Case Report

Transcending history: The revolution of TMLI in BMT

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Abstract

Background: Total Marrow and Lymphoid Irradiation (TMLI) is an organ-sparing alternative to Total Body Irradiation (TBI) in conditioning for bone marrow transplantation (BMT), offering precise radiation targeting of marrow and lymphoid tissues.

Case Presentation: We report a case of Relapsed Philadelphia-Positive B-cell Acute Lymphoblastic Leukemia (B-ALL) with T315I mutation who underwent consolidation allogeneic stem cell transplantation with TMLI-based conditioning.

Methods: TMLI was delivered at 13.5 Gy in 9 fractions (2 fractions per day – 6 hours apart for 5 days) using multiple VMAT plans on a Varian TrueBeam Linear Accelerator. Target volumes included the entire skeletal and lymphatic systems.

Results: The patient tolerated treatment well, with only grade II mucositis. Neutrophil and platelet engraftment occurred on Days +11 and +13, respectively. No infections were observed post-transplant. Chimerism analysis on Days +30 and +60 confirmed 100% donor cell engraftment. She remains clinically stable at last follow-up.

Conclusion: This case illustrates the feasibility, safety, and clinical efficacy of TMLI as part of a myeloablative conditioning regimen for high-risk ALL. TMLI offers precise dose delivery to hematologic targets with reduced toxicity, representing a promising modality in contemporary transplant conditioning

Key words: Total Body Irradiation; TBI; Bone Marrow Transplant; Acute Leukaemia; Inotuzumab; Haemato-oncology

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1. Introduction

Total Body Irradiation (TBI) as a conditioning regimen in Bone Marrow Transplant (BMT) is a cornerstone in haemato-oncology ever since the 1970s (1) and it has been irreplaceable historically (2). Although higher TBI doses are associated with better disease control, reduced risk of marrow rejection and lesser incidence of graft versus host disease (GVHD), the TBI-related toxicities negate any potential survival advantage (3), (4). With higher doses come higher toxicities and various techniques have been employed to deliver TBI with optimum radiation dose-fractionation with or without myeloablative chemotherapy (2). However, this modality does not spare the organs-at-risk (OAR) from

radiation except the lungs and has an inherent potential for larger heterogeneities in absorbed radiation dose across the entire body. Total Marrow and Lymphoid Irradiation (TMLI) uses advanced conformal radiation techniques that deliver higher doses specifically to the bone marrow and lymphoid tissues, the primary reservoirs of hematologic malignancies (5) while achieving reasonably safer tolerance doses to rest of the OAR (6), (7). TMLI is used in both myeloablative and reduced-intensity conditioning regimens, and has shown particular promise in relapsed or refractory settings and in patients who are ineligible for full-intensity TBI (7), (8), (9).

1.1. Case Presentation

28-year-old female was evaluated for leucopoenia during her second pregnancy. Bone marrow evaluation showed features of Acute Leukaemia with 92% blasts. Flow cytometry was suggestive of B-cell Acute Lymphoblastic Leukaemia (B-ALL) with aberrant CD13 expression. She was started on BFM-95 induction chemotherapy (10) along with Dasatinib (BCR-ABL positive). Post induction chemotherapy, bone marrow was in remission with Minimal Residual Disease (MRD) negative. During follow-up after 6 months, peripheral blood picture showed 8% blasts with flow cytometry suggestive of disease relapse – B-ALL with CD22 showing moderate expression. Next-Generation Sequencing (NGS) panel showed BCR-ABL fusion positive. BCR-ABL quantitative Polymerase Chain Reaction (PCR) was found to be 68.603%. Imatinib resistance mutation analysis reported T315I mutation. Cerebrospinal fluid cytology was negative for malignant cells indicating a CNS-1 disease process (11). She completed two cycles of Inotuzumab based systemic therapy following which bone marrow evaluation showed disease in remission with MRD negative status. Repeat BCR-ABL quantitative PCR was 0.253%. She was taken up for consolidation with allogenic stem cell transplant.

2. Materials and Methods

This case of Relapsed Philadelphia (BCR-ABL) Positive B-ALL with T315I mutation was considered for TMLI based BMT conditioning after due discussions in the multi-disciplinary tumour board with close coordination of the haemato-oncology team.

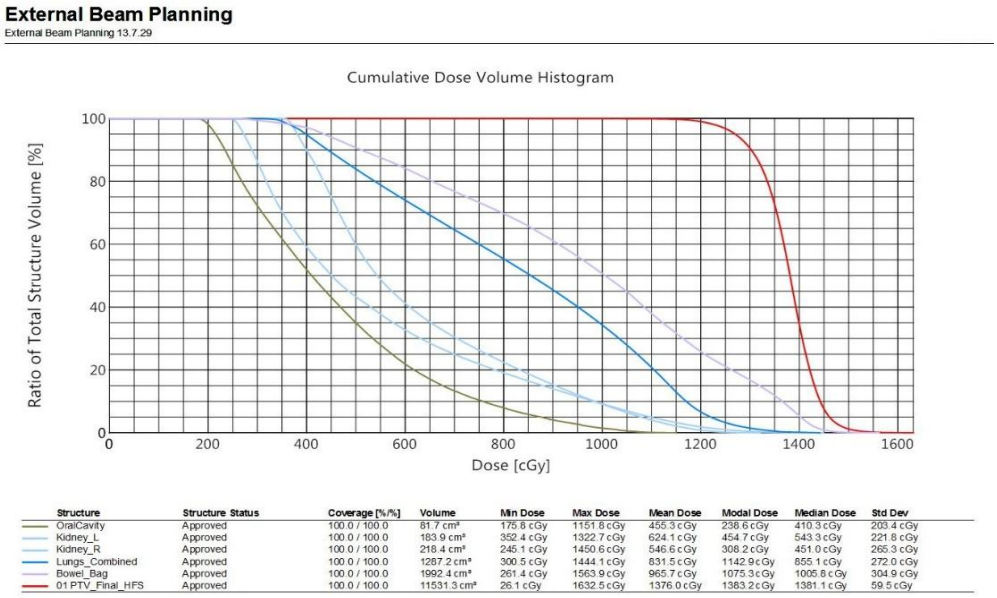
Positioning and Simulation: The patient with a height of 155cm was positioned supine within a customizable whole-body vacuum bag filled with polystyrene beads (Vac-Lok) that can be moulded to the person's body contour, ensuring neutral alignment of the body. A three-point thermoplastic mask was secured over a standard neck support to immobilize the head. The upper body and torso including bilateral shoulders, arms, forearms, and hands (folded to make a fist) were positioned close to the lateral sides of the body, while the lower body, pelvis and bilateral knees were comfortably supported and adjusted to an appropriate height within the Vac-Lok. The Vac-Lok captured firm impressions of the heels and toes to assist with repositioning. Surface laser guidance was used to ensure straight alignment and positioning of the patient within the Vac-Lok reducing the margin for rotational and translational errors later during treatment setup. Due to the translational limitations of a Linear Accelerator (LINAC) couch, Computerized Tomography (CT) scan was acquired in two orientations with Head First Supine (HFS) and Feet First Supine (FFS) positions. Prior to CT acquisition, thin radio-opaque guide wires were placed bilaterally along the mid-thigh on the surface, and horizontal reference lines were drawn with matching markers on the vacuum bag to enhance setup reproducibility. Images were acquired with a 5mm slice thickness and extended field of view (eFOV) in free breathing. The initial CT scan was performed from the vertex to the distal thighs. Following this, the patient along with the immobilization setup was rotated 180°, and a second scan was obtained from the toes upward, ensuring the entire vacuum bag and upper thighs were included in the imaging field *(Figure 1*).

Fig (1): Stitched AP Topogram of both HFS and FFS CT images illustrating patient positioning and immobilization

Contour Delineation: The CT image dataset was transferred to the Varian EclipseTM Treatment Planning System (TPS). The target volumes and OAR were delineated in accordance to the standard Radiation Therapy Oncology Group (RTOG) guidelines. The Clinical Target Volume (CTV) encompassed the entire bony skeleton, brain, spleen, and major lymphatic regions. The CTV was delineated in HFS and FFS CT datasets to ensure complete coverage of the osseous structures. Lymphatics delineated included bilateral cervical, supraclavicular, mediastinal, axillary, entire para-aortic chain, external and internal iliac, presacral, obturator and inguinal nodes. OAR delineated were eyes, lens, midline mucosa (oral, pharyngeal, laryngeal, tracheal and esophageal mucosa), lungs, heart, liver, bowel, kidneys, parotids, thyroid, breast, and ovaries. A Planning Target Volume (PTV) margin was generated around the CTV to account for internal organ motion and daily treatment setup variability.

Treatment Planning: A dose of 13.5 Gy in 9 fractions (1.5 Gy per fraction) was prescribed to the PTV. The contoured CT dataset was taken up for external beam radiation therapy (EBRT) planning in the Varian EclipseTM TPS v13.7.29. The radiation dose calculation and optimization were run using the native Acuros XB algorithm to generate a Volumetric Modulated Arc Therapy (VMAT) treatment plan using 6 Mega Voltage (MV) photons. For the HFS-TMLI treatment plan, four isocentres (Head & Neck, Thorax, Abdomen and Pelvis) were utilized and each isocentre was associated with four VMAT arc fields, except for the thoracic isocentre, which required five VMAT arcs. These isocentres were aligned along the longitudinal axis, with no lateral or anteroposterior shifts and these were separated by no more than 24 cm longitudinally. For the FFS-TMLI treatment plan, two isocentres (Proximal Leg and Distal Leg) with each plan consisting of a four-field oblique cross-fire conventional setup was used. The upper border of the proximal

leg field was matched with the junction of the lower border of pelvic field. This composite plan was generated and evaluated having met satisfactory dosimetric parameters (Figure 2) with respect to target volume coverage (Figure 3) and OAR tolerance limits.



Structure	Structure Status	Coverage [%/%]	Volume	Min Dose	Max Dose	Mean Dose	Modal Dose	Median Dose	Std Dev
OralCavity	Approved	100.0 / 100.0	81.7 cm³	175.8 cGy	1151.8 cGy	455.3 cGy	238.6 cGy	410.3 cGy	203.4 cGy
Kidney_L	Approved	100.0 / 100.0	183.9 cm³	352.4 cGy	1322.7 cGy	624.1 cGy	454.7 cGy	543.3 cGy	221.8 cGy
Kidney_R	Approved	100.0 / 100.0	218.4 cm³	245.1 cGy	1450.6 cGy	546.6 cGy	308.2 cGy	451.0 cGy	265.3 cGy
Lungs_Combined	Approved	100.0 / 100.0	1287.2 cm³	300.5 cGy	1444.1 cGy	831.5 cGy	1142.9 cGy	855.1 cGy	272.0 cGy
Bowel_Bag	Approved	100.0 / 100.0	1992.4 cm³	261.4 cGy	1563.9 cGy	965.7 cGy	1075.3 cGy	1005.8 cGy	304.9 cGy
01.PTV_Final_HFS	Approved	100.0 / 100.0	11531.3 cm³	26.1 cGy	1632.5 cGy	1376.0 cGy	1383.2 cGy	1381.1 cGy	59.5 cGy

Fig (2): Cumulative Dose Volume Histogram (DVH) of the final summed EBRT-VMAT plan for TMLI showing satisfactory target volume coverage and OAR tolerance

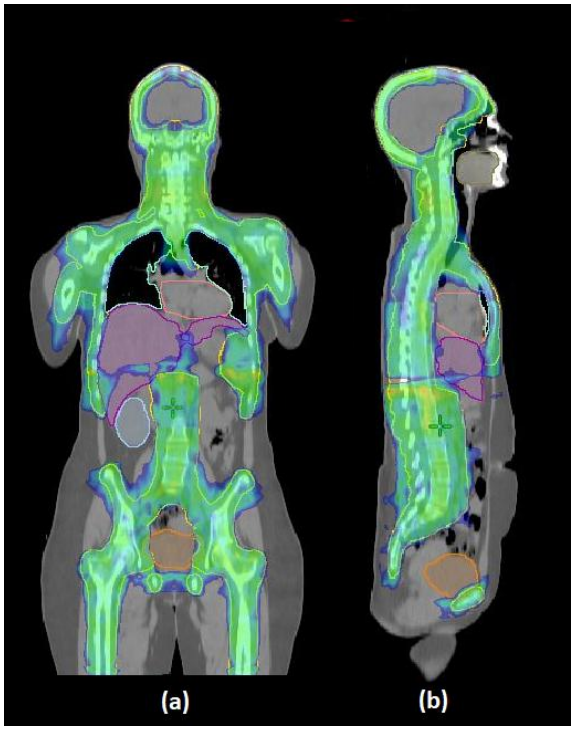


Fig (3): 95% Dose colour wash images of composite VMAT-TMLI plan in (a) Coronal and (b) Sagittal planes showing adequate target volume coverage of total bone marrow and lymphoid chains while significantly sparing the normal tissues including but not limited to the eyes, oral cavity (buccal mucosa), heart, lungs, liver, kidney, bowel, bladder

Treatment Delivery: Prior to treatment delivery, the radiation plan completed a quality assurance program with standard protocol and the treatment was delivered using a VarianTM TrueBeam LINAC equipped with a 120-leaf Multi-Leaf Collimator (MLC). The central 40 leaf pairs had a 5 mm width, while the peripheral 20 pairs featured a 1 cm width. The system supports a maximum field size of 40 × 40 cm^2, with a maximum MLC leaf travel of 15 cm. The prescribed dose of 13.5 Gy in 9 fractions was delivered twice a day with a minimum of six-hour interval between two fractions in a single day for a total of 5 consecutive days (single fraction on the fifth day). Six isocentre plans (Figure 4) were delivered in succession during one fraction of treatment. Treatment setup was verified for each field during each fraction using an onboard Three-Dimensional Cone Beam CT (3D-CBCT) ensuring minimal treatment setup errors and optimal junction matching during treatment delivery. To optimize treatment efficiency, a dedicated setup session was scheduled one day prior to treatment initiation for image acquisition and isocentre verification that assists in determining the optimal patient alignment. The average time in and time out of the patient from the treatment bunker was approximately 85 minutes. The average beam on treatment time for one fraction treatment was approximately 45 minutes.

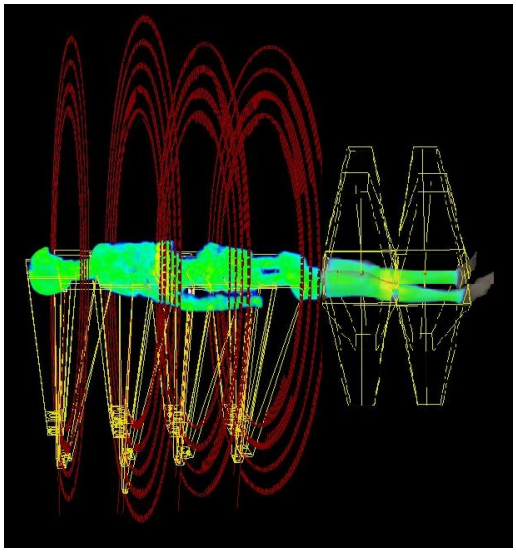


Fig (4): Field arrangements of six isocentres (four VMAT isocentres and two conventional isocentres) for VMAT-TMLI of an adult patient

Haematological Profile: The preparatory regimen for BMT was myeloablative and consisted of TMLI 13.5 Gy in 9 fractions from Day (-8) to Day (-4) and Inj. Cyclophosphamide for 2 days on Day (-3) and Day (-2). The patient tolerated this conditioning regimen well with mild nausea. The donor was a 12/12 Human Leukocyte Antigens (HLA) matched sibling and Granulocyte Colony-Stimulating Factor (G-CSF) mobilised Peripheral Blood Stem Cell (PBSC) harvest was done. Cyclosporine was administered from Day (-1) with subsequent doses titrated as per serum levels monitored periodically. The harvested PBSC was transfused on Day (0) with an uneventful procedure and GVHD prophylaxis with Methotrexate (Leucovorin rescue) and Cyclosporine was started from Day (+1). The trajectory of blood counts (Figure 5) was monitored closely to assess the status of engraftment with an absolute neutrophil count of >500/mm3 achieved on Day (+11) and an unsupported platelet count of >20,000/mm3 achieved on Day (+13)

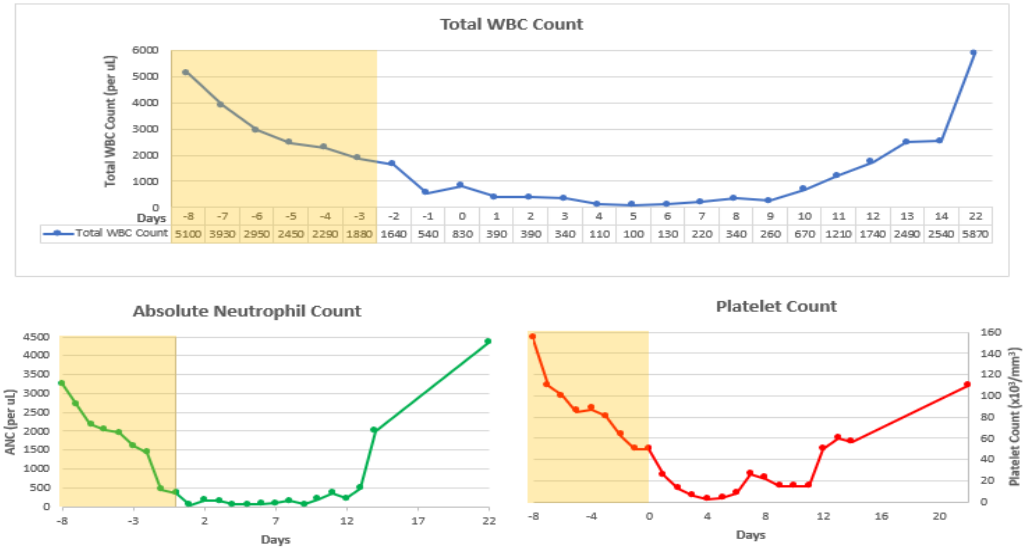


Fig (5): Graph depicting the temporal dynamics of haematological parameters during the entire duration of BMT with highlighted portion (Day-8 to Day-4) of TMLI: Total White Blood Cell Count, Absolute Neutrophil Count and Platelet Count

3. Discussion

TBI has been a historically proven cornerstone in BMT and with this paradigm shift from total body to targeted precision, TMLI heralds a significant improvement over traditional TBI in several respects such as OAR sparing (12), higher doses to target sites and dose escalation (5) translating to improved tolerability with a potential for improved outcomes (6). Implementing TMLI in regular clinical practice can be cumbersome since it is a time and labour-intensive process. In our experience, the simulation in itself consumed approximately two hours, with complete target volume delineation and OAR contouring taking up six hours, multiple VMAT plans with optimization taking three hours per plan and treatment times extending up to 160 minutes every day. However, this effort is translated to better patient outcome with this case reporting only grade-II mucositis and blood product support with 11 units of single donor platelet and 3 units of random donor platelets over a duration of 25 days. The overall treatment tolerability was better. The patient was afebrile throughout her post-transplant period with serial blood, urine and serum showing no laboratorial evidence of bacterial, fungal or viral infections. Chimerism by panel of polymorphic short tandem repeat (STR) markers done on Day (+30) and Day (+60) showed 100% donor cells indicating complete graft acceptance and a successful marrow transplant in this case of high risk ALL. The patient remains clinically stable at last follow-up – Day > (+75) .

4. Conclusion – From Protocol to Practice

TMLI is the future, with increasing adoption in leading cancer centres worldwide, it is poised to become a standard-of-care modality in transplant conditioning. Clinical trials are ongoing to evaluate its long-term impact on relapse rates, survival outcomes, and quality of life compared to TBI. Multiple other studies are looking into dose escalated TMLI with a less chemo-intensive conditioning regimen for better tolerability. As the precision of cancer therapy continues to evolve, TMLI exemplifies how technological innovation can translate into safer, more effective, and more patient-friendly treatment paradigms.

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