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Considerations for intensity modulated total body or total marrow and lymphoid irradiation

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ABSTRACT

We compiled a sampling of the treatment techniques of intensity-modulated total body irradiation, total marrow irradiation and total marrow and lymphoid irradiation utilized by several centers across North America and Europe. This manuscript does not serve as a consensus guideline, but rather is meant to serve as a convenient reference for centers that are considering starting an intensity-modulated program.

Introduction

Over the last two decades, multiple centers have developed and implemented intensity-modulated total body irradiation (IM-TBI), total marrow irradiation (IM-TMI) and total marrow and lymphoid irradiation (IM-TMLI) using modern linear accelerators (linac) and image-guidance [1–18]. Common to these techniques are the treatment of the patient in the supine position at the machine isocenter, volumetric imaging for image guidance, and inverse optimization within a treatment planning system (TPS). This differs significantly from the conventional TBI treatment techniques outlined in AAPM TG-29 [19]. Conventional TBI relied on large treatment vaults with extended distances, manual calculations using physical measurements of the patient in the treatment position, compensators to provide a uniform dose and blocks for organ sparing. In contrast, IM-TBI, IM-TMI and IM-TMLI are products of technological advancements enabling intensity modulated radiation therapy (IMRT) and advanced on-board imaging.

This manuscript summarizes the treatment techniques employed by several centers experienced in (i) IM-TBI: University of Texas Southwestern Medical Center (UTSW) [4,6], New York University (NYU) [11], IRCCS Ospedale Policlinico San Martino [14,15,18], City of Hope (COH) [20], University of Alabama at Birmingham (UAB), University of California San Diego (UCSD) and Cleveland Clinic (CC)[3] and (ii) IM-TMI/TMLI: University of Texas MD Anderson Cancer Center (MDACC) [21], IRCCS Ospedale Policlinico San Martino [5], COH [22,23], IRCCS Humanitas Research Hospital [10,12,13,18], University of Illinois Hospital (UIH) [2,7,17] and Nova Scotia Health (NSH) [9,16].

The aim of this work is to provide a convenient treatment reference for centers starting an IM-TBI or IM-TMI/TMLI program. For brevity, comprehensive details have been omitted from the manuscript.

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Table 1
IM-TBI for seven centers across North America and Europe.

Center	UTSW	NYU	San Martino	COH	UAB	UCSD	CC
CT Simulation	HFS and FFS with overlap in the femur. 5 mm slice thickness	HFS, FFS if the patient > 198 cm in length. 10 mm slice thickness	HFS and FFS. 5 mm (young pediatrics) or 10 mm slice thickness	HFS for upper body, FFS for legs with overlap in pelvic region. Slice thickness is 5 mm for plans on TrueBeam (TB) and 7.5 mm for plans on Tomotherapy.	HFS for upper body, FFS for legs. 3 mm slice thickness	HFS and FFS with overlap in the femur 5 mm slice thickness	HFS and FFS with overlap in pelvic region. 5 mm slice thickness
Immobilization	Rotational TBI frame [4,6], full body vacuum bag with 3-point mask integrated to the frame for CSI boosts. Legs flat with arms are on torso sides. Civco AccuForm headrest.	Two Orfit All-in-one (AIO) boards that serve to attach several thermoplastic three masks [11]	Three thermoplastic masks on AIO board. Legs are slightly bent using a fixation system for knees and feet. Arms are on torso sides.	Thermoplastic mask from head to shoulder region with AccuForm cushion and Silverman headrest, full body VakLok bag, feet board with mask.	S-frame with headrest and a full-body vacuum bag	S-frame with headrest and a full body vacuum bag	A full body vacuum bag with a baseplate in the bag to hold a 3-point open face mask for head [3]
Treatment Machine	VMAT for the upper body (3–4 isos) AP-PA for the lower body (2–3 isos) [6]	VMAT for the upper body (4 isos) AP-PA for the lower body (3 isos) [11]	Helical Tomotherapy	Helical Tomotherapy VMAT (TB) for upper body, AP-PA for the lower body	VMAT	VMAT for the upper body (3–4 isos) AP-PA for the lower body (2–3 isos) Or all VMAT	VMAT for the upper body (3–4 isos) AP-PA for the lower body (2 isos) [3]
Photon Energy	10 MV upper body 6 MV lower body	6 MV	6 MV FFF	6 MV FFF (Tomotherapy) 6 MV (TrueBeam)	6 MV	6 MV 10 MV FFF (obese patient)	6 MV 10 MV (obese patient)
Dose Rate	Nominal 40 MU/min	Nominal 600 MU/min for all fields. Average 150–250 MU/min	Nominal 1000 MU/min	850–1000 MU/min, effective 135–180 MU/min on two different versions of the Tomo. 600 MU/min and effective 135–160 MU/min (TrueBeam)	100 MU for Lung/Chest, 600 MU else	Nominal 100 MU/min for lung/Chest Nominal 600 MU/min else	200 MU/min at lung isocenter. 600 MU/min for all other isocenters
Prescription	12 Gy in 6 or 8 Fx BID 2 or 4 Gy single Fx	12 Gy in 8 Fx BID 13.2 Gy in 8 Fx BID	12 Gy in 6 Fx BID 9.9 Gy in 3Fx once daily 2 Gy single Fx	12 Gy in 8 Fx BID 13.2 Gy in 8 Fx BID	12 Gy in 6 Fx BID 8 Gy in 4 Fx once daily 2 Gy single Fx	12 Gy-13.2 Gy in 6–8 Fx BID or as defined by the transplant protocol 2 or 4 Gy single Fx	12 Gy in 8 Fx BID
Target definition	Body contracted by 5 mm and subtract the lungs and heart	Body contracted 5 mm and subtract the lungs and kidneys	Body contracted by 5 mm subtract lungs contracted by 5 mm (myeloablative only). 5 mm virtual bolus during optimization [14].	Body contracted by 3 mm and subtract the lungs and Kidney Margin. Kidney Margin: 1 cm lateral, 1 cm inferior, 1 cm superior and 0 cm medial [20].	Body contracted by 5 mm and subtract the lungs	Body contracted by 5 mm and subtract the lungs	Body contract 3 mm in all directions and subtract the lungs and kidneys [3]
Objectives	$V_{Rx} \geq 90\%$ $D_{max} <= 150\%$ (AP-PA junctions) [6]	$V_{Rx} > 90\%$ $D_{98\%} > 85\%$ $D_{2cc} < 130\%$ No large breaks in the 85% IDL [11]	$V_{95\%} \geq 95\%$ $D_{max} \leq 110\%$	$V_{Rx} > 85\%$ $D_{max} < 130\%$ [20]	$D_{90\%}$ between 90 and 100% $D_{max} < 140\%$	$V_{Rx} \geq 90\%$ $D_{max} <= 150\%$	$V_{95\%} > 95\%$ $V_{110\%}$ ALARA ($\leq$ ~10%-20%) [3]
Constraints	• Heart and lungs $D_{mean} < 75$ %Rx Lung contracted by 1 cm $D_{mean} < 50$ %Rx Kidneys $D_{mean} =$ Rx All other OARs $D_{0.125cc} < 125$ %Rx [6]	• Each Lung $D_{mean} < 8$ Gy, $D_{0.1cc} < 120\%$ Each kidney $D_{mean} < 11$ Gy, $D_{0.1cc} < 120\%$ Bowel, spinal cord, brain and oral cavity $D_{0.1cc} < 125\%$ [11]	• Lungs Dmean ≤ 8 Gy Possible dose reduction for eyes/lenses, heart and kidneys	• Lungs $D_{mean} < 8$ Gy Heart, kidneys, esophagus, oral cavity, breasts, parotids, thyroid, stomach, bowel, ovary, bladder, optic nerve, eyes and lens $D_{max} \leq 115\%$ [20]	• Lung $D_{mean} < 60$–75 % Rx Spinal cord, heart, bowel, stomach, brain and oral cavity $D_{0.125cc} < 15$ Gy Spinal cord $D_{min} > 90\%$ and $D_{max} < 110\%$ Kidney	• Lungs $D_{mean} < 8$ Gy Kidney $D_{max} < 13$ Gy All other OARs $D_{max} < 125\%$	• Lung $D_{mean} \leq 80$ %Rx (adult) or ≤ 8 Gy (pediatric) patients. Kidneys $D_{mean} \leq 6$ Gy[3]

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Table 1 (*continued*)

Center	UTSW	NYU	San Martino	COH	UAB	UCSD	CC
					$D_{0.3cc} < 13$ Gy		
Boost volumes	SIB 18 Gy in 8 Fx BID for CSI 12 Gy TBI	6 Gy in 3 Fx whole brain prior to IM-TBI	Testis boost of 4 Gy on the last Fx	No boost	No boost	No boost	No boost
TPS	Eclipse v16.1	Eclipse v15.6	Accuray Precision v3.3	Accuray Precision v3.3 Eclipse v16.1.	Eclipse v16.1	Eclipse V16.1	Pinnacle v16.2 and v16.4
Dose calculation algorithm and grid	AAA and 5 mm	AAA and 5 mm	Precision CCC and 1.5 mm	Precision CCC (Tomo) or AAA (TB) with 2.5 mm	AAA and 2.5 mm	AAA and 5 mm	Adaptive Convolution and 5 mm
Patient setup and alignment	SGRT for initial setup, CBCT of the thorax and an additional CBCT of the head if the CSI is being boosted	CBCT and kV orthogonal pairs	Long scan MVCT	MVCT (Tomo) CBCT and kV orthogonal pairs (TB)	CBCT	SGRT for initial setup and monitoring CBCT (lungs) and KV orthogonal pairs	CBCT (lungs) and kV orthogonal pairs except the legs[3]
Routine QA	Patient-specific IMRT QA (Film and chamber). γ: 3%/2mm, 10% threshold, 90% pass rate. Chamber point dose within 5% 2nd MU verification of AP-PA fields using RadCalc	Patient-specific IMRT QA γ: 3%/2mm, 90% pass rate (ArcCHECK QA), 4%/3mm, 95% pass rate (Portal dosimetry), 10% threshold	Patient-specific IMRT QA (ArcCHECK QA) γ: 3%/2mm, 10% threshold, 90% pass rate. Ionization chamber point dose at isocenter within 5%	Patient-specific IMRT QA γ: 3%/3mm, 10% threshold, 95% pass rate.	Patient-specific IMRT QA; γ: 5%/3mm, 10% threshold, 95% pass rate *in vivo* dosimetry on request	Patient-specific IMRT QA; γ: 3%/3mm, 10% threshold, 90% pass rate (Portal Dosimetry) *in vivo* dosimetry on request 2nd MU verification of AP/PA fields using ClearCalc	Patient-specific IMRT QA; γ: 3%/3mm, 10% threshold, 90% pass rate (Portal Dosimetry) *in vivo* dosimetry on Fx1 Mosfet +/- 20% individually and +/- 5% average
Number of patients annually	25	15	5	20	60	30	30
Percent of adult and pediatric patients	55% / 45%	100% / 0%	10% / 90%	95% / 5%	80% / 20%	80%/20%	90% / 10%
Exclusion criteria	IGRT couch weight limit	Trial exclusion criteria	None	Trial exclusion criteria [20]	Height > 1.96 m	Trial exclusion criteria IGRT couch weight limit	IGRT couch weight limit

References to relevant work have been added throughout the text and tables, which can provide more details for those considering adopting a similar approach. Table 1 and Table 2 provides a summary of IM-TBI and IM-TMI techniques, respectively.

Patient simulation

IM-TBI and IM-TMI/TMLI requires CT scans of the entire patient volume, using both head-first-supine (HFS) and feet-first-supine (FFS) scans. This is necessary due to limitations in scan length and couch motion. Both techniques utilize some form of patient immobilization that can range from a custom rotational body frame or commercially available frames. Both routes utilize commercially available thermoplastic masks, vacuum bags, or a combination of both. For c-arm linacs, the maximum height or weight limitations can exclude patients for IM-TBI or IM-TMI/TMLI.

Treatment planning

Treatment planning utilizes the clinical TPS with inverse optimization algorithms whereby target volumes and organs-at-risk are delineated and dosimetric objectives and constraints are specified for optimization. The type of plan varies depending on the treatment linac. C-arm linacs utilize volumetric modulated arc therapy (VMAT) with or without 3D anterior-posterior fields (AP-PA for treatment of the lower extremities). The VMAT isocenters cover either the full body or the head-to-pelvis region with the remaining lower extremities covered by AP-PA fields. The number of isocenters depends on the patient height with most centers utilizing 3–8 isocenters along the cranial-caudal direction. Tomotherapy is the other option utilized by centers, in which a helical plan is delivered for the entire length of the target volume. This is typically split into two plans for HFS and FFS delivery [5]. While not utilized by centers surveyed, it is also possible utilize fixed gantry angles with TomoDirect for IM-TBI [24,25].

IM-TBI target volume can vary from institution, typically including the entire body with at least the lungs and 3–5 mm of skin removed. Additionally, centers may remove the heart and kidneys from the target volume. For IM-TBI, the removed organs are prescribed a different dose (Table 1). IM-TMI and IM-TMLI utilize a variety of targets that have evolved as each center developed their program as shown in Table 2. Compared to conventional techniques, the IMRT approach further limits the mean and maximum dose to critical organs. Additionally, dose uniformity of the plan is allowed to escalate, for example, up to 110–150% in the junction between AP-PA fields in the legs depending on the center. Additionally, automation can play a large role in decreasing the planning time for IM-TBI [11,26] and IM-TMI [27], in which the time can be reduced to under two hours for IM-TMI and 2–6 h for TBI.

The prescription for IM-TBI was inherited from conventional TBI, with non-myeloablative treatments consisting of a single dose of 2–4 Gy and myeloablative treatments consisting of 6–8 fractions BID of with a total dose of 12–13.2 Gy. Similar to the target volume definition, IM-TMI prescriptions can vary substantially between centers. Interestingly, IMRT has enabled simultaneous integrated boosts (SIB) for the

Table 2
IM-TMI and IM-TMLI for six centers across North America and Europe.

Center	MDACC	San Martino	COH	Humanitas	UIH	NSH
CT Simulation	HFS and FFS scan. Arms relaxed close to the sides and propped up with the vacuum bag. Hand in a fist conformed into the bag. 2.5 mm slice thickness (to accommodate auto-contouring tools)	HFS and FFS 10 mm slice thickness	HFS for upper body, FFS for legs. 5 mm (TrueBeam) or 7.5 mm (Tomotherapy) slice thickness	HFS and FFS 5 mm slice thickness	HFS 3 mm slice thickness	HFS: from 5 cm above vertex of head to mid thighs, FFS: 5 cm below feet to 10 cm above mid-thigh marks. 5 mm slice thickness [9]
Immobilization	Full-body vacuum bag, plastic index bars, regular density head rest, 5-point head neck and shoulders mask indexed to board that is conformed into the vacuum bag.	Three thermoplastic masks on AIO board. Legs are slightly bent using a fixation system for knees and feet. Arms are on torso sides and are slightly bent to put hands on inguinal region [5,18]	Thermoplastic mask from head to shoulder region with AccuForm cushion and Silverman headrest, full body VakLok bag,feet board with mask.	Homemade immobilization all-body frame in which 3 masks are adopted [10,13,18]	Aquaplast Brainlab frameless mask, Alpha-cradle, Civco Body Pro-Lok SBRT table [7]	S-frame mask, fixator board, indexed vac lock elevated slightly by Civco elevation blocks. Foot strap around feet [9]
Treatment Machine	VMAT for upper body, 3D for legs	Helical Tomotherapy	Tomotherapy or VMAT for upper body, 3D AP-PA for the lower body (TrueBeam)	VMAT	VMAT [2]	VMAT for upper body, POP with MLC shielding of gonads if needed
Photon Energy	6 MV	6 MV FFF	6 MV FFF (Tomotherapy) 6 MV (TrueBeam)	6 MV	6 MV 10 MV for an obese patient	6 MV
Dose Rate	Nominal 600 MU/min for all arcs, except for arcs going through the lungs use nominal 200 MU/min.	Nominal 1000 MU/min.	850–1000 MU/min, effective 135–180 MU/min on two different versions of the Tomo. 600 MU/min and effective 135–160 MU/min (TrueBeam)	Nominal 600 MU/min.	Nominal 600 MU/min	Nominal 600 MU/min
Prescription	12 Gy in 4 Fx once daily	12 Gy in 3 Fx once daily	12 Gy in 8 Fx BID [22] 18, 19, 20 Gy in 10 Fx BID [23]	2 Gy single fraction [43]	9 Gy in 6 Fx BID 6 Gy in 4 Fx BID + 1 Fx TBI	12 Gy in 6 Fx BID
Target definition	Bone marrow and spleen with a 7–10 mm margin, subtracted out lungs, kidneys and brain and contracted 3 mm from skin. Some dose to lymph nodes, liver and brain are also desired (3–5 Gy)	Six PTVs are considered (Head, Thorax, Lumbar, Pelvic, Arms and Legs). PTVs = Bones plus 3–10 mm. A 3–5 mm "smart" skin crop is done on PTVs (e.g., the shoulder and hands regions are not cropped) [5]	Skeletal bone, major lymph node chains, ribs, sternum and skull to full prescription dose 12, 18–20 Gy. No dose escalation (12 Gy) [22]: Spleen to 12 Gy; Brain and testes to 12 Gy for all patients with ALL. Brain and testes spared for all other patients. Liver and kidney are spared for all patients.Dose Escalation (18–20 Gy) [23]: Spleen and splenic-hilar nodes to full dose. Liver and porta-hepatic nodes, and brain kept at 12 Gy. Testes 12 Gy for AML, 16 Gy for ALL.	Lymph nodes with 5 mm margin, spleen with a 5–8 mm margin and bones with a 2 mm margin (10 mm in the arms and legs). The whole wall chest was considered to account for breathing motion	Head to mid-femur bones plus 3 mm, arm and leg bones excluded [7]	CTV: Skeletal bones from vertex of skull to middle of thighs, brain, and spinal cord. Exclude mandible, metacarpals, and phalanges. PTV: CTV plus soft tissues between adjacent bones (e.g., intercostal tissues, soft tissues between radius and ulna).
Objectives	$D_{90\%} \geq$ 11–12 Gy $D_{1\%} \leq$ 120–130%	$V_{95\%} \geq$ 90–95% $D_{max} \leq$ 110%	$V_{Rx} >$ 85% $D_{max} <$ 135–145%	$V_{98\%} =$ 98% $D_{max} <$ 125–130%	$D_{95\%} =$ Rx $D_{max} <$ 140% [7]	$V_{10.8Gy} =$ 100% $D_{max} <$ 125–130% $V_{110\%} <$ 40% [9]
Constraints	• Lungs, kidneys, lymph node basins, liver, brain, heart, liver $D_{mean} \leq$ 5–7 Gy	OARs have to follow our dose constraints protocol: Lungs $D_{mean} <$ 7.5 Gy Heart $D_{mean} <$ 7.0 Gy Kidneys $D_{mean} <$ 5.5 Gy Brain $D_{mean} <$ 8.5 Gy Bowel $D_{mean} <$ 6.0 Gy Lenses $D_{mean} <$ 3.0 Gy Testis $D_{mean} <$ 2 Gy Other OARs in general $D_{mean} <$ 6 Gy	• Avoidance organs with dose sparing include eyes, lens, parotids, thyroid, esophagus, oral cavity, lungs, heart, kidneys, stomach, upper GI and lower GI tract, rectum, bladder, and in women breast, uterus and ovaries [22–23]. D_{80}, D_{50}, D_{10} to be within the range of previous TMLI plans No dose escalation (12 Gy) [22]: Mean	• ALARA ($D_{mean} <$ 50% for all OARs)	• Mean dose to brain, heart, lungs, bowel, liver, kidneys, eyes, oral cavity, and lenses to be within recent 5-year standard deviation and within RapidPlan estimation range [8]	• Top priorities for sparing are lungs, liver and heart ($D_{mean} <$ 50%) [9]

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Table 2 (*continued*)

Center	MDACC	San Martino	COH	Humanitas	UIH	NSH
			organ dose constraints for right and left lung 4 Gy, right and left kidney 4 Gy, liver 4 Gy and heart 6 Gy Dose escalation (18–20 Gy) [23]: Mean lung dose ≤ 8 Gy			
Boost volumes	No boost	SIB 15 Gy in 3 Fx once daily (PET+, rarely done)	No boost	We use SIB in case of small PET positive uptake of 4 Gy (V95%= V95%; the plan is optimized alone and added to the TMLI delivery).	No boost	No boost
TPS	Raystation v10A and v11B	Accuray Precision v3.3	Accuray Precision v3.3 and Eclipse v16.1.	Eclipse v15.6	Eclipse v16.1	Eclipse v15.6
Dose calculation algorithm and grid	CCC and 5 mm	Precision CCC and 1.5 mm	Precision CCC (Tomotherapy) or AAA (TrueBeam) with 2.5 mm	AAA and 2.5 mm	AXB and 2.5 mm	AAA and 2.5 mm
Patient setup and alignment	CBCT (lungs) and kV orthogonal pairs with AP kV after longitudinal iso shift	The alignment is previously performed using 5 mask markers and lasers. Then the alignment and positioning are verified and corrected through a long-scan MVCT.	MVCT (Tomotherapy) CBCT and orthogonal pairs (TrueBeam)	CBCT for each isocenter [13]	kV orthogonal pairs	kV orthogonal pairs, obliques for spine alignment [16]
Routine QA	Patient-specific IMRT QA (ArcCheck). γ: 3%/3mm, 10% threshold, 95% pass rate	Patient-specific IMRT QA γ: 3%/2mm, 10% threshold, 90% pass rate. Ionization chamber at isocenter dose within 5%	Patient-specific IMRT QA γ: 3%/3mm, 10% threshold, 95% pass rate; dose within 5%	Patient-specific IMRT QA (portal dosimetry) γ: 3%/3mm, 10% threshold, 90% pass rate In vivo dosimetry with Gafchromic films [12]	Patient-specific IMRT QA (ArcCheck) γ: 3%/2mm, 10% threshold, 90% pass rate [17]	Patient-specific IMRT QA (portal dosimetry) γ: 3%/3mm, 10% threshold, 95% pass rate. Independent MU check for POP fields
Number of patients annually	5	5	50	20	10	14
Percent of adult and pediatric patients	100% / 0%	100% / 0%	95% / 5%	100% / 0%	100% / 0%	100% / 0%
Exclusion criteria	Trial exclusion criteria [21]	None	Trial exclusion criteria [22,23]	Trial exclusion criteria [43]	None	IGRT couch weight limit

treatment of sanctuary sites or regions of high F-18 uptake. However, others still rely on sequential boosts to manage these regions, typically 6 Gy in 3 fractions before the TBI treatment for whole brain or 4 Gy in 1 fraction to the testes.

Quality assurance

IM-TBI and IM-TMI/TMLI universally utilize patient-specific IMRT quality assurance (QA). While the exact implementation can vary, a gamma criterion of a dose plane is used at a minimum. In vivo dosimetry is generally reserved for commissioning of the program and unique situations after the program is established.

Treatment delivery

Most conventional TBI studies require a dose rate between 10 and 20 cGy/min [19,28,29] to reduce normal tissue toxicity. However, other studies report no statistically significant dose rate effect on toxicity [30–33]. As such, IM-TBI programs may use a higher and more variable dose rate. This is acknowledged in the most recent ACR practice parameters [34] in which further studies are needed to determine the acceptable dose-rate for toxicity reduction.

Akin to the standard IMRT workflow employed by clinics, IM-TBI and IM-TMI often utilizes volumetric image guidance to align a patient prior to treatment. Additionally, planar imaging and surface guidance can be utilized to aide in patient alignment [35]. When shifting between different isocenters, the type and amount of imaging to verify alignment varies with the immobilization utilized.

Clinical outcomes

Currently, there is a need for reporting of large population dosimetry and outcome data as these techniques are implemented. Current literature outcome data for IM-TBI and IM-TMI is limited, with retrospective analysis requiring a large effort from each individual institute. However, several institutes have recently published their clinical outcome data for IM-TMI and IM-TBI and are summarized below.

For IM-TMI, Haraldsson *et al.* reported a 1-year graft-versus-host disease-free, relapse-free survival (GRFS) for their IM-TMI program (n = 37) of 67.5% and 80.5% for all patients treated and patients with a matched unrelated donor, respectively, at 12 Gy in 6 fractions BID. For comparison, their historical conventional TBI (cTBI) program had GRFS of 39.4% and 42.3% for these populations [36]. They reported one incident of idiopathic pneumonia syndrome for each group, a grade 4 event for IM-TMI and one grade 5 event for cTBI.

Several groups have investigated dose escalation for IM-TMI. Patel *et al.* investigated doses of 3, 6, 9 and 12 Gy with the dose delivered twice a day in 1.5 Gy fraction sizes, approximately 8 h apart. They reported (n =

14) an overall survival (OS) and relapse-free survival (RFS) of 50% and 43% with a median follow-up of 1126 days [37]. All patients experienced oral mucosal toxicity (grade 2 or less), however, 100% in the 12 Gy and 100% in the 6 Gy arm experienced a grade 2 toxicity. Wong *et al.* reported their institute experience for dose-escalation IM-TMLI at 20 Gy in 10 fractions BID with a 2-year OS and GRFS of 86.7%, and 59.3%, respectively, for acute myeloid leukemia (AML) patients in complete remission. While relapsed or refractory AML patients the OS decreased to 48% at 1-year [38]. Similarly, Hui *et al.* have dose-escalated IM-TMI to the bone marrow in 3 Gy intervals (15 or 18 Gy in 3 Gy fractions) while limiting the dose to vital organs at 13.2 Gy. 50% of the 18 Gy patients had treatment related mortality, whereas the 15 Gy level was better tolerated [39]. They are currently investigating the effects of larger 5 Gy per fraction doses.

For IM-TBI, Zhang *et al.* reported with 1- and 2-year OS (n = 44) of 90% and 79% and RFS of 88% and 71%, respectively, for low dose and high dose regimes 2 Gy in 1 fraction (n = 12) or 12 Gy in 6 or 8 fractions BID (n = 32). Four patients (9%) developed grade 3 + pneumonitis. Three cases were in the setting of documented respiratory infection and likely multifactorial, whereas only one case was likely related to radiation. Mucositis was the most severe acute toxicity observed, with 71% developing grade 3 + mucositis; 54% required total parenteral nutrition for grade 4 mucositis. Mucositis was likely multifactorial in the setting of concomitant chemotherapy and transplant toxicity and not believed to be directly related to TBI [6]. Similarly, Konishi *et al.* reported their findings reported a 2-year OS and disease-free survival of 69% and 64% (n = 39) for 12 Gy in 6 fractions. Additionally, they observed 64% patients having a grade 1–2 mucosa toxicity, with no grade 3 + toxicities [40]. Keit *et al.* have investigated oral mucosal sparing in their program after observing 2 grade 5 mucositis events (out of 15 patients treated using IM-TBI). In the following 16 patients, the mucosa mean dose was decreased to 6.9 Gy from 14.1 Gy. However, there was no statistical difference among toxicities at the time of reporting; importantly though, no further Grade 5 toxicities occurred after implementation [41]. Lastly, Ladbury *et al.* have recently compared their comparison of cTBI and IM-TBI. In the study 26 patients received cTBI and 13 received IM-TBI. 5-year estimated OS was 68% and 60% for IM-TBI and cTBI, respectively. Acute grade 2–4 toxicities were 41.7% and 79.2% for IM-TBI and cTBI, respectively [42].

Conclusion

IM-TBI and IM-TMI/TMLI have been well-developed since their initial development over the last two decades. In this brief report, we put together a set of descriptive data which will be useful for those considering moving to IM-TBI and IM-TMI/TMLI. Naturally, a true consensus of IM-TBI and IM-TMI/TMLI is not possible considering the heterogeneity of the regimens, but we hope this work would be the premise for redacting a more articulate report that clearly defines constraints, mode of boosts execution, dose-rate, etc… This works could also facilitate some homogenization of pre-transplant radiotherapy program, which would result in an easier comparison between techniques in terms of toxicity for example retrospective, given the great difficulty in conducting prospective studies in this area.

We hope that this document provides a springboard for centers considering implementing these techniques. All the authors are available for contact for those seeking guidance in starting a program.

Author contribution

David Parsons, Tze Yee Lim, Jose R. Teruel, Paulina Galavis, Stefano Agostinelli, Jieming Liang, Pietro Mancosu, Amanda Cherpak, Dennis N. Stanley, Kang-Hyun Ahn, Bingqi Guo, Yesenia Gonzalez and Grace Gwe-Ya Kim were all involved in compiling the survey data and revised the manuscript.

David Parsons, Jay Burmeister, Jeffrey Y.C. Wong, Xuejun Gu and Grace Gwe-Ya Kim conceived the initial survey questions and material and revised the manuscript.

David Parsons drafted the manuscript.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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