Total marrow and lymphoid irradiation as conditioning in haploidentical transplant with posttransplant cyclophosphamide

Monzr M. Al Malki,1 Joycelynne Palmer,2 Ni-Chun Tsai,2 Sally Mokhtari,3 Susanta Hui,4 Weimim Tsai,1 Ibrahim Aldoss,1 Haris Ali,1 Ahmed Aribi,1 Thai Cao,5 Mathew Mei,1 Karamjeet S. Sandhu,1 Tanya Siddiqi,1 Stephen J. Forman,1 Ryotaro Nakamura,1 Guido Marcucci,1 Anthony Stein,1 Jeffrey Y. C. Wong,4,* and Joseph Rosenthal6,*

1Department of Hematology and Hematopoietic Cell Transplantation, 2Department of Computational and Quantitative Medicine, 3Department of Clinical and Translational Project Development, and 4Department of Radiation Oncology, City of Hope National Medical Center, Duarte, CA; 5Kaiser Permanente, Duarte, CA; and 6Department of Pediatrics, City of Hope National Medical Center, Duarte, CA

Posttransplant cyclophosphamide (PTCy) platform has shown low rates of graft-versus-host disease (GVHD) and nonrelapse mortality (NRM) after haploidentical hematopoietic cell transplantation (HaploHCT). However, because of the limited disease control, relapse rate remains a major cause of treatment failure in high-risk patients. Total marrow and lymphoid irradiation (TMLI) allows for delivery of high radiation to bone marrow and other targeted structures, without increasing off-target radiation exposure and toxicity to end organs. In this phase 1 trial, 31 patients with high-risk and/or active primary refractory leukemias or myelodysplastic syndrome underwent peripheral blood stem cell HaploHCT with TMLI, fludarabine, and cyclophosphamide as the conditioning regimen. Radiation dose was escalated in increments of 200 cGy (1200-2000 cGy). GVHD prophylaxis was PTCy with tacrolimus/mycophenolate mofetil. Grade 2 toxicities by the Bearman scale were mucositis (n = 1), hepatic (n = 3), gastrointestinal (n = 5), and cardiac (n = 2). One patient (1800 cGy) experienced grade 3 pulmonary toxicity (dose-limiting toxicity). At a follow-up duration of 23.9 months for the whole cohort; 2-year NRM was 13%. Cumulative incidence of day 100 grade 2 to 4 and 3 to 4 acute GVHD was 52% and 6%, respectively. Chronic GVHD at 2 years was 35%. For patients treated with 2000 cGy, with a median follow-up duration of 12.3 months, 1-year relapse/progression, progression-free survival, and overall survival rates were 17%, 74%, and 83%, respectively. In conclusion, HaploHCT-TMLI with PTCy was safe and feasible in our high-risk patient population with promising outcomes.

Introduction

Haploidentical hematopoietic cell transplantation (haploHCT) offers a potentially curative therapy for patients with hematologic malignancies lacking a fully matched donor, making transplant available to nearly all eligible patients.1,2 An approach using unmanipulated bone marrow (BM)3 or peripheral blood stem cells (PBSCs)4 followed by immunosuppression with high-dose posttransplant cyclophosphamide (PTCy) as graft-versus-host disease (GVHD) prophylaxis has demonstrated acceptably low incidence of nonrelapse
mortality (NRM) and GVHD. Yet, a shortcoming of this regimen continues to be graft failure and the relatively high rates of relapse.3,5

In a recent retrospective study by the Center for International Blood and Marrow Transplant Research, myeloablative regimens for haploHCT were shown to be associated with lower relapse rate and better disease-free survival (DFS) compared with reduced intensity conditioning (RIC), at least in younger patients with acute leukemias and myelodysplastic syndrome (MDS).6 An incremental increase in radiation dose in total body irradiation (TBI) results in a lower risk of disease progression/relapse after HCT; however, the beneficial impact of higher doses is offset by higher regimen-related toxicities and deaths.7,8 Furthermore, there has been a large heterogeneity in the dose coverage to lungs using conventional TBI.9

We have pioneered and developed total marrow and lymphoid irradiation (TMLI) that allows for precise delivery of increased intensity treatment through sculpting irradiation to sites with high disease burden or higher risk for disease involvement or relapse while sparing healthy tissues.10-14 We have shown that TMLI at 2000 cGy in combination with chemotherapy (cyclophosphamide and etoposide) is safe and results in a relatively low NRM rate and no increased risk of GVHD in patients with relapsed/refractory acute leukemias undergoing HCT in the match donor setting,11,15 but no data are available in the setting of haploHCT.

In this study, we investigated the safety and feasibility of dose escalation of TMLI when combined with fludarabine and cyclophosphamide for conditioning before T cell–replete haploHCT with PTCy in patients with high-risk acute myeloid or lymphoblastic leukemia (AML or ALL, respectively) and MDS.

**Subjects and methods**

**Clinical protocol**

This single-institution phase 1 trial with expansion cohort tested escalating doses of TMLI when given as conditioning regimen for haploHCT. Our primary objectives were to establish the recommended phase 2 dose (RP2D) of TMLI in this regimen and to describe the toxicities at each dose level (DL). Secondary objectives included estimation of overall survival (OS), DFS, cumulative incidence of relapse/progression (RP), NRM, acute/chronic GVHD, and an assessment of radiation dose to target and off-target organs.

This trial was registered with clinicaltrials.gov (#NCT02446964) and approved by the City of Hope institutional review board. An assurance was filed with and approved by the Department of Health and Human Services. Informed consent was obtained for all study participants in compliance with the Declaration of Helsinki.

Patients with high-risk and/or active primary refractory or relapsed AML (classified per Döhner et al),16 ALL (classified per Moorman et al),17 or MDS (classified per Revised International Prognostic Scoring System [IPSS-R])18 aged 12 to 60 years with adequate organ function and an available haploididentical donor were eligible. Patients with prior history of radiation therapy of more than 20% of BM-containing areas or any area exceeding 2000 cGy were excluded. Graft source was PBSCs for all patients.

**TMLI**

TMLI was delivered at 8 to 10 planned doses ranging from 1200 to 2000 cGy, administered in twice daily fraction over 4 to 5 days, as published previously.10,11,19 Briefly, all patients underwent computed tomography simulation and were treated on a TomoTherapy system (Accuray, Sunnyvale, CA). For treatment planning purposes, the target organs included the bone and BM, major lymph node chains, spleen, testes, liver, and brain. All other organs (such as lungs, heart, small and large intestine, kidneys, eyes, lenses, oral cavity, bladder, parotid glands, stomach, and esophagus) were identified as organs at risk, and efforts were made to minimize dose to these organs. Because of dose sparing of the gastrointestinal (GI) tract and the oral cavity, mesenteric lymph nodes, Waldeyer ring lymph nodes, and the mandible were not included as target regions. Doses to BM, major lymph node chains, and testes were escalated up to 2000 cGy, but doses to liver, porta hepatitis, and spleen were kept at 1200 cGy. Brain was treated to 1200 cGy only in patients with ALL with a history of positive cerebrospinal fluid while the skull was considered a targeted organ.

**Preparative regimen and GVHD prophylaxis**

The study schema is depicted in Figure 1A. Palifermin (60 µg/kg per day) was administered from day −10 to day −8 before HCT.20 Patients received cyclophosphamide (14.5 mg/kg per day) on days −7 and −6. Escalating doses of TMLI (Figure 1B) were delivered concurrently with fludarabine (25 mg/m2 per day) from day −7 to day −3. GVHD prophylaxis consisted of high-dose PTCy (50 mg/kg per day) on days +3 and +4, followed by granulocyte colony stimulating factor (5 µg/kg) on day +5 until absolute neutrophil count > 1500. Tacrolimus and mycophenolate mofetil were initiated on day +5 and continued until day +180 and +35, respectively, if no active GVHD was developed.

**Flow cytometry and GVHD biomarkers**

Peripheral blood was collected on days 30, 100, and 180 after HCT. For Treg staining, PBMCs were surface stained for CD3, CD4, CD25, and CD127 (eBioscience) and intracellularly stained for Foxp3 using Foxp3/Transcription Factor Staining Buffer Set (eBioscience). All other antibodies were purchased from eBioscience. Flow cytometry was performed using a BD FACSCelesta (BD Biosciences), and data were analyzed using Flowjo software (Tree Star).

Serum samples were obtained on weekly basis for 4 weeks and were analyzed for GVHD biomarkers using the Luminex FlexMap 3D bead array technology. Multiplex kits were purchased from R&D Systems, and assays were performed according to the manufacturer’s instructions in the analytical Pharmacology Core Facility.

**BM examinations**

Trephine biopsies were obtained before TMLI and at 1 year after transplant. Samples were prospectively analyzed by immunohistochemistry staining with CD34 antibody (Ventana Roche). Marrow samples were also evaluated for cellularity and vessel density and quantified by a certified pathologist.

**Statistical considerations**

Dose-limiting toxicity (DLT) was defined as any of the following that were assigned an attribution level of at least possibly related to TMLI: For nonhematologic toxicities, any regimen-related grade 3 or 4 toxicity per Bearman toxicity grading scale,21 and for nonhematologic toxicities that are not part of the Bearman toxicity, any grade 4 toxicity per NCI Common Terminology Criteria for Adverse Events (CTCAE) v4.03, except for metabolic/electrolyte disturbances and...
### TMLI radiation therapy for haploidentical hematopoietic cell transplantation

**A.** Study schema: patients received palifermin (60 μg/kg per day) for 3 days, starting on day -10 before stem cell infusion. PTCy was administered at 14.5 mg/kg per day on days -7 and -6. TMLI at the scheduled dose was delivered concurrently with fludarabine (25 mg/m² per day) for 5 days from day -7 to day -3. GvHD prophylaxis consisted of posttransplant cyclophosphamide (50 mg/kg per day) on days 1-3 and 1-4, GCSF (5 μg/kg) starting on day +5 and continued until days +1500, and tacrolimus and mycophenolate mofetil starting on day +5 and continued until days +90 and +35, respectively.

**B.** TMLI dose levels and number of patients accrued at each dose level.

| Dose level | # of patients | Fraction and schedule | Total dose |
|------------|---------------|-----------------------|------------|
| 1          | 3             | 150 cGy BID × 4 days | 1200 cGy   |
| 2          | 6             | 175 cGy BID × 4 days | 1400 cGy*  |
| 3          | 3             | 200 cGy BID × 4 days | 1600 cGy*  |
| 4          | 7             | 200 cGy BID 4.5 days | 1800 cGy*  |
| 5          | 12            | 200 cGy BID × 5 days | 2000 cGy*  |

*Liver and spleen limited to 1200 cGy. Brain was treated with 1200 cGy in patients with ALL with history of positive CSF.

**C.** TMLI dose distribution colorwash map in a representative patient with AML who was treated at a TMLI dose of 2000 cGy.

**D.** Mean organ doses at each TMLI dose level for all patients (n = 31). G-CSF granulocyte colony stimulating factor.

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**Figure 1.** TMLI radiation therapy for haploidentical hematopoietic cell transplantation. (A) Study schema: patients received palifermin (60 μg/kg per day) for 3 days, starting on day -10 before stem cell infusion. PTCy was administered at 14.5 mg/kg per day on days -7 and -6. TMLI at the scheduled dose was delivered concurrently with fludarabine (25 mg/m² per day) for 5 days from day -7 to day -3. GvHD prophylaxis consisted of posttransplant cyclophosphamide (50 mg/kg per day) on days 1-3 and 1-4, GCSF (5 μg/kg) starting on day +5 and continued until days +1500, and tacrolimus and mycophenolate mofetil starting on day +5 and continued until days +90 and +35, respectively. (B) TMLI dose levels and number of patients accrued at each dose level. (C) TMLI dose distribution colorwash map in a representative patient with AML who was treated at a TMLI dose of 2000 cGy. (D) Mean organ doses at each TMLI dose level for all patients (n = 31). G-CSF granulocyte colony stimulating factor.
Table 1. Patient, disease and transplant characteristics

| Variable                          | Median (range) or N (%) |
|----------------------------------|-------------------------|
| **Patient sex**                  |                         |
| Female                           | 12 (39)                 |
| Male                             | 19 (61)                 |
| **Patient’s age at transplant (y)** | 37 (21-58)            |
| **Donor’s age at transplant (y), n = 30** | 29 (12-68)            |
| **Sex of donor/recipient**       |                         |
| Female/male                      | 7 (23)                  |
| Other                            | 24 (77)                 |
| **Number of mismatches**         | 5 (2-6)                 |
| **Disease diagnosis**            |                         |
| AML                              | 17 (65)                 |
| ALL                              | 13 (42)                 |
| MDS                              | 1 (3)                   |
| **Cytogenetic risk at diagnosis**|                         |
| AML*                             |                         |
| Intermediate                     | 8 (28)                  |
| Advance                          | 9 (29)                  |
| ALL†                             |                         |
| Favorable                        | 3 (10)                  |
| Unfavorable                      | 10 (32)                 |
| MDS‡                             |                         |
| High risk                        | 1 (3)                   |
| **Disease status before conditioning** |                   |
| AML/ALL                          |                         |
| CR1 with poor risk cytogenetics  | 14 (45)                 |
| CR2/CR3                          | 9 (29.5)                |
| Active disease                   | 7 (22.5)                |
| MDS                              |                         |
| High risk relapsed               | 1 (3)                   |
| **Time from diagnosis to transplant (mo)** | 7.1 (2.7-62.7)     |
| **Donor CMV status**             |                         |
| Negative                         | 11 (35)                 |
| Positive                         | 20 (65)                 |
| **Patient CMV status**           |                         |
| Negative                         | 4 (13)                  |
| Positive                         | 27 (87)                 |
| **HCT comorbidity index**        |                         |
| 0                                | 14 (45)                 |
| 1-2                              | 9 (29)                  |
| ≥3                               | 8 (26)                  |
| **Disease risk index**           |                         |
| Low                              | 1 (3)                   |
| Intermediate                     | 11 (35)                 |
| High                             | 12 (39)                 |
| Very high                        | 7 (23)                  |
| Karnofsky performance status at HCT |                  |
| ≥80                              | 31 (100)                |

AML cytogenetic risk classification was done per ELN recommendations.16
ALL cytogenetic risk classification was done per Moorman et al.17
MDS cytogenetic risk classification was done per Revised International Prognostic Scoring System (IPSS-R), Della Porta et al.18

Results

Patient and disease characteristics

We accrued 31 eligible patients from June 2015 to October 2018. Patient and transplant characteristics are summarized in Table 1. Median age at the time of HCT was 37 years (range, 21-58 years), with 5 (16%) patients being older than 50 years old at the time of HCT. All patients had Karnofsky performance status (KPS) of ≥80. HCT comorbidity index was ≥3 in 26% of patients (range, 0-6). Two patients presented with pre-HCT extramedullary disease (EMD); 1 at the left distal humerus and the other at the mediastinal mass. EMD at the time of HCT was recorded only in 1 patient with mediastinal mass-EMD. Patients were transplanted for AML (n = 17), ALL (n = 13), or MDS (n = 1). At the time of HCT, patients with AML and ALL were in first complete remission (CR) with poor risk cytogenetics (n = 14), or CR2/CR3 (n = 9), or had active disease (n = 7). The disease risk index was high/very high in 82% of treated patients (n = 19).

TMLI radiation therapy

TMLI was delivered to sculpt radiation dose to lymph nodes and bone/BM in each patient. (Figure 1C) Mean organ doses at each DL for each organ is shown in Figure 1D. The mean organ doses of TMLI at all DLS compared favorably with those reported with standard TBI of 1200 to 1320 cGy, where mean lung doses are approximately 900 cGy28 (Table 2).
Safety of TMLI for Haplo-HCT

Bearman toxicities for each DL are detailed in Table 3. At DL-5 (2000 cGy), 8 patients developed grade 1 and 1 patient developed grade 2 mucositis (stomatitis per Bearman toxicity scale), attributed to radiation and chemotherapy. Pulmonary toxicities were seen in 2 patients: 1 patient at DL-3 (1600 cGy) had grade 1, and the other patient at DL-4 had grade 3 pulmonary toxicity that was considered DLT. Six patients developed cardiac toxicities (4 had grade 1, and 2 had grade 2), 17 developed GI toxicities (12 had grade 1, and 5 had grade 2), and 8 developed hepatic toxicities (5 had grade 1, and 3 had grade 2).

Engraftment and HCT outcomes

Neutrophil recovery was achieved in 97% (95% CI: 91-100) of patients by day 28. All patients achieved neutrophil recovery at a median of 17 days (range, 13-38 days). Platelet recovery was achieved in 93% (n=28/30) of patients at a median of 28 days (range, 16-133 days), and 1 patient died at day +34 and therefore was not evaluable. This patient died of sinusoidal obstruction and was heavily pretreated for refractory AML with 5 prior salvage lines of therapy, including CD33 antibodies-drug conjugate.

Cumulatively, there were no deaths within the first 30 days after transplant and only 1 between days +30 and +100. The cumulative incidence of NRM at 100 days and 2 years were 3% (95% CI: 0.5-22) and 13% (95% CI: 5-33), respectively. Causes of death were disease relapse/progression (n=8), multiple organ failure (n=3, including the patient with sinusoidal obstruction), infection (n=1), and GVHD (n=1).

With the median follow-up of 23.9 months of the surviving patients, 12 patients relapsed, of whom only 4 received TMLI at the 2000-cGy dose. Extramedullary relapse was detected in the central nervous system without BM involvement in 1 patient at 29 months after HCT. None of the patients with pre-HCT-EMD presented with extramedullary relapse. All patients who were treated with 2000 cGy (n=12) achieved CR by day 30. With a median follow-up duration of 12.3 months among the surviving patients at DL-5, 1-year NRM, relapse, DFS, and OS rates were 9% (95% CI: 1-60), 17% (95% CI: 5-59), 74% (95% CI: 39-91), and 83% (95% CI: 46-95), respectively. See supplemental Table 2 for overall rates of survival (progression-free and overall), relapse/progression, and NRM in all patients at 1 and 2 years after HCT.

GVHD outcomes

The cumulative incidence of grade 2 to 4 and 3 to 4 acute GVHD (aGVHD) at day +100 were 52% (95% CI: 37-73) and 6% (95% CI: 2-25), respectively, with a median time to onset of 35 days (range, 4-112 days). Of the 23 patients who developed aGVHD, 87% were responsive to steroids.

Chronic GVHD (cGVHD) occurred in 10 of the 30 patients surviving beyond 100 days, with 4 patients having moderate to severe (2 moderate and 2 severe) disease by the National Institutes of Health consensus grading. By day +365, the cumulative incidence of cGVHD and moderate to severe cGVHD was 23% (95% CI: 12-45) and 10% (95% CI: 3-30), with the median time to onset being 308 days (range, 98-516 days). At the time of this report, none of the patients died because of complications of cGVHD.

Cumulative incidence of acute or cGVHD were not significantly different with higher TMLI doses when we compared $1800$ to $2000$ cGy for aGVHD, no vs yes, $P=0.52$; aGVHD, none-1 vs grade 2-4, $P=0.21$; cGVHD, no vs yes, $P=0.25$; Figure 2A-C). Specifically, there was no statistical difference in the cumulative incidence of GI aGVHD based on TMLI doses (53% vs 31%, $P=}$

| Grade | 1 2 1 2 1 2 1 2 1 2 | 1 2 1 2 1 2 1 2 1 2 |
|-------|---------------------|---------------------|---------------------|---------------------|
| Organ assessed | 1 2 1 2 1 2 1 2 1 2 | 1 2 1 2 1 2 1 2 1 2 |
| Bladder | 0 0 0 0 0 0 0 0 0 0 | 1 0 |
| Cardiac | 1 0 0 0 0 0 0 0 1 1 | 1 1 |
| CNS | 0 0 0 0 0 0 0 0 0 0 | 0 0 |
| GI | 1 1 1 1 0 0 2 3 0 0 | 7 2 |
| Hepatic | 1 1 1 1 0 0 2 3 0 0 | 2 0 |
| Pulmonary | 0 0 0 0 1 0 0 0 0 0 | 0 0 |
| Renal | 0 0 0 0 0 0 0 0 0 0 | 0 0 |
| Stomatitis | 0 2 1 0 0 0 0 2 1 0 | 8 1 |

*Dose-limiting toxicity.
Immune reconstitution, cytokine release syndrome, and infections

Cellular immune recovery was measured on days 30, 100, and 180 after HCT by flow cytometry (supplemental Figure 1). Cellular immune reconstitution was not impacted by the dose of radiation to the marrow/lymph nodes when we compared higher dose (≥1800 cGy) to lower dose (<1800 cGy) for each lymphocyte subset at the 3e abovementioned time points (supplemental Figure 1). Cytokine release syndrome (CRS) at any grade was developed in 30 patients (97%). None of the patients developed grade 3 to 4 CRS, 13 patients (43%) had grade 2, and the rest (57%) had grade 1 CRS.

Infectious complications were recorded from day 29 to day 110 and graded per The Blood and Marrow Transplant Clinical Trials...
Network (BMT CTN), version 4.03 (Table 4). Cytomegalovirus (CMV) viremia was detected in 21 patients (7 patients had G2 and 14 had G1). Other viral infections included respiratory infections (n = 9), BK virus cystitis (n = 7; all had grade 1), and Human Herpesvirus 6 (HHV-6) (n = 7; all but 1 has G1). Gram-positive and -negative bacterial infection were detected in 10 and 5 patients, respectively, and only 7 patients (all grade 1) developed C. difficile colitis.

**GVHD biomarker analysis**

Of the 6 GVHD biomarkers, levels of Reg3A\(^{30,31}\) were longitudinally evaluated and compared in patients undergoing TMLI at a higher dose (≥1800 cGy; n = 16) vs lower dose (<1800 cGy; n = 10). We observed no statistically significant difference in the Reg3A levels between high- and low-TMLI doses; however, there was a trend toward greater Reg3A levels in higher vs lower TMLI dose group on day 21 (median, 11504.1; range, 2836.4-37427.4 vs 8058.6; range, 2468.5-10742.4; P = .09; supplemental Figure 2).

We next examined the relationship between the TMLI dose and the dose delivered to the GI tract and found a positive dose correlation. We next examined the relationship between the TMLI dose and the dose delivered to the GI tract and found a positive dose correlation.

**BM recovery**

At 1-year after HCT, BM cellularity was in a normal range (~50%) in most cases (n = 5/7). There were no dose-dependent changes in BM cellularity. No obvious change was noted in vessel density between pre- and postirradiated marrows highlighted by CD34-IHC at 1200 and 1400 cGy; however, vessel density was increased between pre- and postirradiated marrows at higher DLs (1600, 1800, and 2000 cGy; supplemental Figure 4).

**Discussion**

In this phase 1 trial, consistent with our earlier experience with TMLI for matched related donor HCTs,\(^{11}\) we demonstrated that TMLI dose-sparing nonhematopoietic and uninvolved organs can be safely escalated to 2000 cGy when combined with haploHCT followed by PTCy and result in low rates of NRM on day 100 and 2 years. The rationale for not exceeding 2000 cGy was based on lung doses at this level, which were comparable to that of standard TBI using 50% lung transmission blocks. Our data indicated that 2000 cGy (RP2D) was clinically tolerable, with median doses delivered to the nontargeted healthy organs remaining below the corresponding doses delivered by TBI, leading to low incidence and grade of pulmonary, cardiac, GI, and hepatic toxicity.

Our study population was enriched with patients with high-risk disease characteristics including active disease (26%), high/very high disease risk index (62%), and unfavorable/adverse leukemia risk by cytogenetic and molecular markers (65%); however, 1-year relapse rate in the R2PD cohort was promising. EMD relapse is a potential concern with TMLI, particularly in patients with extramedullary disease before transplant. In our study, only 1 patient (3%), who did not have pre-HCT-EMD, was presented with EMD relapse. CRS rate in this trial was consistent with our institutional rate.\(^{32}\) Despite of the short follow-up period, short-term outcomes indicated that optimizing the conditioning regimen intensity could overcome the arguably higher rate of relapse described in earlier reports in this population.\(^{3,4}\)

The escalated radiation dose to the BM from 1200 to 2000 cGy did not impact the recovery of hematopoiesis, confirmed by excellent engraftment rates. When we compared patients receiving lower and higher TMLI doses, immune cell subsets recovery was not significantly impacted by TMLI dose. Immune reconstitution and infection rates/severity were similar between our study and what has been reported in patients undergoing haploHCT with PTCy.\(^{33}\)

Gut radiation dose has been linked to severe GI tissue destruction, resulting in more antigen presentation and higher incidence and severity of GVHD.\(^{34}\) In our study, with increasing TMLI doses, there was a subsequent increase in gut radiation dose. However, the incidence and severity of GvHD was comparable to published data in PBSCT-haploHCT with PTCy platform.\(^{4,35}\) These comparable outcomes could be because of the sparing/lower dose of radiation to the gut during conditioning in our study. In fact, when we measured plasma levels of Reg3A as a marker of gut injury and GVHD, we could not find a correlation between levels of Reg3A and TMLI or gut dose.

Although increasing BM targeted radiation may increase therapeutic benefit, potential damage and delayed recovery of BM environment elements (eg, hematopoietic stem cells and vasculature) become essential as reported earlier.\(^{36}\) In this cohort, we evaluated BM cellularity at 1 year, most cases were found to be as expected after transplant and according to patient age, with increased vessel density when higher doses of TMLI were administered, which was of unknown significance/impact. This secondary evaluation of trephine biopsy sample, although limited, suggest normal BM recovery. Further studies are in process to measure details of BM recovery with a larger sample size. Moreover, immune reconstitution, infection rates, and severity were similar to what has been reported in this population using PTCy as GVHD prophylaxis.\(^{33}\) In addition, recovery of immune cellular subsets were not significantly impacted by dose escalation for TMLI when we compared patients receiving lower and higher TMLI doses.

In conclusion, our data indicate that TMLI-based conditioning regimen is safe and feasible in the setting of PBSC HaploHCT. We successfully delivered higher doses of radiation to the marrow without increasing the organ toxicity. In this high-risk patient population,

**Table 4. Infection outcomes per CTN grading**

| Category | <1800 cGy | ≥1800 cGy |
|----------|-----------|-----------|
| **Bacterial** | | |
| C. difficile | 2 | 0 | 0 | 5 | 0 | 0 | 7 |
| Gram negative | 1 | 1 | 0 | 1 | 2 | 0 | 5 |
| Gram positive | 4 | 1 | 0 | 1 | 4 | 0 | 10 |
| **Viral** | | |
| BK | 3 | 0 | 0 | 4 | 0 | 0 | 7 |
| CMV | 7 | 3 | 0 | 7 | 4 | 0 | 21 |
| HHV6 | 2 | 0 | 1 | 4 | 0 | 0 | 7 |
| HSV | 1 | 0 | 0 | 1 | 0 | 0 | 2 |
| Respiratory | 1 | 3 | 1 | 0 | 3 | 1 | 9 |
| **Fungal** | | |
| Mold | 0 | 0 | 0 | 0 | 0 | 1 | 2 |
| Yeast | 0 | 0 | 0 | 0 | 0 | 2 | 2 |
promising results with low disease relapse was achieved without increasing rates of GVHD or TRM compared with standard prepara-
tive regimens. Given the small sample size of our phase 1 trial
(n = 31), we did not have the power to investigate the benefit of
our TMLI regimen according to the disease (AML vs ALL). However,
Areas for improvement based on confirmed safety profile of TMLI and short-term HCT outcomes of efficacy, we are currently accruing patients on a phase 2 study (#NCT04262843), using our RP2D of 2000 cGy in the setting of HaploHCT with PTCy. Our phase 2 trial has been designed to investi-
gate the efficacy of TMLI at 20 Gy in 2 separate arms of (1) patients with AML or MDS and (2) patients with ALL.

Last, the delivery of TMLI requires intensity-modulated radiation therapy technology, specifically arc or helical delivery of intensity-modulated radiation therapy. These technologies are installed in almost all hospital-based radiation oncology programs and are also in community-based practices. At City of Hope, we deliver TMLI using equipment from Accuray, Inc. (Tomotherapy) and Varian, Inc. (TrueBeam), which is available in the United States, Europe, Asia, Central America, and South America. Efforts are currently being made to extend the TMLI platform to other centers at national and international levels.

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Authorship
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ORCID: M.M.A.M., 0000-0001-8226-471X; H.A., 0000-0002-9728-7292; T.S., 0000-0001-5292-8298; R.N., 0000-0002-9082-0680.

Correspondence: Monzr M. Al Malki, Department of Hematology and Hematopoietic Cell Transplantation, City of Hope National Medical Center, 1500 E. Duarte Rd, Duarte, CA 91010; e-mail: malmalki@coh.org.

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