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Supplementary appendix

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Supplement to: Wong JYC, Filippi AR, Scorsetti M, et al. Total marrow and total lymphoid irradiation in bone marrow transplantation for acute leukaemia. *Lancet Oncol* 2020; **21:** e477–87.

Intensity Modulated Radiation Therapy to deliver Total Body Irradiation

Conventional standard total body irradiation (TBI) is the most non–conformal example of radiation therapy and is limited in its ability to spare normal organs. As TBI requires the full skeleton length to be irradiated, a field with long axis >2 m is required to effectively cover the body extension of an adult. Usually fully opening jaws collimators at 45° and gantry at 90° are considered to maximize the length. This geometry allows obtaining a diamond shaped magna field with diagonal dimension >2 m at source skin distance (SSD) of 4 m. Usually only lungs are attempted to be spared thanks to lung blocks manually placed along the radiation field.[1] Lung blocks can be designed from radiographs obtained while the patient is in the standing treatment position. The blocks cover the central portion of the lung, with approximately 1 or 2 cm between the edge of the lung shadow on the film and the edge of the block (Figure 1).
Multiple studies have documented the risk of pulmonary toxicity associated with TBI which includes interstitial pneumonitis, infectious pneumonia, diffuse alveolar hemorrhage, and respiratory failure with grade 3–5 pulmonary toxicity of 33%.[2] Recent published studies highlight the need for better lung sparing. Esiashvili et al analyzed data from a Children's Oncology Group (COG) trial in pediatric leukemia patients undergoing TBI and reported that mean lung dose of less than 8 Gy was associated with improved overall survival.[3] Moreover, they concluded that lung shielding during TBI is not standardized, lung doses can range from 50% to the full TBI dose, and that future TBI treatments should attempt to limit the lung dose. This finding justifies the need for more modern radiation techniques such as intensity modulated radiation therapy (IMRT) to deliver TBI and to better spare critical organs such as lung. Zhuang et al demonstrated that by using IMRT one can achieve better lung sparing with TBI. As shown in the Supplemental Figures 1 and 2, IMRT was able to reduce the median lung dose from 8–9 Gy to 5–6 Gy or less.[4] Finally Shinde et al. reported on pulmonary complications of 142 TMLI patients and found that mean lung less than 8 Gy correlated with significantly less pulmonary complications.[5] Dose rate to the lung did not impact complications so implementing IMRT TBI as a new standard should be feasible.

Recently some centers have used helical tomotherapy (HT) based IMRT or volumetric modulated arc therapy (VMAT) based IMRT to deliver standard TBI.[4,6–10] Gruen et al. performed HT–based–TBI in children at a total radiation dose of 12 Gy and limited mean lung dose to approximately 10 Gy; there were no grade 3 or 4 side effects.[11] Sarradin et al. performed TBI using IMRT on 11 patients at a starting dose of 12 Gy. They were able to spare lung mean dose to ~8·7 Gy, and no patient had radiation pneumonitis but very limited follow–up.[8]

VMAT–based–TBI has been described in the literature with guidelines for use and implementation. Myeloablative TBI doses have been delivered with VMAT via a similar technique by Springer et al.[7] Initially, only lungs were excluded in the delivery of the radiation, similar to standard conventional TBI. However, for patients with renal insufficiency and prior brain radiation, the kidneys and brain were also used as avoidance structures in the radiation planning to minimize doses to these additional normal organs. In another study 30 patients with AML or ALL were treated with VMAT–based–TBI.[12] Mean lung and kidney doses were restricted to less than 10 Gy.

Other centers have combined TBI at full dose or partial doses with TMI to select targets areas as a form of localized boost. Corvo et al. demonstrated the feasibility of adding a 2 Gy HT–based–TMI boost to bone marrow and spleen

after standard TBI 12 Gy (2 Gy BID) using a linear accelerator and cyclophosphamide in 15 patients with acute myeloid leukemia (AML) and acute lymphoid leukemia (ALL).[13] With a median follow–up of 310 days, they reported a cumulative TRM rate of 20%, relapse rate of 13%, and disease free survival rate of 67%. Jiang et al. recently reported results of combining cyclophosphamide and HT–based–TBI to 10 Gy with simultaneous integrated boost to 12 Gy to bone marrow and sites of CNS and extramedullary leukemia to 12 Gy in 14 patients with high risk or relapsed/refractory ALL.[14]

In summary, IMRT delivery of TBI compared to traditional methods results in superior organ sparing which should translate into improved clinical outcomes.

Figure 1.Sup: Dose color wash of patients treated with TBI using a conventional AP and PA fields with 50% lung transmission block (left) or IMRT (right). The IMRT plan demonstrates better lung sparing and higher dose homogeneity along the body.

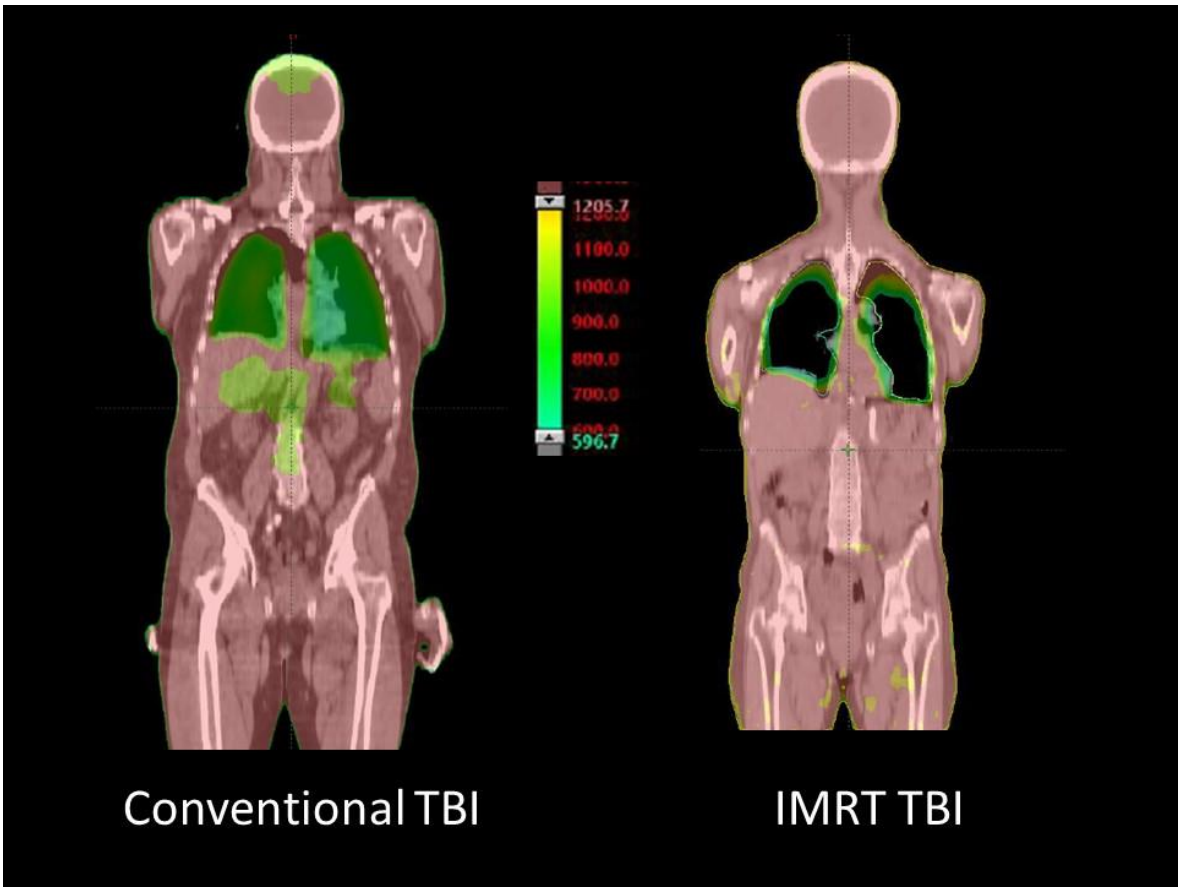

Figure 2.Sup: DVH comparison of lung doses with conventional TBI and IMRT TBI.[4]

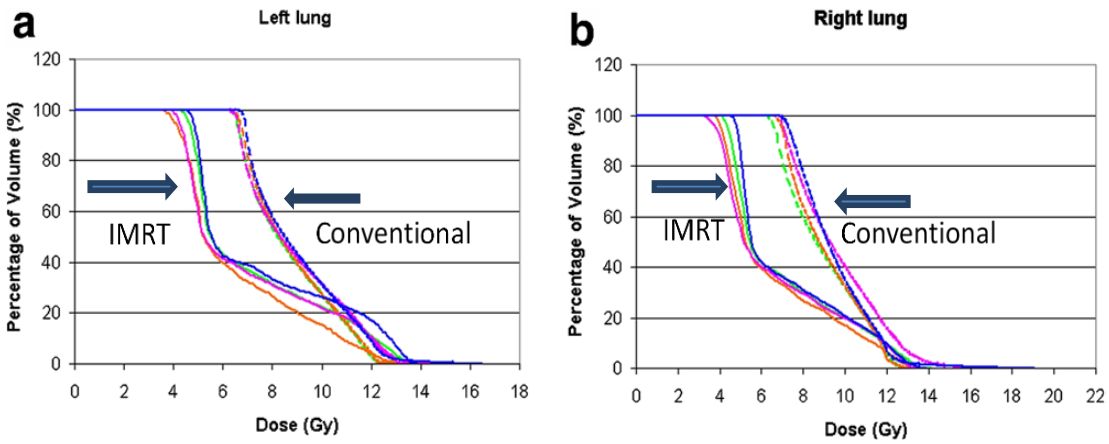

Table 1.Sup: TMI and TMLI Trials in Patients with Acute Leukemia or Advanced Hematologic Malignancies (includes ongoing trials)

Institution NCT Trial No.*	Type of Trial	Type of HCT	Disease Type	Targets	TMI Dose (Gy)	Fractionation and Schedule	Chemotherapy
City of Hope[15] 00540995	Phase I	Allogeneic	AML relapsed or refractory with active disease Not eligible for standard HCT	bone, nodes, testes, spleen, 12 Gy liver, brain	12, 13·5	1·5 BID	BU 4800 uM*min VP16 30 mg/kg
City of Hope[16] 02446964	Phase I	Allogeneic	AML, ALL relapsed or refractory with active disease Not eligible for standard HCT	bone, nodes, testes, spleen, 12 Gy liver, brain	12 to 20	1·5–2 Gy BID	Cy 100 mg/kg VP16 60 mg/kg
City of Hope[17,18] 02094794	Phase II	Allogeneic	AML or ALL, IF, relapsed or > CR2	bone, spleen, node, 12 Gy liver, brain	20	2 Gy BID	Cy 100 mg/kg VP16 60 mg/kg
City of Hope 03467386	Pilot	Allogeneic	AML CR1 or CR2	bone, spleen, node, 12 Gy liver, brain	20	2 Gy BID	pTCy 50 mg/m^2/d x 2
City of Hope[19,20] 00544466	Pilot	Allogeneic	Advanced disease > 50 yrs old or co–morbidities ineligible for standard myeloablative regimens	bone, nodes, spleen, ALL testes, brain	12	1·5 Gy BID	Flu 25 mg/m^2/d x 4 Mel 140 mg/m^2
City of Hope 00800150	Phase I	Allogeneic	Advanced disease > 50 yrs old or co–morbidities ineligible for myeloablative regimens	bone, nodes, spleen, ALL testes, brain	12	1·5 Gy BID	Flu 25 mg/m^2/d x 4 Mel 140 mg/m^2
City of Hope[21] 02446964 (21)	Phase I	Allogeneic haplo–identical	AML, ALL, MDS CR1 high risk, CR2, CR3, refractory	bone, spleen nodes 12 Gy liver, spleen 16 Gy testes ALL 12 Gy brain ALL	12 to 20	1·5–2 Gy BID	Flu 25 mg/m^2/d x 5 Cy 14·5 mg/kg/d x 2 ptCy 50 mg/kg/d x 2
City of Hope 03490569	Phase I	Allogeneic matched	AML, ALL, MDS > 55 yrs old or co–morbidities ineligible for standard myeloablative regimens	bone, spleen nodes 12 Gy spleen 16 Gy testes ALL	12 to 20	1·5–2 Gy BID	Flu 30 mg/m^2/d x 3 Mel 100 mg/m^2
City of Hope 03490569	Phase I	Allogeneic haplo–identical	AML, ALL, MDS > 55 yrs old or co–morbidities ineligible for standard myeloablative regimens	bone, spleen nodes 12 Gy spleen 16 Gy testes ALL	12 to 20	1·5–2 Gy BID	Flu 30 mg/m^2/d x 3 Mel 100 mg/m^2 ptCy 50 mg/d x 2
U. Illinois, Chicago[22] 00988013	Phase I	Allogeneic	Refractory or relapse AML, ALL, MDS, MM, CML	bone	3 to 12	1·5 Gy BID	Flu 40 mg/m^2/d x 4 BU 4800 uM*min
U. Illinois, Chicago 03121014	Phase II	Allogeneic	Poor risk, refractory or relapse AML, MDS	bone	9	1·5 Gy BID	Flu 40 mg/m2/d x 4 BU 4800 uM*min
U. Illinois, Chicago 02333162	Phase I	Allogeneic	recurrent AML, ALL, MDS undergoing second HCT	bone	NS	BID over 2–5 days	Flu, Mel
Case Comprehensive Cancer Center 02129582	Phase I	Allogeneic	High risk AML, ALL, NHL, HL, MM, MDS, CLL, CML ineligible for full myeloablative regimen	bone	NS	BID over 4 days	Flu, Bu
U. Minnesota[23] 00686556	Phase I	Allogeneic	High risk ALL, AML CR2, CR3, Relapse, IF	bone	15, 18	3 Gy QD	Flu 25 mg/m^2/d x 3 Cy 60 mg/m^2/d x 2
Ohio State[24] 02122081	Pilot	Allogeneic	High risk AML, ALL, MDS > 50 yrs old or comorbidities unable to undergo TBI based regimens;	bone, brain, testes	12	2 Gy BID	Cy
U. Perugia[25] 03977103	Phase II	Allogeneic haplo–identical	AML in CR1, CR2, PR	bone nodes 11·7 Gy	13·5 Gy TMI	1·5 Gy BID 1·3 Gy BID	TT 2·5 mg/kg/d x 2 Flu 30 mg/kg/d x 5 Cy 15 mg/kg/d x 2 T–cell manipulated graft
Indiana U. 03696537	Phase I/II	Allogeneic	Relapsed/refractory ALL, AML, MDS, CML ages 18–65	bone	NS	BID over 10 days	Flu 30 mg/m^2/d x 5

Institution NCT Trial No.*	Type of Trial	Type of HCT	Disease Type	Targets	TMI Dose (Gy)	Fractionation and Schedule	Chemotherapy
Beijing 307 Hospital 03048223	Phase I	Allogeneic	High risk AML, ALL (IF, relapse, > CR2)	bone, lymph nodes	12 – 20	4 Gy QD	Cy 60 mg/kg/d x 2
Beijing 307 Hospital 03408210	Pilot	Allogeneic	AML, ALL in CR1 or CR2	bone, lymph nodes	12	4 Gy QD	Cy 60 mg/kg/d x 2
University Hospitals of Geneva 03262220	Pilot	Allogeneic	Hematologic malignancy CR1, CR2, or CR3 Age 40 – 80 yrs old	bone	12 (13·5 to active BM)	4 Gy QD with 4·5 Gy QD boost to active BM	

* Listed at www.clinicaltrials.gov

HCT = hematopoietic cell transplantation; AML = acute myelogenous leukemia; ALL = acute lymphoblastic leukemia; MM= multiple myeloma; NHL = non–Hodgkin's lymphoma; HL = Hodgkin's lymphoma; MDS = myelodysplastic syndrome; TBI = total body irradiation; TMI = total marrow irradiation; TMLI = total marrow and lymphoid irradiation; CR1 = first complete remission; CR2 = second complete remission; CR3 = third complete remission; IF = induction failure; QD = once per day; BID = twice per day; Bu = busulfan; Cy = cyclophosphamide; ptCy = post–transplant Cy; Flu = fludarabine; Mel = melphalan; VP–16 = etoposide; Gy = Gray

Table 2.Sup: Comparison of TBI versus TMI/TMLI Planning and Preparation

TBI	TMI/TMLI
• TBI Measurement: thickness, SSD, positioning, gantry angle, hand position • CT Simulation for chest wall e boost treatment planning	• Immobilization • Whole body CT simulation
• TBI calculation • Fabricate compensator and lung blocks • Set up – lung block placement and port films • Generate e boost plan to chest wall • 2nd calculation QA verification	• Contour • Plan optimization • Phantom QA
• Position standing – harness and lung blocks • Treatment: 20 min beam–on time for 2 Gy fraction	• Position in mask and vac–lock • Treatment: 35–50 min beam–on time for 2Gy fraction

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