		yes	no
Choroid Plexus Papilloma	No	Yes	regardless	yes	no
(malignancy questionable)	YES	regardless	CR or PR	yes	no
	YES	regardless	SD or PD	yes	yes
Choroid Plexus	No	No		yes	no
Carcinoma	No	YES	CR or PR	yes	no
WHO grade III	No	YES	SD or PD	yes	yes
(no doubt)	YES	regardless	regardless	yes	yes

Radiation doses are described in radiotheapy table 2

CLINICAL TARGET VOLUMES / TREATMENT TECHNIQUES

Neuroaxis irradiation

Whole Brain or "Helmet" -Field

Clinical target Volume
The cranial volume should include the whole skull, the cribriform fossa, the temporal fossae, the posterior fossa including the craniotomy and neck scar, and the spinal cord to, or below, the C3 - C4 interspace where it will adjoin the spinal volume.

Radiotherapy Fields
The whole brain is treated using two parallel opposed lateral portals (33, 50). It is essential that the portals encompass both temporal lobes and the cribriform plate. The central ray is stationary, 3 cm posterior to the eyelid markers at the level of the block margin, inferior to the middle cranial fossa. The distance to the eyelid surface has to be respected to protect the contralateral lens from the divergent beam. The superior field border should be located at least 5 cm superior to the vertex to allow shortening of the helmet field when the junction with the adjacent spine field is shifted, unless asymmetric collimators are used. Collimator rotation helps to adapt the helmet portals to the divergent beam of the adjacent spine field. The patient's eye lenses, face and pharynx are shielded by customized blocks. Blocks are shaped so that the portals include the cribriform plate (safety margin of at least 5mm) and the middle cranial fossa (safety margin: 1 cm) down to the 3rd / 4th or 4th / 5th vertebral interspace (the whole vertebral body is included). A repeat CT-examination can check the field margins to ensure reliable coverage of the clinical target volume (32).

Dose specification
The cranial dose must be specified on the central axis in the midplane of the opposed fields according to the ICRU – 50 rules.

Spinal field

Clinical target volume
The spinal volume should cover the spinal dural sac from the junction with the cranial volume down to the level of S2. The width of the vertebrae should be covered with an allowance for scoliosis or rotation of the vertebral column, but a spade should not be used to cover the spinal nerve roots.

Radiotherapy Fields
The spinal canal receives irradiation to a single, direct, dorsal portal. The spinal portal should be 5-6 cm wide (without additional enlargement in the sacral region). In children younger than 7-8 years, 4.0cm may be sufficient. It should extend inferiorly to the second sacral segment. In adolescents, the available field length of cobalt units or linear accelerators may not suffice, thus making necessary irradiation to two dorsal portals. In this case, care has to be taken that the abutting borders of the whole brain and spinal portals do not receive under- or over-dosage. Therefore, the depth of the dose maximum has to be determined using a lateral CT scanogram

in the treatment (prone) position. As an alternative to CT scanograms, lateral simulator films with metal skin markers can be used. Patient positioning is checked simultaneously.

Dose specification
The depth of the dose maximum has to be determined using a lateral CT scanogram or a lateral simulation film in the treatment (prone) position. It is necessary to calculate the minimum and maximum depth of the target volume at the posterior edge of the vertebral bodies. The points of maximum depth are at C7 and L5. The spinal dose must be recorded as a maximum and minimum according to the maximum and minimum depths of the posterior vertebral bodies and the doses should be prescribed to the minimum. These doses, and whether or not a compensator is used, are to be recorded on the RADIOTHERAPY DATA sheet. If the calculated dose to these points varies by more than 10%, then a compensator must be designed to improve the uniformity of dose in this region.

In the case of fast electrons, the energy should be chosen such that the 90% isodose line encompasses the deepest part of the target volume; the dose specification is made at the 90% isodose.

Field matching

Dependent on the divergence of treatment beams of the upper spinal field, collimator rotation is used for optimal matching of adjacent portals of the lateral helmet fields and the spinal field. There should be no gap between the two fields. To smooth out hot and cold spots beneath the surface, the junctions of the whole brain and spinal portals are shifted three times, 2 cm in the cranial direction. The adjacent two spinal fields are matched on the depth of the dose specification (the dorsal border of the vertebral bodies) leaving a skin gap of at least 1.0cm.

Radiation treatment of the tumor region ("Involved-Field")
(as sole treatment / as boost after craniospinal irradiation)

The planning target volume of the boost - field in conventional radiotherapy should be restricted to the primary tumor site defined postoperatively. It is mandatory to perform computer assisted treatment planning. Target volumes will be defined according to the ICRU 50. The clinical target volume (CTV) encompasses the visible tumor as seen on MR (T2 weighted images) with an additional margin of 0.5 cm. If surgery was performed, postoperative delineation of residual disease will be used for treatment planning. The preoperative scans are used to identify regions of possible tumor infiltration. It is not necessary to entirely encompass areas of cerebral edema. The planning target volume (PTV) encompasses the CTV with an additional margin according to the precision of treatment technique (0.2 - 0.5 cm if rigid head fixation and 0.5 - 1.0 cm if a conventional face masks/head shell is used) depending on the department's policy. When defining the clinical target volume anatomical borders must be considered.

Not permitted for the choroid plexus tumor study are: local boost, brachytherapy, gamma knife, seed implantation, hypofractionation, or hyperfractionation.

Dose specification
Radiation dose specification for irradiation of the tumor region is done according to the ICRU rules. The ICRU reference point by definition is located in the center of the target volume (100 %). Dose inhomogeneity within the target volume should not exceed the tolerance limits of 95 % and 107 %. To spare adjacent, healthy tissue CT-supported treatment planning is required in most cases.

Radiotherapy - Table 2:
Treatment volumes and dose prescriptions
according to the radiotherapy fields - described in radiotherapy Table 1

Craniospinal Irradiation				
Part of CNS	Number of fractions	Dose per fraction	Total dose	Duration (weeks)
Cerebrum	22	1.6 Gy	35.2 Gy	4.5
Spinal axis	22	1.6 Gy	35.2 Gy	4.5
Tumor/boost	+11	1.8 Gy	+ 19.8 Gy	+2.2
Metastases	+8	1.8 Gy	+ 14.4 Gy	
Total /tumor	25		55.0 Gy	6.7
Total / metastases			49.6 Gy	

Irradiation of tumor sites				
Part of CNS	Number of fractions	Dose per fraction	Total dose	Duration (weeks)
Tumor region	25	1.8Gy	54.0Gy	5

Radiotherapy Patient Positioning

Neuroaxis Irradiation
The patient is to be treated in an immobilization device in the prone position to provide a stable and reproducible treatment delivery. The spine should be made as straight as possible. The immobilization device should consist of a complete head shell, but a whole body cast is recommended. Alternatively vacuum pillows can be used.

Irradiation of the Tumor Region ("Involved-Field")
The patient is treated in the supine position. It is recommended that an individualized face mask is used to guarantee the reproducibility of head positioning. Head rests should be chosen in order to provide sufficient head inclination so that anterior-posterior beams will not traverse the lenses of the eyes.

Radiotherapy Documentation

It is mandatory to document the field alignment using simulator films and polaroid photographs. At the start of radiotherapy, verification films should be obtained of each irradiated field. Portal films should be repeated once a week. Precise application of radiotherapy is essential for both tumor control and reduction of side-effects. To give recommendations for optimal treatment techniques, it is necessary to analyse the radiation protocols, the prescription of target volumes, doses and the accuracy of treatment delivery.

Therefore, it is requested that the following data (copies) be sent to the reference center for Radiotherapy.

-radiation protocols
-simulation films
-portal films
-computer assisted treatment plans
-Polaroid pictures of patient positioning and field alignment
-Evaluation forms
* Patient data (Appendix)
* Toxicity (Appendix)
- Treatment technique / dose prescription (Appendix
-)

Acute treatment toxicity of radiotherapy
Especially in patients that previously received chemotherapy, neuraxis irradiation may lead to severe suppression of hemopoiesis, as it covers a large volume of hemopoietic bone marrow. The use of the growth factor G-CSF may help overcome myelosuppression and shorten detrimental treatment breaks. Steroid prophylaxis of cerebral edema is mandatory during whole brain irradiation. If acute brain edema occurs, steroids should be given intravenously. Radiation esophagitis may require analgesics and antifungal medication. The acute maximal toxicity and myelotoxicity during irradiation should be documented on the evaluation sheets.

Routine laboratory tests during radiotherapy
2 x weekly: red and white blood cell counts, platelet counts. If the patient is receiving steroid medication: blood glucose 1x weekly. Before and at the end of radiotherapy: sodium, potassium, calcium, GOT, GPT, Gamma-GT, LDH, creatinine, BUN, AFP, ß-HCG, hormones of the pituitary axis (TSH, growth hormone, ACTH, FSH/LH

).

STUDY PROTOCOL

Prior to adjuvant treatment: After maximal possible tumor resection, tumor sample will be sent to the pathology reference centre and the first registration (Form 1) will be sent to the international study centre. Tumor staging will be performed including lumbar puncture, MRI, physical exam (including neurological exam), white blood cell count, hemoglobin, platelets, differential Na, K, Ca, P, ALT/GOT, AST/GPT, bilirubin, and LDH. Creatinine, and Urea will be measured in blood for patients who will receive adjuvant treatment. Patients/Parents will be informed about the study. In case of consent of the patient/parents and in case the participating centre has decided to contribute to both, the registation study and the treatment study, the second registration (Form 2) will be sent after the staging is completed. The international study centre will send the results of the randomization back to the treating physician and to the national representative. The randomization will be either to the carboplatin arm of the study or to the cyclophosphamide arm.

Carboplatin Arm, CarbEV – Protocol:
One chemotherapy block contains: VP16 100 mg/m^2 over 1 hour on days 1-5, carboplatin 350 mg/m^2 over 1 hour on day 2 and 3, vincristine 1.5 mg/m^2 iv push on day 5. A total of six blocks are given in 4 weeks intervals (day1 to day1). After the first two blocks, response will be evaluated including all exams, done prior to the second registration. Further surgery will be considered after these exams, and the result will be reported in Form 3 to the international study center and the national representative. After the surgery the chemotherapy carries on for four further blocks. The small group of patients, who are over 3 years of age, will receive radiation after two blocks of chemotherapy, followed by four further blocks of chemotherapy. After 6 blocks of chemotherapy, further surgical resection will again be considered.

Cyclophosphamide Arm, CycEV - Protocol:
One chemotherapy block contains: VP16 100 mg/m^2 over 1 hour on days 1-5, cyclophosphamide 1 g/m^2 over 1 hour on day 2 and 3, vincristine 1.5 mg/m^2 on day 5. A total of six blocks are given in 4 week intervals (day1 to day1). After the first two blocks, response will be evaluated including all exams, done prior to the second registration. Further surgery will be considered after these exams, and the result will be reported in Form 3 to the international study center and the national representative. After the surgery, the chemotherapy carries on for four further blocks. The small group of patients, who are over 3 years of age, will receive radiation after two blocks of chemotherapy, followed by four further blocks of chemotherapy. After 6 blocks of chemotherapy, further surgical resection will again be considered.

After completing the adjuvant treatment
After six blocks of chemotherapy, the staging will be repeated, and further surgery will be considered. The result will be reported centrally to the international study coordinator (Form 4), who will forward the information to the appropriate national representative. Follow up information will be sent once per year (Form5) and whenever tumor progression is observed. Only tumor progression (but not unchanged tumor status) will be forwarded to the national representatives.

CHOROID PLEXUS TUMOR CHEMOTHERAPY: CYCLOPHOSPHAMIDE ARM CycEV

Week	Study/Chemo	Date
0	MRI: *CR -/- residual tumor* *(please circle the best description)*	
0	1,2,3,4,5,6, 7 send slides, register	
1	1,2,3,4,5,CycEV____/____/_____	
2	1,2,3,4	DD MM YY
3	1	
4	1	
5	1,2,3,4,CycEV_____	
6	1,2,3,4,5,7	
7	1, MRI: *CR / PR / SD / PD /CCR* *(please circle the best description)*	
8	consider surgery again *>**3y age:** wk 8 Start **irradiation*** *wk 14 complete irradiation*	
9/*15*	1,2,3,4, CycEV_____/_____/____	
10/*16*	1,2,3,4	DD MM YY
11/*17*	1	
12/*18*	1	
13/*19*	1,2,3,4, 7*CycEV____/_____/____	
14/*20*	1,2,3,4,5	DD MM YY
15/*21*	1	
16/*22*	1	
17/*23*	1,2,3,4,CycEV____/_____/_____	
18/*24*	1,2,3,4	DD MM YY
19/*25*	1	
20/*26*	1	
21/*27*	1,2,3,4,CycEV____/_____/_____	
22/*28*	1,2,3,4,5	DD MM YY
23/*29*	1	
24/*30*	1	
25/*31*	1	
26/*32*	1,	
27/33	1 MRI: *CR / PR / SD / PD /CCR* *(please circle the best description)*	
28/34	1 2,3,4,5,6,7 *Please circle abnormal results*	
29/35	consider surgery again	

italic week numbers refer to patients who are >3 years

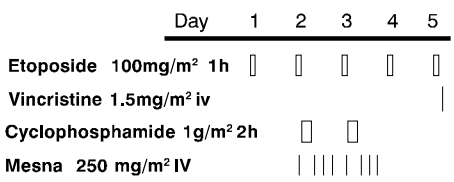
Abbreviations:

Studies:
1: white blood cell count, hemoglobin, platelets, differential
2: Na, K, Ca, P,
3: ALT/GOT, AST/GPT, bilirubin, LDH
4: Creatinine, Urea
5: 24 hour creatinine clearance or glomerular filtration rate
6: audiology
7: LP
7*: LP only, when previously positive.

MRI Response:
CR: complete remission (no tumor left)
PR: partial response (tumor size <50%)
SD: stable disease (tumor >50% <125%)
PD: progressive disease (tumor > 125%)
CCR: continuation of complete remission after gross total resection

For more detailed definitions see protocol

CycEV



Send registrations (week 0), response evaluation (week 7), end of treatment form (week 35), and this roadmap to:

Johannes Wolff,
Alberta Children's Hospital
1820 Richmond Road S.W. Calgary
Alberta, Canada, T2T 5C7
Fax: Canada 403 228 4196
Tel: Canada 403 229 7272
Email:
johannes.wolff@crha-health.ab.ca

CHOROID PLEXUS TUMOR STUDY *CycEV Infusion plan*
CYCLOPHOSPHAMIDE / ETOPOSIDE / VINCRISTINE

Name: _____ Date of birth: _____

Height:_____cm Weight: _____kg Surface area: _____m^2

Requirements for this block: White blood cell count over 2000, platelet count over 100,000, no hematuria. Read dose modification guidelines for **age adjustment** and side effect adjusted dosing.

DAY 1

Hr 0 – Hr 1 **Etoposide (VP-16)** _____mg (100mg/m²) in _____mL (250ml/m²) in D5W.45%NaCl IV over 1 hour.
Anaphylactic precautions for etoposide
Hr 1 – Hr 24 D5W.45%NaCl at _____ml/hr (125ml/m²/hr) IV.

Day 2

Hr 0 – Hr 1 **Etoposide (VP-16)** _____mg (100mg/m²) in _____mL (250ml/m²) D5W.45%NaCl IV over 1 hour.
***Ensure urine SG < 1.015 and negative for blood prior to giving cyclophosphamide.*
Hr 1- Hr 3 **Cyclophosphamide** _____mg (1000mg/m²) and **Mesna** _____mg (250mg/m²) in _____ mL D5W.45%NaCl IV over 2 hours.

Hr 3 – Hr 24 D5W.45%NaCl at _____ml/hr (125mg/m²/hr) IV.
Hr 5, 9, 13 **Mesna** _____mg (250mg/m²) in 50mls D5W.45%NaCL IV over 15 minutes.

Day 3

Hr 0 – Hr 1 **Etoposide (VP-16)** _____mg (100mg/m²) in _____mL (250ml/m²) D5W.45%NaCl IV over 1 hour.
Ensure urine SG < 1.015 and negative for blood prior to giving cyclophosphamide.
Hr 1- Hr 3 **Cyclophosphamide** _____mg (1000mg/m²) and **Mesna** _____mg (250mg/m²) in _____ mL D5W.45%NaCl IV over 2 hours.
Hr 3 – Hr 24 D5W.45%NaCl at _____ml/hr (125mg/m²/hr) IV.
Hr 5, 9, 13 **Mesna** _____mg (250mg/m²) in 50mls D5W.45%NaCL IV over 15 minutes.

Day 4

Hr 0 – Hr 1 **Etoposide (VP-16)** _____mg (100mg/m²) in _____mL (250ml/m²) D5W.45%NaCl IV over 1 hour.
Hr 1 – Hr 24 D5W.45%NaCl at _____ml/hr (125ml/m²/hr) IV.

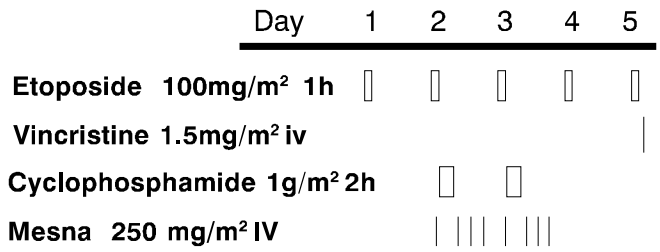
Day 5

Hr 0 – Hr 1 **Etoposide (VP-16)** _____mg (100mg/m²) in _____mL (250ml/m²) D5W.45%NaCl IV over 1 hour.
Hr 1 **Vincristine** _____mg (1.5mg/m²:maximum dose = 2mg) IV push.

Signatures: Date:_____

Ordered:_____ Checked:_____

CycEV



Explanation / Abbreviations used in the infusion plan:

D5%W0.45%NaCl = Dextrose 5% (5g/100ml) and NaCl 0.45% (0.45g/100ml) in sterile water (H_2O).

Body surface area (m^2): square root of (Body weight in kg / body height in cm/3600). You should get results such as: infants: 0.2, 30 kg children:1, adults: 1.7

Maintenance: Fluid intake is defined for this protocol as 100 ml/kg for the first 10 kg of body weight of the patient, 50 ml/kg for the 2nd 10 kg and 20 ml/kg for the remainder of the body weight per 24 hours. *E.g. 9 kg body weight: 900 ml per 24 hours. 19 kg body weight: 1000 + 450 = 1450 ml per 24 hours. 29 kg body weight: 1000 + 500 + 180 ml = 1680 ml per 24 hours.* Divide these numbers by 24 to obtain ml/hr.

Anaphylaxis precaution for Etoposide: As per institutional guideline: One option is to start with Diphenhydramine Hydrochloride (Benadryl) 1 mg/kg. Glucocorticoids should be avoided prior to and during carboplatin since induction of resistance against carboplatin cannot be excluded.

Hr: hour

IV: Intravenous

PO: per os = oral

TID: Three times per day

Antiemetic Treatment as per institutional guidelines: One option is Ondansetron 5 mg/m^2 for children or 8 mg total for adults PO or IV. TID. Glucocorticoids should be avoided if possible.

The infusion plan is a suggestion, it is not mandatory for the CPT-study. The infusion plan may be altered according to instituional / national guidelines. However, the drug choices and dosages are not to be modified without communication with the national representative.

Dose Modifications - Cyclophosphamide Block *CycEV*

Creatinine higher than the upper limit of the institutional normal range, but lower than twice the average institutional normal level measured for the first time*:* Add one day of hydration after vincristine. Measure creatinine weekly until the next block.

Creatinine higher than the institutional upper normal level but lower than twice the institutional average level, measured repeatedly with no signs of improvement*:* reduce cyclophosphamide by 25%, measure creatinine weekly.

Creatinine over 2 x average institutional level, measured for the first time*:* reduce cyclophosphamide by 35%.

Creatinine over 2 x average institutional level, measured repeatedly without signs of improvement*:* reduce cyclophosphamide by 50%.

Creatinine over 2 x average institutional level with further deterioration: substitute cyclophosphamide with procarbazine 50 mg/m^2 x 5 days.

Hematuria

Microhematuria: In case of microhematuria (measurable with laboratory methods but not grossly visible in urine): Double the Mesna for the ongoing and all of the following chemotherapeutic cycles.

Macrohematuria: In case of macrohematuria during a cycle: stop Cyclophosphamide infusion, give Mesna in twice the dose (500 mg/m^2) every 4 hours. In case of continuation of severe macrohematuria or clots in urine, a urinary catheter and Mesna bladder installation may help. Reduce cyclophosphamide in the following cycles by 50% for each of the two infusion days.

White Blood Cell Count

White blood cell count below 2000 at the planned point in time to start the block: wait and repeat CBC delay up to 3 weeks. If G-CSF is available, give G-CSF to recover white blood cell count. Discontinue G-CSF at least 48 hours prior to restarting the next chemotherapy and give G-CSF after each of the following blocks starting at day 9 after starting the chemotherapeutic block. In case the white blood cell count recovers during the waiting period with or without G-CSF, restart the next block with the originally planned dose. In case waiting with or without G-CSF results in white blood cell counts only between 1000 and 2000*:* calculate the absolute neutrophil count (=absolute counts of neutrophil granulocytes + absolute counts of neutrophil bands). If ANC > 500: Restart chemo with 20% reduction of Etoposide, and 20% reduction of Cyclophosphamide. The Etoposide reduction is done by deleting day 1 of the block and keeping the doses of day 2 to day 5 identical. The cyclophosphamide reduction is done by reducing the dose every day by 20%. If any of the drugs had been reduced already by other reasons compared to the previous block, do not reduce it further. If after waiting with or without G-CSF, the white blood cell count is between 1,000 and 2,000 and the ANC is between 200 and 500*:* reduce the cyclophosphamide dose by 35%, delete Etoposide on day 1 and day 5 (=40% reduction) and give Vincristine one day earlier (day 4 instead of day 5 at 100% of the dose). If after 3 weeks of waiting with or without G-CSF, the white blood cell count is still below 1000 or the ANC is below 200, and the patient has received at least 3 cycles of chemotherapy*:* discontinue chemotherapy. If the patient has not yet received 3 cycles of

chemotherapy: wait up to a further 3 weeks and proceed then with the same dose reductions.

Fever and neutropenia after the previous block: If the patient had relevant fever and neutropenia after the previous block*:* Doses of Etoposide and Cyclophosphamide will be reduced by 20% compared to the previous block. Neutropenia in this context is defined as white blood cell count below 1000 or ANC below 500. Significant fever is defined by: over 38.5 for more than 3 days or drop in blood pressure or drop in oxygen saturation during the fever.

Platelet Count

Platelet counts below 100,000: repeat blood cell counts and wait up to three weeks. If the platelet count recovers within 3 weeks*:* Proceed with the originally planned doses. If after 3 weeks of waiting, the platelet count is between 50,000 and 100,000: delete day one of Etoposide (=20% reduction of total Etoposide) and reduce Cyclophosphamide dose by 20*%.* If after 3 weeks of waiting, the platelet count does not recover higher than 50,000, and the patient has received at least 3 blocks of chemotherapy*:* discontinue chemotherapy*.* If, after 3 weeks of waiting, the platelet count does not recovery up to 50,000 and the patient has not received at least 3 blocks of chemotherapy yet*:* wait for further recovery of the platelet count up to 5 more weeks and then reduce the Cyclophosphamide dose by 50%, delete Etoposide on day 1 and day 5 and give Vincristine on day 4 instead of day 5.

Thrombocytopenia after the previous block: In patients with platelet count reductions below 20,000 for more than 3 days or patients who received platelet transfusions because of thrombocytopenia*:* Cyclophosphamide and Etoposide from the previous block should be reduced by 20% for the following block.

Polyneuropathy: If patients walk unsteadily due to polyneuropathy (areflexia and time relation to Vincristine, as opposed to central nervous system alterations caused by tumor or surgery*):* the Vincristine dose will be reduced by 50%. In case of further deterioration, Vincristine will be avoided until recovery, upon which point, it will be restarted at the 50% dose level. Chemotherapy will not be delayed due to polyneuropathy.

Constipation: In case of constipation or abdominal pain: give Lactulose (1mg/kg/day in divided doses). Enhance laxative treatment according to institutional guidelines. If, despite maximal laxative treatment, constipation deteriorates to abdominal pain*:* reduce Vincristine by 50%. In case of further deterioration, delete Vincristine from the chemotherapy. In case of ileus: delete Vincristine.

Age adjusted doses:
Patients older than 60 years of age: reduce dose as calculated per m^2 by 30% in the first block. When there are no relevant side effects after that block: increase the dose in steps of 10% for each block up to 100% of the originally planned dose.

Patients below one year of age: Use dosing calculated by body weight. Conversion of body surface to body weight dose: dose per m^2 divided by 30 = dose per kg.

Patients younger than 3 months of age: Reduce dose (calculated per kg) by 1/3.

Patients younger than 1 month of age: Reduce dose (calculated per kg) by 50%.

Patients younger than 2 weeks of age: Do not start chemotherapy before they reach 2 weeks of age.

***Termination of treatment by delay*:** When delays sum up to a total length of one year of treatment, chemotherapy is terminated. – Please notify the study coordinator.

CHOROID PLEXUS TUMOR CHEMOTHERAPY: CARBOPLATIN ARM CarbEV

For more detailed definitions see protocol

Week	Study/Chemo Date
0	MRI: *CR -/- residual tumor* *(please circle the best description)*
0	1,2,3,4,5,6,7 send slides, register
1	1,2,3,4, CarbEV____/_____/____
2	1,2,3,4 DD MM YY
3	1
4	1
5	1,2,3,4, CarbEV___/___/_____
6	1,2,3,4,5,6,7 DD MM YY
7	1, MRI: *CR / PR / SD / PD /CCR* *(please circle the best description)*
8	consider surgery again >3y age: wk 8 start irradiation wk 14 complete irradiation
9/15	1,2,3,4,5,CarbEV____/___/_____
10/16	1,2,3,4 DD MM YY
11/17	1
12/18	1
13/19	1,2,3,4, 7*CarbEV_____/____/___
14/20	1,2,3,4 DD MM YY
15/21	1
16/22	1
17/23	1,2,3,4,5 CarbEV____/____/____
18/24	1,2,3,4 DD MM YY
19/25	1
20/26	1
21/27	1,2,3,4,6,CarbEV____/_____/_____
22/28	1,2,3,4 DD MM YY
23/29	1
24/30	1
25/31	1
26/32	1
27/33	1 MRI: *CR / PR / SD / PD /CCR* *(please circle the best description)*
28/34	1 2,3,4,5,6 *Please circle abnormal results*
29/35	consider surgery again

italic week numbers refer to patients who are >3 years

Abbreviations:

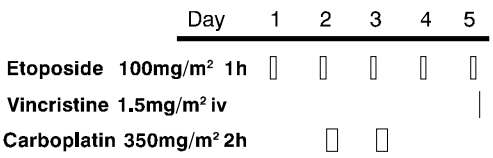
Studies:

1: white blood cell count, hemoglobin, platelets, differential
2: Na, K, Ca, P,
3: ALT/GOT, AST/GPT, bilirubin, LDH
4: Creatinine, Urea
5: 24 hour creatinine clearance or glomerular filtration rate
6: audiology
7: LP
7*: LP only, when previously positive.

MRI Response:

CR: complete remission (no tumor left)
PR: partial response (tumor size <50%)
SD: stable disease (tumor >50% <125%)
PD: progressive disease (tumor > 125%)
CCR: continuation of complete remission after gross total resection

CarbEV



Send registrations (week 0) response evaluation (week 7), end of treatment evaluation (week 28/*34*), and this roadmap to:

Johannes Wolff,
Alberta Children's Hospital
1820 Richmond Road S.W. Calgary
Alberta, Canada, T2T 5C7
Fax: Canada 403 228 4196
Tel: Canada 403 229 7272
Email:
johannes.wolff@crha-health.ab.ca

CHOROID PLEXUS TUMOR STUDY *CarbEV Infusion plan*
CARBOPLATIN / ETOPOSIDE / VINCRISTINE

Name: _____ Date of birth: _____

Height:_____cm Weight: _____kg Surface area: _____m^2

Requirements for this block: White blood cell count over 2000, platelet count over 100,000, no hematuria. Read dose modification guidelines for **age adjustment** and side effect adjusted dosing.

DAY 1

Hr 0 – Hr 1 **Etoposide (VP-16)** _____mg (100mg/m²) in _____mL (250ml/m²) in D5W.45%NaCl IV over 1 hour.
Anaphylactic precautions for etoposide
Hr 1 – Hr 24 D5W.45%NaCl at _____ml/hr (125ml/m²/hr) IV.

Day 2

Hr 0 – Hr 1 **Etoposide (VP-16)** _____mg (100mg/m²) in _____mL (250ml/m²) D5W.45%NaCl IV over 1 hour.
***Ensure urine SG < 1.015 and negative for blood prior to giving carboplatin.*
Hr 1- Hr 3 **Carboplatin** _____mg (350mg/m²) in _____ mL D5W.45%NaCl IV over 2 hours.
Hr 3 – Hr 24 D5W.45%NaCl at _____ml/hr (125mg/m²/hr) IV.

Day 3

Hr 0 – Hr 1 **Etoposide (VP-16)** _____mg (100mg/m²) in _____mL (250ml/m²) D5W.45%NaCl IV over 1 hour.
Ensure urine SG < 1.015 and negative for blood prior to giving carboplatin.
Hr 1- Hr 3 **Carboplatin** _____mg (350mg/m²) in _____ mL D5W.45%NaCl IV over 2 hours.
Hr 3 – Hr 24 D5W.45%NaCl at _____ml/hr (125mg/m²/hr) IV.

Day 4

Hr 0 – Hr 1 **Etoposide (VP-16)** _____mg (100mg/m²) in _____mL (250ml/m²) D5W.45%NaCl IV over 1 hour.
Hr 1 – Hr 24 D5W.45%NaCl at _____ml/hr (125ml/m²/hr) IV.

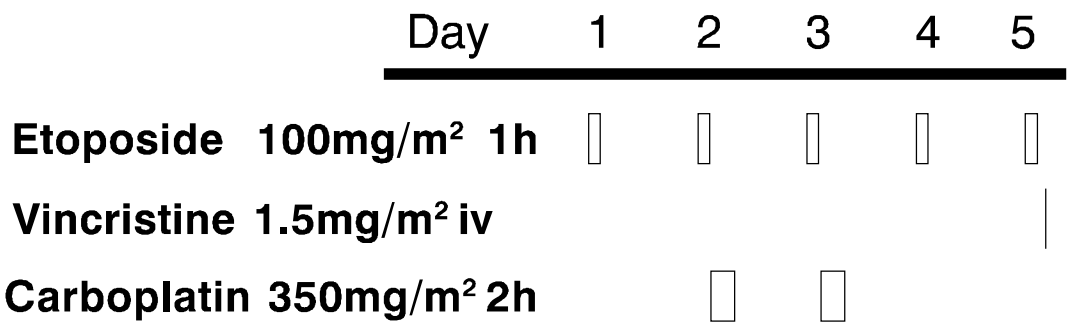
Day 5

Hr 0 – Hr 1 **Etoposide (VP-16)** _____mg (100mg/m²) in _____mL (250ml/m²) D5W.45%NaCl IV over 1 hour.
Hr 1 **Vincristine** _____mg (1.5mg/m²:maximum dose = 2mg) IV push.

Signatures: Date:_____

Ordered:_____Checked:_____

CarbEV



Explanation / Abbreviations used in the infusion plan:

D5%W0.45%NaCl = Dextrose 5% (5g/100ml) and NaCl 0.45% (0.45g/100ml) in sterile water (H_2O).

Body surface area (m^2): square root of (Body weight in kg / body height in cm/3600). You should get results such as: infants: 0.2, 30 kg children:1, adults: 1.7

Maintenance: Fluid intake is defined for this protocol as 100 ml/kg for the first 10 kg of body weight of the patient, 50 ml/kg for the 2nd 10 kg and 20 ml/kg for the remainder of the body weight per 24 hours. *E.g. 9 kg body weight: 900 ml per 24 hours. 19 kg body weight: 1000 + 450 = 1450 ml per 24 hours. 29 kg body weight: 1000 + 500 + 180 ml = 1680 ml per 24 hours.* Divide these numbers by 24 to obtain ml/hr.

Anaphylaxis precaution for Etoposide: As per institutional guideline: One option is to start with Diphenhydramine Hydrochloride (Benadryl) 1 mg/kg. Glucocorticoids should be avoided prior to and during carboplatin since induction of resistance against carboplatin cannot be excluded.

Hr: hour
IV: Intravenous
PO: per os = oral
TID: Three times per day
Antiemetic Treatment as per institutional guidelines: One option is Ondansetron 5 mg/m^2 for children or 8 mg total for adults PO or IV. TID. Glucocorticoids should be avoided if possible.

The infusion plan is a suggestion, it is not mandatory for the CPT-study. The infusion plan may be altered according to instituional / national guidelines. However, the drug choices and dosages are not to be modified without communication with the national representative.

Dose Modifications - Carboplatin Block (CarbEV)

Creatinine higher than the upper limit of the institutional normal range, but lower than twice the average institutional normal level documented for the first time*:* Add one day of hydration after Vincristine. Measure creatinine weekly until the next block.

Creatinine higher than the institutional upper normal level but lower than twice the institutional average level, documented over two courses of chemotherapy with no signs of improvement*:* reduce Carboplatin by 25%, measure creatinine weekly.

Creatinine over 2 x average institutional level, documented for the first time*:* reduce Carboplatin by 35%.

Creatinine over 2 x average institutional level, documented over two courses of chemotherapy without signs of improvement: substitute Carboplatin with Carboplatin 250 mg/m^2 over 22 hours x 2 days. – Continue to check creatinine. Carboplatin is less nephrotoxic but not completely free of nephrotoxicity.

Audiology:

Hearing loss more than 30 dB at 3000 Hz but less than 50 dB at 3000 Hz measured for the first time*:* reduce Carboplatin by 30%.

Hearing loss more than 50 dB measured repeatedly with further deterioration: substitute platinum drugs with procarbazine 50 mg/m^2 x 5 days.

White Blood Cell Count:

White blood cell count below 2000 at the planned point in time to start the block*:* wait and repeat CBC twice weekly, up to 3 weeks delay. If G-CSF is available, give G-CSF to recover white blood cell count. Discontinue G-CSF 48 hours prior to restarting the chemotherapy. Give G-CSF after each of the following blocks starting at day 9 after starting the chemotherapeutic block. In case the white blood cell count recovers during the waiting period with or without G-CSF: restart the next block with the originally planned dose. In case waiting with or without G-CSF results in white blood cell counts only between 1000 and 2000*:* calculate the absolute neutrophil count (=absolute counts of neutrophil granulocytes + absolute counts of neutrophil bands). ANC > 500: Restart chemotherapy with 20% reduction of Etoposide, and 20% reduction of Carboplatin. The Etoposide reduction is done by deleting day 1 of the block and keeping the doses of day 2 to day 5 identical. The Carboplatin reduction is done by reducing the dose every day by 20%. If any of the drugs had been reduced already for other reasons compared to the previous block, do not reduce it further. If after waiting 3 weeks past the due date, the white blood cell count is still between 1,000 and 2,000 or the ANC is between 200 and 500: reduce the Carboplatin dose by 35%, delete Etoposide on day 1 and day 5 (=40% reduction) and give Vincristine one day earlier (day 4 instead of day 5 at 100% of the dose). If after 3 weeks without G-CSF, the white blood cell count is still below 1000 or the ANC is below 200, and the patient has received at least 3 cycles of chemotherapy*:* discontinue chemotherapy. If the patient had not yet received 3 cycles of chemotherapy: wait until a further 3 weeks and proceed then with the same dose reductions.

Platelet Counts

Platelet counts below 85,000: repeat blood cell counts twice weekly and wait up to three weeks. If the platelet count recovers within 3 weeks: Proceed with the originally planned doses. If after 3 weeks of waiting, the platelet count is only between 50,000 and 85,000*:* delete day one (=20% reduction) of total Etoposide and reduce platinum dosage by 20%. If after 3 weeks of waiting, the platelet count does not recover higher than 50,000, and the patient has received at least 3 blocks of chemotherapy*:* discontinue chemotherapy. If, after 3 weeks of waiting, the platelet count does not recover up to 50,000 and the patient has not received at least 3 blocks of chemotherapy yet*:* wait for further recovery of the platelet count for up to 5 more weeks and then

reduce the platinum dose by 50%. Delete Etoposide on day 1 and day 5 and give Vincristine on day 4 instead of day 5.

Thrombocytopenia after the previous block: In patients, who had less than 20,000 platelets for more than 5 days or in patients who received platelet transfusions because of thrombocytopenia: Carboplatin and Etoposide from the previous block should be reduced by 20% for the following block.

***Fever and neutropenia** after the previous block:* If the patient had relevant fever and neutropenia after the previous block: Doses of Etoposide and Carboplatin will be reduced by 20% compared to the previous block. Neutropenia in this context is defined as white blood cell count below 1000 or ANC below 500. Significant fever is defined by: over 38.5 for more than 3 days or drop in blood pressure or drop in oxygen saturation during the fever.

Polyneuropathy: If patients walk unsteadily due to polyneuropathy (areflexia and time relation to vincristine, as opposed to central nervous system alterations caused by tumor or surgery), the Vincristine dose will be reduced by 50%. In case of further deterioration, Vincristine will be avoided until recovery, at which point it will be restarted at the 50% dose level. Chemotherapy will not be delayed due to polyneuropathy.

***Constipation*:** In case of constipation or abdominal pain, give Lactulose (1mg/kg/day in divided doses). Enhance laxative treatment according to institutional guidelines. If, despite maximal laxative treatment, constipation deteriorates to abdominal pain: reduce Vincristine by 50%. In case of further deterioration: delete Vincristine from the chemotherapy. In case of ileus: delete further Vincristine.

Age adjusted doses:

Patients older than 60 years of age: reduce dose as calculated per m^2 by 30% in the first block. When there are no relevant side effects after that block: increase the dose in steps of 10% for each block up to 100% of the originally planned dose.

Patients below one year of age: Use dosing calculated by body weight. Conversion of body surface to body weight dose: dose per m^2 divided by 30 = dose per kg. Substitute D5%W0.45%NaCl with D5%W0.2% NaCl or equivalent infusion with less sodium.

Patients younger than 3 months of age: Reduce dose (calculated per kg) by 1/3.

Patients younger than 1 month of age: Reduce dose (calculated per kg) by 50%.

Patients younger than 2 weeks of age: Do not start chemotherapy before they reach 2 weeks of age.

***Termination of treatment by delay*:** When delays sum up to a total length of one year of treatment, chemotherapy is terminated . Therefore, the total duration of therapy (including delays) will be one year, even if not all scheduled chemotherapy courses have been given. Notify the study coordinator, when treatment is terminated (fax to +1 403 229 7684).

TUMOR STAGING / RESPONSE CRITERIA

After maximal initial surgery, tumor staging will be done. This will include a physical exam (including neurological exam), neuroimaging and a lumbar puncture (LP).

The diagnostic imaging is to be done earlier than 72 hours after tumor resection. Later scanning will not allow differentiation between reactive angiogenesis and residual tumor, both of which are contrast enhancing. The preferred method is magnetic resonance imaging (MRI). Axial T1 weighted images and proton weighted images of the brain without contrast, followed by contrast enhanced axial T1 and 2-3 further planes of the brain and sagittal and axial contrast enhanced spinal images should be done at this point in time. Not all national groups participating in this study have been able to commit to MRI imaging in this time frame. As the primary question of this study measured survival, this does not exclude these groups from the study. Patients without imaging can not be evaluated for response (secondary objective).

For the definition of tumor resection, this study follows the usual Gnekow-criteria (Gnekow et al 1995).

M1 status (tumor cells in cerebrospinal fluid but no indication of metastasis on diagnostic imaging/MRI) has become increasingly rare with the improvements of diagnostic imaging. In early postoperative phase, surgical debris may mimic tumor cells. Therefore, an initial pathological lumbar puncture without correlate in diagnostic imaging, should be repeated at day 14 post surgery. Unquestionable M1 findings at this point in time classify the disease as metastatic. Questionable findings are to be discussed with the national representative, and if appropriate, with the international study coordinator and the reference pathologist. The final decisions, if a disease will be classified as metastatic in the terms of this protocol will made **by the national representatives,** who are able to read the reports and discuss the findings with the treating physicians in their own languages.

Drawing blood for measuring CEA (carcinoembryonic antigen, Paulus 1990, Kato 1996) as a potential tumor marker for CPC is encouraged, in order to gain experience on the national/group level, but it is not a mandatory part of the study.

Evaluation criteria:

Survival time: The primary objective of the main phase of this study will be to compare the drugs Cyclophosphamide and Carboplatin. This will be done by comparing survival times. The survival time is defined as the time from starting the adjuvant treatment protocol of this study until the end of the observation (censored data) or the death of the patient. For this analysis, there will be no difference between death caused by tumor progression, treatment related (toxic) reasons, or unrelated reasons.

Event free survival time: The event free survival time in this study is the time between starting the protocol and the end of the observation time (censored data) or an event. Events in this definition are: death (any reason), tumor progression, and second malignancy.

Resectability after chemotherapy: Since several individual observations have suggested, that chemotherapy in addition to shrinking CPC in 20-40% of the patients, may also make them

more resectable by reducing their vascularity, this study will attempt to measure this in a standardized way. Resectability will be measured by the success of the surgery performed after the second block of chemotherapy. The classification of resection will follow the Gnekow criteria (Gnekow 1995).

Response to Chemotherapy: The classical response criteria for phase II studies will be evaluated as a secondary objective. It will be measured after the second block.

CR: Complete Response (no tumor left): this includes all patients with stable or improving neurological status, who had measurable evidence of tumor prior to starting the adjuvant treatment, but who show evidence of complete tumor disappearance and no new evidence for tumor recurrence. Disappearance of tumor cells from cerebrospinal fluid (CSF) is included in this definition.

PR: Partial Response: this includes all patients with stable or improving neurological status, who had measurable evidence of tumor prior to starting the adjuvant treatment, but who show evidence of tumor shrinkage of 50% or more of the largest measurable diameter, or who have a decrease of 50% or more in the number of tumor cells in the CSF without reaching CR.

SD: Stable Disease this includes all patients with measurable evidence of tumor prior to starting the adjuvant treatment, but whose tumor has shrunk by less than 50%, has remained unchanged or has grown by less than 25% of the largest measurable diameter, or whose tumor cell number in the CSF has decreased by less then 50% or increased to less than 125% of the original number.

PD: Progressive Disease this includes all patients with measurable evidence of tumor prior to starting the adjuvant treatment, but whose tumor has grown by 25% or more of the largest measurable diameter, or whose tumor cell number in the CSF has increased by 25% or more.

DATA ANALYSIS

(Chapter modified by R. Sposto 06.2000)

Prephase:

The prephase of the choroid plexus tumor study is observational. It serves to determine the feasibility of the study. Most critical is the number of randomized patients, from whom follow up data arrive at the international office in Calgary. A table will contain the number of patients from each participating nation (1) registered - (2) randomized and - (3) randomized with follow up information for each 3 month period since the study is activated. Following the experience of other international studies, it is assumed, that the enrollment will increase over the first three years after activating the study. Predicted numbers for three categories for the first year are: 8 – 4 – 0, and for the second year: 30 – 20 – 4, respectively. The total number and the increase with time will be used to estimate the number of patients available for the following main phase of the study. The final analysis of the prephase will be the calculation of accrual time and observation time necessary for the following main phase of the choroid plexus tumor study.

This study will be considered feasible to continue after the prephase, if sufficient numbers of patients can be randomized within five years to provide a reasonably precise comparison of the effect of CDDP vs Cyc on survival. Although preliminary data are somewhat uncertain, it is reasonable to assume that 50% of patients will be alive at 4 years and that approximately 25% will be long-term survivors.

The table below shows the minimum yearly accrual rate as a function of total years of accrual and the number of years of follow-up for the last randomized patient. This computation is based on a two-sided log rank test with 5% type I error and 80% power to detect a halving of the failure rate, with a 2.5%/year loss-to-follow-up rate (Sposto 1985).

	Minimum required yearly accrual by years of accrual and years of follow-up		
	3 years follow-up	4 years follow-up	5 years follow-up
5 years accrual	33	30	29
6 years accrual	27	25	24
7 years accrual	22	21	20
8 years accrual	19	18	17.

This study will be considered feasible if final analysis within 10 years of study activation will result in power specified above. Based on the table above, a minimum annual accrual of 20 randomized patients per years will be a reasonable goal.

In the evaluation of the pre-phase of the study, the average yearly accrual between month 7 and month 24 will be computed, and compared to the target accrual rate of 20 per year.

As a secondary objective, the prephase will also gain administrative and organizational experience for a study performed worldwide in adults and children. Two ways of communication will be offered for the prephase: Internet/Email and FAX. The experience of the first two years will determine if both ways are indeed necessary. Primary communication partners for treating physicians are the national study representatives. Those representatives will give feedback on how well the protocols run in their nations. At the end of the prephase, the need for translating the protocol into other languages will be determined based on those comments.

Main Phase:

The primary objective will be addressed in a comparison of two randomized treatment groups using the "intend to treat" definition for these groups. The only difference between the two treatment groups is the use of carboplatin in one and cyclophosphamide in the other arm of the study. The primary endpoint is overall survival after start of adjuvant treatment. Kaplan Meier-projected overall survival curves will be produced to make sure that the curves do not cross. The log rank test will then be used to compare the two treatment groups. Homogeneity of the composed groups will be checked for: age, gender, tumor location, degree of resection, compliance to randomization, irradiation, and discontinuation of treatment.

Secondary objective resectability: The success of surgery after the first two cycles of chemotherapy will be compared between the two treatment arms. The percentage of patients with secondary complete remission from those with incomplete primary resection, will be used to analyze this question. In this way, tumors with complete response and tumors which could be completely resected after two cycles of chemotherapy, will be counted together. The frequency will be compared among the two treatment arms using the Chi-square test.

Secondary Objective Response: The frequency of partial or complete response after two cycles will be compared among the two treatment arms using the chi square test.

Secondary objective SV40: The prognosis of tumors with or without SV40 will be compared using overall survival time as endpoint and Kaplan Meier survival estimates and log rank tests as statistical methods similar to the analysis of the primary objective.

The prognostic relevance of histological parameters, including SV40 detection, proliferation, and malignancy markers will be addressed in the histological reference centre. The histological parameters will be evaluated and encoded as described in the pathology section. The database will be merged with the clinical database and the parameters will be analyzed in univariant and multivariant analyses parallel to the analyses of the clinical variables using the same endpoints and statistical methods. These data will also be used as a hypothesis generating tool to determine the frequency of SV40 antigen in various subpopulations. It is, for instance, possible that SV40 positive tumors have different age, gender or location distribution as compared to SV40 negative tumors. This will allow a generation of a hypothesis about the pathogenesis of the tumors.

A multivariate analysis using the Cox regression model will gain further information on the relevance of these variables, and can be used for analyzing the treatment results when the groups turn out to be inhomogeneous in a prognostic relevant parameter.

QUALITY CONTROL

Quality control of this multidisciplinary, intercontinental study will be done in a network setting with different assignments for different tasks:

Chemotherapy quality control will be done by the national representatives, the international study coordinator, and the data monitor. The international study coordinator will monitor in detail the toxicity data of the first two blocks of chemotherapy, and the residual sequelae after completion of the protocol. Data for this control are included in the forms 3 and 4. In addition, timing of the chemotherapy, and compliance with randomization will be monitored using the roadmaps, which are submitted for each patient. The data monitor will, on a semiannual base, review these data based upon the report of the international study coordinator. The national representatives will monitor the study based upon the national requirements. They will receive copies of all forms from patients in their nation from the international study coordinator, as soon as they come in. In addition, the national representatives will ask for further data on a national basis, as appropriate for the local regulations and the local available resources in the participating centres.

Radiotherapy quality control will be done by the international radiotherapy reference center, using the forms included in this protocol. These forms will be filled in by the local radiation oncologists/radiotherapists and be sent directly to the radiotherapy reference center, where they are reviewed on an ongoing basis. If communication is necessary, the reference center will contact the local radiotherapy centre directly, and inform the international study centre if appropriate. The radiation reference center will participate in creating the reports mentioned below.

Neuropathology quality control will be done by the international neuropathology reference center. Submitted material includes slides and reports of the local neuropathologist. Review of slides and special stainings will depend on additional laboratory funding. Presently, in the absence of funding, the slides will be stored and reviewed once per year. In case of disagreement with the primary pathologist, the reference center will contact the local neuropathologist/pathologist as appropriate for the clinical situation, and the culture of the center. For the purpose of the study, the histological diagnosis of the reference center will be used for data analysis.

Neurosurgery quality control will be done by the neurosurgery reference center in coordination with the national groups. The international study coordinator will forward the surgical information (operative notes, local classification of degree of resection as reported on the forms) to the neurosurgery reference center. However, the national representatives might have a better insight into the success and morbidity of neurosurgery as reported by the various centers. Therefore, in case of an apparent need for communication, the reference neurosurgeon will contact the national study representatives first.

Diagnostic Imaging quality control will be done on a national base by the national representatives according to national/group guidelines. Standards of various nations differ largely in this discipline. At present, an international quality control could not be agreed upon in the intercontinental setting of the choroid plexus tumor study. The national representatives will describe their experience to the group as a part of the reports at the end of the pre-phase. Based on these reports, imaging guidelines will be considered for the mainphase of the study.

PROTOCOL MODIFICATIONS

1. Planned major modification: This study starts with a prephase, the objective of which is to evaluate feasibility and available patient numbers for the study. Unless the study closure criteria apply earlier, the prephase will be two years. Prior to starting the main phase, a large international discussion will occur similar to, but faster than the discussion to start the study. In this discussion, the time necessary to perform a randomized phase III study with the available patient numbers will play the dominant role. The treatment protocol, particularly the chemotherapy and the radiotherapy guidelines, as well as the mode of communication will be reviewed using the experience of the prephase. Leadership and reference centers might be reconsidered. Because the outcome of this discussion is unpredictable, the various national groups cannot commit in advanced to the main phase. By the end of the discussion, the international study coordinator will again ask for commitment to participation similar to the prephase.

2. Unplanned Minor Treatment-Modifications: Minor modifications of the protocol, such as alterations to the guidelines provided with the protocol that do not affect the scientific objectives of the study, may be requested by the data monitor, any member of the protocol committee, any member of the reference centers, or any SIOP member who has enrolled at least one patient into the randomization part of the study. The request will be in the form of a finally useful wording for a protocol amendment. General nonspecific recommendations will not be considered. The international study coordinator and the biostatistician of the study will decide if the requested alteration is indeed minor. In they disagree, the data monitor will make the decision. In case the requesting member is one of the three, one of the national representatives will substitute for the role of the requesting person. The international study coordinator will bring the request to a vote in the protocol committee via email. Simple majority of the votes received back within 10 days will determine the protocol alteration. If the committee voted for the alteration, the international study coordinator will inform all national representatives and the scientific committee of SIOP about the changes. Informing and obtaining approval of local ethic committees will be the responsibility of the local institutions, which are notified by their national representatives.

3. Unplanned Major Protocol Modifications: Major protocol modifications include anything that affects the primary objective of the protocol, in particular the choice of the dosing of the chemotherapeutic agents. The decision-making process will be similar to the unplanned minor treatment modifications with the exception that the period of voting will be 1 month as opposed to 10 days, and that the number of votes received must be 50% or larger of the number of persons eligible to vote.

4. Minor Modification Without Impact on Treatment: Minor modifications without impact on the patient's treatment and without impact on the primary objective may be based on a less rigorous review process. Examples include the change of an address or telephone number of one of the reference centers or corrections of critical typographical errors. Those changes will be made by the international coordinator in communication with the appropriate reference center or the data monitor. The international study coordinator is committed to keeping those changes to a minimum. Should changes be unavoidable, the information about the amendment will follow the same routes as mentioned above. Addition of new national representatives and translations of the protocol or parts (Consent form) to more languages, will not be documented as amendments.

5. Study closure: The study can be closed for one of five reasons: 1. Insufficient Accrual 2. Completed Accrual, 3. Closure caused by new information, 4. Closure requested by the Monitor, and 5. Closure due to unexpected high toxicity. Details are described below:

Insufficient Accrual: The study will be closed if insufficient accrual occurs. Necessary accrual is defined by:
First year - 8 patients, 3 of which are randomized.
End of the second year: 10 patients in total, at least 5 of which are randomized.
At the end of the second year, continuation of the study will be evaluated. At that time also, the closure limits for the following years will be determined. In general, the accrual has to be sufficient, so that an answer to the primary study question appears possible.

Completed Accrual: The Prephase of the study will be closed, if all of the following requirements have been completed unexpectedly early. There will not be a closure of single strata of this study:
Randomized patients below 3 years of age: 50.
Randomized patients older than 3 years of age: 40.
The Main phase of the study will be closed, when the accrual is complete. The number of patients necessary will be calculated at the end of the prephase. It is estimated, that this number will be approximately 90 randomized patients.

Closure caused by new information: This study is based on a systematic literature review. Medical science makes inconsistent and somewhat unpredictable progress. It is possible that new information will become available, which makes the continuation of the study unreasonable. The study coordinator, data monitor, and biostatistician will make this decision after consulting with members of the protocol committee. In this case, a new treatment protocol will be written and substituted for this study. The old study will not be closed unless the new study has passed all committees and achieved ethical approval (IRB approval) in at least one center.

Closure requested by the Monitor: The study coordinator will prepare a report on a half-yearly basis. He/she will submit this report via e-mail to the data monitor. Specifically, this report will include the number of patients registered, the number of patients reported as deceased, and significant side effects from treatment. The data monitor can request closure of the study. This will be discussed with the biostatistician and the study coordinator. In case of disagreement, the arguments will be presented to the scientific committee of SIOP.

Closure due to unexpected high toxicity: The chemotherapy in this protocol in not novel. The toxicity can be predicted. Monitoring toxicity is done in three ways: (1) Reasons for protocol deviations and toxic death from chemotherapy are elements of the Form 3 (response to treatment after two cycles), (2) Reasons for protocol deviations, toxic death, and toxicity at the end of treatment are elements of the Form 4 (end of treatment), (3) the national representatives will keep close informal contacts with the treating physicians according to their national guidelines. In case of unexpected toxicity, they will contact the international study coordinator. The study will be closed or significantly modified if toxic death from treatment occurs in the following frequency: 1 in the first 5 patients, 2 in the first 20 patients, 3 in the first 50 patients, 4 in the first 100 patients. Only toxic deaths clearly caused by the chemotherapy are counted in this respect. In case of unexpectedly high but not deadly toxicity, the study coordinator will consult the members of the protocol committee by email to implement amendments to the protocol or close the study.

REPORTS, PUBLICATIONS

An annual short report will be submitted as an abstract for each SIOP meeting to be published in Medical and Pediatric Oncology.

After completing the prephase, a complete report will be made by the international study coordinator, and sent to the national representatives, all reference centers of the study, the data monitor and the scientific committee of SIOP. Based upon his report, the protocol committee will decide which publications should be written and will assign this task to certain members.

The results of the primary objective of the main phase will be presented, and publication assignments will be given in a similar way as in the prephase. It is to be expected, that more than one publication will be written.

Assignments for writing will be distributed as homogenously as possible among the participating continents and medical specialties. For instance, publication of the primary objective of the main phase should be assigned to the international study coordinator, but the next chemotherapy questions should be assigned to another person such as the national representative of the group which entered most patients or the biostatistician. Data of other subspecialties such as neurosurgery, neuropathology and, radiation therapy should be summarized and published by those representatives. None of these assignments will be made before the data are available. If a consensus about these assignments can not be reached in the large group of the protocol committee, a subcommittee will be formed by the international study coordinator, the data monitor, and the reference neuropathologist, neurosurgeon, radiation oncologist, the biostatistician, and the three national representatives, which enrolled most patients into the study. The decision will then be made by majority vote.

National groups, provided they mention their link to the SIOP study and their results match with their data in the SIOP database, can publish results of national series.

ETHICAL CONSIDERATIONS

Patients with choroid plexus tumors deserve medical progress as much as patients with any other deadly disease. Unfortunately the disease is so rare, that meaningful clinical studies are very difficult and economic interest in performing clinical studies is non-existent. A clinical study has to be done in an intercontinental setting, using minimal resources. This makes compromises in many areas necessary, including the details of ethical considerations mentioned in the protocol, which aren't possible to cover by all national standards.

The study aims to create data that will impact on treatments for improved survival of patients with choroid plexus tumors. The treatment included in this protocol is not new. Variations of the drug combinations used here have been used in many chemotherapy protocols for brain tumor patients. The drugs used are licensed in all countries, from which the international study coordinator could get the appropriate information. The drugs are not expensive, and will not create a burden on any national or institutional budget, beyond the normal treatment given to these patients outside of this protocol. The protocol will also not create any data, which could be used by a pharmaceutical company to license anything such as a new drug. A financial compensation for participation on the study is not possible.

This international study follows the declaration of Helsinki (see appendix) and the good clinical practice (GCP) guidelines (ICH-GCP 6.2.5) assured by a specific independent review performed by the German cancer society (Deutsche Krebsgesellschaft) done in June 2000, as close as possible in this setting. However, institutional/local ethical approval shall follow accepted national practice. Accepted national procedures for patient consent as documented shall be used.

Participation in this study is voluntary. No compensation for participation can be provided to the patients or their families or participating centers. In the event that physical injury occurs as a result of this study, treatment for injury will be available as in any case of treatment-related injury according to local institutional guidelines. Neither the treating hospitals, the study coordinating center, nor the University of Calgary and the Alberta Children's Hospital, which host the study coordinating center, can provide reimbursement for medical care or other compensation. Acknowledgement of this has to be a part of the consent form of the information sheet provided to the patients/parents by the treating institution according to local/national regulations.

Patients, and if appropriate their parents, shall be informed about the study. Guidelines for the information to be given may follow the patient information sheet. Translations of this Information sheet to the national languages are encouraged. Patients/parents will then be asked for consent to participate in the study. A sample consent form, as standardized at the Alberta Children's Hospital and the University of Calgary, are included as appendix. Translation and modification according to national guidelines are encouraged. Should the patients/parents give informed consent, the registration will be done.

The data submitted to the study centre will contain the name, first name and data of birth. This reflects the standard for registration in the North American Children's Oncology Group, the German Society for Pediatric Oncology and Hematology and most other national groups. Data will be made anonymous prior to submission for publication, external review, data monitoring or any communication not particularly necessary for the care of this particular patient. All communication with the treating physician, and the national representative will include anonymous information, if this is preferred by the data submitting person. In this case, the

further communication will be via use of a patient number assigned by the international study coordinator. The submitting physician will enter this number instead of the name into the appropriate fields of the forms 2-5. The international database will also provide anonymity, and will be password protected in a locked office at the international study center. The power of this computer will be turned off, unless someone is physically working on it. The personal data connecting the numbers with the patients' names will not be kept in computer format, but instead will be documented on paper and locked in the same office. Data transmission will be done in various ways. Some national groups, such as the Children's Oncology Group, have developed direct remote data entry protocols for clinical studies. Those data are transmitted via the internet. This study allows such a data entry. The data transmission has been tested in the development phase of the study in an intercontinental setting. Data transmitted in this way will be printed and the personal data will be deleted as soon as it has arrived at the international data center. Some national guidelines/laws do not allow such data entry. For those centers, the data forms in the appendix of this protocol have been developed. They may be transmitted via fax or regular mail. If mail is chosen, the centers are encouraged to follow-up the second form (second registration) with a phone call to the data manager of the international study center, to ensure that the results of the randomization reached the treating center in time.

ECONOMIC CONSIDERATIONS

National: Choroid plexus tumors are rare. Running this study will not have a relevant influence on any health care budget. Success of the study, which means increased numbers of survivors, will also not increase national tax revenues significantly either. However, when this is viewed as a pilot for worldwide clinical studies including pediatric and adult patients, it could start a series of other studies for rare diagnoses, which as a whole will have economic impact.

Study coordination: This protocol is written, so that it can potentially run without financial support. Many of the participating members have academic positions, and consider the invested time an element of their protected research time. Others are willing to donate their time. However, the likelihood of success is much higher, when funding becomes available. The international study coordinator intends to seek financial funding as soon as the study is officially finalized. In addition, the national representatives and reference centres are encouraged to approach independent national sources.

Treating Institution: The treatment recommended here is inexpensive. In July 2000 expenses for chemotherapeutic agents used in this protocol were in Canada: Etoposide 100 mg vial = $13.50, VCR 1 mg vial = $3.85, Carboplatin 450 mg vial = $54.95, Cyclophosphamide 1 g vial = $8.25, Mesna 1 g vial = $48.07. Most patients are infants, but the age range might go up to adult patients. Assuming a patient with 1 m^2 body surface (older child), the following costs will accrue for medication:

1 block CarbEV:		**1 block CycEV:**	
VP16 5x100mg : $67.50		VP16 5x100mg : $67.50	
VCR 2x1mg : $7.70		VCR 2x1mg : $7.70	
Carboplatin $109.90		Cyc 2x1g : $16.50	
Total:	$185.10	Mesna 2x1g : $96.14	
		Total:	$187.84

6 blocks for a 1 year treatment will sum up to: $1110.60 for CarbEV and to $1127.04 for CycEV.

Additional costs for supplies, such as syringes and tubing, are in the same order of magnitude as the chemotherapeutic agents. Supportive care drugs are dependent on institutional guidelines. High costs can be caused by GCSF or Ondansetron, when the institution chooses to use them. Further costs will be created by diagnostic imaging. Three MRIs are required for the study, but experience shows, that further MRIs or CCTs are necessary for clinical reasons throughout the treatment. Patients older than three years will receive irradiation. Some of these patients will require sedation during irradiation. However, none of these costs are caused by the study, as they simply reflect the standard of care as evident from the literature and summarized in the protocol. Direct study costs are only the working time invested to fill in the five forms, and the costs for communication such as FAX or Email, and the costs to send out the histological slides. Reverse participation in the study offers a high quality consultation system for clinical questions arising during treatment, and a second opinion on the histological diagnosis, which might be more valuable than the invested time for documentation.

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APPENDICES

INTERNATIONAL STUDY FOR THE TREATMENT OF CHOROID PLEXUS TUMORS

INFORMATION FOR PATIENTS AND PATIENTS' FAMILIES

This document is meant to inform you about choroid plexus tumors, the treatment, and the international choroid plexus tumor study, for which we are asking your support. This should give general information about the most frequently asked questions at the beginning of brain tumor treatment. It should supplement but not substitute the information provided to you by treating physician.

What is a tumor? A tumor is tissue which grows at a time and in a location of the body where it is not supposed to grow. Like all tissues, a tumor is made out of cells. These cells share many characteristics with normal body cells, from which they probably arise. Tumor cells, however, differ from normal cells in that they keep proliferating even when this is not beneficial for the remainder of the organism. Regulatory mechanisms which stop proliferation in normal cells are not functioning enough in tumor cells, while mechanisms making them grow are over-active. Various tumor types comprise a large spectrum with regards to how much they differ from normal cells. At one end of the spectrum are benign tumors. In general, these tumor cells closely resemble certain types of normal cells. They grow slowly, do not infiltrate surrounding normal tissue, and they stay in the place of their origin. At the other end of the spectrum is the malignant tumor, which is also called 'cancer'. These tumor cells proliferate quickly, infiltrate normal tissue, and can separate from the normal tumor, adhere in a different place of the body, continue to grow there and form a second tumor in this place. These distant tumors are called 'metastases'.

What is the choroid plexus? Choroid plexus is normal tissue in the brain which produces cerebral spinal fluid. It is located in normal fluid spaces at the centre of the brain, which are called 'ventricles'. There is a lateral ventricle on the right, and one on the left, as well as a third and a fourth ventricle at the middle of the brain. The cerebral spinal fluid is a clear, water-like fluid which slowly flows from the lateral to the third and then to the fourth ventricle, after which it leaves the middle of the brain to be reabsorbed in the tissue surrounding the central nervous system. Tumors arising from the choroid plexus are called 'choroid plexus papilloma' when they are relatively benign, or 'choroid plexus carcinoma' when they are more malignant.

What is the cause of choroid plexus tumors? There are four main groups of causes which are discussed in cancer research: inherited susceptibility for cancer, radioactivity, chemicals, and viruses. With respect to choroid plexus tumors, a link has been described to a familial syndrome called Li-Fraumeni syndrome. In those families, breast cancer, sarcoma, leukemia, and other brain tumors are more frequent. It is caused by an alternation of the p53 gene. In addition, there is experimental evidence that the Simian virus 40 (SV40) can cause choroid plexus tumors in animals. This virus is otherwise harmless to humans and it is still not clear if it can really cause choroid plexus tumors in humans. The international study for choroid plexus tumors attempts to answer this question.

How frequent are choroid plexus tumors? This type of tumor is very rare. Exact numbers are not known. However, it can be estimated that 1,500 new tumors of this type occur in the world per year. Most of these tumors occur in infants, but they can occur at any age. The exact distribution and frequency is unknown. The international study attempts to create more reliable data to clarify these points.

Is the tumor deadly? Yes - if there was no treatment, a fatal outcome from the disease is most likely. But this tumor can be treated, and the treatment will quite frequently be successful. The likelihood of a successful outcome depends on many variables, such as the age of the patient, the location and size of the tumor, and whether or not the tumor has already spread (metastasized). Overall, about half of the patients survive for 10 or more years after the diagnosis, which comes close to a cure from the tumor disease. The two most important factors which determine whether or not an individual will be in the group of survivors, are the microscopic picture of the tumor (benign or malignant, papilloma or carcinoma), and if the tumor could be completely surgically removed. Patients who have choroid plexus papilloma, which can be completely removed, have an excellent prognosis when compared to other tumor diseases. In most of these patients, the tumor will not recur, and even with recurrence, it might still be possible to treat successfully. On the other end of the spectrum are patients with choroid plexus carcinoma, which cannot be surgically removed. Without further treatment such as irradiation and chemotherapy, these patients will most likely die. This study is meant to standardize and improve the treatment of choroid plexus tumors so that the overall outcome will be better in the future.

What is known about treatment results in choroid plexus tumors? Unfortunately, relatively little reliable evidence is available about the best treatment for patients with choroid plexus tumors. This is because the tumor is so rare that treatment studies can hardly accumulate enough patients to generate significant information. In general, the best level of evidence are statistically significant results of a randomized trial. In that study-type, two equal groups of patients are treated with different protocols, the treatment results are compared later to show which of the treatments were more effective. This kind of evidence is not available for choroid plexus tumors. However, there is a large number of smaller case series, or single case reports published in the literature. Taking this information together, it is generally felt that surgical tumor removal is highly beneficial for the patients. Two other treatment modalities frequently used are irradiation and chemotherapy. When all published cases are combined and patients who received, or did not receive irradiation are compared, the survival rates of patients with irradiation tends to be higher. This type of analysis is strongly suggestive that irradiation can help in this disease. Unfortunately, there are sources of errors occurring in these analyses which cannot be excluded entirely. Therefore, it is likely, but not certain that irradiation will increase the cure rates in choroid plexus tumor patients. The information about chemotherapy is even less certain. This is partially because there are many different types of chemotherapy and lumping all these drug treatments together could give misleading results because only one type of chemotherapy might be helpful. However, few reports have described tumor shrinkage after chemotherapy was given, which again suggests that chemotherapy is helpful. **In summary,** only very little information is available about which type of treatment is most helpful. There is some evidence that surgery, irradiation, and chemotherapy can be beneficial. This evidence is strongest in the case of surgery and weakest in the case of chemotherapy. The international treatment study is the first attempt to treat two equal groups of patients and to compare the treatment results so that more evidence will be available in the future.

What is irradiation and how does it work against tumors? The type of irradiation used in medical treatment is called gamma irradiation. It is somewhat similar to diagnostic x-rays. An invisible beam travels through the body, delivering energy to biological structures. Certain molecules including oxygen are altered, thereby making the molecules more reactive. The genetic material (DNA) of proliferating cells is susceptible to alterations in this process. There is some repair of those alterations in living cells, but when the alterations become too many, the cell will die. In principle, irradiation harms both tumor and normal cells, but the tumor cells are

generally more susceptible for two reasons. On the one hand, tumor cells proliferate faster, but on the other, the repair mechanisms in normal cells are more effective than in cancer cells. Therefore, in an ideal situation, just enough radiotherapy will be given to kill the tumor cells, but allow the normal cells to recover. In practice, radiotherapy will start with an explanation by the radiation oncologist (doctor for irradiation) to patients and their families about the treatment details and side effects. Subsequently, the irradiation is planned. One important element of this is the irradiation field. The field will be chosen so that the least amount of normal tissue will be within the irradiation beam. It is crucial that the body position is exactly the same for each treatment session so that the preplanned field does not miss the tumor and does not include more normal tissue than necessary. Especially with children, many precautions need to be taken to make sure the body position is identical in each session. The actual treatment is a short period of a few minutes given once per day, five days per week, over a period of approximately 6 weeks. Most of the patients do not need to stay in the hospital during this time, as continuous infusion is not required. Irradiation side effects reflect the harm of the normal tissue in the irradiation beam. The different tissue types vary in their susceptibility for irradiation harm. The skin frequently becomes red towards the end of the treatment, similar to a sun burn. The hair within the irradiation field will fall out and might not come back. On the lower border of the middle of the brain is a hormone producing gland, which is called the “pituitary gland”. If this gland is in the irradiation field, various hormone deficiencies are likely to occur. Most frequently, the growth hormone will be missing. This is important in children, as they slow down in growth compared to their age mates. Growth hormones can be replaced if it is missing. This replacement treatment can be considered after the tumor treatment has been completed. It is not a major problem during the first year of tumor treatment. When the brain is in the irradiation field, brain function such as intelligence can be reduced after irradiation. This side effect is largely dependent on the developmental stage of the brain. It is much worse when the maturing brain of infants is treated with radiotherapy than when older children or adults receive the same treatment. In general, irradiation of infant’s brains is therefore avoided in treatment plans. It is hard to decide at which age exactly the benefit of radiotherapy exceeds the harm it can potentially do. The limit is also dependent on the tumor type. For choroid plexus tumors, the international study committee has decided to adapt the most frequently used limit of the 3rd birthday. Within this study, radiotherapy is not given to patients younger than three years of age, while it is delivered to those 3 years and older.

What is chemotherapy and how does it work? Chemotherapy of cancer is a generic term, describing a large variety of treatments which include agents given to the patient in order to kill tumor cells. It is most frequently given systemically, which means to the whole body, and most of the treatments share some mechanisms of action and some side effects. Most of the agents included in chemotherapy are derived from plants (such as vincristine and etoposide used in this study). Some are chemically engineered (such as carboplatin and cyclosphosphamide used in this study). The chemotherapeutic agents used in this study are given directly into the blood. They reach the tumor cells with the blood supply inside the tumors. Similar to irradiation, chemotherapy kills growing cells, which can include both tumor cells and normal cells, and side effects arise from the harm to normal tissue. One can categorize chemotherapy side effects into two groups: A) non specific, mostly temporary side effects, which may occur with any type of chemotherapy. Those side effects are considered acceptable up to a certain level. B) The other category includes permanent harm to certain organs which may or may not occur and which should be avoided if possible. The most frequent types of side effects in the first category, the temporary side effects, include nausea/vomiting, hair loss, and low blood counts. Nausea and vomiting occur predominantly during and shortly after the chemotherapy is given. These side effects diminish the day after the chemotherapy. Hair loss begins several days or a few weeks after the chemotherapy protocol has started, and does not get better before the

whole protocol is finished. Low blood cell counts occur one to two weeks after each chemotherapeutic block. The blood counts must recover before the next chemotherapy is given. Low blood cell counts affect three distinct types of blood cells: red blood cells (erthyrocytes), white blood cells (leukocytes), and blood platelets (thrombocytes). The function of red blood cells is to transport oxygen from the lung to the other tissues such as brain or muscle. If the red blood cell count is low, the person will be pale and will feel weak. This can be treated by giving the patient someone else's red blood cells (transfusion). The white blood cells are part of the immune system which fights infections. If the white blood cell count is low, it might not be physically noticeable, but if an infection occurs at this time, the infection can be much more dangerous than in a person with normal white blood cell counts. Therefore, in the case of fever after chemotherapy, patients and their families should immediately consult the treating physician. Often antibiotic treatment will be necessary to support the immune system in fighting the infection. The normal function of platelets is to stop bleeding. A low number of platelets in blood can cause nose bleeds or formation of tiny red spots in the skin which indicate small hemorrhages. None of these two signs are very dangerous, but hemorrhages can occur in other places as well. Of most concern, is development of a hemorrhage inside of the brain if a brain tumor patient bumps his head. To prevent this, if the platelet count in blood reaches a dangerously low level, platelets from a different person can be given. As a standard part of chemotherapy treatment, blood counts are frequently checked to ensure that they are not too low, or if they are declining, to treat the problem early enough. This is a well-established standardized way to deliver chemotherapy which is quite safe, as it is based on experience of treating many thousands of patients in similar ways. The specific agents used in this study have been well known for a long time. They are described below in more detail, especially with respect to specific side effects which have a certain pattern for each agent. One has to keep in mind, however, that any chemotherapeutic agent can potentially harm any organ, and a complete list of side effects regardless of frequency would be quite long. Therefore, focus is put on those which could reasonably be expected. One should also keep in mind, that none of the described side effects below necessarily need to happen. Many patients go through chemotherapy experiencing only hair loss, nausea, and low blood counts, but none of the other side effects. In fact, frequent criticisms from former cancer patients is that physicians over-emphasized possible side effects at the beginning of the treatment, which scared them more than necessary.

Vincristine is a plant-derived agent diluted as clear fluid in small volumes and given as intravenous (directly in blood) injection. It functions by blocking the cell division in its final moments before one cell turns into two (mitosis). Arresting cells during this moment eventually leads to cell death. Most of the specific side effects occur because Vincristine also slows the speed at which some nerves transmit signals. This can result in numbness, tingling and clumsiness. Some patients walk unsteadily, and need to hold onto something. Also the intestinal coordination of bowel movements can be jeopardized, resulting in constipation and abdominal pain. Pain may also occur in the jaw or the feet. Those side effects are reversible. But, the process of reversibility is slower than in the case of low blood counts. It can take months or even up to two years. The reversibility is faster and more complete in children than in adults. Vincristine is given as a part of the chemotherapy course every four weeks, up to six injections in the international choroid plexus tumor study.

VP16 (Etoposide) is a lipid soluble plant-derived agent which requires additional solvents to dilute it in water. It is given as a clear solution infusion over one hour. The molecule enters the cells and blocks "topoisomerase II", a cellular molecule. Topoisomerase II works on the genetic material of the cell (DNA) in many processes such as cell proliferation and repair of DNA damage. This is believed to be especially effective in combination with other agents such as

carboplatin or cyclophosphamide, which result in DNA repair. Specific side effects of VP16 include acute allergic reactions which can occur even when the drug is given for the first time. In those occasions, the patient can develop a skin rash, difficulties in breathing or low blood pressure. It requires immediate attention as it sometimes can become life threatening. VP 16 may rarely also result in a sore mouth or slower nerve function. In addition, there is evolving data suggesting that VP16 can cause a second malignancy, especially leukemia in very rare cases. VP16 is given in this protocol, because it was part of most of the reported successful treatments of choroid plexus tumors. In fact, unlike other drugs, VP16 has even been able to shrink a choroid plexus carcinoma of one patient when given as a single agent. In this protocol, VP16 is given as part of the chemotherapeutic block on five consecutive days, over one hour each. Six of these blocks are given in a total of one year.

Carboplatin is a small inorganic platinum compound which is given as a water solution in an infusion. Inside the cell, the molecule changes and thereby becomes activated. It then binds to the genetic material (DNA) of cells with two bindings linking various parts of the DNA molecule together. This makes it difficult for the cell to read and replicate the DNA, and therefore makes cell proliferation difficult. Specific side effects of carboplatin include kidney damage, low platelet counts, and more rarely, hearing loss. The kidney damage can reduce the overall kidney function, making the it less efficient at cleaning waste and some toxins from blood. A reduced function means that kidneys will be slower in this process. It might also mean that kidneys excrete molecules with urine which should remain in the blood. In those cases, life long supplementation with electrolytes such as phosphate might become necessary. The kidney damage almost never reaches a degree in which dialysis becomes necessary. As a part of the protocol, kidney function will be checked with blood and urine levels of creatine. This is a good early indicator of the beginning of kidney damage before it becomes relevant. Hearing loss caused by carboplatin affects the ear's ability to hear very high sounds first. This can be monitored in hearing tests, and it will show up on these tests before the hearing loss affects daily life function such as the understanding of spoken language. In the international choroid plexus tumor study, carboplatin is given with each course of chemotherapy in 2 hour infusions on two consecutive days. In addition, prior to, and after carboplatin infusions, high volumes of fluid without carboplatin are infused. This serves to protect kidneys which are less susceptible to platinum damage when they are producing large volumes of urine.

Cyclophosphamide is an organic chemical compound containing nitrogen and phosphorus. The molecule by itself is not toxic. However, after it is infused into blood, it is metabolized in liver to create an effective chemotherapeutic molecule which reaches the tumor cells via the blood. Inside cells, it binds to the genetic material (DNA), making DNA replication for cell proliferation difficult or impossible. Eventually, the cell dies when too many cyclophosphamide molecules are bound to the DNA. Specific side effects of cyclophosphamide include nausea and vomiting kidney damage, bleeding and inflammation of the urinary bladder, and inability to have children. Similar to carboplatin, kidney damage can result in slower cleaning of waste and toxins from blood, as well as in loss of electrolytes which should remain in blood. This may result in the need of life-long supplementation of electrolytes, such as phosphate, but almost never results in the need for dialysis. The inability to have children affects male patients more than females. It is caused by a low sperm number, not by the inability for a penis erection. Sexuality is normally not affected by this side effect. Bladder bleeding is caused by waste product from a cyclophosphamide byproduct, which stays in urine and harms the adjacent bladder walls. It can almost completely be prevented when an additional drug is given prior to and after cyclophosphamide. The name of this additional drug is **mesna**. It binds to the toxic byproducts of cyclophosphamide and inactivates them. Within the international choroid plexus tumor study, cyclophosphamide is given as two-hour-infusions on two consecutive days. Prior to and after

these infusions, high volumes of infusions within chemotherapeutic drugs are given so that the kidneys will excrete large volumes of water. At this stage, the kidneys are less susceptible to chemotherapy side effects. Mesna is given in four-hour intervals, once prior, and three times after the cyclophosphamide infusion as short infusions over 15 minutes.

Supportive medication: Together with the actual chemotherapeutic agents, frequent supportive medication is given to reduce side effects of the chemotherapy. The supportive agents will follow the institutional guidelines and are not standardized for the International choroid plexus tumor study. Supportive agents might include **G-CSF**. This is a hormone which increases white blood cell counts. It is given by injections below the skin when white blood cell counts are low. The most detrimental part of this treatment is the daily poke, which might be especially bothersome for young children. In addition, G-CSF can cause local inflammations and allergic reactions. **Mesna** is given together with cyclophosphamide to prevent bladder bleeding. It is given as short term infusions over 15 minutes and may also, in rare cases, result in allergic reactions such as skin rash as well as fever, tiredness, and nausea. Anti-allergic medications, such as **diphenhydramine** is frequently used together with the chemotherapeutic agent, VP16. It may cause tiredness, dry mouth, full bladder, and allergic reactions.

What is the purpose of the international choroid plexus tumor study? This study serves several objectives. The primary objective is to find out which of the two DNA binding agents mentioned above, carboplatin or cyclophosphamide is more effective in choroid plexus tumor treatment. Half of the patients will have cyclophosphamide and the other half of the patients will have carboplatin as a DNA binding agent in their chemotherapeutic protocols. The remainder of the protocol, which includes the other agents mentioned above, as well as irradiation for patients over 3 years of age, will be the same in both groups of patients. The surviving times and the number of surviving patients will be compared among the two treatment groups in order to answer the primary question. In addition, the study will, as a secondary objective, address the role of SV40 in these tumors. This virus might cause some of the choroid plexus tumors. Tumor slides will be examined for the presence of SV40. The characteristics of the patients with SV40 positive tumors will be compared to those with SV40 negative tumors. This will provide us with data, which could help us find out if there is a certain type of choroid plexus tumor caused by SV40. Comparing these data with survival will further allow better prognostic predictions for new patients in the future and might alter the recommendations as to which patients should and which patient should not receive treatment after surgery. This part of the study will include patients who receive treatment after surgery, as well as those for whom treatment after surgery is not recommended. The study has a two year prephase followed by a main phase of approximately 5 years. In the prephase, the number of patients who will be enrolled in the study will be observed. This number is necessary to calculate the feasibility and exact time necessary to do the main phase. Presently the study is in the prephase.

What are the down sides of participating in the international choroid plexus tumor study? When the consent form for registering into the study has been signed, and when adjuvant treatment is indicated, the study coordinating centre will make a randomized decision as to which patient will receive carboplatin and which patient will receive the cyclophosphamide treatment arm of the study. Signing the consent form means agreeing with the randomized decision, which is unknown at the timepoint when the consent has to be signed. There is no evidence that could give an answer as to which of the two treatment arms is superior. If, however, anyone believes he knows the answer already, this person should not allow randomization, but make the decision himself. He or she can still participate in the second part of the study, which addresses what causes the tumor and the prediction of prognosis, when permission is given for their data to be submitted to the study coordinating centre. Data

submission is the second potential down side of participating in this study. This clinical study cannot be performed unless some personal data such as name, first name, date of birth, and city of treatment are known to the study coordinating centre. After signing the consent form, these data will be submitted in a form. The study coordinating centre commits to the best possible confidentiality when dealing with these data. There is however, never an absolute certainty against unexpected events which could make some data available to a person who should not have access to them. Anyone who feels uncomfortable with this should not consent to registration.

What is the benefit of participating in this study? The study protocol was written after extensive research and international discussions in order to find the best possible treatment. In other diseases, such efforts have resulted in increased survival rates, which is also the objective for the international group with this protocol. However, after this work is done, the study protocol will be available to everyone. The registration is voluntary. However, as this is an effort to increase knowledge to improve the outcome of future patients, and as this can only succeed with voluntary participation of patients, their families, and their health care givers, it might appear that participation is the 'right thing' to do. This comfort to do the right thing is the only benefit the study can give to its participants. Unfortunately, there is no financial compensation or fee for service available. The authors of the study protocol and this information form ask you to participate for the benefit of future patients even if they cannot provide you with a benefit.

What should be done next? This form is only a part of the process of giving information prior to treatment. The most important part of this is the personal discussion with the treating health care giver. It is the experience of previous families in the same stressful situation, that focussing on the right questions can be difficult in this discussion. After reading through this, you should think about the priority of the questions. Which are the most important points you want to have covered in the discussion with your health care giver? Turn this information form around and write your questions on the backside. Following the discussion with your physician, you will be asked to sign the consent form for the study. If no additional treatment after surgery is necessary, the study will only include submission of data. If, additional treatment is indicated, this study has two parts: collecting data about the biology of the tumor and a randomized treatment plan. In this case, you will have to consent to both elements separately. Subsequently, the registration will happen and the decision as to which treatment arm will be used will be send from the study coordinating centre to your health care giver. Chemotherapy will then start. For patients older than three years of age, irradiation will be a part of the treatment. It will be given after the second course of chemotherapy. The younger patients will carry on with chemotherapy, skipping the irradiation. During that time, patients and their families frequently accumulate a significant amount of important paper work. Keeping everything together is recommended. You may start by putting this information sheet in a binder.

Sincerely

Johannes Wolff

For many people from all around the world, who participated in putting the study together.

CHOROID PLEXUS TUMOR STUDY
CONSENT FORM

This consent form, a copy of which has been given to you, is only part of the process of informed consent. It should give you the basic idea of what the research project is about and what your participation will involve. If you would like more details about something mentioned, or information not included here, you should feel free to ask. Please take the time to read this carefully and to understand any accompanying information.

I, _____ willingly agree to participate (allow my child to participate) in this investigation, which has been explained to me by Dr. _____. This is a treatment protocol designed to increase the chance of survival. In order to improve such protocols, clinical information will be collected, summarized, and reported. This information will contain some personal information such as name, first name, date of birth, and city of treatment. The information will be forwarded to the study coordinating centre, the Alberta Children's Hospital in Calgary. The address is: 1820 Richmond Road SW., Calgary, AB, Canada T2T 5C7. The study coordinator is Dr. Johannes Wolff. The data, which allows identification of the patient, will be kept confidential. However, absolute certainty that no data can ever become accessible to someone not involved in this study, cannot be guaranteed. Provided that all possible precautions are taken, I accept the remaining risk of data safety.

The protocol is meant to treat patients with choroid plexus tumors. Two treatment arms are included. They differ by one agent. This is carboplatin in one treatment arm and cyclophosphamide in the other treatment arm. The other chemotherapeutic agents given as a part of the protocol are VP16, and vincristine. I have had sufficient access to information about these chemotherapeutic agents. I agree with the decision of which treatment arm will be done by the study coordinating centre and I commit to following this treatment decision.

As a part of the study, tumor material will be sent to the central reference institution for neuropathology. There, it will be viewed and examined, and remaining tissue will be stored to answer future potential research questions about this tumor. I understand, that this is also a process involving personal information which will be kept as confidential as possible. I agree with sending both tissue and information, and with storage of tumor material in the neuropathology reference centre.

Participation in this study is voluntary. No compensation for participation will be given. In the event that physical injury occurs as a result of this study, treatment for injury will be available. I (my child) understand(s), however, that neither the treating hospital, the study coordinating centre, nor the University of Calgary and the Alberta Children's Hospital, which host the study coordinating centre, can provide reimbursement for medical care or other compensation. I (my child) understand(s) that I am (he/she is) free to withdraw consent for participation in this treatment protocol or any other elements of the consent at any time without prejudice to subsequent care: refusal for participation will involve no penalty or loss of benefits. I am (my child is) free to seek care from a physician of my (his/her) choice at any time. If I (my child) withdraw(s) or do not take part in this study I (my child) will continue to receive care.

My (my child's) signature on this form indicates that I have (my child has) understood to my (my child's) satisfaction, the information regarding my (my child's) participation in the research project and agree to participate as a subject. In no way does this waive my (my child's) legal rights or release the investigators, sponsors, or involved institutions from their legal rights and

professional responsibilities. I am (my child is) free to withdraw from this study at any time without jeopardizing my (my child's) health care. My (my child's) continued participation should be as informed as my (my child's) initial consent, so I (my child) should feel free to ask for clarification of any information throughout my (my child's) participation.

If you (your child) has further questions concerning matters related to this research, please contact: Dr. Johannes Wolff, (403)229-7256, in Calgary, Alberta, Canada.

_____
_____
_____
_____

If you have any questions concerning your rights as a possible participant in this research, please contact the Office of Medical Bioethics, Faculty of Medicine, University of Calgary at (403)220-7990.

A copy of this consent will be given to you (your child). Please keep it for your (your child's) record and future reference. The investigator will, as appropriate, explain to you (your child) the research and your (your child's) involvement and will seek your (your child's) ongoing cooperation throughout the project.

_____
Name

_____
Signature of Subject or signature
or responsible proxy, if applicable

_____
Name of witness

_____
Signature of investigator

_____
Date

Choroid Plexus Tumor Study: Paper- Form 1: first registration

Please fax to: +1 403 229 7684 or: +1 403 228 4196 with operation- -, pathology- and MRI- reports

Patient: Name_____ **First name:**_____
Date of Birth: ___/____/_____(DD/ MM / YYYY) **Gender**: 1 male ___2 female ____
Reporting Institution: (name, address)_____
_____
Contact Fax number:_____ Phone number: _____
Contact person in reporting institution:_____

Primary tumor location:
1 right lateral ventricle:_____
2 left lateral ventricle:_____
3 third ventricle: _____
4 fourth ventricle: _____
5 cerebello pontine angle:_____
6 others (specify): _____

Are there secondary tumor locations?:
1 No_____
2 yes_____
if yes, specify where:_____
_____
_____

Surgery date (most recent resection): ____/____/_____(fax the reports if available)
DD / MM/YYYY

Surgeon's opinion on completeness of the most recent resection:
1 no visible tumor left (gross total resection): _____
2 minimal tumor tissue left, (less than 2 mm tumorsheat):_____
3 still macroscopically visible tumor present: _____

Pathology: primary / local pathology result:
1 Choroid plexus papilloma (CPP): _____
2 Atypical CPP: _____
3 Choroid plexus carcinoma (CPC):_____
4 Others (specify): _____
_____

Reporting Pathologist:
Number of specimen:_____
Pathologist:_____
Phone number:_____
City:_____
Institution:_____

(Please fax pathology report, if available)
Have the slides already been sent to the pathology reference centre? Yes __/ No: __

Postoperative imaging: CT-date: **____/____/_____** MRI date:**____/____/_____**
DD / MM/YYYY DD / MM / YYYY

Result of postoperative imaging: **(Please fax imaging report, if available)**
1 no suspicion of residual tumor: _____
2 lesion visible, nature of lesion unclear: _____
3 clearly still residual tumor present: _____
if tumor present: primary lesion? Yes ___No ____
metastasis / secondary lesion? Yes ___No ___

Agreement of the patient / legal guardian **for electronic data processing** for the study has been documented according to the local laws and guidelines: Yes _____No_____

Signature: _____Name of signing person (please print):_____

Choroid Plexus Tumor Study: FAX- Form 2: second registration

Please fax to: +1 403 229 7684 or: +1 403 228 4196 together with OR -, pathology and MRI report

Patient: Name_____ **First name:**_____
Date of Birth: ____/_____/_____ (DD / MM / YYYY)

Reporting Institution: (name, address)_____
_____
Contact Fax number:_____ Phone number: _____
Contact person in reporting institution:_____

Postoperative imaging MRI date:**____/____/_____** (DD / MM/YYYY)

Result of postoperative imaging: **(Please fax imaging report, if available)**
1 no suspicion of residual tumor: _____
2 lesion visible, nature of lesion unclear: _____
3 clearly still residual tumor present: _____
if tumor present: primary lesion? Yes ___No ____
metastasis / secondary lesion? Yes ___No ___

Result of Pathology Reference centre:
Diagnosis: Number of specimen:_____
1 Choroid plexus papilloma (CPP): _____
2 Atypical CPP: _____
3 Choroid plexus carcinoma (CPC):_____

Has the patient previously been treated with irradiation or chemotherapy: Yes _____ No _____

Requirements for starting adjuvant treatment:

Result of patient (most recent):	**Requirements of study:**
White blood cell count: _____	(over 2000 / ul)
Platelet count:_____	(over 85,000 / ul)
Creatinine : normal _____abnormal_____	(in normal range of local laboratory)
Audiology: normal _____abnormal_____	(hearing loss < 30 dB at 3 kHz).

The patient/legal guardian has **agreed** to follow the **randomization,** and this has been documented according to local guidelines: Yes _____ No_____

The institution will follow the **randomization** and will **submit the follow-up data:**
Yes ____ No_____

Signature:_____ **Name (please print)**:_____

Date of signature: ___ /____/_____(DD / MM / YYYY)

CP Tumor Study: **FAX- Form 3:** Response to Chemotherapy (page 1 of 3)

Please fax to: +1 403 229 7684 or: +1 403 228 4196 together with MRI report
Feel free to submit additionally - comments, discharge summaries or tumor board minutes

Patient: Name_____ **First name:**_____
Date of Birth: ____/_____/_____ (DD / MM / YYYY)

Reporting Institution: (name, address)_____
_____
Contact Fax number:_____ Phone number: _____
Contact person in reporting institution:_____ __

Treatment randomization: Carboplatin arm:_____ Cyclophosphamide arm:_____

The treatment followed the randomization and the study protocol: Yes ____ No_____
Reasons of deviation: _____
_____
_____

MRI prior to chemotherapy: ____/_____/_____(DD / MM / YYYY)
First day of **first chemotherapy** block: ____/_____/_____(DD / MM / YYYY)
First day of **second chemotherapy** block**: ____/_____/_____**(DD / MM / YYYY)
MRI after chemotherapy: ____/_____/_____(DD / MM / YYYY)

Result of comparing the two MRIs (prior to – and – after chemotherapy):
_____1 CCR: (continuous complete remission): no evidence of tumor in either MRI
_____2 CR: (complete remission) clear evidence of complete tumor disappearance
_____3 PR: (partial remission) tumor shrinkage to less than 50% of first MRI (measurements in 2 dimensions)
_____4 SD: (stable disease) tumor size between 50% and 125% of the first MRI (measurements in 2 dimensions)
_____5 PD: (progressive disease) tumor growth to more than 125% of the first MRI (measurements in 2 dimensions)

Patient status: alive_____ Death_____, unknown: _____
If alive: last date, known to be alive: ____/_____/_____(DD / MM / YYYY)
If death, date of death: ____/_____/_____(DD / MM / YYYY)
cause of death: _____progressive disease
_____surgery
_____chemotherapy
_____unknown
_____others, please specify:
_____

Signature:_____ **Name (please print)**:_____
Date of signature: ___ /____/_____(DD / MM / YYYY)

See following 2 pages for documentation of toxicity!

Choroid Plexus Tumor Study: **FAX- Form 3:** Response to treatment (page 2 of 3)

Please fax to: +1 403 229 7684 or: +1 403 228 4196 together with MRI report

Patient: Name_____ **First name:**_____

Date of Birth: ____/_____/_____ (DD / MM / YYYY)

Toxicity of the first block of chemotherapy: Please circle the appropriate grades:

	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Leukopenia	> 4.0 x 10^9/L	3.0-3.9 x 10^9/ L	2.0-2.9 x 10^9/L	1.0-1.9 x 10^9/L	< 1.0 x 10^9/L
Thrombocytopenia	> 100 x 10^9/L	75-99 x 10^9/L	50-74 x 10^9/L	25-49 x 10^9/L	< 25 x 10^9/L
Nausea/Vomiting	none	nausea	transient vomiting	vomiting requiring therapy	intractable vomiting
Oral	no change	soreness/ erythema	erythema, ulcers; can eat solids	ulcers; requires liquid diet only	alimentation not possible
Diarrhea	none	transient < 2 days	tolerable, but > 2 days	intolerable, requiring therapy	haemorrhagic dehydration
Serum creatinine	Within normal limits	< 1.5 x N	1.5-3.0 x N	3.1-6.0 x N	> 6.0 x N
GFR	> 110 ml/min./ 1.73m^2	90-110 ml/min/ 1.73m^2	70-89 ml/min/ 1.73 m^2	50-69 ml/min/ 1.73 m^2	< 50 ml/min/ 1.73 m^2
Bilirubin	Within normal limits	____	< 1.5 x N	1.5-3.0 x N	> 3.0 x N
ALT/AST	Within normal limits	< 2.5 x N	2.6-5.0 x N	5.1- 20 x N	> 20.0 x N
Metabolic disturbances	none	slight water imbalance	moderate water imbalance	severe water imbalance	untreatable water imbalance
Skin	no change	erythema	dry desquamation	moist desquamation	exfoliate dermatitis: necrosis
Neurotoxicity: central	alert	transient lethargy	somnolence <50% of time and/or mild disorientation	somnolence >50% of time and/or severe disorientation	coma
Neurotoxicity: peripheral	none	paraesthesiae and/or decreased tendon reflexes	severe paraesthesiae and/or mild weakness	intolerable paraesthesiae and/or marked motor loss	paralysis
Hearing: objective	no change	20-40 db loss > 4 kHz	> 40 db loss > 4 kHz	> 40 db loss > 2 kHz	> 40 db loss < 2 kHz
Hearing: subjective	no change	loss on audiometry only	tinnitus, soft splash	loss correctable with hearing aid	deafness not correctable
Infection	none	minor infection	moderate infection	major infection	major infection with hypotension

Choroid Plexus Tumor Study: **FAX- Form 3:** Response to treatment (page 3 of 3)

Please fax to: +1 403 229 7684 or: +1 403 228 4196 together with MRI report

Patient: Name_____ **First name:**_____

Date of Birth: ____/_____/_____ (DD / MM / YYYY)

Toxicity of the second block of chemotherapy: Please circle the appropriate grades:

	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Leukopenia	> 4.0 x 10^9/L	3.0-3.9 x 10^9/ L	2.0-2.9 x 10^9/L	1.0-1.9 x 10^9/L	< 1.0 x 10^9/L
Thrombocytopenia	> 100 x 10^9/L	75-99 x 10^9/L	50-74 x 10^9/L	25-49 x 10^9/L	< 25 x 10^9/L
Nausea/ Vomiting	One	nausea	transient vomiting	vomiting requiring therapy	intractable vomiting
Oral	no change	soreness/ erythema	erythema, ulcers; can eat solids	ulcers; requires liquid diet only	alimentation not possible
Diarrhea	none	transient < 2 days	tolerable, but > 2 days	intolerable, requiring therapy	haemorrhagic dehydration
Serum creatinine	Within normal limits	< 1.5 x N	1.5-3.0 x N	3.1-6.0 x N	> 6.0 x N
GFR	> 110 ml/min./ 1.73m^2	90-110 ml/min/ 1.73m^2	70-89 ml/min/ 1.73 m^2	50-69 ml/min/ 1.73 m^2	< 50 ml/min/ 1.73 m^2
Bilirubin	Within normal limits	____	< 1.5 x N	1.5-3.0 x N	> 3.0 x N
A LT/AST	Within normal limits	< 2.5 x N	2.6-5.0 x N	5.1- 20 x N	> 20.0 x N
Metabolic Disturbances	none	slight water imbalance	moderate water imbalance	severe water imbalance	untreatable water imbalance
Skin	no change	erythema	dry desquamation	moist desquamation	exfoliative dermatitis: necrosis
Neurotoxicity: central	alert	transient lethargy	somnolence <50% of time and/or mild disorientation	somnolence >50% of time and/or severe disorientation	coma
Neurotoxicity: peripheral	none	paraesthesiae and/or decreased tendon reflexes	severe paraesthesiae and/ or mild weakness	intolerable paraesthesiae and/ o r marked motor loss	paralysis
Hearing: objective	no change	20-40 db loss >4 kHz	> 40 db loss > 4 kHz	> 40 db loss > 2 kHz	> 40 db loss < 2 kHz
Hearing: subjective	no change	loss on audiometry only	tinnitus, soft splash	loss correctable with hearing aid	deafness not correctable
Infection	none	minor infection	moderate infection	major infection	major infection with hypotension

Choroid Plexus Tumor Study: **FAX- Form 4:** End of treatment **-Page 1 of 2-**

Please fax to: +1 403 229 7684 or: +1 403 228 4196 together with MRI and irradiation report
Feel free to submit additionally - comments, discharge summaries or tumor board minutes

Patient: Name_____ **First name:**_____
Date of Birth: ____/_____/_____ (DD / MM / YYYY)
Reporting Institution: (name, address)_____
_____
Contact Fax number:_____ Phone number: _____
Contact person in reporting institution:_____

Treatment randomization: Carboplatin arm:__ Cyclophosphamide arm:_____
The treatment followed the randomization and the study protocol: Yes ____ No_____
Reasons of deviation: _____
_____
_____

Chemotherapy:
First day of **first chemotherapy** block: ____/_____/_____(DD / MM / YYYY)
First day of **last chemotherapy** block: ____/_____/_____(DD / MM / YYYY)
How many blocks of chemotherapy had the patient in total? _____
Comments:_____
_____

Irradiation:
First day of **irradiation**: ____/_____/_____(DD / MM / YYYY)
Last day of **irradiation:** ____/_____/_____(DD / MM / YYYY)
Total irradiation dose given:_____Gy
Did the irradiation follow the study protocol: Yes ____ No_____
Reasons for deviations: _____
_____
Comments:_____

Surgery:
Was a further surgical resection performed during adjuvant treatment ? Yes ___ No___
Date of further surgery: ____/____/_____ (fax the reports, if available)
DD / MM/YYYY
Surgeon's opinion on completeness of the further resection:
1 no visible tumor left (gross total resection): _____
2 minimal tumor tissue left, (less than 2 mm tumorsheat):_____
3 still macroscopically visible tumor present: _____

Form 4, Page 2 of 2, Patient name: _____

Recurrence: No_____Yes_____,
Date of first CT/MRI showing the recurrence____/_____/_____(DD/MM/YYYY)
Location of recurrence: _____
_____

Alive: _____

Date last seen: ____/_____/_____(DD/MM/YYYY) (=last day known to be alive)
Date of **most recent MRI**: ____/_____/_____(DD/MM/YYYY)
Result of most recent MRI:
1 no suspicion of residual tumor: _____
2 lesion visible, nature of lesion unclear: _____
3 clearly still residual tumor present: _____
if tumor present: primary lesion? Yes ___No ____
Metastasis / secondary lesion? Yes ___No ___

Date of treatment end evaluation: _____/_____(MM/YYYY)
White blood cell count:_____, Hemoglobin:_____
Platelet count: _____
Na, K, Ca, P: normal_____abnormal :_____ values:_____
ALT/GOT, AST/GPT, bilirubin, LDH:
normal_____abnormal :_____ values:_____
Creatinine, Urea:
normal_____abnormal :_____ values:_____
24 hour creatinine clearance or glomerular filtration rate:
normal_____ abnormal :_____ values:_____
Audiology: normal_____ abnormal :_____
Worst hearing loss at 3,000 Hz:_____dB, which side ? right ___left___
Worst hearing loss at 4,000 Hz:_____dB, which side ? right ___left___

Dead: _____ *please submit autopsy report, or mortality review, if available*
date of death: ____/_____/_____(DD / MM / YYYY)
cause of death:
_____progressive disease
_____surgery
_____chemotherapy
_____unknown
_____others, please specify:
_____

Signature:_____ **Name (please print)**:_____

Date of signature: ___ /____/_____(DD / MM / YYYY)

Choroid Plexus Tumor Study: **FAX- Form 5:** Follow up

Please fax to: +1 403 229 7684 or: +1 403 228 4196 together with MRI report in case of recurrence
Feel free to submit additionally - discharge summaries or tumor board minutes without translation
Page 1 of 1

Patient: Name_____ **First name:**_____
Date of Birth: ____/_____/_____ (DD / MM / YYYY)
Reporting Institution: (name, address)_____
_____
Contact Fax number:_____ Phone number: _____
Contact person in reporting institution:_____

Recurrence: No_____Yes_____,
Date of first CT/MRI showing the recurrence____/_____/_____(DD/MM/YYYY)
Location of recurrence:_____
_____

Status:
Alive: _____
Date last seen: ____/_____/_____(DD/MM/YYYY)
Date of **most recent MRI**: ____/_____/_____(DD/MM/YYYY)
Result of most recent MRI:
1 No suspicion of residual tumor: _____
2 lesion visible, nature of lesion unclear: _____
3 clearly still residual tumor present: _____
if tumor present: primary lesion? Yes ___No ____
Metastasis / secondary lesion? Yes ___No ___

Dead: _____
date of death: ____/_____/_____(DD / MM / YYYY)
cause of death:
_____progressive disease
_____surgery
_____chemotherapy
_____unknown
_____others, please specify:
_____

please submit autopsy report, or mortality review, if available

Signature:_____ **Name (please print)**:_____
Date of signature: ___ /____/_____(DD / MM / YYYY)

Radiotherapy Data Form

SIOP CHOROID PLEXUS TUMOR STUDY

Please send to the Radiotherapy Reference centre
Rolf - D. Kortmann, Department of Radiotherapy, University of Tübingen
Hoppe-Seyler-Str. 3, D - 72076 Tübingen, Germany
Telephone.: +49/7071/29 8 21 66
Fax: +49/7071/29 58 94
e-mail : rdkortma@med.uni-tuebingen.de

Study ID (national)				
Reg. # (international)				
Initials				
	L	F	M	F
date of birth				
	M M		D D	Y Y

(page 1of 6)

I) PATIENT - DATA

Surname _____First name_____Date of birth_____

Sex _____(male=1, female=2)

Diagnosis_____

Clinic/Radiotherapy _____
Start of treatment _____*End of treatment* _____

	Total dose (Gy)	Single dose (Gy)	Fractions/week
Tumor/boost			
Cerebrum			
Spinal canal			
Metastases			

	Total dose (Gy)	Single dose (Gy)	Fractions/week
Tumor region "Involved-field"			

Interruption / Break of treatment _____(yes=1, no=2)
Interruption / interval : from _____ to _____ _____days
Reason _____

_____

SIOP CHOROID PLEXUS TUMOUR STUDY

Form: RADIOTHERAPY
(page 2 of 6)

Study ID (national)	
Reg. # (international)	
Initials	L F M F
date of birth	M M D D Y Y

II) ACUTE MORBIDITY / MODIFIED WHO SCORE

1. NEUROTOXICITY

Headache : __ (0 nil, 1 slight, 2 moderate, 3 severe)

Nausea / Vomiting : __ (0 no, 1 intermittent, 2 continuous)

Epilepsy :__ (0 nil, 1 well controlled under medication, 2 poorly controlled under medication)

2. INFECTIONS : ____ (0 nil, 1 bacterial, 2 viral, 3 fungal, 4 combination, 5 others, 6 not isolated)

3. SKIN *:* ___ (0 none, 1 slight erythema, hair loss, dry desquamation, 2 marked erythema, moderate oedema, 3 moist desquamation, marked oedema, 4 ulceration, necrosis)

4. MUCOSA : _____ (0 none, 1 slight erythema, 2 patchy mucositis, moderate edema, 3 patchy mucositis, marked oedema, 4 confluent mucositis, necrosis, ulceration)

SIOP CHOROID PLEXUS TUMOUR STUDY

Form: RADIOTHERAPY
(page 3 of 6)

Study ID (national)	
Reg. # (international)	
Initials	L F M F
date of birth	M M D D Y Y

III) MYELOTOXICITY

	Date	***Value***
WBC-Nadir		***(x10^9/l)***
Platelets-Nadir		***(x10^9/l)***
Blood count/start of treatment		
WBC		***(x10^9/l)***
Platelets		***(x10^9/l)***
Blood count/end of treatment		
WBC		***(x10^9/l)***
Platelets		***(x10^9/l)***
Administration of growth factors	***(yes=1, no=2)***	
Transfusion/Erythrocytes	***(yes=1, no=2)***	
Transfusion/Platelets	***(yes=1, no=2)***	

SIOP CHOROID PLEXUS TUMOR STUDY
Form: RADIOTHERAPY
(page 4 of 6)

Study ID (national)				
Reg. # (international)				
Initials				
	L	F	M	F
date of birth				
	M M		D D	Y Y

IV) DOSE PRESCRIPTION / TREATMENT TECHNIQUE

A . CRANIOSPINAL AXIS

"HELMET - TECHNIQUE"

Linear accelerator (energy)_____MV CO-60____(yes=1,no=2)

Lateral, isocentric opposed fields___ (yes=1,no=2)

If 2, further details:_____

SPINAL AXIS

Linear accelerator (energy)_____MV CO-60____(yes=1,no=2)

Depth dose 1____cm Depth dose 2___cm SSD :____cm

Maximum dose ____ Minimum dose____

Electron fields___ (yes=1,no=2) Energy :_____MeV

Dose specification ____% Isodose (Electron-Field)

POSITIONING AIDS

Individual face mask :____(yes=1,no=2)

Vacuum pillows :____(yes=1,no=2)

Immobilization cast :____(yes=1,no=2)

Others :____(yes=1,no=2)

Others / detail _____

SIOP CHOROID PLEXUS TUMOUR STUDY

Form: RADIOTHERAPY
(page 5 of 6)

Study ID (national)				
Reg. # (international)				
Initials				
	L	F	M	F
date of birth				
	M M		D D	Y Y

BOOST TO TUMOR BED

Linear accelerator (energy)_____MV CO-60____(yes=1,no=2)

CT-assisted plan___ (yes=1,no=2)

3-D treatment planning___ (yes=1,no=2)

Lat.opp.fields __(yes=1,no=2) Multi-field technique__(yes=1,no=2)

Wedge filters :___(yes=1,no=2) Rotation____(yes=1,no=2)

Dose/Reference-point_____Gy

max._____% Min._____% "hot spot" _____%

Image fusion (MR /CT) for treatment planning:___ (yes=1,no=2)

Dose to critical organs :

Pituitary gland	____,___Gy	Optic chiasm	____,___Gy
Hypothalamus	____,___Gy	Brain stem	____,___Gy
left optic nerve	____,___Gy	right optic nerve	____,___Gy
left eye lens	____,___Gy	right eye lens	____,___Gy

POSITIONING AIDS

Individual, conventional face mask :____(yes=1,no=2)

Rigid head fixation using face mask :____(yes=1,no=2)

Stereotactic immobilization device (i.e. Gill-Thomas-Cosman ring) :____(yes=1,no=2)

Others :____(yes=1,no=2)

Others / detail _____

REMARKS: _____

SIOP CHOROID PLEXUS TUMOR STUDY
Form: RADIOTHERAPY
(page 6 of 6)

Study ID (national)				
Reg. # (international)				
Initials				
	L	F	M	F
date of birth				
	M M	D D	Y Y	

IV) DOSE PRESCRIPTION / TREATMENT TECHNIQUE

B. "INVOLVED - FIELD"

Linear accelerator (energy)_____MV CO-60____(yes=1,no=2)

CT-assisted plan___ (yes=1,no=2)

3-D treatment planning___ (yes=1,no=2)

Lat.opp.fields __(yes=1,no=2) Multi-field technique__(yes=1,no=2)

Wedge filters :___(yes=1,no=2) Rotation____(yes=1,no=2)

Dose/Reference-point_____Gy

max._____% Min._____% "hot spot" _____%

Image fusion (MR /CT) for treatment planning:___ (yes=1,no=2)

Dose to critical organs :

Pituitary gland	____,___Gy	Optic chiasm	____,___Gy
Hypothalamus	____,___Gy	Brain stem	____,___Gy
left optic nerve	____,___Gy	right optic nerve	____,___Gy
left eye lens	____,___Gy	right eye lens	____,___Gy

POSITIONING AIDS

Individual, conventional face mask :____(yes=1,no=2)
Rigid head fixation using face mask :____(yes=1,no=2)

Stereotactic immobilization device (i.e. Gill-Thomas-Cosman ring) :____(yes=1,no=2)

Others :____(yes=1,no=2)

Others / detail _____

REMARKS: _____

SIGNATURE: _____ **DATE:**_____

DECLARATION OF HELSINKI

Recommendations guiding physicians in biomedical research involving human subjects

Adopted by the 18th World Medical Assembly Helsinki, Finland, June 1964
amended by the 29th World Medical Assembly Tokyo, Japan, October 1975
and the 35th World Medical Assembly Venice, Italy, October 1983
and the 41st World Medical Assembly Hong Kong, September 1989
and the 48th General Assembly Somerset West, Republic of South Africa, October 1996

INTRODUCTION

It is the mission of the physician to safeguard the health of the people. His or her knowledge and conscience are dedicated to the fulfillment of this mission.

The Declaration of Geneva of the World Medical Association binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act only in the patient's interest when providing medical care which might have the effect of weakening the physical and mental condition of the patient."

The purpose of biomedical research involving human subjects must be to improve diagnostic, therapeutic and prophylactic procedures and the understanding of the etiology and pathogenesis of disease.

In current medical practice most diagnostic, therapeutic or prophylactic procedures involve hazards. This applies especially to biomedical research.

Medical progress is based on research which ultimately must rest in part on experimentation involving human subjects.

In the field of biomedical research a fundamental distinction must be recognized between medical research in which the aim is essentially diagnostic or therapeutic for a patient, and medical research, the essential object of which is purely scientific and without applying direct diagnostic or therapeutic value to the person subjected to the research.

Special caution must be exercised in the conduct of research which may effect the environment, and the welfare of animals used for research must be respected.

Because it is essential that the results of laboratory experiments be applied to human beings to further scientific knowledge and to help suffering humanity, the World Medical Association has prepared the following recommendations as a guide to every physician in biomedical research involving human subjects. They should be kept under review in the future. It must be stressed that the standards as drafted are only a guide to physicians all over the world. Physicians are not relieved from criminal, civil and ethical responsibilities under the laws of their own countries.

I. BASIC PRINCIPLES

1. Biomedical research involving human subjects must conform to generally accepted scientific principles and should be based on adequately performed laboratory and animal experimentation and on a thorough knowledge of the scientific literature.

2. The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol which should be transmitted for consideration, comment and guidance to a specially appointed committee independent

of the investigator and the sponsor, provided that this independent committee is in conformity with the laws and regulations of the country in which the research experiment is performed.

3. Biomedical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a medically qualified person and never rest on the subject of the research, even though the subject has given his or her consent.

4. Biomedical research involving human subjects cannot legitimately be carried out unless the importance of the objective is in proportion to the inherent risk to the subject.

5. Every biomedical research project involving human subjects should be preceded by careful assessment of predictable risks in comparison with foreseeable benefits to the subject or to others. Concern for the interests of the subject must always prevail over the interests of science and society.

6. The right of the research subject to safeguard his or her integrity must always be respected. Every precaution should be taken to respect the privacy of the subject and to minimize the impact of the study on the subject's physical and mental integrity and on the personality of the subject.

7. Physicians should abstain from engaging in research projects involving human subjects unless they are satisfied that the hazards involved are believed to be predictable. Physicians should cease any investigation if the hazards are found to outweigh the potential benefits.

8. In publication of the results of his or her research, the physician is obliged to preserve the accuracy of the results. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.

9. In any research on human beings, each potential subject must be adequately informed of the aims, methods, anticipated benefits and potential hazards of the study and the discomfort it may entail. He or she should be informed that he or she is at liberty to abstain from participation in the study and that he or she is free to withdraw his or her consent to participation at any time. The physician should then obtain the subject's freely-given informed consent, preferably in writing.

10. When obtaining informed consent for the research project, the physician should be particularly cautious if the subject is in a dependent relationship to him or her or may consent under duress. In that case, the informed consent should be obtained by a physician who is not engaged in the investigation and who is completely independent of this official relationship.

11. In case of legal incompetence, informed consent should be obtained from the legal guardian in accordance with national legislation. Where physical or mental incapacity makes it impossible to obtain informed consent, or when the subject is a minor, permission from the responsible relative replaces that of the subject in accordance with national legislation.

    Whenever the minor child is in fact able to give consent, the minor's consent must be obtained in addition to the consent of the minor's legal guardian.

12. The research protocol should always contain a statement of the ethical considerations involved and should indicate that the principles enunciated in the present Declaration are complied with.

II. MEDICAL RESEARCH COMBINED WITH PROFESSIONAL CARE

(Clinical Research)

1. In the treatment of the sick person, the physician must be free to use a new diagnostic and therapeutic measure, if in his or her judgment it offers hope of saving life, re-establishing health or alleviating suffering.
2. The potential benefits, hazards and discomfort of a new method should be weighed against the advantages of the best current diagnostic and therapeutic methods.
3. In any medical study, every patient - including those of a control group, if any - should be assured of the best proven diagnostic and therapeutic method. This does not exclude the use of inert placebo in studies where no proven diagnostic or therapeutic method exists.
4. The refusal of the patient to participate in a study must never interfere with the physician-patient relationship.
5. If the physician considers it essential not to obtain informed consent, the specific reasons for this proposal should be stated in the experimental protocol for transmission to the independent committee.
6. The physician can combine medical research with professional care, the objective being the acquisition of new medical knowledge, only to the extent that medical research is justified by its potential diagnostic or therapeutic value for the patient.

III. NON-THERAPEUTIC BIOMEDICAL RESEARCH INVOLVING HUMAN SUBJECTS

(Non-Clinical Biomedical Research)

1. In the purely scientific application of medical research carried out on a human being, it is the duty of the physician to remain the protector of the life and health of that person on whom biomedical research is being carried out.
2. The subjects should be volunteers - either healthy persons or patients for whom the experimental design is not related to the patient's illness.
3. The investigator or the investigating team should discontinue the research if in his/her or their judgment it may, if continued, be harmful to the individual.
4. In research on man, the interest of science and society should never take precedence over considerations related to the well-being of the subject.