Total marrow and total lymphoid irradiation in bone marrow transplantation for acute leukaemia

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The use of total body irradiation as part of conditioning regimens for acute leukaemia is progressively declining because of concerns of late toxic effects and the introduction of radiation-free regimens. Total marrow irradiation and total marrow and lymphoid irradiation represent more targeted forms of radiotherapy compared with total body irradiation that have the potential to decrease toxicity and escalate the dose to the bone marrow for high-risk patients. We review the technological basis and the clinical development of total marrow irradiation and total marrow and lymphoid irradiation, highlighting both the possible advantages as well as the current roadblocks for widespread implementation among transplantation units. The exact role of total marrow irradiation or total marrow and lymphoid irradiation in new conditioning regimens seems dependent on its technological implementation, aiming to make the whole procedure less time consuming, more streamlined, and easier to integrate into the clinical workflow. We also foresee a role for computer-assisted planning, as a way to improve planning and delivery and to incorporate total marrow irradiation and total marrow and lymphoid irradiation in multi-centric phase 2–3 trials.

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Introduction

Total body irradiation has been an integral component of conditioning to allogeneic haematopoietic stem-cell transplantation (HSCT) for both acute myeloid leukaemia and acute lymphoblastic leukaemia.[1] One of the primary aims of total body irradiation is to eradicate malignant cells from the bone marrow, lymph nodes, and circulating blood. Unlike chemotherapy, radiation delivery to leukaemic sites is not dependent on blood supply or influenced by inter-patient variability of drug absorption, metabolism, biodistribution, or clearance kinetics, and can also reach sanctuary sites such as the brain or testes.[2] Moreover, total body irradiation provides a powerful means of immunosuppression to prevent rejection of donor haematopoietic cells.[2]

The standard total body irradiation technique is unable to irradiate the target without exposing healthy structures to the full planned dose. Late toxicities are most evident in paediatric patients—including growth impairment, neurocognitive decline, long-term endocrinological toxicity, and secondary malignancies—but also represents a clinically significant concern for older patients (eg, risk of lung damage).[3,4] Traditional methods of delivering total body irradiation were developed more than 60 years ago through the pioneering work of Edward Donnall Thomas, using two opposing radiation fields with the patient positioned on a specific couch in a dedicated large-size radiotherapy room.[5]

A clearer understanding of the technical and clinical limitations of total body irradiation, in the context of evolving conditioning strategies, might provide the basis for developing more targeted approaches. The use of total body irradiation is declining mainly because of concerns of toxicities and as a result of the introduction of alternative approaches.[6,7] Chemotherapy-only myeloablative and reduced-intensity conditioning regimens with low-dose total body irradiation have been introduced for elderly patients, or patients with comorbidities.[8] Additionally, the haematology perspective has evolved from viewing allogeneic HSCT primarily as cytotoxic to a form of immunological therapy that relies on the graft-versus-tumour effect.[9] Total body irradiation no longer appears to be the primary conditioning modality, but is added when increased cytoreduction and immunosuppression are needed. When using total body irradiation with this goal, the need for reducing toxicity through technical optimisation and new approaches emerges as one of the most promising topics for future research programmes.[10]

A more selective irradiation of bone marrow, lymph nodes, and circulating blood could redefine the use and possibly expand the role of radiotherapy in HSCT conditioning.[11] Such targeted approaches are often referred to as total marrow irradiation and total marrow and lymphoid irradiation. The term total marrow irradiation has been used when the target structure is bone marrow only (figure 1A), whereas the term total marrow and lymphoid irradiation has been used to reflect the addition of lymph node chains and the spleen as target regions (figure 1B). These technical solutions are made possible through recent developments of image-guided intensity-modulated radiotherapy (IMRT) to large regions of the body, offering radiation oncology and transplant teams unprecedented control of radiation dose delivery to target regions and organs at risk. Despite being introduced 15 years ago,[11] the use of total marrow irradiation or total marrow and lymphoid irradiation is limited to a few centres,[11–16] and total body irradiation has not yet been replaced on a large scale.[10] In this Review, we highlight the clinical potential of total marrow irradiation and total marrow and lymphoid irradiation, based on the first promising clinical findings, and we discuss the current roadblocks for widespread use of these forms of precise radiotherapy for conditioning before HSCT. We then focus on the need to integrate the technical progress in planning and delivery into multidisciplinary research platforms for implementation of clinical trials and protocols.

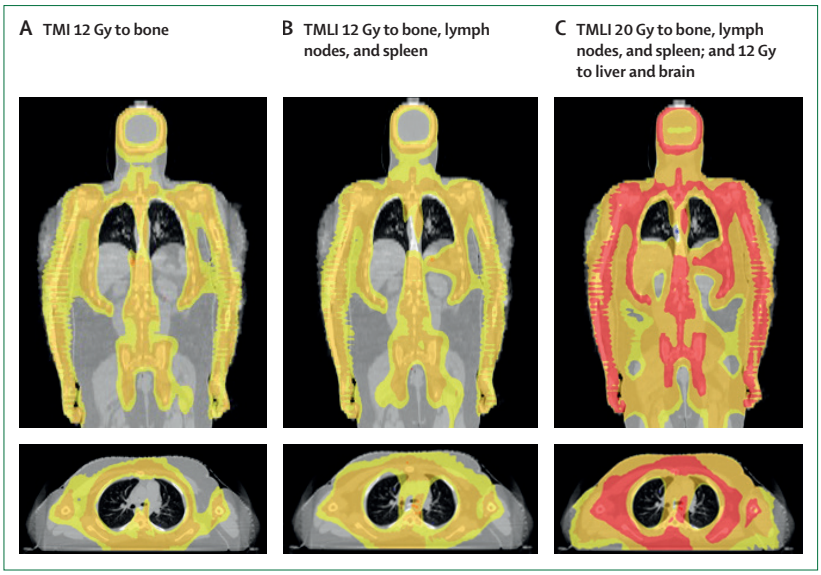


Figure 1: **Dose-colour graphical representation of TMI and TMLI**
TMI=total marrow irradiation. TMLI=total marrow and lymphoid irradiation.

Treatment planning feasibility and dosimetry verification

Studies of the feasibility of total marrow irradiation or total marrow and lymphoid irradiation using IMRT have been done since 2005 (table 1). The primary aim of these studies was to achieve full coverage of the bone marrow (total marrow irradiation) or the bone marrow plus the lymphoid system (total marrow and lymphoid irradiation) while saving nearby healthy tissues.

The first attempts of total marrow irradiation or total marrow and lymphoid irradiation were done with a helical tomotherapy system, a device combining a helical CT scanner and a linear accelerator. In this rotational IMRT technique, the patient is positioned on a couch and is irradiated while the couch is continuously moved through the helical tomotherapy system. From a geometrical point of view, rotational techniques are favourable for total marrow irradiation, as both the target (total marrow) and the healthy tissues around the target have considerable cylindrical symmetry. The first treatment planning feasibility studies of helical tomotherapy-based total marrow irradiation showed that good target coverage could be achieved while reducing the doses to key normal tissue by about 35–70%, compared with the standard total body irradiation approach.[11,12]

The next step forward was the use of a standard linear accelerator to deliver total marrow irradiation, using a number of static (so-called step-and-shoot) IMRT fields.[13,14] The first study of total marrow irradiation based on IMRT showed an adequate target coverage with dose reduction to normal tissues in the range 29–65%, in comparison with conventional total body irradiation.[14]

A further technological innovation appeared in 2011, when the concept of volumetric modulated arc therapy (VMAT)—ie, rotational IMRT on a conventional linear accelerator—was adapted to total marrow irradiation.[15,16] VMAT-based total marrow irradiation was found to provide adequate target coverage with dose reductions in normal tissues similar to those obtained with helical tomotherapy and IMRT.[15,16] A key advantage of VMAT-based total marrow irradiation was a reduction in the beam-on-time—ie, the time it takes to deliver each fraction of radiation, from about 45–50 min reported for static field IMRT[14] to 13–18 min.[15,16]

All these early reports explored approaches of total marrow irradiation based on helical tomotherapy, IMRT, and VMAT for the irradiation of the upper body, since helical tomotherapy and linear accelerators, as well as CT scanners, are limited to treatment and scanning lengths of less than 140 cm. The lower extremities were usually treated with a second treatment plan using a simplified beam geometry, accepting suboptimal doses in the junction between the two plans since there are fewer radiation sensitive normal tissues in the lower extremities. Subsequently, researchers showed the feasibility of helical tomotherapy[17,18] and VMAT[19] in irradiating the whole patient length with two simultaneously optimised IMRT plans, allowing a robust plan-to-plan junction management.

Further studies in this area have looked at approaches to optimise the clinical workflows, by improving efficiency and precision of the treatment. For example, the beam-on-time was reduced for helical tomotherapy-based total marrow irradiation from 50 min to 20 min maintaining the same mean doses to nearby healthy tissues.[17,20,21] Takahashi and colleagues[22] implemented a fast total marrow irradiation patient localisation method by topographic orthogonal imaging, aiming to scan the whole patient in 1 min instead of 15 min required for the standard imaging approach of the helical tomotherapy treatments. However, a few years later, the same consortium analysed pre-treatment imaging from six centres, but none used the proposed method.[23]

Finally, studies have shown that there is reasonably good agreement between planned and delivered doses for total marrow irradiation or total marrow and lymphoid irradiation techniques for both helical tomotherapy-based total marrow irradiation[11,24–26] and VMAT-based total marrow irradiation.[15,16,27,28] Efforts have also been made to reduce the time needed to do a patient-specific dose verification.[29]

Clinical trials in acute leukaemia

A widespread adoption of total marrow irradiation or total marrow and lymphoid irradiation in conditioning regimens requires the demonstration of superior outcomes in comparison with total body irradiation, with respect to either reduced toxicity or improved disease control. Although total marrow irradiation was first evaluated in patients with multiple myeloma,[10,12,30–32] the majority of trials have focused on acute myeloid

	Technique	Design	Dose	Target	Prescription	Aim	Quality assurance	Result	Notes
Hui et al (2005)[11]	HT	TMI *vs* TBI	1·65 Gy × 8 fractions	Bones	V95%=100%	Feasibility of HT	TLD in an anthropomorphic phantom	Doses reduced to 35–70%; TLD within 7%	1 pz; only upper body BOT 31 min
Wong et al (2006)[12]	HT	TMI and TMLI *vs* TBI	1·2 Gy × 10 fractions	TMI: bones; TMLI: bones and lymph nodes, liver, spleen, brain	V100%=80%	Feasibility of dose escalation with HT	Not shown	1·7-times to 7·5-times reduction in median organ doses; potential escalation up to 20 Gy	Feasibility on 2 pz and 1 treated pz (first worldwide); BOT 50 min
Aydogan et al (2006)[13]	SF-IMRT	TMI *vs* TBI	2 Gy × 6 fractions	Bones	Not shown	Feasibility of SF-IMRT	Not shown	It is feasible	1 pz; three plans with separate isocentres (using dose-plan-based technique); BOT 14·5 min; dose rate: 400 MU/min
Wilkie et al (2008)[14]	SF-IMRT	TMI	1·5 Gy × 8 fractions	Bones	V99%=99%	Feasibility SF-IMRT in anthropomorphic Rando phantom	TLD in an anthropomorphic phantom in 22 positions plus solid water phantom with ion chamber and film	The doses to critical structures were reduced by 29–65%; TLD within 3·5% and ionisation chamber measurement within 3%	Evaluation of junctions; DTDT estimated 1 h
Aydogan et al (2011)[15]	VMAT	TMI *vs* TBI	2 Gy × 6 fractions	Bones	V100%=95%	Feasibility of VMAT	2D-diode detectors matrix plus ion chamber	Similar to SF-IMRT; OARs doses <50%; GAI (3 mm, 3%)=98·1; the absolute point dose differences <3% in the junction region	6 pz; for each pz, three plans of three arcs; BOT 18 min; SF-IMRT 45 min
Fogliata et al (2011)[16]	VMAT	TMI	2 Gy × 6 fractions	Bones and chest wall	V100%=85%	Feasibility of VMAT	Epid dosimetry	Mean dose to OARs <45%; GAI (3 mm, 3%)=94·3 (SD 5·1%)	5 pz; for each patient, single plan with eight overlapping co-planar arcs; BOT 13 min
Zeverino et al (2012)[17]	HT	TMI	2 Gy in 1 fraction	Bones	V100%=50%	Plan matching between upper-body and lower-body by HT	Dose-point and film-plane measurements	Homogeneity at junction level <10%	First study of lower-body part with HT; BOT ranging from 24 min to 35 min for 2 Gy
Mancosu et al (2015a)[19]	VMAT	TMI and TMLI	TMI: 2 Gy × 6 fractions; TMLI: 2 Gy in 1 fraction	TMI: bones; TMLI: bones and major lymph nodes, spleen	TMI: V80%=100%; TMLI: V98%=98%	Plan matching between upper-body and lower-body by VMAT	Not shown	Dosimetric field junction is possible with optimal target coverage	First study of lower-body part with VMAT; 21 patients plus 144 shifted plans for plan robustness
Han et al (2012)[20]	VMAT *vs* HT	TMLI	1·5 Gy × 8 fractions	Bones and major lymph nodes, spleen	V100%=85%	To compare VMAT with HT	Not shown	Comparable dose coverage to the target volumes and sparing of normal organ dose	4 patients; AP-PA fields for the lower extremities; VMAT plan; BOT 1122 s (range 998–1224) for HT and 628 s (range 602–674) for VMAT
Surucu et al (2012)[27]	VMAT	TMI	1·5 Gy × 8 fractions	Bones	V99%=99%	Dosimetric validation of VMAT	Anthropomorphic phantom plus 39 TLDs; 2D-diode detectors matrix plus water equivalent phantom	Median dose difference: 0·5% (range −4·3% to 6·6%)	Phantom study; optimisation time 8 h; VMAT better sparing than SF-IMRT
Mancosu et al (2015b)[28]	VMAT	TMLI	2 Gy in 1 fraction	TMI: bones; TMLI: bones and major lymph nodes, spleen	TMI: V80%=100%; TMLI: V98%=98%	Bi-dimensional in-vivo verification	2DFilm with dose evaluation	GAI (5 mm, 5%) >95% in all cases	Phantom plus 3 patients; CBCT was acquired for each session; action level of 1 mm

AP-PA=anterior-posterior and posterior-anterior. BOT=beam-on-time. CBCT=cone-beam CT. DTDT=door-to-door time. GAI (3 mm, 3%)=Gamma agreement index with distance to agreement 3 mm and dose difference 3%. Epid=electronic portal imaging device. HT=helical tomotherapy. MU=monitor unit. OARs=organs at risk. SF-IMRT=static field intensity-modulated radiotherapy. TBI=total body irradiation. TLD=thermoluminescent dosimeter. TMI=total marrow irradiation. TMLI=total marrow and lymph node irradiation. VMAT=volumetric modulated arc therapy. V95%=100%=volume receiving 95% of the prescription dose should be covered by 100% of the target volume.

Table 1: **Feasibility studies of TMI and TMLI**

leukaemia and acute lymphoblastic leukaemia, using either total marrow irradiation or total marrow and lymphoid irradiation as a strategy to improve outcomes in refractory or relapsed patients.

Clinical strategies that have been or are currently investigated include the following: dose escalation to improve disease control with acceptable toxicity in patients with advanced refractory or relapsed disease;[33–38]

adding total marrow irradiation or total marrow and lymphoid irradiation to reduced-intensity conditioning regimens to improve disease control with acceptable toxicity;[39–41] adding total marrow irradiation or total marrow and lymphoid irradiation to established regimens that use strategies after HSCT to reduce graft-versus-host disease;[42–44] and total marrow irradiation or total marrow and lymphoid irradiation to improve disease control in patients who are in first remission as an alternative to conventional total body irradiation (appendix pp 5, 6). Table 1 summarises these clinical strategies.

See Online for appendix

Dose-escalated total marrow irradiation and total marrow and lymphoid irradiation

The rationale for dose escalation relies on the presence of a radiation dose-response effect for acute leukaemia, as suggested by retrospective total body irradiation series.[45,46] Although higher doses of total body irradiation were associated with better disease control than with lower doses in patients with myeloid leukaemia, the increased risk of toxicities related to total body irradiation negated any potential survival advantage in two prospective studies.[47,48]

Two phase 1 trials have evaluated total marrow and lymphoid irradiation dose escalation from 12 Gy up to 20 Gy (at 2 Gy per fraction) to the whole target, except for the radiation dose to the liver and brain, considered as part of the target, which was kept at 12 Gy (figure 1C).[33,34]

In the first trial, 51 patients with relapsed or refractory acute myeloid leukaemia and acute lymphoblastic leukaemia underwent a conditioning regimen of escalating doses of total marrow and lymphoid irradiation ranging from 12 Gy to 20 Gy delivered on days –10 to –6 with etoposide (60 mg/kg, day –4) and cyclophosphamide (100 mg/kg, day –2).[33] All but one patient had detectable blasts in the bone marrow (median 52% involvement [range 5–98]), and 27 patients had circulating blasts in the week before HSCT conditioning. Dose-limiting toxicity was observed in only one patient at the 15 Gy dose level (Bearman scale grade 3 mucositis)[49] and no further dose-limiting toxicities were observed up to 20 Gy. All patients engrafted without delays. Treatment-related morbidity rates were 4% at day 100 and 8% at 1 year. With a median follow-up of 25 months in surviving patients, the 1-year overall survival was 56% while progression-free survival was 40%. Similar results have been reported for the successor phase 2 trial of 20 Gy total marrow and lymphoid irradiation with cyclophosphamide and etoposide in 57 patients, with a 6% non-relapse mortality rate, 67% overall survival, and 48% progression-free survival (all rates at 1 year).[35,36] These studies showed that total marrow and lymphoid irradiation at 20 Gy can be safely delivered in combination with etoposide and cyclophosphamide with non-relapse mortality rates less than 10%. The regimen was shown to be effective for patients with relapsed or refractory acute leukaemia.

In the second phase 1 trial, the total marrow and lymphoid irradiation dose was escalated up to 15 Gy (two fractions of 1·5 Gy per day, days –8 to –4) with busulfan (4800 micromolar[μM] × min, days –12 to –8) and etoposide (30 mg/kg, day –3) in 20 patients with advanced acute myeloid leukaemia who were not eligible for standard HSCT regimens; 19 patients had detectable marrow blasts and 13 patients had circulating blasts during the week before HSCT conditioning.[34] Dose-limiting toxicities of stomatitis and sinusoidal obstructive syndrome were seen at 13·5 Gy, making dose-escalation to 15 Gy not feasible with this regimen.[34]

In a phase 1 trial, Patel and colleagues[37] reported results of treatment with total marrow irradiation (two fractions of 1·5 Gy per day, on days –8 to –5) plus fludarabine (40 mg/m² per day for 4 days) and busulfan (4800 μM × min). A maximum tolerated dose of 9 Gy was established. All 14 patients engrafted, and with a median follow-up of 3·1 years, non-relapse mortality was 29%, relapse-free survival was 43%, and overall survival was 50%. A phase 2 trial (NCT03121014) evaluating 9 Gy total marrow irradiation with fludarabine and busulfan is ongoing.

Hui and colleagues[38] reported on a phase 1 trial combining dose-escalated total marrow irradiation from 12 Gy up to 18 Gy with fludarabine (25 mg/m², days –9 to –7) and cyclophosphamide (60 mg/m², days –8 and –7). All 14 patients engrafted. Three (50%) of six patients at the 18 Gy dose level had treatment-related mortality, establishing 15 Gy as the maximum tolerated dose. Other groups are evaluating larger fraction sizes of up to 5 Gy in ongoing trials (appendix pp 5, 6).[50]

Total marrow irradiation or total marrow and lymphoid irradiation as part of reduced-intensity conditioning regimens

Non-myeloablative and reduced-intensity conditioning regimens are defined by their lower non-relapse mortality than that of myeloablative conditioning regimens and their suitability for older patients or those with comorbidities. They are primarily used as a method of immunosuppression to allow engraftment of donor cells, and rely more on graft-versus-tumour effects than on direct eradication of leukaemic cells.[8] A graft-versus-tumour (or graft-versus-leukaemia) effect is also an important contributing factor to leukaemia control in patients undergoing allogeneic HSCT. As with graft-versus-host disease, a graft-versus-tumour effect is due to the genetic differences between the donor and recipient. Donor-derived T cells have an important role. It is strongly associated with the development of graft-versus-host disease, but can also occur independent of clinically significant graft-versus-host disease.[9] A graft-versus-tumour effect can be observed in patients undergoing myeloablative and reduced-intensity conditioning regimens. However, for patients at higher risk of relapse, a more efficient cytoreduction might be needed. With this rationale, Rosenthal and colleagues[51] evaluated the

feasibility of combining 12 Gy total marrow and lymphoid irradiation (two 1·5 Gy fractions per day, days –7 to –4) with an established reduced-intensity conditioning regimen of fludarabine (25 mg/m^2 per day, days –7 to –4) and melphalan (140 mg/m^2, day –2) in patients who were ineligible for standard total body irradiation because of their age (>50 years) or existing comorbidities.[39,40] 61 patients were entered into this trial with a median age of 55 years (range 9–70) and with a median follow-up of 7·4 years. All patients engrafted successfully. 2-year overall survival was 54%, event-free survival was 49%, and non-relapse mortality was 30%; at 5 years, the overall survival was 42% and event-free survival was 41%. The addition of total marrow and lymphoid irradiation to fludarabine and melphalan conditioning was feasible, with favourable outcomes and with a non-relapse mortality rate that was similar to that previously reported for fludarabine and melphalan alone.[51]

Recently Welliver and colleagues[41] reported results of an ongoing trial evaluating total marrow irradiation and cyclophosphamide in patients with high-risk acute myeloid leukaemia, acute lymphoblastic leukaemia, or myelodysplastic syndrome who were older than 50 years or with comorbidities, and unable to undergo standard myeloablative total body irradiation. Sixteen patients were enrolled, and with a median follow-up of 14 months, the relapse rate was 0%, and the median OS was 313 days (20–784).

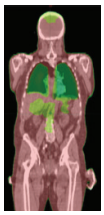
Total marrow irradiation or total marrow and lymphoid irradiation added to regimens that use strategies to reduce graft-versus-host disease

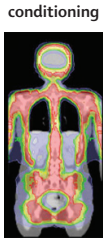
Promising strategies to reduce graft-versus-host disease include the use of post-transplant cyclophosphamide,[52,53] and T-regulatory and T-conventional (T-reg/T-con) adoptive immunotherapy.[44,54] These strategies are especially important in patients undergoing haploidentical HSCT. A haploidentical match means the donor and recipient are identical at one HLA haplotype. Since all biological parents and children and half of siblings share one HLA haplotype, there is a high likelihood of identifying an eligible donor, making donors available to a wider range of patients. A major drawback of haploidentical HSCT, especially after myeloablative conditioning, has been high rates of graft rejection and severe graft-versus-host disease.

The effects of high dose post-transplant cyclophosphamide on the incidence and severity of graft-versus-host disease were investigated by Luznik and colleagues.[52] The rationale for post-transplant cyclophosphamide is that recently activated alloreactive T cells are selectively sensitive to the toxic effects of cyclophosphamide. Clinical trials have evaluated the safety and efficacy of this strategy to prevent graft rejection and graft-versus-host disease after non-myeloablative conditioning (combined with fludarabine, cyclophosphamide, and 2 Gy total body irradiation) and T-cell-replete bone marrow transplantation from haploidentical-related donors.[55] These studies showed low incidences of non-relapse mortality and graft-versus-host disease. The relapse rates were relatively high, interpreted as related to a diminished or delayed graft-versus-leukaemia effect or to the conditioning regimen not being of sufficient intensity.

To potentially improve upon this approach, Al Malki and colleagues[42] recently presented results using a regimen that replaced the low-dose total body irradiation with myeloablative doses of total marrow and lymphoid irradiation (12–20 Gy) with the goal of decreasing relapse rates while keeping non-relapse mortality at an acceptable level. This phase 1 trial included 29 patients with high-risk acute myeloid leukaemia, acute lymphoblastic leukaemia, or myelodysplastic syndrome who received stem cells from haploidentical donors and reported a maximum tolerated dose for total marrow and lymphoid irradiation of 20 Gy. Total marrow and lymphoid irradiation (2 Gy twice a day, days –7 to –3) was combined with a regimen of fludarabine (25 mg/m² per day, days –7 to –4), cyclophosphamide (14·5 mg/kg per day, days –7 and –6), and post-transplant cyclophosphamide (50 mg/kg, days 3 and 4). All patients engrafted, and at 1 year the cumulative incidence of relapse or progression was 24% and overall survival was 83%. Cumulative incidence of grades 2–4 acute graft-versus-host disease was 61%. Day 100 non-relapse mortality rate was 4%, and 1-year non-relapse mortality was 9%.[43]

Alternative strategies have been developed by Martelli and colleagues[54] who showed that a co-infusion of FoxP3+ T-reg and T-con cells prevented graft-versus-host disease by suppressing alloreactive T-cell proliferation, without inhibiting non-alloreactive T cells and therefore, not inhibiting immunologic reconstitution and graft-versus-leukaemia effects. Adding T-reg/T-con adoptive immunotherapy to myeloablative single fraction or fractionated total body irradiation conditioning regimens resulted in low graft-versus-host disease and relapse rates. To further reduce toxicities of the conditioning regimen and to be able to adopt this approach to an older population, total body irradiation was replaced with total marrow and lymphoid irradiation. Aristei and colleagues[44] presented results from an ongoing phase 2 trial of patients with acute myeloid leukaemia using T-reg/T-con adoptive immunotherapy combined with myeloablative total marrow and lymphoid irradiation (13·5 Gy to the bone marrow and 11·7 Gy to the lymph nodes, in nine fractions) plus thiotepa plus fludarabine followed by haploidentical HSCT. Preliminary findings have been reported in 20 patients (median age 58 years and 14 in first complete remission), showing a 40% incidence of grades 2–4 acute graft-versus-host disease, and no patients with chronic graft-versus-host disease. Cumulative incidence of treatment-related mortality was 32%. 14 (70%) of 20 patients were alive and relapse-free with a median follow-up of 30 months.





	Leukaemia eradication	Immuno-suppression	Engraftment	Treatment planning	Delivery	Late toxicity
TBI conditioning	+++	+++	+++	+++	++	+
TMI or TMLI conditioning	+++	+++	+++	+	++	+++

Figure 2: **Graphic comparison of TMI or TMLI *vs* TBI in terms of therapeutic effect, radiation planning and delivery, and toxicity profile**
Plus sign represents a 3-point rating scale, with three plus signs indicating the best and one plus sign the worst. TBI=total body irradiation. TMI=total marrow irradiation. TMLI=total marrow and lymphoid irradiation.

Total marrow irradiation or total marrow and lymphoid irradiation in patients in first remission as a possible alternative to total body irradiation

Total marrow irradiation and total marrow and lymphoid irradiation are under investigation for patients who have a lower tumour burden and would normally be eligible for standard total body irradiation conditioning regimens, such as patients with acute myeloid leukaemia and acute lymphoblastic leukaemia in first or second remission. Trials are currently ongoing, and the results have yet to be published (appendix pp 5, 6). Total marrow and lymphoid irradiation to 20 Gy (2 Gy given twice per day for 5 consecutive days) and post-transplant cyclophosphamide (50 mg/kg per day for 2 days); total marrow irradiation to 12 Gy (4 Gy daily) combined with pre-transplant cyclophosphamide (60 mg/kg per day for 2 days); and total marrow irradiation to 12 Gy (4 Gy daily) alone in older patients (40–80 years) are currently being evaluated.

Long-term toxicities with total marrow irradiation and total marrow and lymphoid irradiation

Long-term toxicities following total marrow irradiation or total marrow and lymphoid irradiation in a series of 142 patients treated from 2005 to 2016 were reported in 2019 and 2020.[56,57] Thyroid, renal, pulmonary, and ophthalmologic toxicity status up to 8 years after HSCT were monitored. The median dose was 14 Gy (range 10–19). A fractionation schedule of 1·5–2·0 Gy (two fractions per day) for 4–5 days was used. The dose rate was approximately 2 Gy/min. The crude incidence of radiation pneumonitis was one (<1%) of 142. Mean lung dose of 8 Gy or less predicted for significantly lower combined rates of pulmonary infection and pneumonitis at 2 years (21% *vs* 32% for >8 Gy; p=0·01) and 6 years (28% *vs* 54%; p=0·01). No radiation-induced renal toxicity was noted. Hypothyroidism occurred in eight (6%) of 134 patients and cataract formation in ten (7%) of 142. These data indicate that total marrow irradiation or total marrow and lymphoid irradiation was associated with reduced toxicities compared with that historically reported for conventional total body irradiation.

The results of this study also addressed concerns that the higher radiation dose rates (≥2 Gy/min) used to deliver total marrow irradiation might result in more substantial toxicities and non-engraftment compared with conventional total body irradiation, which is delivered at rates of 0·3 Gy/min or less. The low incidence of late toxicities suggests that the higher dose rate did not contribute to organ dysfunction. Dose-rate effects might also have been mitigated by dose reduction to the organs at risk as well as fractionation. These observations are consistent with published pre-clinical studies evaluating dose-rate effects.[58,59] Besides, an increase in non-engraftment has not been reported with doses up to 20 Gy.

Does organ sparing increase relapse rates after total marrow irradiation and total marrow and lymphoid irradiation?

The general reduction in mean dose to multiple organs achieved by total marrow irradiation or total marrow and lymphoid irradiation could potentially be risky because of sparing of leukaemia cells present in these regions. To evaluate this possible effect, Kim and colleagues[60] reported on a series of extramedullary recurrences in 101 patients undergoing allogeneic HSCT with total marrow irradiation as part of the conditioning regimen. With a median follow-up of 13 months, 13 patients developed extramedullary relapses at 19 sites. The site of relapse was not dose dependent, with nine relapses occurring in the target region (≥12 Gy), five relapses in regions receiving 10·1–11·4 Gy, and five relapses in regions receiving 3·6–9·1 Gy. The risk of extramedullary relapse was similar to standard total body irradiation, and the use of total marrow irradiation did not appear to increase the risk of relapse in non-target regions.

Concerns have also been raised that total marrow irradiation, which is delivered sequentially and not simultaneously to all parts of the body, could result in a reduction of dose to circulating leukaemia cells, potentially increasing relapse rates. This hypothesis was addressed by Molloy,[61] who showed that for typical blood circulation times, dose heterogeneity to circulating blood was clinically acceptable if the dose was fractionated and the treatment times for each fraction were 20 min or more. They concluded that development of conformal, sequential total body irradiation and total marrow

	Trial phase	NCT trial number*	Number of patients	Eligibility criteria	Targets	TMI dose (fractionation)	Chemotherapy	NRM and survival data
Stein et al (2017)[33]	Phase 1	02446964	51	AML, ALL relapsed or refractory	Bone, lymph nodes, testes, spleen; 12 Gy liver and brain	12–20 Gy (1·5–2·0 twice a day)	Cyclophosphamide (100 mg/kg); etoposide (60 mg/kg)	100-day NRM 3·9%, 1-year NRM 8·1%; 1-year PFS 40%; 1-year OS 55·5%; 2-year OS 41·5%
Wong et al (2013)[34]	Phase 1	00540995	20	AML relapsed or refractory	Bone, lymph nodes, testes, spleen; 12 Gy liver and brain	12 Gy, 13·5 Gy (1·5 twice a day)	Busulfan (4800 μM × min); etoposide (30 mg/kg)	NRM eight (40%) of 20; five (25%) of 20 complete remission at 20·8–49·4 months
Stein et al (2017; 2019)[35,36]	Phase 2	02094794	57	AML or ALL, induction failure, relapsed or >CR2	Bone, spleen, lymph nodes; 12 Gy liver and brain	20 Gy (2·0 twice a day)	Cyclophosphamide (100 mg/kg); etoposide (60 mg/kg)	100-day NRM 4%, 1-year NRM 6%; 1-year PFS 48%; 1-year OS 67%
Patel et al (2014)[37]	Phase 1	00988013	14	Refractory or relapse AML, ALL, MDS, MM, CML	Bone	3–12 Gy (1·5 twice a day)	Fludarabine (40 mg/m² per day for 4 days); busulfan (4800 μM × min)	NRM 29%; RFS 43%; OS 50%
Hui et al (2017)[38]	Phase 1	00686556	12	High risk ALL, AML, CR2, CR3, relapse, induction failure	Bone	15 Gy, 18 Gy (3·0 twice a day)	Fludarabine (25 mg/m² per day for 3 days); cyclophosphamide (60 mg/m² per day for 2 days)	1-year NRM 42%; relapse rate 36%; 1-year DFS 22%; 1-year OS 42%
Rosenthal et al (2011; 2018)[39,40]	Pilot	00544466	61	AML, ALL, >50 years or comorbidities	Bone, lymph nodes, spleen, ALL testes, brain	12 Gy (1·5 twice a day)	Fludarabine (25 mg/m² per day for 4 days); melphalan (140 mg/m²)	2-year NRM 30%, 5-year NRM 33%; 2-year EFS 49%, 5-year EFS 41%; 2-year OS 50%, 5-year OS 42%
Welliver et al (2018)[41]	Pilot	02122081	15	High-risk AML, ALL, MDS, >50 years or comorbidities unable to undergo TBI-based regimens	Bone, brain, testes	12 Gy (2·0 twice a day)	Cyclophosphamide	NRM four (25%) of 16; median OS 313 days
Al Malki et al (2019);[42] Arslan and Al Malki (2020)[43]	Phase 1	02446964	29	AML, ALL, MDS CR1 high risk, CR2, CR3, refractory, haploidentical	Bone, spleen, lymph nodes; 12 Gy liver and spleen; 16 Gy testes ALL; 12 Gy brain ALL	12–20 Gy (1·5-2·0 twice a day)	Fludarabine (25 mg/m² per day for 5 days); cyclophosphamide (14·5 mg/kg per day for 2 days); post-transplant cyclophosphamide (50 mg/kg per day for 2 days);	1-year NRM 9·3%; 1-year OS 83%; 1-year relapse rate 24%
Aristei et al (2020)[44]	Phase 2	03977103	20	AML in CR1, CR2, PR, haploidentical donor	Bone; 11·7 Gy lymph nodes	13·5 Gy (1·5 twice a day)	Thiotepa (2·5 mg/kg per day for 2 days); fludarabine (30 mg/kg per day for 5 days); cyclophosphamide (15 mg/kg per day for 2 days); T-cell manipulated graft	NRM six (30%) of 20; 14 (70%) of 20 alive and relapse-free; no chronic graft versus host disease

ALL=acute lymphoblastic leukaemia. AML=acute myeloid leukaemia. CML=chronic myeloid leukaemia. CR1=first complete remission. CR2=second complete remission. CR3=third complete remission. DFS=disease-free survival. EFS=event-free survival. MDS=myelodysplastic syndromes. MM=multiple myeloma. NRM=non-relapse mortality. PFS=progression-free survival. PR=partial response. OS=overall survival. RFS=relapse-free survival. TBI=total body irradiation. TMI=total marrow irradiation. TMLI=total marrow and lymphoid irradiation. μM=micromolar. *Listed at www.ClinicalTrials.gov.

Table 2: **TMI and TMLI trials in patients with acute leukaemia**

irradiation delivery techniques should not be withheld based on concerns of circulating blood dose heterogeneity.

Discussion and future challenges

In the field of radiation oncology, the transfer of technical innovations to clinical trials often proceeds at a slow pace. This delay is particularly evident when complex planning and delivery solutions are made possible by a combined effort of medical physicists and engineers in pioneer studies but are challenging to implement in clinical trials because of the lack of radiotherapy equipment or expert staff and the high costs.[62–65] The introduction of high-precision novel techniques for radiation-based conditioning in acute leukaemia might represent a typical example. The studies reviewed herein showed that total marrow irradiation or total marrow and lymphoid irradiation is feasible and might offer an efficient and precise radiation conditioning regimen to patients with acute leukaemia undergoing allogeneic HSCT. However, few prospective trials have been conducted so far, they have all been phase 1 and 2 with small sample sizes. Despite these limitations, the findings obtained by different research groups indicate the following: total marrow irradiation and total marrow and lymphoid irradiation can be successfully integrated into either myeloablative or reduced-intensity conditioning regimens as an alternative to total body irradiation; first long-term toxicity data showed a reduction in pulmonary, thyroid, eye, and kidney toxicities; and dose escalation to the bone marrow is feasible, with an acceptable toxicity profile, giving a new experimental therapeutic option that could be available for high-risk patients, with encouraging

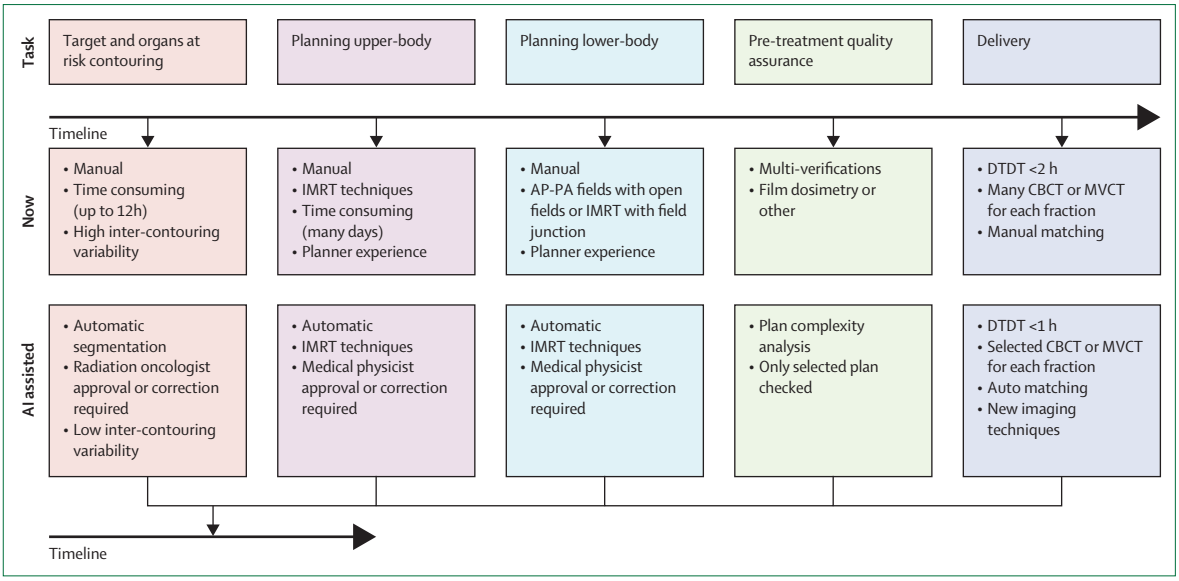


Figure 3: **Potential AI approaches for automatic or semi-automatic optimisation of target delineation and radiation planning of TMI and TMLI**
AI=artificial intelligence. AP-PA=anterior-posterior and posterior-anterior. CBCT=cone beam CT. DTDT=door-to-door time. IMRT=intensity-modulated radiotherapy. MVCT=mega voltage CT.

relapse and survival rates. Figure 2 and table 2 summarises these findings.

A technological gap currently limits the widespread introduction of total marrow irradiation and total marrow and lymphoid irradiation as modern alternatives to total body irradiation. Precise radiotherapy still represents a challenge, because of difficulties in target contouring, sophisticated planning, and prolonged fraction delivery time (appendix p 7). Schultheiss and colleagues reported that manual contouring of targets and normal tissues took 12–16 h.[66] Plan optimisation based on iterative trial-and-error attempts could require several days to obtain adequate dose distributions. In addition, the time required to treat a patient with helical tomotherapy-based or VMAT-based total marrow irradiation exceeds the time required for total body irradiation.

However, VMAT can be delivered on all modern radiotherapy machines, and therefore most centres worldwide could potentially deliver either total marrow irradiation or total marrow and lymphoid irradiation, without the need for a dedicated large bunker, as is the case for standard total body irradiation. One major challenge—again related to the need to accumulate clinical experience in prospective trials—is to develop planning and delivery methods that might facilitate radiation oncology departments in introducing total marrow irradiation or total marrow and lymphoid irradiation in their clinical practice.[6,7,10] A first step could be the transition towards delivering total body irradiation using approaches based on IMRT, which is happening in an increasing number of centres. This topic is not the focus of the present Review, but we have included a detailed discussion in the appendix (pp 1–4).

Beyond technical optimisation, the design of new clinical trials requires specific clinical endpoints. In most centres, both haematology and radiation oncology teams would probably be more interested in a trial investigating superiority rather than merely demonstrating slightly inferior long-term toxicity, in particular for adult patients. The increasing use of non-total body irradiation-containing regimens and the rapid development of chimeric antigen receptor T cells and other cellular therapies should also be considered.[67] In this scenario, a study implementing total marrow irradiation or total marrow and lymphoid irradiation as a way to selectively escalate the dose to the target structures for high-risk patients seems to be the most reasonable research strategy. However, it should be done with clear technical indications on the use of precise radiotherapy.

Artificial intelligence (AI) approaches such as convolutional networks, holistically nested networks, or other customised network architectures could be beneficial for treatment planning contouring of normal organs, as well as for fast semi-automatic planning (figure 3).[68,69] Automatic and knowledge-based planning optimisation solutions are being developed and successfully tested in other settings.[70,71] The use of these advanced tools could be crucial for the progress of total marrow irradiation and total marrow and lymphoid irradiation, and their incorporation into multi-centre clinical trials.

A necessary next step would be to push forward research in computer-assisted or AI methods to facilitate the use of total marrow irradiation or total marrow and lymphoid irradiation in multiple sites using various radiotherapy planning and delivery systems. The collaboration between medical physicists and clinicians

Search strategy and selection criteria

We identified references for this Review through searches of PubMed, Scopus, and ClinicalTrials.gov for articles published in English from Jan 1, 2005, to March 1, 2020. The following search terms were considered: ("total marrow irradiation" OR "total marrow") AND ("radiation therapy" OR "radiotherapy") AND "acute Leukaemia". Title, abstract, and keywords were included in the query. We considered further references from the bibliographies of retrieved articles. We also identified articles through searches of our own files. We included literature published as abstracts at international meetings. The final reference list was generated on the basis of originality and relevance of the scope of this Review. We divided articles into feasibility and clinical studies. An article was included in the clinical group when it reported detailed data for outcome or toxicities, or both, after total marrow irradiation or total marrow and lymphoid irradiation treatment, in particular information about study design (retrospective, prospective, case series, or case report); number of patients, their age (mean, range), and sex; definition of acute and late radiotherapy toxicity profile; and outcome in terms of tumour control and toxicity profile. All other studies were included in the feasibility group.

in this field appears indispensable for the future of radiation-containing regimens and their rational use. Multi-centre trials are needed to rapidly advance this emerging area and answer important questions that remain. The future adoption of total marrow irradiation or total marrow and lymphoid irradiation will most likely be within transplant programmes that are already using total body irradiation-based conditioning regimens. Primary goals are the development of new regimens able to improve outcomes in high-risk patients, where the standard of care is suboptimal. Outcome analyses from data collected by the international HSCT databases will also be essential. The Centre for International Blood and Marrow Transplant Research (Milwaukee, WI, USA) is now collecting mean lung, kidney, heart, thyroid, and gut dose in all patients undergoing total marrow irradiation or total marrow and lymphoid irradiation, which will allow for dose-toxicity and outcome studies in the future. Ultimately these efforts need to show that conditioning regimens based on precise radiotherapy offer advantages over already established regimens. The use of total marrow irradiation or total marrow and lymphoid irradiation holds substantial promise and will help redefine and expand the role of radiotherapy in HSCT.

Conclusions

Total marrow irradiation and total marrow and lymphoid irradiation hold the potential to fully replace total body irradiation in radiation-containing conditioning regimens for acute leukaemia. The associated incidence of late toxic effects appears modest, and targeted dose escalation showed promising results for high-risk patients. Total marrow irradiation and total marrow and lymphoid irradiation are feasible and could be introduced in the majority of radiotherapy departments. However, as robust prospective data are lacking and there are several technical obstacles, total marrow irradiation and total marrow and lymphoid irradiation should still be part of research programmes. An ideal approach for their full development would be the design of a multi-centre trial, focused on selected clinical objectives and disease settings, and including an active technical part aimed at further optimising the planning and delivery of total marrow irradiation and total marrow and lymphoid irradiation.

Contributors

JYCW, ARF, and PM did the Review structure, literature search, figures, tables, and data discussion. MS, SH, and LPM did the data discussion and references cross-check. All authors were responsible for the preparation and writing of the Review, and approved the final version.

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