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Original Article

# Towards homogenization of total body irradiation practices in pediatric patients across SIOPE affiliated centers. A survey by the SIOPE radiation oncology working group

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ABSTRACT

*Background and purpose:* To reduce relapse risk, Total Body Irradiation (TBI) is part of conditioning regimens for hematopoietic stem cell transplantation (HSCT) in pediatric acute leukemia. The study purpose was to evaluate clinical practices regarding TBI, such as fractionation, organ shielding and delivery techniques, among SIOPE affiliated radiotherapy centers.

*Methods:* An electronic survey was sent out to 233 SIOPE affiliated centers, containing 57 questions about clinical practice of TBI. Surveys could be answered anonymously.

*Results:* From over 25 countries, 82 responses were collected. For TBI-performing centers, 40/48 irradiated ≤10 pediatric patients annually (range: 1–2 to >25). Most indications concerned acute lymphoblastic leukemia (ALL) or acute myeloid leukemia (AML). Four different fractionation schedules were used, of which 12 Gy in 6 fractions was applied in 91% for ALL and 86% for AML. Dose reduction to the lungs, mostly to a mean dose of 8–10 Gy, was applied by 28/33 centers for ALL and 19/21 centers for AML, in contrast to much less applied dose reduction to the kidneys (7/33 ALL and 7/21 AML), thyroid (2/33 ALL and 2/21 AML), liver (4/33 ALL and 3/21 AML) and lenses (4/33 ALL and 4/21 AML). Conventional TBI techniques were used by 24/29 responding centers, while 5/29 used advanced optimized planning techniques.

*Conclusion:* Across SIOPE, there is a high level of uniformity in fractionation and use of lung shielding. Practices vary regarding other organs-at-risk shielding and implementation of advanced techniques. A SIOPE radiotherapy working group will be established to define international guidelines for pediatric TBI.


Chemotherapy cures most children with hematologic malignancies. However, some 15% of all children with acute leukemia (acute lymphoblastic leukemia (ALL) or acute myeloid leukemia (AML)) and high risk features or relapse, benefit from donor (allogeneic) hematopoietic stem cell transplantation (HSCT) [1]. HSCT for hematologic malignancies is usually preceded by a conditioning regimen with myeloablative doses of chemotherapy (mostly treosulfan or busulphan-based) or with Total Body Irradiation (TBI), often combined with etoposide or cyclophosphamide [1].

TBI dose schedules range from a single dose between 5–10 Gy to a fractionated dose of 8–14.4 Gy once- or twice-daily over

*Abbreviations:* ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; $EQD_2$, equivalent total dose in 2 Gy fractions; Gy, Gray; HSCT, (allogeneic) hematopoietic stem cell transplantation; IMRT, intensity-modulated radiotherapy; OAR, organ(s)-at-risk; SIOPE, The European Society for Paediatric Oncology; TBI, Total Body Irradiation; TMI, Total Marrow Irradiation; TMLI, Total Marrow and Lymphoid Irradiation; TLI, Total Lymphoid Irradiation; VMAT, volumetric modulated arc therapy.

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3–4 days [2–5]. In the long term, TBI is associated with well-known side-effects, such as cataract, hypothyroidism, interstitial pneumonitis and lung fibrosis, renal dysfunction, sinusoidal obstruction syndrome, decreased gonadal function and infertility, growth inhibition, as well as a higher risk of secondary malignancies [6–15]. TBI below the age of 3–4 years induces more multi-organ dysfunction and neurocognitive abnormalities, and is generally not performed [11,16]. Fractionated TBI, especially with doses <14.4 Gy, incurs less acute and late effects, including secondary malignancies, compared to single high-fraction dose TBI [14,17–21].

For AML, chemotherapy-only regimens are the mainstay for conditioning, but TBI-containing regimens are also employed in e.g. high-risk recurrent cases [22–25]. For ALL, conditioning with a combination of chemotherapy and TBI has mostly shown better leukemic control [26–29]. An ongoing international randomized controlled trial in ALL (ALL SCTped 2012 FORUM, EudraCT number: 2012-003032-22), comparing chemotherapy-only conditioning with chemotherapy plus TBI conditioning, has stopped randomization prematurely due to superior overall and event-free survival rates in the TBI-containing arm [29,30]. Based on this trial, chemotherapy plus TBI is once more the first choice for ALL HSCT conditioning in children $\geq$48 months of age.

TBI-providing pediatric radiotherapy centers should carefully evaluate how late effects could be mitigated without compromising efficacy. The implementation of modern conformal radiotherapy techniques like rotational intensity-modulated radiotherapy (IMRT) (e.g. volumetric modulated arc therapy (VMAT), helical tomotherapy) could be beneficial to achieve both a homogeneous dose delivery to the target volume of the body, and dose reduction for organs-at-risk (OAR) [31,32]. Other approaches to spare OAR are in use as well, such as total marrow and/or lymphoid irradiation (TM(L)I) [32–34].

Some years ago, the International Lymphoma Radiation Oncology group presented guidelines for TBI in adults [35]. For growing children, several considerations regarding total dose, fractionation and organ shielding may be of even more interest than for adults. The lack of a specific pediatric guideline, and the low numbers of pediatric patients treated in each center makes international collaboration necessary to achieve homogenization of TBI practices. The first step in establishing such collaboration, is to evaluate the degree of heterogeneity in clinical practice. Therefore, the purpose of this study was to map the current clinical practice of myeloablative TBI across SIOPE-affiliated radiotherapy centers by means of a survey.

## Materials and methods

To collect information on the current practice of myeloablative TBI across SIOPE-affiliated countries (https://www.siope.eu/about-siope/members/), an online accessible survey with a maximum of 57 questions was designed using Survey Monkey (SVMK Inc., CA, USA).

In the context of the Joint Action on Rare Cancer (JARC) project, endorsed by the European Union, pediatric radiotherapy departments have been mapped in 2019 [36]. The survey was sent to one radiation oncologist per center; a total of 233 centers in 33 countries were contacted.

Participants could choose to participate anonymously or to mention their name and affiliation.

The survey focused on clinical aspects of myeloablative TBI in pediatric patients. It included multiple-choice questions with room for remarks, as well as several open-ended questions. Depending on the given answers, certain questions were skipped if not applicable. Questions were asked regarding the center's frequency of pediatric myeloablative TBI performance annually; TBI indications; age characteristics of pediatric TBI patients; total TBI doses and fractionation schedules; OAR shielding / underdosing; use of conventional or advanced optimized radiotherapy techniques for TBI; use of CT for TBI planning; and potential application of TM (L)I. A follow-up survey with 8 additional questions regarding boost doses and use of anesthesia (sedation) was sent to 27 known TBI-performing survey participants in September 2020. Responses were collected via Survey Monkey and analyzed at the departments of radiation oncology in Utrecht UMC and LMU Munich. Survey respondents were invited for a web-based live discussion of the results and to join a TBI working group. These participants evaluated the survey outcomes and resulting manuscript as co-authors.

Regarding the evaluation of differences in lung shielding dose, the equivalent total dose in 2-Gy fractions ($EQD_2$) was calculated for different fractionation schedules; for leukemia-dose effect with an $\alpha/\beta$ ratio of 10, and for lung toxicity (fibrosis) dose–effect with an $\alpha/\beta$ ratio of 3. $EQD_2$ was calculated by $EQD_2 = D\ (d + (\alpha/\beta))/(2+(\alpha/\beta))$, without correction for overall treatment time (OTT) since all fractionation schemes were completed within 3–4 days.

## Results

Between January 31 and March 1, 2020, 82 responses were collected (35% return rate), from at least 25 out of 33 countries as could be derived from non-anonymous participation. In September 2020, 18 responses to the follow-up survey were collected. Since answers in the survey could be skipped by respondents, results are given as absolute numbers of centers providing information.

Fifty-two centers in 16 countries, out of 82 participating centers, performed TBI with myeloablative radiotherapy doses for pediatric patients; 48 of these respondents answered multiple questions. Thirty centers did not perform TBI in children. Major reasons for not performing TBI were referral to another center ($n$ = 17), technical limitations ($n$ = 8), and/or no TBI under sedation possible ($n$ = 2).

Across the centers, there was a great variety in the total number of pediatric TBI's performed annually: 1–2 (10/48); 3–5 (16/48); 6–10 (14/48); 11–15 (5/48); 16–20 (2/48); >25 (1/48).

For ALL, respondents indicated that TBI was performed in their center in case of high-risk disease at first presentation (19/37), at first recurrence (30/37), and at second recurrence (14/37). For AML, TBI was performed in case of high-risk disease at first presentation (8/22); at first recurrence (13/22), and at second recurrence (11/22).

Most centers performed TBI in 6–10 pediatric patients with ALL (range 1–2 to 21–25) per year, and in 1–2 pediatric patients with AML (range 1–2 to 11–15) per year (Fig. 1).

The minimum age for TBI as conditioning for HSCT in pediatric ALL and AML patients, as responded by 15 and 10 participants respectively, varied from 2 years (12%), through 3–4 years (50%), to 5 years (12%) old. One center did not have a minimum age cut-off, 2 others responded that it depended on risk or indication. The upper age-limit for "pediatric" patients was 16, 18 or 21 years for 14, 29 and 1 centers, respectively.

Myeloablative TBI was performed with varying dose schedules, but the majority of centers used 12 Gy in 6 fractions of 2 Gy, given as 2 fractions per day over 3 days (91% of centers for ALL and 86% of centers for AML) (Fig. 2). One center spread this dose over 4 days in a 1-2-2-1 fractionation schedule. Other twice-daily schedules were 14.4 Gy in 8 1.8-Gy fractions and 13.2 Gy in 8 1.65-Gy fractions. A once-daily fractionation schedule that was used, was 11 Gy in 4 fractions of 2.75 Gy over 4 days. No center mentioned currently using a single-fraction high dose for TBI in leukemia.

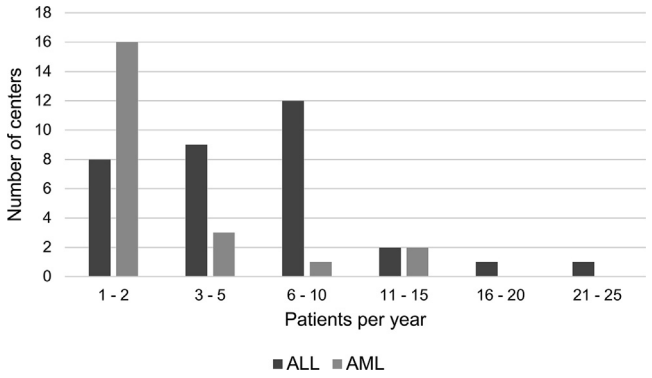


**Fig. 1.** Number of responding centers that treat 1–2, 3–5, 6–10, 11–15, 16–20 or 21-25 pediatric patients per year with myeloablative TBI, for ALL and AML.

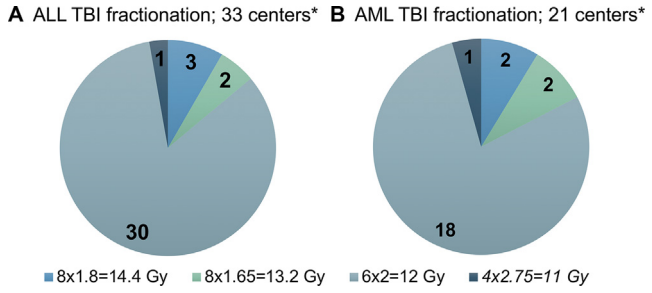


**Fig. 2.** Fractionation schemes as used by responding centers for TBI in HSCT conditioning for ALL (A) and AML (B). Twice-daily fractionation schemes are used, except a once-daily fractionation scheme in *Italic*. *3 (ALL) respectively 2 (AML) centers performed 2 different fractionation schedules.

Boost doses, when indicated, were performed in once-daily fractions as cranial or craniospinal irradiation to doses of 5.4 Gy in 3 fractions, in addition to 14.4 Gy TBI; 6 Gy in 3–4 fractions, in addition to 12 Gy or 14.4 Gy TBI; or 12 Gy in 6 fractions, in addition to 12 Gy TBI (cranial boost: 12/17 centers; craniospinal boost 3/17 centers). When indicated, boost doses on the testes were given to a dose of 4 Gy in 1 fraction in addition to 12 Gy or 14.4 Gy TBI; 6 Gy in 3 fractions in addition to 12 Gy TBI; or 12 Gy in 6 fractions in addition to 12 Gy TBI (11/17 centers). On occasion, a boost of 12 Gy in 6 fractions would be given on other leukemic deposits, in addition to 12 Gy TBI (2/17 centers).

Sedation, if indicated and possible within a center, was no impediment for twice-daily TBI fractionation.

Six respondents reported performing Total Marrow Irradiation (TMI) or Total Lymphoid Irradiation (TLI) for children in their institutes, mostly in special cases after e.g. graft rejection. One center used TMI as standard for all myeloablative treatments in pediatric patients.

Dose reduction for OAR was applied by nearly all of the responding centers: for both ALL (29/33 centers; 88%) and AML (19/21 centers; 90%). A dose-reduction was given on the lungs by most centers; 28/33 centers for ALL and 19/21 centers for AML. The maximal accepted lung dose was mostly 8–10 Gy for a TBI prescription dose of 12 Gy, and 12 Gy for a prescription dose of 14.4 Gy. Fig. 3 represents $EQD_2$ calculations for leukemia-effective dose versus lung-toxicity-dose as utilized in different centers for ALL and AML. A minority of centers performed dose reduction to the kidneys (7/33 centers for ALL and 7/21 centers for AML), lenses (4/33 ALL and 4/21 AML), liver (4/33 ALL and 3/21 AML), or thyroid (2/33 ALL and 2/21 AML) (Table 1).

Most of the responding centers (24/29) used conventional techniques for TBI, while 5/29 centers used advanced optimized techniques for all referred children (Fig. 4). Advanced techniques comprised IMRT, VMAT and helical tomotherapy. The number of pediatric patients receiving myeloablative TBI within these centers were 11–15 (1 center), 6–10 (1 center), and 3–5 (3 centers). Fourteen out of 29 centers performed CT-based planning, with an axial CT slice thickness between 2 and 10 mm.

## Discussion

In this survey on myeloablative TBI practice across SIOPE-affiliated centers, we observed large consistency in dose prescription, indications, age limit for TBI, lung shielding, boost doses, and the use of conventional techniques. However, to further decrease the risk of potential late effects, more research and consensus is needed on the value and relevance of shielding of other organs-at-risk and implementation of advanced radiotherapy techniques for TBI.

In adults, a European survey among 56 centers in 23 countries reported important heterogeneity of TBI techniques [37]. Another recent survey in Australia and New Zealand reported use of mainly fractionated TBI, but heterogeneity in shielding and TBI procedures [38]. Guidelines published by Wong et al. in 2018 gave directions to homogenize indications and procedures for TBI in adults [35].

From the current survey on TBI for children, international consensus can be concluded on factors such as lowest age-limit and use of fractionated schedules instead of single-fraction high dose TBI. A summary of these factors is given in Table 2. Since older publications reported on neuropsychological and other developmental deficiencies, such as growth inhibition and endocrine abnormalities, in very young children after TBI conditioning [11,16], chemotherapy-only conditioning regimes are commonly preferred for children under 2–4 years old. The current FORUM trial uses 4 years as a cut-off for chemotherapy-only versus TBI-based conditioning [29]. Only a few centers in our survey stated to perform TBI for children at or under 2 years old. No responding center is currently performing single-fraction high dose TBI for pediatric leukemia.

Radiation dose reduction to the lungs is clinical practice in almost all responding centers. Reports on lung interstitial disease and associated worse survival odds for doses $\geq$8 Gy in TBI-conditioned patients have been published, and a mean dose reduction to below 8–10 Gy has been advised to reduce risks of pneumonitis or lung fibrosis [6,10,16]. In our survey, 27/33 centers applied lung $EQD_2$ doses between ±7 and ±10 Gy, and some exceptions accepted up to 14.4 Gy.

Practices vary regarding shielding of other organs-at-risk. Only a few centers in our survey performed e.g. kidney, liver, eye/lens or thyroid shielding. Nephrotoxicity after HSCT is ascribed to both chemotherapy and TBI [7,8,24]. A Biologically Effective Dose (BED) of >16 Gy is associated with increased risk of renal dysfunction [8]. Acute and late liver toxicity after combined chemotherapy and TBI conditioning in the form of elevated liver enzymes is described frequently; hepatic sinusoidal obstruction syndrome can occur in up to one-fourth of patients after HSCT, and TBI is thought to be a contributing factor [16,39,40]. Also, children with early liver injury after HSCT, which occurs more often in TBI-containing regimens, are at higher risk of transplantation-related mortality [41]. Specific shielding of the liver is complicated with conventional techniques.

Cataract risk is related to single-dose TBI, corticosteroid-use, and also to chronic graft-versus-host-disease [15]. Eye/lens shielding for reduction of cataract risk may still be relevant in fractionated TBI, since severe cataracts mostly form at BEDs of >40 Gy [7]. Depending on dose rate, 6 fractions of 2 Gy will give a 37–43 Gy BED on the lenses [7]. Therefore, even with fractionated

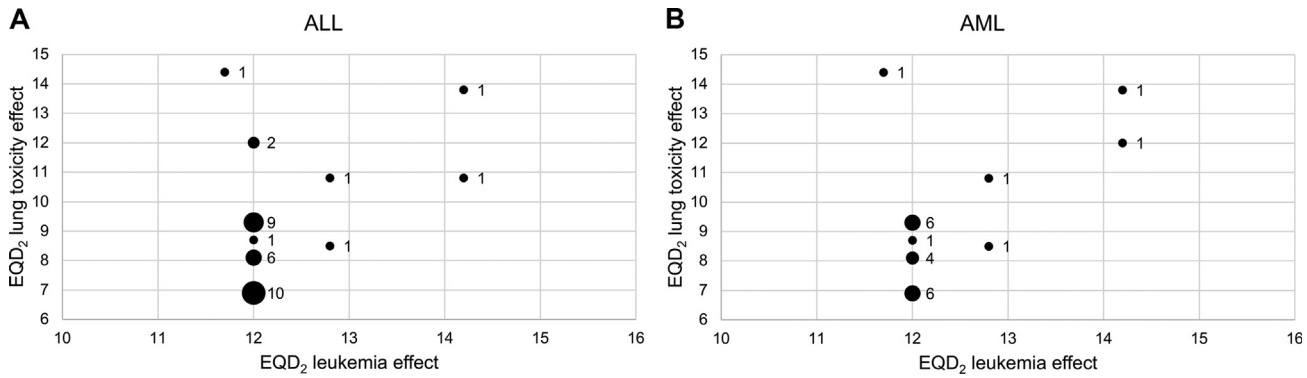


**Fig. 3.** $EQD_2$ for leukemia-dose–effect with an $\alpha/\beta$ of 10 versus lung-toxicity (interstitial fibrosis) dose–effect with an $\alpha/\beta$ of 3, as calculated from maximum accepted lung dose in different centers for different fractionation schemes, for ALL in 33 centers (A) and AML in 22 centers (B). Size of the spheres and adjoining numbers represent number of centers using these $EQD_2$'s.

**Table 1**
Maximum accepted organ doses (lungs, kidneys, liver, thyroid, lenses) for different TBI fractionation schedules in leukemia (ALL and AML), by responding number of centers.

| Organ shielded | Fractionation | Max accepted organ dose (Gy) | ALL No. of centers | AML No. of centers |
|---|---|---|---|---|
| Lungs | 6x2 = 12 Gy | 12 | 2 | |
| | | 10 | 9 | 7 |
| | | 9.5 | 1 | |
| | | 9 | 6 | 4 |
| | | 8 | 10 | 6 |
| | 8 × 1.65 = 13.2 Gy | 12 | 1 | 1 |
| | | 10 | 1 | 1 |
| | 8 × 1.8 = 14.4 Gy | 14.4 | 2 | 1 |
| | | 12 | 1 | 1 |
| | 4 × 2.75 = 11 Gy | 12 | 1 | 1 |
| Kidneys | 6 × 2 = 12 Gy | 12 | 24 | 13 |
| | | 10 | 3 | 2 |
| | | 8 | | 1 |
| | | 6 | 1 | 1 |
| | 8 × 1.65 = 13.2 Gy | 12 | 1 | 1 |
| | | 10 | 1 | 1 |
| | 8 × 1.8 = 14.4 Gy | 14.4 | 2 | 1 |
| | | 12 | 1 | 1 |
| | 4 × 2.75 = 11 Gy | 12 | 1 | 1 |
| Liver | 6 × 2 = 12 Gy | 12 | 25 | 15 |
| | | 10 | 1 | 1 |
| | | 8 | 1 | |
| | | 6 | 1 | 1 |
| | 8 × 1.65 = 13.2 Gy | 13.2 | 1 | 1 |
| | | 10 | 1 | 1 |
| | 8 × 1.8 = 14.4 Gy | 14.4 | 3 | 2 |
| | 4 × 2.75 = 11 Gy | 12 | 1 | 1 |
| Thyroid | 6 × 2 = 12 Gy | 12 | 27 | 16 |
| | | 8 | 1 | 1 |
| | 8 × 1.65 = 13.2 Gy | 13.2 | 1 | 1 |
| | | 10 | 1 | 1 |
| | 8 × 1.8 = 14.4 Gy | 14.4 | 3 | 2 |
| | 4 × 2.75 = 11 Gy | 12 | 1 | 1 |
| Lenses | 6 × 2 = 12 Gy | 12 | 25 | 14 |
| | | 10 | 2 | 2 |
| | | 6 | | 1 |
| | | 4 | 1 | |
| | 8 × 1.65 = 13.2 Gy | 13.2 | 1 | 1 |
| | | 4 | 1 | 1 |
| | 8 × 1.8 = 14.4 Gy | 14.4 | 3 | 2 |
| | 4 × 2.75 = 11 Gy | 12 | 1 | 1 |

TBI, cataracts are diagnosed during follow-up in a high percentage of children [13]. Eye shielding does not seem to increase the risk of central nervous system recurrence [42]. Optimized techniques may provide a better opportunity to reduce lens doses without decreasing the central nervous system dose.

Shielding of the thyroid may reduce the risk of hypothyroidism, thyroid nodules and thyroid carcinoma, which, according to older publications with very long follow-up, occur in >10% of the children after HSCT with TBI [13,15]. Other second cancers after HSCT are not related to the type of conditioning (with or without TBI),

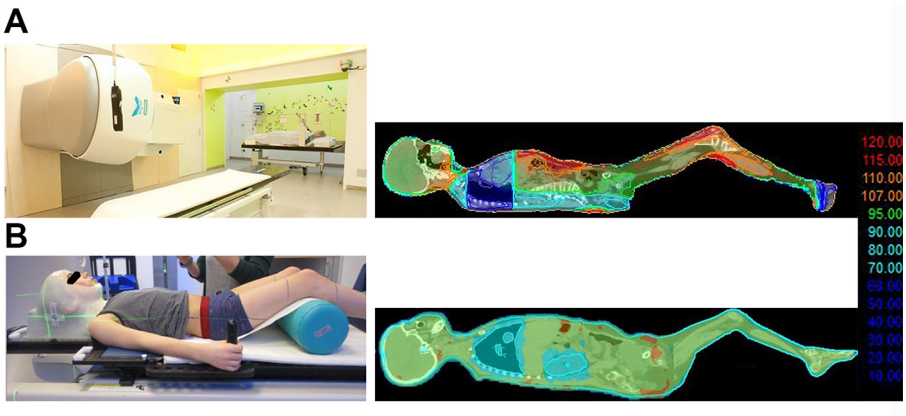


**Fig. 4.** (A) Example of a treatment room setup for conventional TBI and of a conventional TBI plan using lateral photon beams. (B) Example of a patient table setup for TBI by means of an advanced radiotherapy technique and of a VMAT plan dose distribution. *Relative isodose values depicted on the side of the plan images.*

**Table 2**
Summary of guiding clinical principles regarding pediatric myeloablative TBI, as followed by the majority of responding centers.

| TBI factor | Guiding principle |
|---|---|
| Most prevalent indications | High-risk and recurrent ALL and AML |
| Age | No TBI < 3 years of age |
| Fractionation | 12 Gy in 6 fractions of 2 Gy, b.i.d. |
| Organ dose reduction | Mean lung dose 8–10 Gy ($EQD_2$ 6.9–9.3 Gy) |
| Boost, if indicated (cumulative dose) | Cranial irradiation (18–24 Gy)<br>Testes irradiation (18–24 Gy) |
| Sedation, if indicated | Twice-daily sedation can be routinely performed |

but are more often diagnosed after HSCT in second remission than in first remission [14,15].

Conventional TBI techniques are standard of care in the majority of responding centers. The use of lead shielding can reduce the dose to particular OAR. However, leukemic compartments in the beam behind the shields are underdosed as well. One advantage of modern rotational techniques is the possibility to decrease the doses in specific OAR while increasing homogeneous target coverage in the rest of the body at the same time [43–47]. TLI/TMI/TMLI approaches aim to protect even more OAR while specifically delivering the dose in lymphoid / marrow tissues to pursue an anti-leukemic effect [33,34,48], or to induce less graft-versus-host-disease [32].

The use of modern TBI techniques with integrated shielding could maximally reduce OAR doses to mitigate late effects, without increasing risk of leukemia recurrences. Further research and consensus meetings can result in broadly supported guidelines.

For inverse optimized delivery techniques, a CT-based planning is indispensable. In our survey, we found that 50% of the responding centers were using CT-based planning, which would be the first step for the introduction of modern techniques. The entire process of advanced optimized techniques is technically more challenging than the conventional techniques and can take several hours of contouring, 30 h for dose calculation and optimization, 6–8 h for quality assurance and between 40 and 120 min for one treatment session, depending on patient height and fraction dose [31,43–46,49], which may be explanatory factors for the limited implementation at the present time. If performance of advanced optimized techniques can become more standardized, less time-consuming and thus more user- and patient-friendly, widespread implementation could be achieved.

Although a 35% overall return rate is in line with comparable surveys [37,50], the weakness of our current study is that only 30–40 participants filled out a significant part of the survey. On the other hand, a representative number of countries across SIOP Europe have participated in the survey, including low- and middle income countries.

The establishment of a collaborative platform in which clinical and technical issues are discussed, is the next step in a process to create more homogeneity in pediatric myeloablative TBI approaches. The platform should consist of clinicians, physicists and technicians willing to improve outcomes and to facilitate broader study and interpretation of side-effects. The objective is to reach final consensus on TBI fractionation schedule(s), selection and dose constraints of the organs-at-risk, on the technical aspects of overarching advice on treatment-planning and –delivery for modern TBI, as well as the potential role of TMI, TLI and TMLI techniques.

In conclusion, myeloablative TBI in the conditioning of HSCT for pediatric acute leukemia is a relatively infrequent procedure in many radiotherapy departments. Nonetheless, there is international uniformity regarding fractionation schedules, age limits, the use of boost doses and the need for lung shielding. Practices vary regarding shielding of other organs-at-risk. Conventional techniques are applied more frequently than advanced optimized techniques. Improving clinical outcomes and reduction of toxicity may be possible through collaborative development of international guidelines for myeloablative TBI in pediatrics.

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## Conflict of interest

Nothing to declare.

## References

[1] Copelan EA. Hematopoietic stem-cell transplantation. N Engl J Med 2006;354:1813–26.

[2] Kal HB, Loes van Kempen-Harteveld M, Heijenbrok-Kal MH, Struikmans H. Biologically effective dose in total-body irradiation and hematopoietic stem cell transplantation. Strahlenther Onkol 2006;182:672–9.

[3] Clift RA, Buckner CD, Appelbaum FR, Bearman SI, Petersen FB, Fisher LD, et al. Allogeneic marrow transplantation in patients with acute myeloid leukemia in first remission: a randomized trial of two irradiation regimens. Blood 1990;76:1867–71.

[4] Willemze AJ, Geskus RB, Noordijk EM, Kal HB, Egeler RM, Vossen JM. HLA-identical haematopoietic stem cell transplantation for acute leukaemia in children: less relapse with higher biologically effective dose of TBI. Bone Marrow Transplant 2007;40:319–27.

[5] van Kempen-Harteveld ML, Brand R, Kal HB, Verdonck LF, Hofman P, Schattenberg AV, et al. Results of hematopoietic stem cell transplantation after treatment with different high-dose total-body irradiation regimens in five Dutch centers. Int J Radiat Oncol Biol Phys 2008;71:1444–54.

[6] Sanders JE. Late effects in children receiving total body irradiation for bone marrow transplantation. Radiother Oncol 1990;18:82–7.

[7] Kal HB, van Kempen-Harteveld ML. Induction of severe cataract and late renal dysfunction following total body irradiation: dose-effect relationships. Anticancer Res 2009;29:3305–9.

[8] Kal HB, van Kempen-Harteveld ML. Renal dysfunction after total body irradiation: dose-effect relationship. Int J Radiat Oncol Biol Phys 2006;65:1228–32.

[9] Komori K, Hirabayashi K, Morita D, Hara Y, Kurata T, Saito S, et al. Ovarian function after allogeneic hematopoietic stem cell transplantation in children and young adults given 8-Gy total body irradiation-based reduced-toxicity myeloablative conditioning. Pediatr Transplant 2019;23:e13372.

[10] Esiashvili N, Lu X, Ulin K, Laurie F, Kessel S, Kalapurakal JA, et al. Higher reported lung dose received during total body irradiation for allogeneic hematopoietic stem cell transplantation in children with acute lymphoblastic leukemia is associated with inferior survival: a report from the Children's Oncology Group. Int J Radiat Oncol Biol Phys 2019;104:513–21.

[11] Smedler A-C, Winiarski J. Neuropsychological outcome in very young hematopoietic SCT recipients in relation to pretransplant conditioning. Bone Marrow Transplant 2008;42:515–22.

[12] Legault L, Bonny Y. Endocrine complications of bone marrow transplantation in children. Pediatr Transplant 1999;3:60–6.

[13] Faraci M, Barra S, Cohen A, Lanino E, Grisolia F, Miano M, et al. Very late nonfatal consequences of fractionated TBI in children undergoing bone marrow transplant. Int J Radiat Oncol Biol Phys 2005;63:1568–75.

[14] Baker KS, Leisenring WM, Goodman PJ, Ermoian RP, Flowers ME, Schoch G, et al. Total body irradiation dose and risk of subsequent neoplasms following allogeneic hematopoietic cell transplantation. Blood 2019;133:2790–9.

[15] Lee CJ, Kim S, Tecca HR, Bo-Subait S, Phelan R, Brazauskas R, et al. Late effects after ablative allogeneic stem cell transplantation for adolescent and young adult acute myeloid leukemia. Blood Adv 2020;4:983–92.

[16] Mulcahy Levy JM, Tello T, Giller R, Wilkening G, Quinones R, Keating AK, et al. Late effects of total body irradiation and hematopoietic stem cell transplant in children under 3 years of age. Pediatr Blood Cancer 2013;60:700–4.

[17] Cohen A, Rovelli A, Bakker B, Uderzo C, van Lint MT, Esperou H, et al. Final height of patients who underwent bone marrow transplantation for hematological disorders during childhood: a study by the Working Party for Late Effects-EBMT. Blood 1999;93:4109–15.

[18] Ogilvy-Stuart AL, Clark DJ, Wallace WH, Gibson BE, Stevens RF, Shalet SM, et al. Endocrine deficit after fractionated total body irradiation. Arch Dis Child 1992;67:1107–10.

[19] Thomas BC, Stanhope R, Plowman PN, Leiper AD. Endocrine function following single fraction and fractionated total body irradiation for bone marrow transplantation in childhood. Acta Endocrinol (Copenh) 1993;128:508–12.

[20] Thomas BC, Stanhope R, Plowman PN, Leiper AD. Growth following single fraction and fractionated total body irradiation for bone marrow transplantation. Eur J Pediatr 1993;152:888–92.

[21] Benyunes MC, Sullivan KM, Deeg HJ, Mori M, Meyer W, Fisher L, et al. Cataracts after bone marrow transplantation: long-term follow-up of adults treated with fractionated total body irradiation. Int J Radiat Oncol Biol Phys 1995;32:661–70.

[22] Sauer MG, Lang PJ, Albert MH, Bader P, Creutzig U, Eyrich M, et al. Hematopoietic stem cell transplantation for children with acute myeloid leukemia-results of the AML SCT-BFM 2007 trial. Leukemia 2020;34:613–24.

[23] Copelan EA, Hamilton BK, Avalos B, Ahn KW, Bolwell BJ, Zhu X, et al. Better leukemia-free and overall survival in AML in first remission following cyclophosphamide in combination with busulfan compared with TBI. Blood 2013;122:3863–70.

[24] Dandoy CE, Davies SM, Ahn KW, He Y, Kolb AE, Levine J, et al. Comparison of total body irradiation versus non- total body irradiation containing regimens for de novo acute myeloid leukemia in children. Haematologica 2020.

[25] Lucchini G, Labopin M, Beohou E, Dalissier A, Dalle JH, Cornish J, et al. Impact of conditioning regimen on outcomes for children with acute myeloid leukemia undergoing transplantation in first complete remission. An analysis on behalf of the Pediatric Disease Working Party of the European Group for Blood and Marrow Transplantation. Biol Blood Marrow Transplant 2017;23:467–74.

[26] Davies SM, Ramsay NK, Klein JP, Weisdorf DJ, Bolwell B, Cahn JY, et al. Comparison of preparative regimens in transplants for children with acute lymphoblastic leukemia. J Clin Oncol 2000;18:340–7.

[27] Bunin N, Aplenc R, Kamani N, Shaw K, Cnaan A, Simms S. Randomized trial of busulfan vs total body irradiation containing conditioning regimens for children with acute lymphoblastic leukemia: a Pediatric Blood and Marrow Transplant Consortium study. Bone Marrow Transplant 2003;32:543–8.

[28] Gupta T, Kannan S, Dantkale V, Laskar S. Cyclophosphamide plus total body irradiation compared with busulfan plus cyclophosphamide as a conditioning regimen prior to hematopoietic stem cell transplantation in patients with leukemia: a systematic review and meta-analysis. Hematol Oncol Stem Cell Ther 2011;4:17–29.

[29] Peters C, Schrappe M, von Stackelberg A, Schrauder A, Bader P, Ebell W, et al. Stem-cell transplantation in children with acute lymphoblastic leukemia: a prospective international multicenter trial comparing sibling donors with matched unrelated donors-The ALL-SCT-BFM-2003 trial. J Clin Oncol 2015;33:1265–74.

[30] Peters C, Dalle JH, Locatelli F, Poetschger U, Pichler H, Sedlacek P, et al. TBI or chemotherapy based conditioning for children and adolescents with ALL: a prospective randomized multicenter-study 'FORUM' on behalf of the AIEOP-BFM-ALL-SG, IBFM-SG, INTREALL-SG and EBMT-PD-WP. European Hematology Association Library. 2020; 294922.

[31] Springer A, Hammer J, Winkler E, Track C, Huppert R, Bohm A, et al. Total body irradiation with volumetric modulated arc therapy: dosimetric data and first clinical experience. Radiat Oncol 2016;11:46.

[32] Paix A, Antoni D, Waissi W, Ledoux MP, Bilger K, Fornecker L, et al. Total body irradiation in allogeneic bone marrow transplantation conditioning regimens: a review. Crit Rev Oncol Hematol 2018;123:138–48.

[33] Patel P, Aydogan B, Koshy M, Mahmud D, Oh A, Saraf SL, et al. Combination of linear accelerator-based intensity-modulated total marrow irradiation and myeloablative fludarabine/busulfan: a phase I study. Biol Blood Marrow Transplant 2014;20:2034–41.

[34] Ocanto A, Escribano A, Glaria L, Rodriguez I, Ferrer C, Huertas C, et al. TLI in pediatric patients. Clin Transl Oncol 2020;22:884–91.
[35] Wong JYC, Filippi AR, Dabaja BS, Yahalom J, Specht L. Total body irradiation: guidelines from the International Lymphoma Radiation Oncology Group (ILROG). Int J Radiat Oncol Biol Phys 2018;101:521–9.
[36] Janssens GO, Timmermann B, Laprie A, Mandeville H, Padovani L, Chargari C, et al. Recommendations for the organisation of care in paediatric radiation oncology across Europe: a SIOPE-ESTRO-PROS-CCI-Europe collaborative project in the framework of the JARC. Eur J Cancer 2019;114:47–54.
[37] Giebel S, Miszczyk L, Slosarek K, Moukhtari L, Ciceri F, Esteve J, et al. Extreme heterogeneity of myeloablative total body irradiation techniques in clinical practice: a survey of the Acute Leukemia Working Party of the European Group for Blood and Marrow Transplantation. Cancer 2014;120:2760–5.
[38] Fog LS, Wirth A, MacManus M, Downes S, Grace M, Moggre A, et al. Total body irradiation in Australia and New Zealand: results of a practice survey. Phys Eng Sci Med 2020.
[39] Chou RH, Wong GB, Kramer JH, Wara DW, Matthay KK, Crittenden MR, et al. Toxicities of total-body irradiation for pediatric bone marrow transplantation. Int J Radiat Oncol Biol Phys 1996;34:843–51.
[40] Rosler P, Christiansen H, Kortmann RD, Martini C, Matuschek C, Meyer F, et al. Hepatotoxicity after liver irradiation in children and adolescents: results from the RiSK. Strahlenther Onkol 2015;191:413–20.
[41] Radhakrishnan K, Bishop J, Jin Z, Kothari K, Bhatia M, George D, et al. Risk factors associated with liver injury and impact of liver injury on transplantation-related mortality in pediatric recipients of allogeneic hematopoietic stem cell transplantation. Biol Blood Marrow Transplant 2013;19:912–7.
[42] van Kempen-Harteveld ML, van Weel-Sipman MH, Emmens C, Noordijk EM, van der Tweel I, Revesz T, et al. Eye shielding during total body irradiation for bone marrow transplantation in children transplanted for a hematological disorder: risks and benefits. Bone Marrow Transplant 2003;31:1151–6.
[43] Losert C, Shpani R, Kiessling R, Freisslederer P, Li M, Walter F, et al. Novel rotatable tabletop for total-body irradiation using a linac-based VMAT technique. Radiat Oncol 2019;14:244.
[44] Fog LS, Hansen VN, Kjaer-Kristoffersen F, Berlon TE, Petersen PM, Mandeville H, et al. A step and shoot intensity modulated technique for total body irradiation. Tech Innov Patient Support Radiat Oncol 2019;10:1–7.
[45] Ouyang L, Folkerts M, Zhang Y, Hrycushko B, Lamphier R, Lee P, et al. Volumetric modulated arc therapy based total body irradiation: workflow and clinical experience with an indexed rotational immobilization system. Phys Imaging Radiat Oncol 2017;4:22–5.
[46] Tas B, Durmus IF, Okumus A, Uzel OE, Gokce M, Goksoy HS, et al. Total-body irradiation using linac-based volumetric modulated arc therapy: its clinical accuracy, feasibility and reliability. Radiother Oncol 2018;129:527–33.
[47] Gruen A, Ebell W, Wlodarczyk W, Neumann O, Kuehl JS, Stromberger C, et al. Total Body Irradiation (TBI) using Helical Tomotherapy in children and young adults undergoing stem cell transplantation. Radiat Oncol 2013;8:92.
[48] Stein A, Palmer J, Tsai NC, Al Malki MM, Aldoss I, Ali H, et al. Phase I trial of total marrow and lymphoid irradiation transplantation conditioning in patients with relapsed/refractory acute leukemia. Biol Blood Marrow Transplant 2017;23:618–24.
[49] Pierce G, Balogh A, Frederick R, Gordon D, Yarschenko A, Hudson A. Extended SSD VMAT treatment for total body irradiation. J Appl Clin Med Phys 2019;20:200–11.
[50] Holt DE, Hiniker SM, Kalapurakal JA, Breneman JC, Shiao JC, Boik N, et al. Improving the pediatric patient experience during radiation therapy - a children's oncology group study. Int J Radiat Oncol Biol Phys 2020.