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Dose Escalation of Total Marrow Irradiation with Concurrent Chemotherapy in Patients with Advanced Acute Leukemia Undergoing Allogeneic Hematopoietic Cell Transplantation

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Abstract

Purpose—We have demonstrated that toxicities are acceptable with total marrow irradiation (TMI) 16 Gy without chemotherapy or TMI 12 Gy and the reduced intensity regimen of fludarabine/melphalan in patients undergoing hematopoietic cell transplantation (HCT). This study reports on TMI combined with higher intensity chemotherapy regimens on two phase I trials in patients with advanced AML/ALL who would do poorly on standard intent-to-cure HCT regimens.

Methods—Trial 1: TMI on days -10 to -6, VP16 day -5 (60 mg/kg), and cyclophosphamide (CY) day -3 (100 mg/kg). TMI dose (Gy) was 12 (n=3), 13.5 (n=3) and 15 (n=6) at 1.5 Gy BID. Trial 2: Busulfan (BU) days -12 to -8 (800 uM min), TMI days -8 to -4, and VP16 day -3 (30 mg/kg). TMI dose (Gy) was 12 (n=18) and 13.5 (n=2) at 1.5 Gy BID.

Results—Trial 1: 12 patients; median age 33; 6 induction failure (IF), 6 first relapse (1RL); 9 with marrow blasts (10–98%), 5 with circulating blasts (24–85%) and 2 with chloromas. No dose limiting toxicities were observed. Eleven achieved CR at day 30. With a median follow-up 14.75

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months, 5 remain in complete remission from 13.5–37.7 months. **Trial 2:** 20 patients; median age 41; 13 IF, 5 1RL, 2 in 2nd relapse; 19 with marrow blasts (3–100%) and 13 with peripheral blasts (6–63%). Grade 4 dose limiting toxicities were seen at 13.5 Gy (stomatitis and hepatotoxicity). Stomatitis was the most frequent toxicity in both trials.

Conclusions—TMI dose escalation to 15 Gy is possible when combined with CY/VP16 and is associated with acceptable toxicities and encouraging outcomes. TMI dose escalation is not possible with BU/VP16 due to dose-limiting toxicities. Future efforts will focus on whether further dose escalation with CY/VP16 is safe with the goal of improving disease control in this high risk population.

Keywords

total marrow irradiation; bone marrow transplantation; total body irradiation; tomotherapy; acute leukemia

INTRODUCTION

Total body irradiation (TBI) continues to be an important part of conditioning regimens in patients undergoing hematopoietic cell transplantation (HCT). Several randomized trials have demonstrated superior outcomes using TBI compared to non-TBI containing regimens (1). Randomized phase II trials have also demonstrated reduced relapse rates in AML and CML with higher TBI doses (2,3). However, overall survival was unchanged due to an increase in toxicities and treatment related mortality rates. A more targeted form of TBI delivery is therefore needed to allow for dose escalation with acceptable toxicity with the potential to improve outcomes. Recently, we reported on the concept of using a Tomotherapy Hi-Art System to deliver a more targeted, conformal form of TBI, referred to as total marrow irradiation (TMI) (4,5). The initial trial evaluated TMI without concurrent chemotherapy and demonstrated the feasibility to escalate TMI alone to 18 Gy before dose limiting toxicities were observed (6). A subsequent trial at our institution demonstrated that combining TMI at 12 Gy with the reduced intensity chemotherapy regimen of fludarabine (FLU) and melphalan (MEL) was associated with acceptable toxicities in patients undergoing allogeneic HCT who were not eligible for standard TBI regimens due to age (> 50) or co-morbidities (7).

Current trials at our institution are evaluating TMI combined with concurrent higher-intensity chemotherapy conditioning regimens in a younger patient population (< 55) with acute leukemia but who would not benefit from standard HCT regimens because of advanced or refractory disease (8), which is the subject of this report.

PATIENTS AND METHODS

Patient characteristics

The first 32 patients treated from June 2007 to July 2010 with TMI on two separate Phase I trials combining TMI with either cyclophosphamide and etoposide (CY/VP16) or busulfan and etoposide (BU/VP16) are the subjects of this report. Both trials defined acute toxicities as those occurring in the first 30 days after HCT. Dose limiting toxicities were defined as

any grade 4 toxicity by the NCI Common Toxicity Criteria (CTC) version 3 or grade 3 toxicity using the Bearman Toxicity Scale for bone marrow transplantation. Both trials were approved by the Institutional Review Board.

Trial 1: Phase I trial of TMI, cyclophosphamide and etoposide (CY/VP16)

This trial entered patients with ALL who were not in first or second remission. After the MTD for trial 2 (see below) was reached, trial 1 was subsequently amended to also allow entry of patients with AML who were not in first or second remission. Patients were primarily those who were induction failures, in relapse or beyond second remission and therefore not eligible for and would do poorly on other intent-to-cure HCT regimens. Patients were required to be > 21 days post last induction or reinduction and > 6 and < 55 years of age. Prior HCT was not allowed. Prior etoposide, cyclophosphamide, or busulfan was allowed. All patients required a donor from a HLA matched identical sibling, or a 10/10 allele matched unrelated donor. One allele mismatch was allowed. Other entry criteria included: a cardiac ejection fraction of 50%; serum creatinine 1.2 or creatinine clearance > 80 ml/min; DLCO and FEV1 > 50% predicted; and total bilirubin < 1.5 and liver transaminases no greater than five times upper limit of normal.

The conditioning regimen consisted of TMI on days -10 to -6, etoposide at 60 mg/m² intravenously on day -5, and cyclophosphamide at 100 mg/kg intravenously on day -3. Tacrolimus and sirolimus were used for graft versus host disease (GVHD) prophylaxis and palifermin used for mucositis prophylaxis. Established institutional supportive care regimens were utilized to manage nausea, vomiting and infection risks. For the first 100 days after discharge, patients were followed at least weekly with complete differential blood counts and comprehensive metabolic panel. Bone marrow biopsies were performed at approximately 30 days, 100 days and 1 year after HCT. Patients were evaluable for chronic GVHD at or beyond 100 days post HCT.

Trial 2: Phase I trial of TMI, busulfan and etoposide (BU/VP16)

Entry criteria and trial design were identical to that of Trial 1 with the exception that patients with ALL were excluded and palifermin was not routinely administered in all patients. The conditioning regimen consisted of TMI on days -8 to -4, targeted intravenous busulfan at AUC 800 uM*min on days -15 to -9, and etoposide at 30 mg/kg intravenously on day -3.

TMI Technique

Both phase I trials planned for TMI dose escalation in cohorts of 3 to 6 patients per standard phase I trial design. The first three dose levels were defined as 12 Gy, 13.5 Gy and 15 Gy delivered at 1.5 Gy BID over 4 to 5 days. The methodology used to deliver TMI at this institution has been previously described in detail (4,5,9). All patients were treated on a TomoTherapy Unit (Accuray, Inc. Sunnyvale, CA). The lower extremities were treated on a conventional C-arm linear accelerator through standard AP-PA fields.

Two categories of target structures were defined. For bone, major lymph node chains, and testes, the target dose was escalated for each dose level (12, 13.5 and 15 Gy). The remaining target structures were kept at 12 Gy at each dose level and included spleen and splenic-hilar

lymph nodes, liver and porta-hepatic lymph nodes, ribs, sternum, brain and skull, in part to minimize additional dose to lung and minimize pneumonitis risks. Avoidance structures or organs at risk (OAR) were defined as orbits, lens, thyroid, oral cavity, mandible, parotids, larynx, hypopharynx, esophagus, lungs, heart, breast, kidneys, stomach, small and large intestine, rectum and bladder. Plans were designed such that a minimum of 85% of the target structure received the prescribed dose.

TMI treatment planning utilized an organ/target optimization sequence that first optimized dose avoidance to critical organs while the target dose uniformity constraint was relaxed. For the second phase of optimization, the organ doses were kept at a low level while the target dose uniformity was improved by gradually increasing target dose importance and maximum dose penalty. This optimization sequence resulted in lower critical organ doses with acceptable target dose uniformity when compared to our earlier TMI planning approaches which would first optimize target dose uniformity, followed by critical organ dose optimization. A color wash dose distribution of a patient treated on trial 1 is shown (Figure 1).

Statistical Methods

Demographic, disease and treatment characteristics were generated using descriptive statistics. Non-relapse mortality (NRM) was measured from transplant to death from any cause other than disease relapse or disease progression. Non-relapse-related mortality and relapse-related mortality were considered competing risks for mortality.

RESULTS

Trial 1: Phase I trial of TMI + cyclophosphamide and etoposide

Of 12 patients on this trial, 5 had AML, 6 ALL, and 1 mixed lineage; 6 were induction failures and 6 were in first relapse (Supplemental Table 1). Median age was 31 years of age (range: 21–54). Most had advanced disease prior to HCT. Nine had persistent bone marrow blasts ranging from 10–98% involvement (median 58%), 5 had detectable peripheral blasts ranging from 24–85%, and an additional 2 patients had chloromas in the soft tissue or CNS. None had received prior radiotherapy.

TMI doses of 12 Gy were delivered to 3 patients, 13.5 Gy to 3 patients, and 15 Gy to 6 patients. Organ doses are reported as Dx which is the dose to x% of the organ volume. D80, D50 and D10 doses to organs felt to be potentially dose limiting (lung, heart, oral cavity, esophagus, kidneys and small intestine) remained relatively constant with TMI dose escalation with the exception of increases in D10 doses for esophagus and oral cavity (table 1). The median (D50) OAR doses (supplemental table 2) to the lens, eyes and oral cavity were approximately 15–35% of the prescribed dose, and esophagus, lung, kidney and GI tract approximately 35–45% of the prescribed dose. Although the target regions were large and complex in shape, the dose distribution was relatively uniform within each target region as seen with the target structure D80, D50 and D10 doses shown in Gy (table 1) or as a percent of the prescribed dose (supplemental table 3).

Acute toxicities observed during the first 30 days are shown in Table 2. The regimen was relatively well tolerated at 12 and 13.5 Gy. At 15 Gy there was an increase in toxicities with all patients experiencing NCI CTC v3 grade 3 mucositis and fatigue. However, dose limiting toxicities were not observed.

Table 3 summarizes the outcomes for all patients in trial 1. Median follow-up was 14.75 (range: 2.0–37.7) months for all patients and 22.7 (13.5–37.7) months for living patients. Eleven of 12 patients demonstrated complete remission on bone marrow biopsies at day 30. Three of 12 patients experienced acute GVHD (2 grade II and 1 grade III). Six of 9 evaluable patients experienced chronic GVHD, which was extensive in 5 patients.

Six patients have died. Four have died of disease at 2.7, 5.5, 5.6 and 26.3 months. Two died of non-relapse causes. One died of epidermal necrolysis secondary to dilantin within the first 100 days for a 100 day non-relapse mortality rate of 8%. A second patient died at 9.2 months from chronic GVHD. Six patients remain alive, one with disease at 24.7 months and 5 patients (3 ALL, 1 AML, 1 mixed lineage) in complete remission at 13.5 to 37.7 months. Of the five in continuous complete remission, all had significant tumor burden; 3 with 30–80% marrow blasts and 2 with chloromas. The longest survivor who remains in remission at 37.7 months is a 21 year old male with ALL presenting in first relapse with 80% blasts in the marrow.

Trial 2: Phase I trial of TMI + busulfan and etoposide

Of the 20 patients entered, 13 were induction failures, 5 were in first relapse and 2 were in second relapse (Supplemental Table 1). Median age was 41 years of age (range: 23–52). Most had advanced disease prior to HCT. Nineteen had persistent bone marrow blasts ranging from 3–100% involvement (median 50%) and 13 had detectable peripheral blasts ranging from 6–63% (median 12%). None had received prior radiation therapy. Target and OAR doses were similar to those observed in trial 1 (supplemental tables 2 and 3).

Acute toxicities observed during the first 30 days are shown in Table 2. Acute toxicities were greater compared to TMI/CY/VP16 on trial 1. At 12 Gy all 3 patients experienced NCI CTC grade 3 mucositis. At 13.5 Gy dose limiting toxicities were observed for both patients treated at that dose level, with one patient experiencing reversible hepatic veno-occlusive disease and the second patient NCI CTC grade 4 mucositis requiring intubation. As a result additional patients entered received 12 Gy. Although no further dose limiting toxicities were observed, 12 of the 15 additional patients experienced NCI CTC grade 3 mucositis.

Table 4 summarizes the outcomes for all patients on trial 2. Median follow-up was 7.3 (range: 0.7–49.4) months for all patients and 29.0 (20.8–49.4) months for living patients. As with trial 1 a high percentage (17 of 18) achieved complete remission on day 30 bone marrow biopsies. Ten of 20 patients experienced acute GVHD (5 grade II and 4 grade III–IV). Seven of 14 evaluable patients experienced chronic GVHD, which was extensive in 6 patients.

Five patients remain alive and in complete remission at 20.8 to 49.4 months. Fifteen patients have died. Seven died of disease at 1.1 to 15.2 months. Eight patients died of non-relapse

causes, of which 4 died within the first 100 days (3 multi-organ failure and 1 pulmonary complications from infection) for a 100 day non-relapse mortality rate of 20%. The remaining 4 died of non-relapse causes beyond 100 days (2 from chronic GVHD and 2 from infections).

DISCUSSION

Image-guided intensity modulated radiotherapy technologies allow for the delivery of highly conformal dose distributions to large complex target shapes making it ideally suited for the delivery of TMI. We reported the first patient treated with this approach as part of a Phase I tandem autologous HCT trial (4). This trial evaluated toxicities associated with TMI with no concurrent chemotherapy. Dose limiting toxicities were not observed until a TMI dose of 18 Gy, establishing the maximum tolerated dose (MTD) at 16 Gy.

We recently demonstrated that TMI at 12 Gy combined with the reduced intensity regimen of fludarabine and melphalan was associated with acceptable toxicities in patients who would normally not tolerate standard TBI regimens due to age (> 50) or co-morbidities (7). The treatment related mortality rate at one year was 19% which compared favorably to the 30–40% rates reported for fludarabine and melphalan alone (10–12).

The two trials reported here expand upon the scope of the TMI HCT experience at this institution. These trials evaluated the most aggressive TMI-chemotherapy dose escalation regimens to date at this center in patients with advanced acute leukemia who had no option for and would do poorly on standard intent-to-cure HCT regimens.

Trial 1 demonstrated that escalating TMI doses up to 15 Gy combined with cyclophosphamide and etoposide was associated with acceptable toxicities. Dose-limiting toxicities were not observed. Further escalation of TMI dose with this schedule is therefore possible. Responses observed in this poor prognosis population with persistent marrow and peripheral blasts were encouraging. Also encouraging was a non-relapse mortality rate in the first 100 days of 8% and 17% total. This compares favorably to previous studies using TBI (10–12 Gy), cyclophosphamide and etoposide which have reported treatment related mortality rates of 37–50% (13,14).

TMI dose escalation when combined with busulfan and etoposide in a similar population resulted in dose limiting toxicities (Table 2) preventing dose escalation. The increased toxicities are likely related to the use of busulfan. Although complete remission rates were comparable to trial 1, this trial is now closed given the inability to escalate TMI dose.

The toxicities from these trials are compared to TMI trials previously reported from this institution (Table 5). The addition of concomitant chemotherapy significantly increased toxicities, with mucositis being the most significant. Grade 3 mucositis was not observed with TMI alone (6), but increased to 58–85% with the addition of chemotherapy. In addition dose limiting NCI grade 4 and Bearman grade 3 toxicities were seen with the BU/VP16 and FLU/MEL (7) regimens making TMI dose escalation not possible. TMI dose escalation was only possible on trial 1 with the CY/VP16 regimen, possibly due to the chemotherapy regimen used.

The routine use of palifermin on trial 1 may have further reduced mucositis compared to the other TMI trials but is probably not the main factor permitting dose escalation. In the pivotal randomized palifermin trial (15), the incidence of grade 3/4 mucositis with palifermin and TBI 12 Gy/CY/VP16 was still 63% compared to only 1 of 6 on trial 1 with TMI 12–13.5 Gy/CY/VP16, suggesting that the use of TMI was the more important factor. To date we have not seen a correlation between the degree of mucositis and dose to esophagus and oral cavity for a given dose level. This suggests that further refinements in treatment planning are unlikely to substantially reduce mucositis risks.

Questions have been raised as to whether organ sparing may lead to sparing of cancer cells or reduction of the immunosuppression needed for allogeneic HCT. To date all patients have successfully engrafted and there does not appear to be a higher incidence of extramedullary recurrences compared to patients undergoing standard TBI regimens at this center. A corollary to this is whether TMI should be used in patients with known extramedullary disease prior to HCT. For patients with limited extramedullary sites, target structures can include these sites. For patients with extensive extramedullary risk, such as those with skin involvement, modifying the dose distribution similar to standard TBI where the target organ becomes the total body minus defined avoidance structures, such as lung, have been reported and should be considered (16,17).

Since we reported the first patient treated using this technique (4), other groups have reported on their early TMI experience(17–20). Techniques have differed from those reported here and include using Tomotherapy to also sculpt dose to bones of the lower extremities, to deliver dose using a standard TBI dose distribution, or to add TMI as a single fraction boost to standard TBI. Clinical trials will hopefully determine which dose distributions are best for a given patient population.

To our knowledge, the collective institutional experience reported here represents the largest experience of using TMI as part of HCT conditioning regimens reported to date. Based on this experience, a primary advantage of TMI is the ability to escalate target dose with acceptable toxicities and the potential to improve outcomes. A second advantage is that TMI, through a reduction in toxicities, can increase the number of patients able to tolerate radiation conditioning regimens, such as older patients (greater than age 50) or, those with co-morbidities (6).

CONCLUSION

TMI continues to demonstrate promise as a method to escalate dose with acceptable toxicities beyond that achievable with standard TBI. The results reported here demonstrate that TMI can be combined with higher-intensity chemotherapy regimens and that dose escalation to at least 15 Gy with cyclophosphamide and etoposide is possible with acceptable toxicities and encouraging outcomes in very advanced poor risk patients. Future plans are to evaluate whether further escalation of TMI dose in combination with cyclophosphamide and etoposide is safe and to begin to evaluate whether dose escalation can potentially improve disease control in this high risk population.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

1. Hartman AR, Williams SF, Dillon JJ. Survival, disease-free survival and adverse effects of conditioning for allogeneic bone marrow transplantation with busulfan/cyclophosphamide vs. total body irradiation: a meta-analysis. *Bone Marrow Transplant.* 1998; 22:439–443. [PubMed: 9733266]
2. Clift RA, Buckner CD, Appelbaum FR, et al. Allogeneic marrow transplantation in patients with chronic myeloid leukemia in the chronic phase: A randomized trial of two irradiation regimens. *Blood.* 1991; 77:1660–1665. [PubMed: 2015394]
3. Clift RA, Buckner CD, Appelbaum FR, et al. Long-term follow-up of a randomized trial of two irradiation regimens for patients receiving allogeneic marrow transplants during first remission of acute myeloid leukemia. *Blood.* 1998; 92:1455–1456. [PubMed: 9694737]
4. Wong JYC, Liu A, Schultheiss T, et al. Targeted total marrow irradiation using three-dimensional image-guided tomographic intensity-modulated radiation therapy: An alternative to standard total body irradiation. *Biol Blood Marrow Transplant.* 2006; 12:306–315. [PubMed: 16503500]
5. Schultheiss TE, Wong J, Liu A, et al. Image-guided total marrow and total lymphatic irradiation using helical tomotherapy. *Int J Radiat Oncol Biol Phys.* 2007; 67:1259–1267. [PubMed: 17336225]
6. Somlo G, Spielberger R, Frankel P, et al. Total Marrow Irradiation: A new ablative regimen as part of tandem autologous stem cell transplantation for patients with multiple myeloma. *Clin Cancer Res.* 2011; 17:174–182. [PubMed: 21047977]
7. Rosenthal J, Wong J, Stein A, et al. Phase 1/2 trial of total marrow and lymph node irradiation to augment reduced-intensity transplantation for advanced hematologic malignancies. *Blood.* 2011; 117:309–315. [PubMed: 20876852]
8. Duval M, Klein JP, He W, et al. Hematopoietic stem-cell transplantation for acute leukemia in relapse or primary induction failure. *Journal of Clinical Oncology.* 2010; 28:3730–3738. [PubMed: 20625136]
9. Wong JYC, Rosenthal J, Liu A, et al. Image guided total marrow irradiation (TMI) using helical tomotherapy in patients with multiple myeloma and acute leukemia undergoing hematopoietic cell transplantation (HCT). *Int J Radiat Oncol Biol Phys.* 2009; 73:273–279. [PubMed: 18786784]
10. Giralt S, Thall PF, Khouri I, et al. Melphalan and purine analog-containing preparative regimens: reduced intensity conditioning for patients with hematologic malignancies undergoing allogeneic progenitor cell transplantation. *Blood.* 2001; 97:631–637. [PubMed: 11157478]
11. Giralt S, Aleman A, Anagnostopoulos A, et al. Fludarabine/melphalan conditioning for allogeneic transplantation in patients with multiple myeloma. *Bone Marrow Transplant.* 2002; 30:367–373. [PubMed: 12235521]
12. Ritchie DS, Morton J, Szer J, et al. Graft-versus-host disease, donor chimerism, and organ toxicity in step cell transplantation after conditioning with Fludarabine and Melphalan. *Biol Blood Marrow Transplant.* 2003; 9:435–442. [PubMed: 12869957]
13. Giralt SA, LeMaistre CF, Vriesendorp HM, et al. Etoposide, cyclophosphamide, total-body irradiation, and allogeneic bone marrow transplantation for hematologic malignancies. *Journal of Clinical Oncology.* 1994; 12:1923–1930. [PubMed: 8083714]
14. Brown RA, Wolff SN, Fay JW, et al. High-dose etoposide, cyclophosphamide and total body irradiation with allogeneic bone marrow transplantation for resistant acute myeloid leukemia: a

- study by the North American Marrow Transplant Group. *Leuk Lymphoma*. 1996; 22:271–277. [PubMed: 8819076]
15. Spielberger R, Stiff P, Bensinger W, et al. Palifermin for oral mucositis after intensive therapy for hematologic cancers. *N Engl J Med*. 2004; 351:2590–2598. [PubMed: 15602019]
 16. Zhuang AH, Liu A, Schultheiss TE, et al. Dosimetric study and verification of total body irradiation using helical tomotherapy and its comparison to extended SSD technique. *Medical Dosimetry*. 2010; 35:243–249. [PubMed: 19944588]
 17. Penagaricano JA, Chao M, van Rhee F, et al. Clinical feasibility of TBI with helical tomotherapy. *Bone Marrow Transplant*. 2011; 46:935.
 18. Hui SK, Verneris MR, Higgins P, et al. Helical tomotherapy targeting total bone marrow - First clinical experience at the University of Minnesota. *Acta Oncol*. 2007; 46:250–255. [PubMed: 17453378]
 19. Shueng PW, Lin SC, Chong NS, et al. Total marrow irradiation with helical tomotherapy for bone marrow transplantation of multiple myeloma: first experience in Asia. *Technology in Cancer Research & Treatment*. 2009; 8:29–38. [PubMed: 19166240]
 20. Corvo R, Zeverino M, Vagge S, et al. Helical tomotherapy targeting total bone marrow after total body irradiation for patients with relapsed acute leukemia undergoing an allogeneic stem cell transplant. *Radiother Oncol*. 2011; 98:382–386. [PubMed: 21339008]

SUMMARY

Total marrow irradiation (TMI) is associated with reduced doses to normal organs compared to standard TBI. Results reported here demonstrate that TMI dose escalation to 15 Gy combined with cyclophosphamide and etoposide is associated with acceptable toxicities and encouraging outcomes in patients with advanced, refractory acute leukemia undergoing bone marrow transplantation. Studies to evaluate further dose escalation and whether this translates into improved control rates and survival in this high risk population are warranted.

Figure 1.

Dose distribution color wash of a patient treated on trial 1, dose level 3. Target structures bone, lymph nodes, and testes received 15 Gy and spleen and splenic-hilar lymph nodes, liver and porta-hepatic lymph nodes, ribs, sternum, brain and skull received 12 Gy in 10 fractions BID over 5 days.

Table 1
Mean (range) of D80, D50 and D10 Doses to Critical Organs at Risk and Target Structures in Trial 1

Organ at Risk	D80 (Gy)			D50 (Gy)			D10 (Gy)		
	12 Gy (n=3)	13.5 Gy (n=3)	15 Gy (n=6)	12 Gy (n=3)	13.5 Gy (n=3)	15 Gy (n=6)	12 Gy (n=3)	13.5 Gy (n=3)	15 Gy (n=6)
Esophagus	4.1 (4.0-4.3)	4.1 (3.8-4.2)	4.2 (3.6-4.8)	4.8 (4.8-5.3)	5.0 (4.1-5.5)	5.2 (4.1-6.1)	6.5 (5.0-8.0)	7.6 (6.1-8.5)	9.2 (6.3-12.5)
Oral Cavity	2.6 (2.3-2.8)	4.1 (2.0-5.3)	3.4 (2.1-6.3)	2.9 (2.7-3.1)	5.3 (2.6-6.8)	4.2 (3.0-7.7)	5.1 (4.0-6.2)	8.4 (4.9-10.2)	8.8 (5.0-12.7)
Lungs	5.1 (4.7-5.6)	4.8 (4.4-5.5)	4.6 (3.8-5.0)	6.3 (5.6-6.6)	6.6 (5.9-7.3)	6.0 (5.1-6.8)	10.2 (10.1-10.4)	10.4 (9.8-10.7)	10.2 (9.4-11.5)
Small Intestine	4.8 (4.0-5.8)	4.7 (4.1-5.6)	4.7 (3.9-5.1)	6.1 (4.9-7.3)	6.6 (6.2-7.3)	6.2 (5.0-7.5)	10.5 (9.3-11.9)	11.6 (11.3-11.9)	10.7 (9.9-12.9)
Kidneys	6.0 (5.7-6.2)	4.2 (3.9-4.5)	5.1 (4.2-5.6)	7.7 (6.9-8.1)	5.5 (5.1-6.1)	6.2 (4.9-7.1)	11.5 (11.0-12.0)	10.4 (9.1-11.3)	10.6 (10.1-11.2)
Heart	6.0 (5.4-6.6)	6.0 (5.4-6.4)	4.7 (4.0-5.2)	7.5 (6.3-8.3)	8.0 (6.9-8.7)	6.2 (5.4-7.1)	10.4 (8.9-11.5)	11.0 (9.6-11.8)	10.5 (9.6-11.7)
Target Organs									
Bone	12.1 (12.0-12.2)	12.5 (12.2-12.9)	13.1 (12.5-14.0)	13.6 (13.5-13.6)	13.9 (13.8-14.0)	14.1 (14.0-14.2)	15.2 (15.0-15.3)	15.7 (15.4-16.1)	16.1 (15.8-16.4)
Lymph Nodes	12.1 (12.0-12.1)	12.6 (12.2-13.0)	13.1 (12.5-13.9)	13.6 (13.4-13.7)	13.9 (13.7-14.0)	14.1 (13.9-14.2)	14.9 (14.3-15.2)	15.6 (15.4-15.9)	16.0 (15.7-16.4)
Spinal Cord	12.1 (11.8-12.5)	12.8 (12.2-13.6)	13.3 (12.6-14.1)	13.2 (13.1-13.4)	13.5 (13.3-13.6)	13.7 (13.6-13.9)	14.9 (14.3-15.0)	15.4 (15.2-15.9)	15.9 (15.7-16.4)
Liver	12.3 (11.9-12.7)	12.8 (12.2-13.6)	13.3 (12.6-14.1)	12.2 (12.0-12.3)	12.5 (12.4-12.6)	12.9 (12.8-13.0)	12.2 (11.9-12.5)	12.7 (12.6-13.0)	13.3 (13.0-13.5)
Spleen	12.3 (12.0-12.7)	12.7 (12.2-13.4)	13.2-12.6-14.1)	12.3 (12.2-12.3)	12.4 (12.3-12.5)	12.6 (12.4-12.7)	12.1 (11.5-12.5)	12.8 (12.6-13.2)	13.5 (12.9-14.5)
Ribs/sternum	11.8 (11.2-12.3)	12.5 (12.2-12.8)	13.1 (12.7-13.8)	12.0 (12.0-12.1)	12.5 (12.3-12.6)	12.9 (12.7-13.0)	13.2 (12.0-12.7)	13.0 (12.6-13.4)	14.0 (13.3-14.8)
Brain	11.9 (11.8-11.9)	12.1 (12.0-12.2)	12.3 (12.2-12.5)	11.9 (11.7-12.1)	12.2 (12.1-12.3)	12.6 (12.5-12.7)	12.1 (11.8-12.4)	12.5 (12.2-12.8)	12.7 (12.6-13.0)
Skull	11.9 (11.7-12.1)	12.0 (12.0-12.1)	12.3 (12.1-12.4)	12.2 (12.0-12.3)	12.3 (12.1-12.4)	12.5 (12.4-12.8)	12.3 (12.0-12.6)	12.5 (12.4-12.8)	12.7 (12.6-13.0)

Table 2

Toxicities Observed in First 30 Days

	Trial 1 TMI + CY + VP16			Trial 2 TMI + BU+ VP16	
	12 Gy (n = 3)	13.5 Gy (n = 3)	15 Gy (n = 6)	12 Gy (n = 18)	13.5 Gy (n = 2)
NCI Grade 3					
Mucositis	1		6	15	1
Fatigue	1	1	6	15	2
Anorexia	1	2	4	6	
Nausea	1		3	8	
Vomiting			1	2	
Diarrhea				3	
NCI Grade 4 or Bearman Grade 3					
					1 - mucositis 1 - hepatic (SOS *)

* sinusoidal obstructive syndrome

Table 3

Trial 1 Clinical Summary

Pt	Age/sex	TMI Dose (Gy)	Dx	Status	Type of Transplant	% Peripheral Blasts	% BM Blasts	Disease Status @ Day 30	Acute GVHD Grade	Chronic GVHD	Outcome	NRM @ 100 days	Survival (months)
1	44F	12	ALL	IF	MR	51	80	CR	None	Extensive	Relapse DOD	-	26.3
2	21M	12	ALL	1RL	MR	0	80	CR	None	Extensive	Remission Alive	-	37.7
3	34M	12	Mixed lineage	IF	MR	0 Chloromas	0	CR	None	None	Remission Alive	-	25.7
4	20M	13.5	ALL	1RL	MR	0	0	CR	II	Extensive	Relapse AWD	-	24.7
5	24F	13.5	ALL	1RL	MR	0	10	CR	None	None	Relapse DOD	-	5.5
6	53M	13.5	AML	IF	MMU	85	98	CR	II	Extensive	Remission Died from cGVHD	-	9.2
7	35M	15	ALL	1RL	MR	0	30	CR	None	Limited	Remission Alive	-	20.7
8	54F	15	AML	1RL	MMU	70	80	CR	None	NE	Relapse DOD	-	5.6
9	31F	15	AML	IF	MMU	24	58	Persistent Disease	None	NE	Persistent Disease DOD	-	2.7
10	31F	15	ALL	IF	MR	0	50	CR	III	Extensive	Remission Alive	-	16
11	22F	15	AML	1RL	MR	0 Chloromas in CNS	0	CR	None	None	Remission Alive	-	13.5
12	50F	15	AML	IF	MMU	58	40	CR	None	NE	Remission Died from Toxic Epidermal Necrolysis	+	2.0

MR = matched related; MU = matched unrelated; MMU = mismatched unrelated; IF = induction failure; 1RL = first relapse; 2RL = second relapse; CR = complete remission; NA = not available; NE = not evaluable; DOD = Dead of Disease; AWD = alive with disease; NRM = non-relapse mortality

Table 4

Trial 2 Clinical Summary

Pt	Age/sex	TMI Dose (Gy)	Dx	Status	Type of Transplant	% Peripheral Blasts	% BM Blasts	Disease Status @ Day 30	Acute GVHD	Chronic GVHD	Outcome	NRM @ 100 days	Survival (months)
1	34M	12	AML	IF	MR	0	0	CR	II	Extensive	Remission Alive	–	49.4
2	40F	12	AML	IRL	MR	12	60	CR	II	Extensive	Remission Died of cGVHD/ infection	–	9.3
3	52M	12	AML	IF	MR	0	18	CR	None	Extensive	Remission Alive	–	29
4	43M	13.5	AML	IF	MR	41	42	Progressive disease	None	NE	Dead with active disease	+ MOF	1.1
5	29F	13.5	AML	IF	MU	0	100	CR	None	NE	Died of regimen related toxicity	+ Pulmonary	1.4
6	33M	12	AML	IRL	MR	0	6	CR	III	Extensive	Remission Alive	–	38.4
7	51F	12	AML	IF	MMU	6	5	CR	II	Extensive	Died of cGVHD	–	10.7
8	47F	12	AML	2RL	MU	8	17	CR	None	Extensive	Remission Alive	–	22.7
9	30M	12	AML	IF	MR	8	60	CR	II	None	DOD	–	15.3
10	52F	12	AML	IF	MMU	6	8	CR	None	None	DOD	–	9.8
11	49M	12	AML	IRL	MU	0	81	CR	None	Limited	Remission Alive	–	20.8
12	44F	12	AML	IF	MU	63	50	CR	III	None	Remission Died of infection	–	14.4
13	28M	12	AML	IF	MR	0	3	CR	None	None	DOD	–	5.3
14	46M	12	AML	IRL	MU	8	50	CR	II	NE	DOD	–	1.8
15	32F	12	AML	IF	MR	57	80	CR	None	None	DOD	–	4.5
16	42M	12	AML	IRL	MU	52	95	NE	IV	NE	Died of regimen related toxicity (MOF/aGVHD)	+ MOF	0.8
17	35M	12	AML	2RL	MMU	0	41	CR	I	NE	DOD	–	2.0
18	37M	12	AML	IF	MR	49	85	CR	None	None	DOD	–	4.3
19	47F	12	AML	IF	MR	19.	60.	NE	None	NE	Died of regimen related toxicity (MOF/infection)	+ MOF	0.7
20	23F	12	AML	IF	MMU	7	60	CR	IV	None	Remission Died of infection/ cGVHD	–	4.3

MR = matched related; MU = matched unrelated; MMU = mismatched unrelated; IF = induction failure; IRL = first relapse; 2RL = second relapse; CR = complete remission; NA = not available; NE = not evaluable; DOD = Dead of Disease; AWD = alive with disease; NRM = non-relapse mortality; MOF = multi-organ failure

Table 5

Toxicities First 30 days

	Trial 1 (CY/VP16/TMI)		Trial 2 (BU/VP16/TMI)		FLU/MEL/TMI*	MEL → TMI ⁺
TMI Dose (Gy)	12.0, 13.5, or 15.0		12.0 or 13.5		12	10, 12, 14, 16, or 18
Target Organs	Bone, major lymph node chains, spleen, liver, brain, testes		Bone, major lymph node chains, spleen, liver, brain, testes		Bone, major lymph node chains, spleen If ALL: brain, testes	Bone
Chemotherapy	Cyclophosphamide (CY) + Etoposide (VP16)		Busulfan (BU) + Etoposide (VP16)		Fludarabine (FLU) + Melphalan (MEL)	Melphalan (MEL)
Palifermin Used	Yes		No		No	No
Type of Transplant	Allogeneic		Allogeneic		Allogeneic	Tandem autologous
No. of patients	12		20		47	31
Diagnosis	AML, ALL, mixed lineage		AML		AML, ALL, NHL, MDS, CML	MM
Median Age (range)	33 (21–54)		41 (23–52)		55 (12–68)	53 (35–66)
Day 30 Grade 3 Toxicities (NCI CTC)	Nausea 4 (33%) (3 at 15 Gy) Vomiting 1 (8%) (1 at 15 Gy) Mucositis 7 (58%) (6 at 15 Gy) Esophagitis 0 Diarrhea 0		Nausea 9 (45%) Vomiting 1 (5%) Mucositis 17 (85%) Esophagitis 1 (5%) Diarrhea 3 (15%)		Nausea 26 (55%) Vomiting 13 (28%) Mucositis 28 (60%) Esophagitis 2 (4%) Diarrhea 27 (57%)	Nausea 3 (10%) (2 at 18 Gy, 1 at 16 Gy) Vomiting 0 Mucositis 0 Esophagitis 0 Diarrhea 1 (3%) (1 at 18 Gy) Pulmonary 1 (6%) at 18 Gy DLT Hypotension 1 (6%) at 18 Gy DLT
Day 30 NCI CTC v3 Grade 4 or Bearman grade 3 Toxicities	none		Mucositis 1 (5%) at 13.5 Gy Ileus & VOD 1 (5%) at 13.5 Gy		Pulmonary 5 (11%) Renal 4 (9%) Bladder 1 (2%) CNS 1 (2%) Cardiac 2 (4%)	none
Non-relapse mortality at 100 days	1 (8%) (at 15 Gy)		4 (20%) (2 at 13.5 Gy)		7 (15%)	none

* 33 patients previously reported (6)

⁺ 22 patients previously reported (7)