Dutch guideline for Radiotherapy in Acute Lymphatic Leukemia

This guideline mainly follows the study protocols as followed by the Dutch Childhood Oncology Group:

- ALL-11 Treatment study protocol of the Dutch Childhood Oncology Group for children and adolescents (1-19 year) with newly diagnosed acute lymphoblastic leukemia *(version 10 dd 19-03-2020)*
- ALLTOGETHER ALLTogether1 – A Treatment study protocol of the ALLTogether Consortium for children and young adults (1-45 years of age) with newly diagnosed acute lymphoblastic leukaemia (ALL) *(version 1.2, 18-10-2019)*
- EsPhALL2017/COGAALL1631 International phase 3 trial in Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph+ ALL) testing imatinib in combination with two different cytotoxic chemotherapy backbones *(version April 5 2017)*
- IntReALL SR 2010 International Study for Treatment of Standard Risk Childhood Relapsed ALL 2010 *(version 2.1, 20-6-2019)*
- IntReALL HR 2010 International Study for Treatment of High Risk Childhood Relapsed ALL 2010 *(version 1.7, 2-3-2015)*
- ALL SCTped 2012 FORUM Allogeneic Stem Cell Transplantation in Children and Adolescents with Acute Lymphoblastic Leukaemia *(version 6.0, 9-9-2019)*

Further literature references can be found throughout the guideline text.

Background information

Radiotherapy (RT) indications for leukemia have changed significantly over the past few decades, mainly in the direction of reducing the intensity and/or indications based on risk-adapted therapy principles. Late effects from cranial/craniospinal RT, testicular RT, and TBI can adversely affect the quality of life and ultimate survival of children treated for leukemia. In the current Dutch practice, RT is mainly applied for specific indications in central nervous system (CNS) disease, testicular disease and as total body irradiation (TBI) during conditioning for allogeneic stem cell transplantation.

CNS disease

Indications

In general, for children ≥4 years (>48 months) of age in with a primary leukemia diagnosis who have residual CNS leukemia that is refractory to chemotherapy, or those who develop a relapse involving CNS, there is an indication for RT, especially when other CNS-directed therapy has failed.

In the case of a planned TBI in the conditioning scheme for allogeneic stem cell transplantation and indication for CNS-directed RT, the latter should be given as a boost before TBI.

Although some evidence points to reduced risk of post-transplant CNS relapse in children with a history of CNS leukemia at *any* time during their disease who received a cranial RT boost before TBI, this addition did not have an impact on overall or disease free survival (1). Therefore, in case of leukemia recurrence, it is recommended to reserve CNS-directed RT before allogeneic stem cell transplantation for those patients with CNS *relapse*.

In case of previous CNS-directed radiotherapy, adjustments should be made to the radiotherapy dose according to guidelines in the Dose Specification section.

Study protocol indications

In the ALLTogether1 protocol (for therapy regarding initial diagnosis), CNS disease is treated by extra intrathecal therapy. Patients with refractory CNS disease at the end of consolidation 1 are taken off protocol and may be eligible for other clinical trials for resistant ALL or for supplementation of the therapy with CNS-irradiation or other interventions.

In the DCOG-ALL-11 treatment protocol (for therapy regarding initial diagnosis), CNS disease is treated by extra intrathecal therapy according to MR or HR protocols. Patients with refractory CNS disease at day 33 should be discussed with the protocol chairman. No specific mention is made regarding indications for CNS-directed RT in case of residual disease.

In the IntReALL HR 2010 protocol (for therapy regarding relapse), patients with CNS relapse receive CNS-directed RT.

In the IntReALL SR 2010 protocol (for therapy regarding relapse), patients with CNS relapse receive CNS-directed RT if they are not eligible for allogeneic stem cell transplantation (SCT) according to the protocol (typically, patients not eligible for SCT are those with late isolated extramedullary relapse and those with late bone marrow relapse and MRD good response; see details in paragraph 9.2 of the study protocol). Patients receiving SCT go off-study and are treated following the FORUM protocol guidelines. For patients receiving TBI during stem cell transplantation conditioning, potential CSI boost is planned according to the FORUM guidelines (see below in Dose Specification section).

CNS treatment volume

To treat the entire volume at risk, craniospinal axis irradiation (CSI) is recommended, not only cranial irradiation. Some evidence suggests that CSI may improve CNS disease control before allogeneic stem cell transplantation to a greater extent than does cranial RT (2).

Prophylactic cranial irradiation

Prophylactic cranial irradiation (CRT) (in the absence of a planned transplant) was prescribed in many protocols in the past, but has proven to be redundant for event-free survival or overall survival with current systemic and intrathecal treatment protocols (3-7). Prophylactic CRT can be considered rarely and on case-by-case basis for patients with high-risk features, since a meta-analysis found that an increased risk of CNS relapse was only present in a small subgroup (2-3%) of patients with CNS3 disease at diagnosis; however, use of prophylactic radiotherapy did not affect 5-year mortality rates (8). The EsPhALL2017 is the only current study in the Netherlands with an indication for prophylactic CRT, for patients with CNS3 leukemia at diagnosis.

<u>Testicular localization</u>

Testicular involvement is an indication for RT in case of testicular recurrence or with residual disease detected with ultrasound at the end of induction. No standard biopsies should be performed at that time if there is no clinical enlargement or if ultrasound is not suspect (9, 10).

In the ALLTogether1 trial, if patients with an initial testicular leukemia in the High Risk protocol still have biopsy-proven testicular involvement after 3 blocks of HR therapy, it is deemed refractory testicular disease and indication for resistant ALL protocols and / or testicular RT should be discussed.

There is some evidence that RT can be omitted for patients with B-cell ALL with an isolated first testicular relapse at >18 months, who have no more testicular enlargement on ultrasound or no biopsy-proven testicular disease after induction therapy with higher doses of methotrexate (11, 12).

Other extramedullary disease

In the case of persistent leukemia in other extramedullary sites (e.g. mediastinum, lymph nodes, bone, skin or other organs), the study protocol coordinator or disease committee can be consulted regarding indications for radiotherapy. For pediatric ALL, these indications are rare.

Total Body Irradiation

Myeloablative Total Body Irradiation (TBI) can be applied in the context of an allogeneic stem cell transplantation (SCT) protocol. TBI pertains serious risks of late health damage: i.e. secondary malignancies, growth retardation, hormonal failure, cognitive damage. For this reason, a randomized study was conducted in Europe (the FORUM trial) concerning the non-inferiority of chemotherapy (vs radiotherapy) in children with acute lymphoblastic leukemia (ALL). This study was stopped prematurely due to excessive recurrences in the chemo arms. Since then, TBI is again the first choice for conditioning for ALL in children ≥ 4 years of age. CNS toxicity below the age of 4 is high and TBI / CSI is in principal steered clear from. CSI is contra-indicated for children <2 years of age.

Considerations regarding extra CNS toxicity

For any ALL RT, cumulative radiotherapy doses (including previous RT), in particular to the central nervous system, should be taken into account. Even low to moderate doses of CNS RT (i.e., 18-24 Gy) can lead to toxicity that is more severe than would be expected at such doses, largely because of the synergistic effect of RT and CNS-directed chemotherapy. It is advised not to give RT to CNS volumes concurrent with intrathecal or intravenous chemotherapy (13, 14).
In case of known leukencephalopathy with clinical symptoms or clinical myelopathy from systemic / intrathecal treatment before start of CNS-directed RT (15, 16), indications for RT should be reconsidered and discussed with the study / national coordinator. Depending on clinical symptoms and severity of RT indication, it can be decided to not give RT or to adjust the dose.

Diagnostic information before start of radiotherapy

Recent hematological laboratory values

CNS macroscopic involvement: MRI brain before start of chemotherapy and evaluation of response to chemotherapy; cerebrospinal fluid results

Testicular involvement: ultrasound of testis with biopsy (if needed) before start of chemotherapy and evaluation response by ultrasound after chemotherapy. In case of unilateral involvement and orchiectomy, a biopsy of the contralateral testis should be taken during orchiectomy. Testicular contralateral involvement documented by ultrasound alone without clinical enlargement has to be confirmed by biopsy and will be treated like a clinically non-involved testis, until proven otherwise by biopsy. In the DCOG-ALL-11 trial, diagnostics (biopsy) for testicular residual disease are recommended in case of doubtful clinical findings after the M block of systemic treatment.

In the ALLTogether1 trial, if patients with an initial testicular leukemia are stratified to a High Risk protocol in case of (biopsy-proven) incomplete response after consolidation 1. If there still is biopsy-proven testicular involvement after 3 blocks of HR therapy, it is deemed refractory testicular disease.

Timing of radiotherapy in relation to systemic therapy

Overall, radiotherapy in case of residual CNS/testicular disease, in case of no TBI, is given after the end of the intensive chemotherapy phase; this will often mean at the start of the maintenance courses (*exception: EsPhALL see below). Be aware: no CNS-directed RT concurrent with intravenous or intrathecal chemotherapy.

CNS disease

A minimal interval of 2 weeks (preferably 3-5 weeks when feasible) between the last intravenous or intrathecal administration of methotrexate or cytarabine and initiation of CNS-directed RT is recommended. However, in cases in which urgent RT is necessary because of symptoms, shorter intervals of 48 to 72 hours may be considered (17).

In IntReALL SR 2010 protocol, the CSI is scheduled at the beginning of maintenance therapy in SR patients not receiving stem cell transplantation. Patients receiving SCT are treated according to the FORUM protocol guidelines with CSI boost right before TBI.

In IntReALL HR 2010 protocol, the CSI boost is scheduled right before TBI. Patients receiving SCT are conditioned according to the FORUM protocol guidelines.

Testicular disease

In the DCOG-ALL-11 trial, if testicular biopsy after block M is positive, RT will take place after the HR (after block 6 if no SCT; as pre-TBI boost after block 3 if SCT with TBI), or at the end of the 12 weeks MR intensification – thus before the start of maintenance therapy.

In the ALLTogether1 trial, if refractory testicular disease is present after 3 HR blocks, indication for resistant ALL protocols and / or testicular RT should be discussed, including timing thereof.

In IntReALL SR 2010 protocol, testicular radiotherapy is scheduled before the start of maintenance therapy. In case of TBI during conditioning for stem cell transplantation, a testicular boost is given before TBI. Patients receiving SCT are conditioned according to the FORUM protocol guidelines.

In IntReALL HR 2010 protocol, the testicular boost is scheduled right before TBI. Patients receiving SCT are conditioned according to the FORUM protocol guidelines.

TBI

TBI is given during the conditioning regimen before allogeneic stem cell transplantation, according to the specific conditioning protocols, and the last fraction may be given up to a few hours before the transplantation.

If both CSI and TBI are to be given during conditioning for the allogeneic stem cell transplantation, CSI is given in the days just before TBI and thus during the systemic conditioning schedule (e.g. Wed – Thur – Fri CSI / Mon – Tue – Wed TBI).

If both testicular radiotherapy and TBI are to be given during conditioning for the allogeneic stem cell transplantation, testicular radiation is given in the days just before TBI and thus during the systemic conditioning regimen.

Prophylactic cranial RT

* Specific mention of the EsPhALL2017 study for prophylactic CRT: Cranial irradiation will be given to Standard Risk patients with CNS3 leukemia at diagnosis. It will be administered during either a) the first two weeks of the Interim Maintenance phase and completed by Day 14 (SR patients assigned to the EsPhALL arm (arm A), or b) the first 4 weeks of Maintenance therapy and should be completed by Day 29 (SR patients assigned to the Investigational COG Arm). It is recommended that High Risk patients going to HSCT who were CNS3 at diagnosis going to HSCT should receive a cranial boost prior to TBI. In the rare circumstance that an HR patient is unable to proceed to HSCT in CR1 and will continue to be treated per the HR chemotherapy arm (EsPhALl backbone), cranial irradiation should be administered during the first two weeks of the Interim Maintenance phase in HR patients with CNS3 disease at diagnosis.

Target volume Craniospinal Irradiation (CSI)

This follows the guideline as published by the SIOPE (18).

Clinical Target Volume CTV_brain includes the entire cerebrum including the cerebrospinal fluid extension around the optical nerves and the skull base with extra attention for coverage of the lamina cribrosa and the extending cranial nerves.

- N II: entire length of the optic nerve including the optic disc
- N V: Meckel's cave
- N VII+VIII: internal acoustic canal
- N IX+X+XI: 10-15 mm outside tabula interna
- N XII: 10-15 mm outside tabula interna

CTV_spine: includes the full thecal sac, including the recesses in lateral direction. The inferior limit is determined by the visible expansion of the CSF on MRI. According to recent MRI research, the CSF distribution at the sacral plexus appears to be limited to the spinal canal (19). Usually the lower limit of the CTV is S3.

Target volume Testis Irradiation

Gross Target Volume GTV: contralateral testis after orchiectomy or both testes

Clinical Target Volume CTV: scrotal content up until the exit point of the vas deferens towards inguinal

Target volume prophylactic Cranial Irradiation

CTV_brain includes the entire cerebrum including the cerebrospinal fluid extension around the optical nerves and the skull base with extra attention for coverage of the lamina cribrosa and the extending cranial nerves.

- N II: entire length of the optic nerve including the optic disc

- N V: Meckel's cave
- N VII+VIII: internal acoustic canal
- N IX+X+XI: 10-15 mm outside tabula interna
- N XII: 10-15 mm outside tabula interna

The caudal border of historically planned 2D fields was placed to include at least the C2 vertebral level. CTV should therefore extend down until the caudal 5 mm of the C2 vertebra.

Target volume Total Body Irradiation (TBI)

Entire body. Following the local protocol, the lungs, kidneys and lenses should be blocked or receive a lower dose if using dose modulating techniques – maximum dose to lungs, kidnes and lenses should be 10 Gy. Be aware, in case of 2D techniques, not to block the eyes in case of CNS disease and indication for CNS RT.

Dose specification and fractionation

<u># Total Body Irradiation (TBI):</u>

The standard conditioning schedule is 6 x 2 Gy = 12 Gy b.i.d, so 6 fractions twice a day on 3 consecutive days. Time interval between 2 fractions at least 6 hours.

After previous CNS-directed RT, patients who are older than 48 months at the time of conditioning should receive TBI under the following conditions:

- if the previous irradiation free period is ≥24 months, and the prior CNS irradiation does not exceed 18 Gy.
- if the previous irradiation free period is <24 months and the prior CNS irradiation does not exceed 12 Gy.

→ When CNS radiotherapy has previously been given, the TBI dose (and CNS dose) is adjusted depending on age and conditioning schedule (Table extract from FORUM protocol):

Overview: Irradiation plan (TBI and Cranial irradiation)

Age at time of conditioning	CNS-Involvement	Previous irradiation (Cranium) in Gy	Irradiation-free interval	TBI in Gy	CNS –Boost before SCT in Gy	Total dose Cranium
≤48 months or MMD SCT	neg	0		no	no	0
		12		no	no	12
		18		no	no	18
	pos	0		no	no	0
		12		no	no	12
		18		no	no	18
>48 months MSD or MD SCT or MMD BM 8/10	neg	0	<24 months	12	no	12
		12		12	no	24
		18		no	no	18
		0	≥24 months	12	no	12
		12		12	no	24
		18		12	no	30
	"Active" Pos: no randomisation	0	<24 months	12	6	18
		12		12	no	24
		18		no	6	24
		0	≥24 months	12	6	18
		12		12	no	24
		18		12	no	30

- Active positive disease - defined as CNS positivity at the time of relapse diagnosis (if HSCT in CR2) or at time of initial diagnosis (if HSCT in CR1).

Craniospinal Irradiation (CSI):

- 9 x 2 = 18 Gy (or 10-12 x 1.8-1.5 = 18 Gy), fractionation 5x / week (no CSI in children <2 years old)

→ When TBI for allogeneic SCT is given as well, the RT starts with an adjusted CSI dose of 3 x 2 = 6 Gy, followed by TBI 6 x 2 Gy b.i.d.

- If indicated: boost on specific (visible on MRI) locations: 3 x 2 = 6 Gy or 4 x 1.5 = 6 Gy (Total Dose 24 Gy), start before CSI and TBI

→ The (current) cumulative total dose on the brain must not be >24 Gy with (combined) TBI / CNS (+ - boost) irradiation

→ When previous CNS radiotherapy has been given >18 Gy, the CSI dose is adjusted to 10 x 1.5 = 15 Gy

→ When previous CNS radiotherapy >15 Gy has been given less than 24 months before current RT, the CSI dose is adjusted to 10 x 1.5 = 15 Gy

Testicular recurrence or residual disease

- Orchiectomy and reduced RT of contralateral (clinically not suspected) testicle:

→ If no involvement proven by biopsy: 15 Gy in fractions of 1.5 - 1.8 Gy (or cumulative 18 Gy if TBI is given as well)

→ If biopsy-proven involvement (subclinical disease) or no biopsy: 18 Gy in fractions of 1.5 - 1.8 Gy

- One or both testicles clinically involved and no orchiectomy performed:

RT of both testicles 12 x 2 = 24 Gy (or pre-TBI boost 6x2 Gy and therefore cumulative 24 Gy if TBI is given as well)

Prophylactic Cranial Radiotherapy (CRT) in EsPhAll2017 protocol:

- 10x1.8 = 18 Gy, fractionation 5x / week

→ When TBI for allogeneic SCT is given as well, the RT starts with an adjusted CRT dose of 3 x 2 = 6 Gy, followed by TBI 6 x 2 Gy b.i.d.

REFERENCES

1. Gao RW, Dusenbery KE, Cao Q, Smith AR, Yuan J. Augmenting Total Body Irradiation with a Cranial Boost before Stem Cell Transplantation Protects Against Post-Transplant Central Nervous System Relapse in Acute Lymphoblastic Leukemia. Biol Blood Marrow Transplant. 2018;24(3):501-6.
2. Hiniker SM, Agarwal R, Modlin LA, Gray CC, Harris JP, Million L, et al. Survival and neurocognitive outcomes after cranial or craniospinal irradiation plus total-body irradiation before stem cell transplantation in pediatric leukemia patients with central nervous system involvement. Int J Radiat Oncol Biol Phys. 2014;89(1):67-74.
3. Jeha S, Pei D, Choi J, Cheng C, Sandlund JT, Coustan-Smith E, et al. Improved CNS Control of Childhood Acute Lymphoblastic Leukemia Without Cranial Irradiation: St Jude Total Therapy Study 16. J Clin Oncol. 2019;37(35):3377-91.
4. Piette C, Suciu S, Bertrand Y, Uyttebroeck A, Vandecruys E, Plat G, et al. Long-term outcome evaluation of medium/high risk acute lymphoblastic leukaemia children treated with or without cranial radiotherapy in the EORTC 58832 randomized study. Br J Haematol. 2019.
5. Kelly MJ, Trikalinos TA, Dahabreh IJ, Gianferante M, Parsons SK. Cranial radiation for pediatric T-lineage acute lymphoblastic leukemia: a systematic review and meta-analysis. Am J Hematol. 2014;89(10):992-7.
6. Clarke M, Gaynon P, Hann I, Harrison G, Masera G, Peto R, et al. CNS-directed therapy for childhood acute lymphoblastic leukemia: Childhood ALL Collaborative Group overview of 43 randomized trials. J Clin Oncol. 2003;21(9):1798-809.
7. Richards S, Pui CH, Gayon P, Childhood Acute Lymphoblastic Leukemia Collaborative G. Systematic review and meta-analysis of randomized trials of central nervous system directed therapy for childhood acute lymphoblastic leukemia. Pediatr Blood Cancer. 2013;60(2):185-95.
8. Vora A, Andreano A, Pui CH, Hunger SP, Schrappe M, Moericke A, et al. Influence of Cranial Radiotherapy on Outcome in Children With Acute Lymphoblastic Leukemia Treated With Contemporary Therapy. J Clin Oncol. 2016;34(9):919-26.
9. Hijiya N, Liu W, Sandlund JT, Jeha S, Razzouk BI, Ribeiro RC, et al. Overt testicular disease at diagnosis of childhood acute lymphoblastic leukemia: lack of therapeutic role of local irradiation. Leukemia. 2005;19(8):1399-403.
10. Pui CH. Is testicular irradiation necessary for patients with acute lymphoblastic leukemia and testicular relapse? Pediatr Blood Cancer. 2018;65(5):e26977.
11. Barredo JC, Hastings C, Lu X, Devidas M, Chen Y, Armstrong D, et al. Isolated late testicular relapse of B-cell acute lymphoblastic leukemia treated with intensive systemic chemotherapy and response-based testicular radiation: A Children's Oncology Group study. Pediatr Blood Cancer. 2018;65(5):e26928.
12. van den Berg H, Langeveld NE, Veenhof CH, Behrendt H. Treatment of isolated testicular recurrence of acute lymphoblastic leukemia without radiotherapy. Report from the Dutch Late Effects Study Group. Cancer. 1997;79(11):2257-62.
13. Watterson J, Toogood I, Nieder M, Morse M, Frierdich S, Lee Y, et al. Excessive spinal cord toxicity from intensive central nervous system-directed therapies. Cancer. 1994;74(11):3034-41.
14. Magge RS, DeAngelis LM. The double-edged sword: Neurotoxicity of chemotherapy. Blood Rev. 2015;29(2):93-100.
15. Bhojwani D, Sabin ND, Pei D, Yang JJ, Khan RB, Panetta JC, et al. Methotrexate-induced neurotoxicity and leukoencephalopathy in childhood acute lymphoblastic leukemia. J Clin Oncol. 2014;32(9):949-59.

16. Reddick WE, Glass JO, Helton KJ, Langston JW, Xiong X, Wu S, et al. Prevalence of leukoencephalopathy in children treated for acute lymphoblastic leukemia with high-dose methotrexate. AJNR Am J Neuroradiol. 2005;26(5):1263-9.
17. Pinnix CC, Yahalom J, Specht L, Dabaja BS. Radiation in Central Nervous System Leukemia: Guidelines From the International Lymphoma Radiation Oncology Group. Int J Radiat Oncol Biol Phys. 2018;102(1):53-8.
18. Ajithkumar T, Horan G, Padovani L, Thorp N, Timmermann B, Alapetite C, et al. SIOPE - Brain tumor group consensus guideline on craniospinal target volume delineation for high-precision radiotherapy. Radiother Oncol. 2018;128(2):192-7.
19. Wood AM, Lequin MH, Philippens MM, Seravalli E, Plasschaert SL, van den Heuvel-Eibrink MM, et al. MRI-guided definition of cerebrospinal fluid distribution around cranial and sacral nerves: implications for brain tumors and craniospinal irradiation. Acta Oncol. 2019;58(12):1740-4.