Biologic and Image Guided Systemic Radiotherapy

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Abstract

Radiotherapy has traditionally been used as a therapy directed to the primary site of disease to achieve local and regional control. This role is rapidly changing with radiotherapy now playing an integral part of systemic therapy in patients with metastatic disease. Stereotactic body radiotherapy to each oligometastatic site is now actively being evaluated as a means to more definitively control disease and contribute to a longer progression free interval. Irradiation of a tumor site can result in clinically important immuno-modulatory systemic effects which when combined with certain immunotherapy agents can result in abscopal responses at unirradiated sites harboring macroscopic and microscopic disease. Technological advances have now made the delivery of targeted systemic radiotherapy a reality. Systemic radiotherapy can be biologically guided as in the case of radiolabeled peptide analogs or immunologically guided as in the case of radiolabeled antibodies directed against tumor associated antigens. Recent advances in intensity modulated radiation therapy allow for radiation dose sculpting to the entire body resulting in a more targeted form of total body irradiation, also referred to as total marrow irradiation. This targeting is CT image guided to a specific anatomic region, but in the future is expected to incorporate PET and MRI based functional imaging allowing for systemic

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radiotherapy which is biologically guided based on the unique physiologic, phenotypic and genotypic properties of the tumor. This chapter will summarize the progress, current state and future directions of targeted systemic radiotherapy. The treatment of hematopoietic malignancies is used to illustrate important principles which are applicable to other malignant conditions.

Keywords
Total marrow irradiation · Radioimmunotherapy · Total body irradiation · Bone marrow transplantation

1 Introduction

Radiation therapy has traditionally been utilized as a local regional therapy to optimize local control at the primary site or at a symptomatic site of metastatic disease. This treatment paradigm is rapidly changing with radiotherapy now playing a critical role as an integral part of systemic therapy in patients with metastatic disease. For example, a distinct subset of patients with oligometastatic disease is now recognized, with disease characterized by lower tumor burden, limited metastatic sites, and a longer timeline towards progression (Weichselbaum and Hellman 2011). Stereotactic body radiotherapy (SBRT) to each tumor site is now actively being evaluated as a means to more definitively control macroscopic disease and contribute to a longer progression free interval in this population (Salama et al. 2008). Irradiation of a tumor site in patients with metastatic disease can result in clinically important immuno-modulatory systemic effects which when combined with certain immunotherapy agents can result in abscopal immune responses at unirradiated sites harboring macroscopic and microscopic disease (Formenti and Demaria 2012, 2005).

Technological advances have now made the delivery of targeted systemic radiotherapy a reality. Systemic radiotherapy can be targeted to cancer cells at the cellular level. These can be biologically guided as in the case of radiolabeled peptide analogs to somatostatin in the treatment of neuroendocrine tumors, or immunologically guided as in the case of radiolabeled antibodies directed against tumor associated antigens expressed by solid tumors and hematopoietic malignancies, also known as radioimmunotherapy (RIT) (Jurcic et al. 2016).

Recent advances in intensity modulated radiation therapy (IMRT) delivery systems allow for radiation dose targeting and sculpting to the entire body resulting in a more targeted form of total body irradiation (TBI), also referred to as total marrow irradiation (TMI) (Wong et al. 2006, 2009; Schultheiss et al. 2007). This targeted form of systemic radiotherapy is image guided and to specific anatomic regions identified on CT, but in the future is expected to incorporate PET and MRI based functional imaging allowing for image guided targeted systemic radiotherapy to also be biologically guided based on the unique physiologic, phenotypic and

genotypic properties of the tumor. This chapter will summarize the progress, current state and future directions of targeted systemic radiotherapy. Although the treatment of hematopoietic malignancies is used as an example, the principles outlined are applicable to other malignancies.

2 Total Body Irradiation: The Earliest Form of Systemic Radiotherapy

Total body irradiation (TBI) is one of the earliest forms of systemic radiotherapy and understanding its potential benefits and limitations provides the basis for developing new more targeted systemic radiotherapy approaches. TBI is a non-conformal, non-targeted form of systemic radiotherapy and was initially evaluated as a single modality therapy in patients with advanced leukemias, lymphomas and solid tumors. The first leukemia patient was treated with TBI in 1927 (Teschendorf 1927). In 1932 a specially designed room for TBI was developed at Memorial Sloan Kettering (Heublein 1932). In the 1950s units specifically designed to deliver TBI were developed at the Naval Medical Research Unit in Bethesda (Draeger et al. 1953), Oak Ridge National Laboratories (Hayes et al. 1964; Andrews et al. 1962) and City of Hope (Jacobs and Pape 1960, 1961). Jacobs and Marasso at City of Hope reported their four year experience treating 52 patients with advanced acute and chronic leukemia, Hodgkin's and non-Hodgkin's lymphoma, multiple myeloma and a variety of solid tumors (Jacobs and Marasso 1965). Doses as low as 40 cGy resulted in palliation of symptoms in patients with leukemia. Pancytopenia was dose limiting and five patients received autologous or allogeneic marrow reinfusion.

The first use of TBI as part of the conditioning regimen for hematopoietic cell transplant (HCT) delivered the dose in a single fraction and was reported by Thomas et al. (1959). Although engraftment was successful, relapse occurred within 12 weeks suggesting that TBI alone was insufficient to prevent relapse. Since then chemotherapy, usually cyclophosphamide (Cy) has been combined with TBI. Since these initial pioneering efforts, TBI continues to be an important part of conditioning regimens in patients undergoing HCT. In a recent survey of the Center for International Blood and Transplant Research (CIBMTR) Database which surveyed 596 centers in 52 countries and included 219341 patients, TBI was utilized in 46% of patients undergoing allogeneic and 10% of autologous HCT (Hong et al. 2012). The primary indications for HCT in acute myelogenous leukemia (AML) and acute lymphoblastic leukemia (ALL) are patients in first remission with intermediate to high risk features, induction failure, relapse, or in second remission or beyond. Patients with myelodysplastic syndrome (MDS) with high risk features or evolving to an acute state are also candidates for HCT. Patients with chronic myelogenous leukemia (CML) and chronic lymphocytic leukemia (CLL) undergo HCT much less frequently given the efficacy of current systemic therapies.

A primary role of TBI as part of the conditioning regimen just prior to HCT is the eradication of malignant cells. In patients undergoing allogeneic HCT, TBI also provides a powerful means of immunosuppression to prevent rejection of donor hematopoietic cells. TBI offers distinct advantages compared to chemotherapy. Unlike chemotherapy, delivery of radiation therapy to the tumor site is not dependent on blood supply or influenced by inter-patient variability of drug absorption, metabolism, biodistribution, or clearance kinetics. Radiation therapy can reach potential sanctuary sites, such as testes and brain. Chemotherapy resistant clones that develop may still be sensitive to irradiation.

The available data demonstrate that application of the same radiobiologic principles successfully employed for conventional field radiotherapy, such as fractionation, hyperfractionation, and organ shielding, have also helped to improve the therapeutic ratio of TBI with reduced toxicities and improved outcomes (Deeg et al. 1986; Girinsky et al. 2000; Labar et al. 1992; Shank et al. 1990). The effect of dose-rate appears to be modest above 5 centigray (cGy)/minute and diminishes if TBI is fractionated as opposed to a single fraction (Travis et al. 1985; Tarbell et al. 1987; Sampath et al. 2005; Weiner et al. 1986; Ozsahin et al. 1992). Typical TBI schedules today deliver a total dose of 10–16 (Gray) Gy at 1.2–1.35 Gy per fraction three times per day, 1.5–2 Gy per fraction twice a day or 3–4 Gy per fraction once a day with a minimum of 4–6 h between fractions. Patients are usually treated at extended SSD (source to skin distance) to encompass the entire body in a single field. As a result dose-rates are in the range of 5–30 cGy/minute. Many centers utilize lung shielding to reduce median lung doses to 8–10 Gy and reduce the incidence of pneumonitis. Others have utilized renal shielding to reduce long term nephrotoxicity (Rhoades et al. 1997). Hepatic shielding has been attempted by some groups to reduce hepatotoxicity especially when TBI is combined with busulfan (Bu) (Einsele et al. 2003) although one group in a small series of patients concluded that this may increase relapse rates due to under treatment of disease (Anderson et al. 2001).

Non-TBI chemotherapy only conditioning regimens offer no obvious advantage in reducing toxicities or improving control rates compared to TBI containing regimens, and in some randomized trials have been shown to be inferior (Blaise et al. 1992; Dusenbery et al. 1995; Ringden et al. 1996; Bunin et al. 2003). Most studies have compared TBI-Cy to the BuCy regimens. Hartman et al. (1998) performed a meta-analysis of 5 published randomized trials. Survival and disease free survival were better with TBI-based regimens compared to BuCy although the differences were not statistically significant. A significantly greater incidence of sinusoidal obstructive syndrome (SOS) (also known as veno-occlusive disease) was observed with the BuCy regimens. Recently, Gupta et al. (2011) performed a meta-analysis of seven randomized HCT trials involving 730 patients with leukemia randomized between BuCy and TBI-Cy. TBI-Cy was associated with a modest but non-significant reduction in all cause mortality and relapse rates. Since the early randomized trials utilized suboptimal dosing of busulfan, more recent comparison studies have been done. In a prospective cohort comparison study of 1483 patients, patients undergoing intravenous BU regimens experienced a statistically significant

increase in 2 year overall survival (OS) compared to those undergoing a TBI containing conditioning regimen. The survival difference was only seen for early stage AML and not seen for intermediate or advanced AML, CML or MDS, and hepatotoxicity was greater with IV-Bu (Bredeson et al. 2013).

TBI containing and chemotherapy only conditioning regimens have traditionally been myeloablative. Myeloablative regimens are associated with a treatment related mortality (TRM) or no-relapse mortality (NRM) rate of about 20–30%. In a recent summary report of the CIBMTR of patients undergoing a myeloablative regimens prior to HLA matched allogeneic HCT, the main cause of death was relapse of primary disease (48%) but treatment related causes including graft versus host disease (GVHD), infection, and organ failure accounted for 17, 14 and 5% of deaths, respectively. As a result older patients (greater than age 55–60) or patients with co-morbidities are often not able to tolerate standard myeloablative TBI containing regimens.

As a result non-myeloablative (NMA) and reduced intensity conditioning (RIC) regimens have been developed which utilize lower chemotherapy or TBI doses (Deeg and Sandmaier 2010). These regimens are usually associated with fewer acute toxicities, are primarily used as a method of immunosuppression to allow engraftment of donor cells and rely more on graft versus tumor (GVT) effects to eradicate disease. RIC and NMA regimens offer a larger spectrum of patients a HCT option, but being less myeloablative can be associated with increased relapse rates. For example, in a recent multi-center phase III randomized trial, 272 patients, age 18–65 years old with AML in first remission or with MDS, were randomized to either a myeloablative or RIC regimen (Scott et al. 2015). With the RIC group the relapse rate was significantly higher (48.3% vs. 13.5%, $p < 0.01$) and the relapse free survival (RFS) rate was significantly lower (47.3% vs. 67.7%, $p < 0.01$), resulting in an 18 month overall survival difference of 67.7% versus 77.4% ($p = 0.07$).

3 Rationale for Targeted Systemic Radiotherapy and TBI

Targeted forms of TBI and systemic radiotherapy have the potential to significantly reduce organ dose and associated acute and late toxicities. With regards to TBI and HCT, several groups have demonstrated a reduction in radiation related complications with reduction in dose to critical normal organs including pneumonitis, nephrotoxicity and cataract formation (Fig. 1) (Sampath et al. 2005; Cheng et al. 2008; Hall et al. 2015). This could also potentially reduce TRM rates of radiation condition regimens allowing for a broader spectrum of patients to undergo radiation containing conditioning regimens, including patients who are older or those with co-morbidities who would otherwise not tolerate standard TBI.

RIC regimens can be associated with increased relapsed rates as noted earlier. Attempts to add TBI to RIC chemotherapy regimens to improve relapse rates have been challenging because of additional toxicities. For example Petropolous et al.

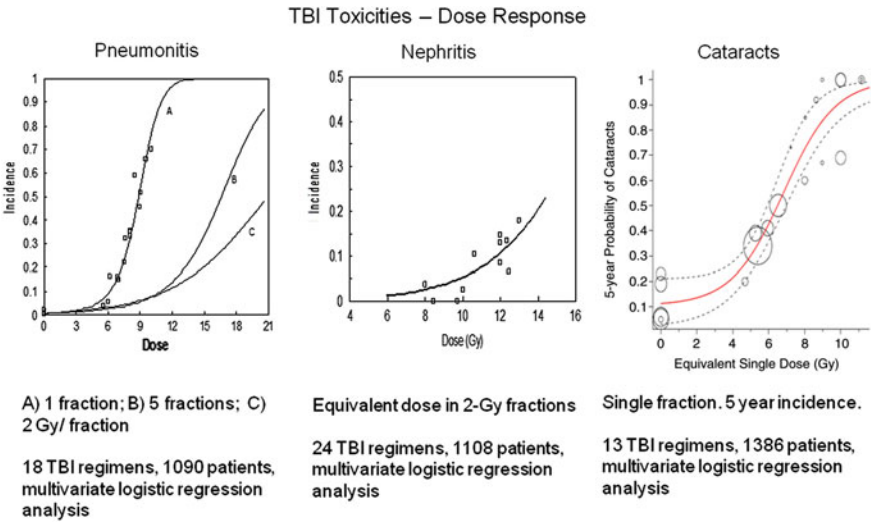

Fig. 1 Select examples of radiation dose-toxicity curves demonstrating that a reduction in dose to normal organs is associated with a decrease in late organ toxicities such as pneumonitis, nephritis and cataract formation (Sampath et al. 2005; Cheng et al. 2008; Hall et al. 2015)

(2006) reported that combining 9 Gy (3 Gy/day) TBI with the RIC regimen fludarabine (Flu) and melphalan (Mel) was not possible in adults because of increased mucositis. More targeted forms of TBI combined with RIC may be better tolerated and may potentially improve relapse rates compared to RIC chemotherapy regimens alone.

The primary reason for a more targeted form of TBI is to improve the therapeutic ratio by reducing normal organ dose and toxicities allowing for the potential to increase dose to tumor and improve long term outcomes. The available clinical data indicate that there is a dose response for most cancers including acute leukemia. Chloromas (also known as granulocytic or myeloid sarcomas) are extramedullary tumors of myeloid leukemia cells. Although relatively radiosensitive, Chak et al. (1983) demonstrated local control rates at 2 Gy per day of approximately 20% at doses less than 10 Gy, 40% at doses of 10–20 Gy and over 80% at doses of >20 Gy. They recommended a dose of 30 Gy at 2 Gy per day for optimal local control. More recently, Bakst et al. observed only one local failure at 6 Gy and recommended at least 20–24 Gy at 2 Gy/day (Bakst and Wolden 2012).

A dose response relationship has also been observed with the TBI experience. Two randomized phase II single institution trials have compared Cy combined with 12 Gy at 2 Gy/day or 15.75 Gy at 2.25 Gy/day. In a trial of 116 patients with CML in chronic phase, the higher dose resulted in a significantly lower relapse rate (0% vs. 25% $p = 0.008$), but higher treatment related mortality rate (24% 12 Gy and 34% 15.75 Gy, $p = 0.13$), and as a result no significant change in overall survival (Clift et al. 1991). In a separate report of 71 patients with AML in first

remission, relapse rate was also decreased with the higher dose (14% vs. 39% $p = 0.06$), but these gains were offset by an increase in TRM rate (38% vs. 19%, $p = 0.05$), resulting in no difference in overall survival between the two arms (Clift et al. 1998). The increase in TRM rate was due to an increase in lung, liver and mucous membrane toxicities (Appelbaum et al. 1992). In several retrospective reports from the group in Genoa (Scarpati et al. 1989), relapse rate and survival was significantly decreased if TBI dose was >9.9 Gy (3.3 Gy/day). In an analysis of the CIBMTR and City of Hope Cancer Center databases, Marks et al. (2006) reported that patients with ALL beyond first remission receiving TBI-CY conditioning regimens had a lower relapse rate and increased disease free survival if the TBI dose was $\geq$13 Gy. Finally, Kal et al. (2006), compared results of different TBI regimens published in three randomized trials, four studies comparing results of two to three TBI regimens, and nine studies reporting on one TBI regimen. Using linear-quadratic principles, a biologically effective dose (BED) was calculated for each TBI regimen to normalize for differences in dose per fraction, number of fractions and dose-rates of the different regimens. Higher BED values were associated with a lower relapse rate and higher disease-free survival and overall survival rates.

In summary, despite use of fractionated schedules and organ shielding, escalation of TBI dose has been difficult due to dose-limiting normal tissue toxicities. This has limited total doses of most TBI conditioning regimens to approximately 16 Gy or less. Gains in disease control with TBI dose escalation are associated with an increase in regimen related toxicities and non-relapse mortality in some studies, resulting in no improvement in overall survival. New more targeted strategies are clearly needed to allow further dose escalation without associated increase in side effects. With regards to HCT, two targeted systemic radiotherapy strategies have been evaluated in the clinic and are discussed below, biologically targeted radioimmunotherapy (RIT) and image guided-IMRT based total marrow irradiation (TMI).

4 Radioimmunotherapy: Biologically Targeted Systemic Radiotherapy

Radioimmunotherapy (RIT) is a form of targeted systemic radiotherapy that utilizes monoclonal antibodies or related immunoconstructs linked to radionuclides. Radiolabeled antibodies have been evaluated as a form of therapy in solid tumors and hematopoietic malignancies. A number of detailed reviews on this topic have been published (Jurcic et al. 2016; Speer 2013). This section will focus on the use of RIT as a form of targeted TBI for leukemia.

The majority of the experience has been with antibodies targeting CD20 on B cells in patients with non-Hodgkin's lymphoma. RIT has also been applied to other hematopoietic malignancies including leukemia. Table 1 lists the antigens that

Table 1 Radioimmunotherapy target antigens in acute leukemia

Target	Disease	Expressed by
CD33	Myeloid leukemia	Promyelocytes to mature myeloid cells AML blasts (not ALL blasts) Not hematopoietic stem cells or ALL blasts
CD45	AML, ALL	Virtually all hematopoietic stem cells except plasma cells 90% of AML and ALL
CD66	AML, ALL	Mature myeloid and monocytic cells Not on AML blasts (relies on cross-fire effect)
CD22	ALL	B-cell acute lymphoblastic leukemia

Table 2 Radionuclides used in RIT of acute leukemia

Radionuclide	Particles emitted	Half life	Energy (MeV)	Path length	Comments
Iodine-131 (^{131}I)	β, γ	8.1 days	0.6	0.8 mm	Dehalogenation
Yttrium-90 (^{90}Y)	β	2.7 days	2.3	2.7 mm	Goes to bone, liver
Rhenium-188 (^{188}Re)	β, γ	17 h	2.1	2.4 mm	Goes to kidney
Bismuth-213 (^{213}Bi)	α, γ	46 min	6.0	84 μm	Requires fast targeting
Actinium-225 (^{225}Ac)	α, γ	10 days	8	50–80 μm	Difficult to generate

radiolabeled antibodies have been developed against to target AML and ALL. Table 2 lists the radionuclides that have been linked to these antibodies and evaluated in clinical trials.

Selection of the appropriate radionuclide for RIT is based on availability, half-life, energy path length, and ease of labeling to the antibody. ^{131}I is both a β and γ emitter. The γ emission allows for imaging and assessing biodistribution of the RIT. The β energy emission provides the therapeutic RIT effect. The disadvantage is that γ radiation travels far and increases exposures to normal tissues as well as to surrounding medical personnel. ^{131}I will also disassociate from the antibody, a process called dehalogenation, especially if the antibody is internalized into the cell after antigen binding, which reduces radiation dose to the target cell.

^{90}Y is a radiometal commonly used in RIT and is a pure β emitter. The mean β emission range is approximately 2.7 mm compared to 0.8 mm for ^{131}I ^{90}Y β emissions travel only a few mm and thus mainly affect the cells which are targeted or adjacent malignant cells through what is termed a cross-fire effect. To monitor biodistribution of ^{90}Y RIT requires the co-administration of the same antibody radiolabeled with the γ-emitting radiometal ^{111}In which allows for visualization biodistribution by planar and SPECT imaging. Some have hypothesized that the path length of ^{90}Y β emissions are too long for the treatment of microscopic disease although there are no clinical data to date to support this.

α emitters are the most recent radioisotope to be exploited. α emitters have higher linear energy transfer (LET) than either γ or β emitters. In addition, the effective range of α emitter's effect is shorter (range of 40–80 μM) thus potentially further reducing the normal toxicity and potentially making it more suitable for the treatment of microscopic disease. The utilization of α-emitters has been limited by their availability and short half-life.

RIT directed against CD33 has been evaluated as single modality therapy in pilot and phase I trials in acute myeloid leukemia. The CD33 antigen is a 67-kD glycoprotein expressed on most myeloid leukemias and leukemia progenitors but not on normal stem cells. Anti-CD33 RIT has been developed and evaluated using the murine M195 and the HuM195 (lintuzumab) humanized antibodies by the group at Memorial Sloan-Kettering Cancer Center (MSKCC). A phase I trial at MSKCC reported on the feasibility of administering ^{131}I-CD33 antibodies (M195 and HuM195) in 31 patients and demonstrated that dose escalation to 135 mCi/m^2 achieved myelosuppression and allowed 8 patients to proceed to bone marrow transplant, with three patients remaining in complete remission at 59, 87, and 90 months (Burke et al. 2003). Rosenblat et al. (2010) evaluated HuM195 anti-CD33 radiolabeled with the α-emitter ^{213}Bi administered after cytarabine in a Phase I/II trial in patients with newly diagnosed, refractory or relapsed AML. The RIT agent was shown to be tolerable at all dose levels. Although 77% of patients had >20% decrease in marrow blasts with the addition of RIT compared to only 40% with cytarabine alone, the response rate was only 19% at the maximum tolerated dose (MTD) of 37 MBq/kg with a median duration of response of 6 months. Due to the short half life of ^{213}Bi, HuM195 has recently been evaluated in a phase I trial labeled with the α-emitter ^{225}Ac by the same group with an overall response rate of 29% reported (Jurcic et al. 2015).

RIT has also been evaluated as part of conditioning regimens in patients with leukemia undergoing allogeneic HCT. RIT has been combined with established myeloablative or reduced intensity regimens. Table 3 lists select trials that have combined RIT with non-TBI conditioning regimens. Marrow doses have ranged from 3 to 47 Gy with mean marrow doses depending on the agent ranging from 11–36 Gy at the MTD. Almost all trials have demonstrated the feasibility of combining RIT with established conditioning regimens and acceptable TRM rates. Results have been are encouraging, although the experience to date has been limited to phase I and II trials, at a limited number of centers, and in a relatively small number of patients.

Combining RIT with TBI containing regimens has also been evaluated and has demonstrated the limits of dose escalation (Table 4). Matthews et al. (1999) combined ^{131}I-BC8 anti-CD45 RIT with the myeloablative conditioning regimen of 12 Gy TBI and Cy is a phase I trial. RIT was escalated based on estimated dose to the bone marrow. One case of non-engraftment occurred with the combination of 12 Gy TBI and 31 Gy RIT. A RIT marrow dose of 24 Gy in combination with 12 Gy TBI was determined to be the MTD. Bunjes et al. (2002) combined ^{188}Re labeled anti-CD66 RIT with myeloablative conditioning regimen which included TBI to 12 Gy. This agent has greater biodistribution and dose to kidney than other

Table 3 Select hct trials combining RIT with myeloablative or reduced intensity conditioning regimens

First Author year	Antibody (target)	No.	Disease	HCT	Marrow dose (Gy)	Response	Toxicities
Burke et al. (2003) Phase I	^{131}I-M195 or Hu195 (CD33)	31	AML relapsed AML refractory CML-AP MDS advanced	Bu/Cy	2.72–14.7	3 CR 59 + , 87 + , and 90 + months	TRM 65%
Pagel et al. (2006) Phase I/II	^{131}I-BC8 (CD45)	46	AML CR1	Bu/Cy	5.3–19 Mean 11.3	3 yr DFS 61%	3 yr TRM 21%
Pagel et al. (2009) Phase I	^{131}I-BC8 (CD45)	58	AML advanced MDS high risk Age >50	RIC: Flu + TBI (2 Gy)	6.3–46.9 At MTD 36	1 yr OS 41%	1 yr TRM 22%
Mawad et al. (2014) Phase I	^{131}I-BC8 (CD45)	58	AML advanced MDS high risk Age <50	RIC: Flu + TBI (2 Gy)	12–43.3 Mean 27	1 yr OS 73% 1 yr RFS 67%	1 yr TRM 0%
Koenecke et al. (2008) Phase I/II	^{188}Re-BW 250/183 (CD66)	21	AML high risk MDS advanced	Bu/Cy or RIC	4.95–21.3 Mean 10.9	DFS 43% median follow-up 42 months	1 yr TRM 28.6%
Ringhoffer et al. (2005) Phase I/II	^{188}Re- or ^{90}Y-BW 250/183 (CD66)	20	AML, MDS Age 55–65	Flu + ATG or Mel	21.9 ± 8.4	1 yr OS 70% 2 yr OS 52%	Cumulative TRM 25%
Lauter et al. (2009) Phase II	^{188}Re-BW 250/183 (CD66)	22	AML advanced Age >54	RIC: Flu/Bu/campath		2 yr OS 40% 2 yr DFS 41%	2 yr TRM 23%

HCT hematopoietic cell transplantation; *RIT* radioimmunotherapy; *AML* acute myelogenous leukemia; *CML-AP* chronic myelogenous leukemia in acute phase; *MDS* myelodysplastic syndrome; *CR* complete remission; *CR1* first complete remission; *Bu* busulfan; *Cy* cyclophosphamide; *RIC* reduced intensity conditioning regimen; *Flu* fludarabine; *TBI* total body irradiation; *Gy* Gray; *ATG* anti-thymocyte globulin; *Mel* melphalan; *DFS* disease free survival; *RFS* relapse free survival; *OS* overall survival; *TRM* treatment related mortality

Table 4 Select HCT Trials Combining RIT and TBI (12 Gy)

First Author year	Antibody (target)	No.	Disease	HCT	RIT marrow dose (Gy)	Response	Toxicities
Appelbaum et al. (1992) Phase I	^{131}I-p67 (CD33)	4	AML Relapse, second CR	Cy/TBI (12 Gy)	1.7–5.56	3 of 4 CR 195–477 days	Low marrow doses
Matthews et al. (1999) Phase I	^{131}I-BC8 (CD45)	44	AML, ALL beyond first remission	Cy/TBI (12 Gy)	4–31 24 at MTD	AML: 7/25 (28%) NED 15-89 months ALL: 3/9 NED at 23, 58, 70 months	One engraftment failure at 31 Gy RIT + 12 Gy TBI
Bunjes (2002) Phase I/II	^{188}Re-BW 250/183 (CD66)	57	High risk AML and MDS $\underline{<}$25% marrow blasts	Cy/TBI (12 Gy) TBI/Cy/TT Bu/Cy	15.5 ± 5.1	DFS 54% DFS 64% (n = 44) if $\underline{\leq}$15% blasts DFS 8% (n = 13) if >15% blasts	14% late renal toxicity Radiation nephropathy in 6 patients (4/6 if > 12 Gy) 26 month TRM 30%
Zenz et al. (2006) Phase I	^{188}Re-BW 250/183 (CD66)	20	Ph + ALL advanced CML	Bu/Cy or Cy/TBI (12 Gy) kidney shielded to 6 Gy	13.3 ± 1.1	4 yr OS 29% relapse rate cumulative 40%	1 yr TRM 20%

HCT hematopoietic cell transplantation; *RIT* radioimmunotherapy; AML = acute myelogenous leukemia; ALL = acute lymphoblastic leukemia; CML = chronic myelogenous leukemia; MDS = myelodysplastic syndrome; CR = complete remission; CR1 = first complete remission; NED = no evidence of disease; Bu = busulfan; Cy = cyclophosphamide; TT = thiotepa; TBI = total body irradiation; Gy = Gray; DFS = disease free survival; OS = overall survival; TRM = treatment related mortality

agents. Late renal toxicity was seen in 14% and in 4 of 6 patients if the total renal dose exceeded 12 Gy. Renal toxicity was reduced in a subsequent study of the same agent when renal shielding was utilized with TBI (Zenz et al. 2006).

RIT as a form of targeted systemic radiotherapy and a form of targeted TBI for acute leukemia patients undergoing HCT is theoretically attractive with encouraging results and acceptable toxicities, yet challenges still remain. The availability of these agents, expertise and resources needed to perform myeloablative RIT is limited to only a few centers. The technology is therefore currently not easily exportable for wide use making further clinical evaluation of these agents beyond the phase I and II trial setting difficult. There is inter-patient variability in the biodistribution and pharmacokinetics for these agents. In many trials, a small subset of patients does not receive the therapy infusion after demonstrating suboptimal biodistribution of the pre-therapy infusion. Although the amount of administered radioactivity and agent is determined by the treating physician, the actual radiation doses to the intended target sites and organs is not and can vary from patient to patient adding a degree of uncertainty to the anticipated toxicities and efficacy.

5 Total Marrow Irradiation: Image Guided Systemic Targeted Radiotherapy

5.1 Background and Rationale

Recent technological advances in radiotherapy systems now allow for the delivery of a image guided IMRT to large regions of the body allowing for more targeted forms of TBI and therefore targeted whole body or systemic radiotherapy. These new forms of image guided targeted TBI are often referred to as total marrow irradiation (TMI). The Tomotherapy HiArt System® was the first system used to deliver targeted TMI. Tomotherapy integrates CT image-guided radiotherapy and helical delivery of IMRT in a single device. Specifically, a 6 MV linear accelerator is mounted on a CT ring gantry and rotates around the patient as the patient translates through the ring. The maximum target size possible is approximately 60 cm in width by approximately 160 cm in length (Beavis 2004). More recently, other groups have successfully used linear accelerators with volumetric arc-based image guided IMRT (also referred to as VMAT) capabilities to deliver TMI (Han et al. 2011; Aydogan et al. 2011; Fogliata et al. 2011; Patel et al. 2014).

The first delivery of TMI as part of the conditioning regimen in patients undergoing autologous or allogeneic HCT began in 2005 (Wong et al. 2006, 2009; Schultheiss et al. 2007; Wong et al. 2013; Somlo et al. 2011; Rosenthal et al. 2011; Stein et al. 2012). Figure 2 shows the typical conformal dose distribution pattern that is achieved to the designated target structure, with simultaneous reduction of dose to critical organs. Table 5 compares the median doses for various normal organs at risk (OAR) delivered through standard TBI to 12 Gy with 50% transmission block lung shielding and electron boost to the underlying chest wall versus TMI to 12 Gy to the

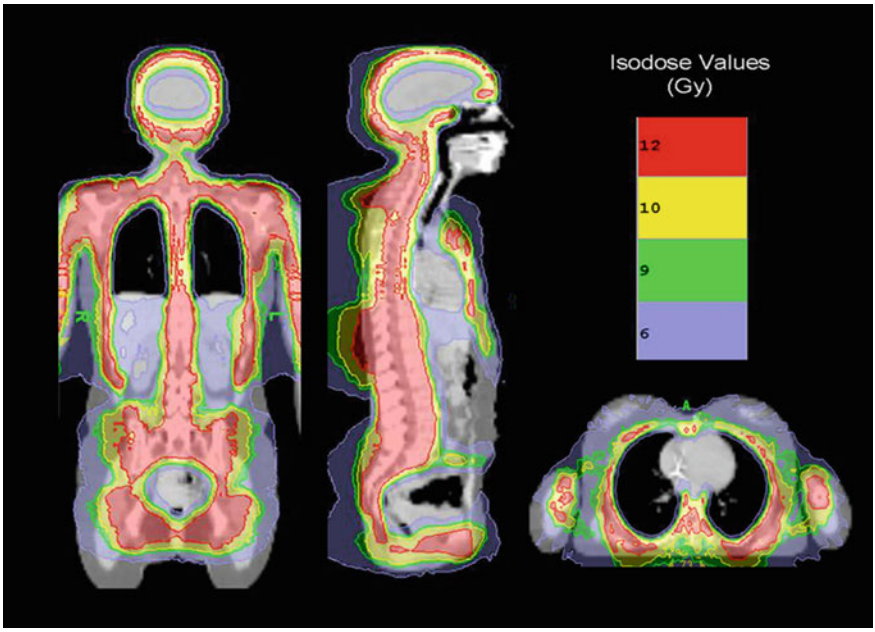

Fig. 2 Radiotherapy dose color wash demonstrating typical dose distribution of a patient treated with TMI. The target structure is skeletal bone

skeletal bone. Significant reduction in dose and volume of organ receiving full dose is observed compared to standard TBI for all critical organs.

This approach offers the treatment team more control of radiation dose delivery to target regions and organs compared to targeted radiopharmaceutical approaches. The physician can simultaneously reduce dose to organs or any other user-defined avoidance structure, while simultaneously increasing dose to particular target regions depending on the tumor burden and clinical situation. Figure 3 shows median organ doses and Fig. 4 lung dose-volume histogram (DVH) plots for standard TBI to 12 Gy versus TMI at 12 and 20 Gy in the same patient. At TMI doses to 20 Gy, median doses to all organs are still below that of TBI to 12 Gy. The lung DVH plots demonstrate that at 20 Gy TMI median lung doses remain below that of TBI 12 Gy with lung shielding but the D_{80} (minimum dose to at least 80% of the lung volume) is comparable, which predicts for similar pneumonitis risks for TMI 20 Gy and TBI 12 Gy. Table 6 compares median organ doses between TMI plans to 12 Gy (target structure is bone) compared to TBI plans to 12 Gy using 50% transmission blocks to shield lung.

5.2 Methodology Used at City of Hope

5.2.1 CT Simulation and Immobilization

All patients undergo CT simulation for treatment planning purposes. The patient is scanned supine with arms at side on a CT simulator. Two planning CT scans are

Table 5 Completed TMI Trials at City of Hope

Type of trial (NCT no.)	Type of HCT	Disease type	No.	Targets (dose)	TMI Dose levels (Gy)	Fraction and Schedule	Chemo-therapy
Phase I (Somlo et al. 2011) (00112827)	Autologous (tandem)	MM stage I-III responding or stable	25	bone	10,12,14,16,18	2 Gy QD-BID x 5 days	Mel
Phase II (Somlo et al.2015) (00112827)	Autologous (tandem)	MM stage I-III responding or stable	54	bone	16	2 Gy BID x 5 days	Mel
Pilot (Rosenthal et al. 2011) (00800150)	Allogeneic	Advanced disease ineligible for myeloablative regimens >50 yrs old, co-morbidities,	33	bone, nodes, spleen, testes, brain	12	1.5 Gy BID x 4 days	Flu/ Mel
Phase I (Wong et al. 2013) (00540995)	Allogeneic	AML, ALL relapsed or refractory with active disease not eligible for standard HCT	20	bone, nodes, testes, spleen, liver, brain	12, 13.5	1.5 BID x 4-5 days	BU/ VP16
Phase I (Stein et al. 2015) (02446964)	Allogeneic	AML, ALL relapsed or refractory with active disease not eligible for standard HCT	51	bone, nodes, testes, spleen, liver, brain	12, 13.5, 15, 16, 17, 18, 19, 20	1.5 BID x 4-5 days	Cy/ VP16

HCT hematopoietic cell transplantation; *AML* acute myelogenous leukemia; *ALL* acute lymphoblastic leukemia; *MM* multiple myeloma; *QD* once per day; *BID* twice per day; *Bu* busulfan; *Cy* cyclophosphamide; *Flu* fludarabine; *Mel* melphalan; *VP-16* etoposide; *TMI* total marrow irradiation; *Gy* Gray

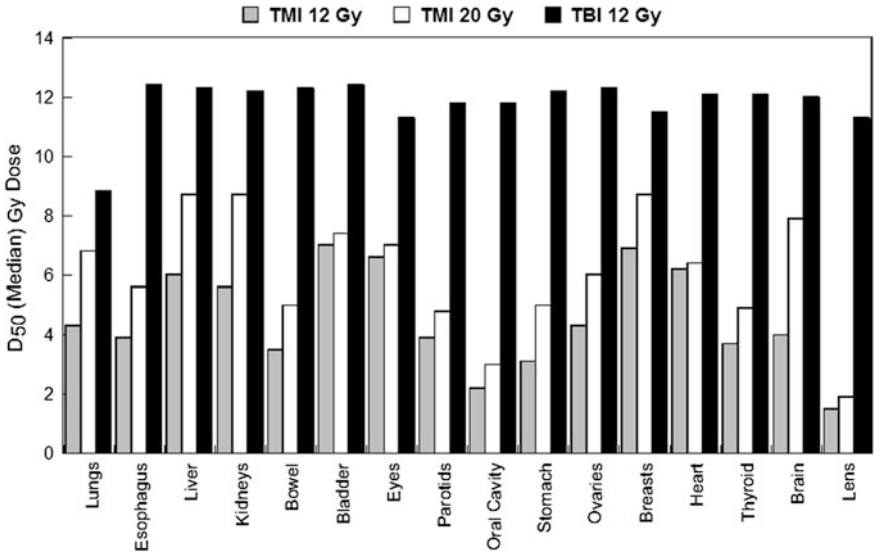

Fig. 3 Median organ doses from treatment plans for TBI 12 Gy, TMI 12 Gy and TMI 20 Gy planned on the same patient. Median organ doses are *lower* with TMI at 20 Gy compared to TBI 12 Gy, predicting that dose escalation of TMI to 20 Gy in patients should result in *lower* organ doses and reduced side effects compared to standard TBI 12 Gy

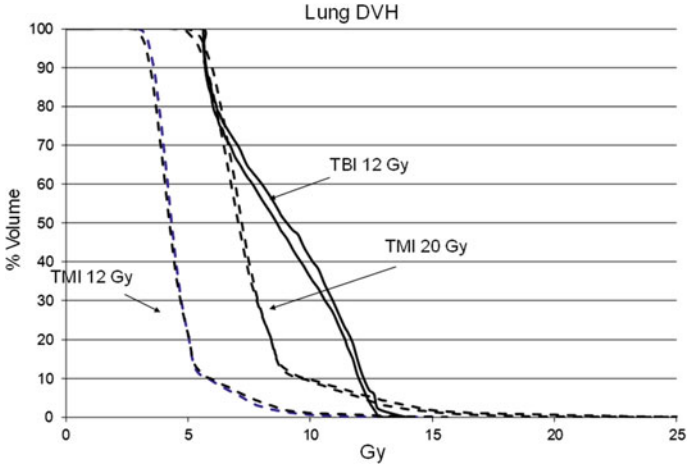

Fig. 4 Comparison of dose-volume histogram (DVH) plots for lung with TMI 12 Gy, TMI 20 Gy versus standard TBI to 12 Gy in the same patient. Standard TBI utilized 10 MV photons to deliver 12 Gy. Fifty percent attenuation blocks were used to shield the lungs. Electrons were used to deliver 6 Gy to the rib cage underlying the lung blocks. The lung DVH plots demonstrate that at 20 Gy TMI median lung doses remain *below* that of TBI 12 Gy with lung shielding but the D_{80} (minimum dose to at least 80% of the lung volume) is comparable, suggesting that pneumonitis risks for TMI 20 Gy may be similar to TBI 12 Gy

Table 6 Median dose to normal organs with TMI compared to standard TBI to deliver 12 Gy

Organ at risk	Median dose (Gy) TMI	Median dose (Gy) TBI	TMI/TBI median dose
Bladder	7.5	12.3	0.61
Brain	7.1	12.2	0.58
Breast	7.7	12.4	0.62
Esophagus	4.9	11.7	0.42
Orbits	6.0	12.0	0.50
Heart	6.1	11.5	0.53
Lens	2.3	10.5	0.22
Liver	6.9	11.7	0.59
Left Kidney	7.4	11.9	0.62
Right Kidney	6.9	11.9	0.58
Left Lung	6.3	9.0	0.70
Right Lung	6.4	9.7	0.66
Optic Nerve	6.4	12.3	0.52
Oral Cavity	2.5	12.5	0.20
Ovary	7.0	12.5	0.56
Parotids	4.6	13.1	0.35
Rectum	4.8	12.6	0.38
Small intestine	5.0	12.5	0.40
Stomach	4.6	11.5	0.40
Thyroid	4.4	12.6	0.35

Data is an average of comparison plans from 6 patients at City of Hope (unpublished data)
Standard TBI utilized 10 MV photons to deliver 12 Gy. Fifty percent attenuation blocks were used to shield the lungs. Electrons were used to deliver 6 Gy to the rib cage underlying the lung blocks

performed, one to plan body regions from head to pelvis and the other to plan for lower extremities. The body CT scan is obtained with normal shallow breathing. 4D CT scan data are acquired for chest and abdomen. If 4D CT is not available, shallow inspiration and expiration breath hold CT scans can be acquired instead. The normal shallow breathing CT data set is used for dose calculation and planning. The 4D CT datasets are registered to the planning CT to account for any organ motion during respiration. AccuForm^{TM} (CIVCO Medical Systems, Kalona, IA) cushion is used in combination with Silverman headrest to support and stabilize the head and neck. A body vac-lok^{TM} bag (CIVCO Medical Systems, Kalona, IA) and a thermoplastic head and shoulder mask are used as additional immobilization devices. The patient's arms, legs and feet are positioned using a vac-lok bag to enhance comfort and repositioning accuracy. Oral contrast is used to help visualize the esophagus. Couch height is approximately 10 cm below the isocenter of the gantry and patient is positioned on the couch so that the top of the head is approximately 5 cm from the end of the couch. Those settings are used to maximize the available length for the CT scanning and treatment delivery.

Target delineation: Target and avoidance structures and normal organs are contoured on an Eclipse™ treatment planning system (Varian Medical Systems, Palo Alto, CA) or similar planning system. Avoidance structures contoured are user defined and usually include lungs, heart, kidneys, liver, esophagus, oral cavity, parotid glands, thyroid gland, eyes, lens, optic chiasm and nerves, brain, stomach, small and large intestine, breasts, rectum, testes, ovary and bladder. Depending on the clinical circumstances, clinical trial or center, potential target structures can include skeletal bone, spleen, testes and major lymph node chains. In some clinical trials brain and liver are target structures. The 4D CT datasets are registered to the planning CT so that the contours of ribs, esophagus, kidneys, spleen and liver are enlarged to account for the organ movements during respiration. An additional 3 to 5 cm margin is usually added to the CTV to define the PTV target. Our center has added up to 10 cm margins in areas where larger setup uncertainty is observed, such as in the regions of the shoulder, arms, thighs, and posterior spinous processes. Spinal cord (part of the target) is outlined separately so to avoid hot spots in the spinal canal during planning. At some centers such as City of Hope, the mandible and maxillary bones are excluded from the target in an effort to minimize oral cavity dose and mucositis.

5.2.2 Treatment Planning with a Helical Tomographic Delivery System (Tomotherapy)

DICOM-RT images are transferred to the Hi-Art™ Tomotherapy treatment planning system (Accuray Inc. Palo Alto, CA). Helical Tomotherapy plan is designed such that a minimum of 85% of the target received the prescribed dose. For the body treatment plan, jaw size of 5 cm, pitch of 0.287 and modulation factor of 2.5 are used for most patients as a balance of treatment time and plan quality. Plan quality index is comprised of target dose uniformity and critical organ doses. Since the first TMI patient treated in 2005, TMI treatment planning efforts at City of Hope have continued to evolve. Median organ doses with current planning methods are now lower than previously published (Wong et al. 2006). Our current approach is to perform plan optimization in two stages. Critical organ sparing is optimized before target dose uniformity optimization is done resulting in being able to escalate target doses without a proportionate increase in normal organ dose (Stein et al. 2015). Legs and feet are planned in Tomo-Direct mode. A 5 cm jaw size is used. Gantry angles of 0 and 180° are selected. Composite dose of body plan and leg plan is generated to double check there is no dose gap or overlap at the junction.

5.2.3 Treatment Planning with a VMAT Conventional Linear Accelerator System

TMI can be planned and treated using a conventional linear accelerators with VMAT capability as well. Multiple dynamic IMRT arcs with usually 3–4 isocenters are used to cover target regions. Collimator angles are varied for each arc to increase the planning degree of freedom and plan quality. After the plan of the body is finalized, the lower extremities are planned with two or three additional AP-PA

fields given the lack of sensitive organs in this area. AP-PA fields are opened at 40 cm × 40cm and gapped at 50% isodose line at midplane (Han et al. 2011; Aydogan et al. 2011).

5.2.4 Treatment Delivery

Our current procedure involves initial laser alignment of the patient in the vac-lok bag and thermoplastic mask. Verification CT positioning scans are performed prior to each treatment session using multiple cone beam CT scans (CBCTs) or one megavoltage CT (MVCT) scan from orbit to ischial tuberosities and is fused to the planning CT. Registration and couch shifts are reviewed and approved by attending physician before treatment is delivered. The Tomotherapy has a maximum treatment length of approximately 150 cm. A jaw size of 5 cm and pitch of 0.287 usually result a beam-on of time of approximately 25 min to treat the upper body. On the Tomotherapy system, the patient translates through the unit head first to treat from the head to proximal thighs and is then re-setup and translates through the unit feet first to treat the lower extremities. Treatment of legs has a beam-on of time of approximately 10 min. With a conventional linear accelerator with VMAT capability, it is recommended the verification CBCT to be performed for each isocenter before treatment delivery. The total treatment time is similar to TMI delivery using a helical topographic approach.

5.2.5 Comparison to TBI Planning and Delivery

Table 7 compares the steps needed to plan and deliver TBI versus TMI. The TBI technique currently used at City of Hope is similar to that developed at Memorial Sloan Kettering Cancer Center (Shank et al. 1990). Briefly, patients are treated using a C-arm linac in the standing position at extended SSD of approximately 400 cm. The most common fractionation schedule is 1.2 Gy three times a day for 10–11 fractions using alternating AP and PA fields. A compensator is made for each patient to achieve a uniform dose. Fifty percent transmission blocks are used to shield the lung for each fraction. Electrons are used to treat the rib cage underlying the lung blocks. The time and resources needed for planning and delivery of TMI is

Table 7 Comparison of TBI versus TMI planning and preparation

	TBI	TMI
Day 1	• TBI measurement: thickness, SSD, positioning, gantry angle, hand position • CT Simulation for chest wall e boost treatment planning	• Immobilization • Whole body CT simulation
Day 2–4	• TBI calculation • Fabricate compensator and lung blocks • Set up—lung block placement and port films • Generate e boost plan • 2nd calculation QA verification	• Contour • Plan optimization • Phantom QA
Day 5	• Position standing—harness and lung blocks • Treatment: 20 min beam-on time for 2 Gy fraction	• Position in mask and vac-lock • Treatment: 35 min beam-on time for 2 Gy fraction

comparable to TBI. Centers actively involved in HCT and already treating patients with TBI should also be able to adopt TMI as part of their HCT program.

5.3 Results of TMI Clinical Trials

Initial preclinical dosimetric studies comparing TMI and TBI demonstrated that TMI could result in median organ doses that were approximately 15–65% of the prescribed dose to the target structure (bone) depending on organ site. These preclinical studies were hypothesis generating and predicted that TMI could result in a reduction of acute toxicities and the potential to dose escalate to marrow without an increase TRM rates compared to TBI containing regimens. Clinical trials would need to validate this hypothesis.

5.3.1 Tandem Autologous Mel-TMI HCT in Multiple Myeloma

The TMI trials at City of Hope have evolved through several phases. Patients undergoing HCT were first treated with TMI containing conditioning regimens in 2005. The initial trial evaluated TMI as part of a conditioning regimen in patients with multiple myeloma undergoing autologous tandem HCT. Since this was the first in human trial evaluating TMI, the trial was designed in part to address initial concerns of possible increased toxicities with TMI due to higher dose-rates compared to TBI. TMI would be evaluated without concurrent chemotherapy using a fractionation schedule and a fraction size comparable to TBI. This would allow us to evaluate the acute toxicities and determine the MTD of TMI alone in this population (Wong et al. 2006; Somlo et al. 2011).

Patients with Salmon-Durie stage I-III multiple myeloma and with stable or responding disease after first line therapy, underwent tandem autologous HCT. The first autologous HCT used the standard conditioning regimen of Mel at 200 mg/m^2. This was followed a minimum of 6 weeks later by a second autologous HCT using TMI as the conditioning regimen. TMI dose was escalated from 10 Gy to 18 Gy at 2 Gy fractions delivered twice a day with a minimum interval between fractions of 6 h. The TMI target structure was bone (Fig. 2). The trial design was a modification of a standard tandem autologous HCT regimen which utilized Mel at 200 mg/m^2 as a conditioning regimen for both tandem HCT.

Of 22 patients, reversible NCI grade 3 non-hematologic toxicities were as follows: nausea/emesis in 3 patients, enteritis in 2 patients and mucositis in no patients. Dose limiting toxicities were not observed until a TMI dose of 18 Gy (1 patient with reversible grade 3 pneumonitis, congestive heart failure and enteritis, and 1 patient with grade 3 hypotension), establishing the MTD at 16 Gy. With dose escalation to 18 Gy, median organ doses still remained below that for standard TBI to 12 Gy (Somlo et al. 2011), ranging from 11 to 81% of the prescribed bone dose.

The observation of radiation pneumonitis in one of three patients at 18 Gy TMI is consistent with predications made by initial preclinical planning studies. Table 8 displays the D_{80}, D_{50} (median) and D_{20} doses points for lung averaged for all

Table 8 Total Lung D_{80}, D_{50} and D_{20} DVH Doses for Patients with Multiple Myeloma Undergoing TMI

	N	D_{80}	D_{50}	D_{10}
TBI 12 Gy[a]	3	7.0	9.4	12.3
TMI 10 Gy	3	4.5	4.9	6.8
TMI 12 Gy	4	5.6	6.2	8.4
TMI 14 Gy	3	6.4	6.9	9.4
TMI 16 Gy	3	6.4	7.1	10.7
TMI 18 Gy	3	6.9	7.6	11.2

[a]Based on TBI plans from first 3 TMI patients (dose level 1) with 50% transmission lung blocks and 6 Gy electron boost to underlying chest wall
D_{80} minimum dose to that 80% of the organ receives; D_{50} minimum dose that 50% of the organ receives; D_{20} minimum dose that 20% of the organ receives

patients at each dose level. This shows the D_{80} point of 6.9 Gy which is similar to the D_{80} of 7 Gy which is observed with standard TBI to 12 Gy with 50% transmission lung blocks.

A phase II tandem autologous HCT trial of Mel followed by 16 Gy TMI has been completed (Somlo et al. 2015). A total of 54 patients were entered on the Phase I and II trials. No grade 4 toxicities, treatment related mortality, or non-engraftment was observed in either the Phase I or II trials. The median age was 54 years (31–67). Four patients were stage I, 18 stage II and 32 stage III. Forty-four of the 54 pts received TMI (28 at the MTD of 16 Gy). Best responses included complete response in 22, very good partial response in 8 and partial response or stable disease in 14. Median follow-up of alive pts was 73 months (27–117). In an intent-to-treat analysis median progression free survival (PFS) for the 54 pts was 52 months (95% CI 34.4-not reached), and median overall survival (OS) was not reached. PFS and OS at 5 years was 43% (95% CI 31–59) and 66% (95% CI 54–81), respectively. For pts enrolled at 16 Gy, the PFS and OS at 5 years were 48% (34–69) and 73% (59–90). The authors concluded that TMI of 16 Gy was feasible following Mel and the long-term safety and PFS/OS were encouraging.

5.3.2 TMLI (Total Marrow and Lymphoid Irradiation) Added to an Established RIC Regimen (Flu-Mel) as a Conditioning Regimen for Allogeneic HCT in Older Patients with Acute Leukemia

As noted earlier RIC regimen can be associated with an increase in relapse rates (Scott et al. 2015), yet adding standard TBI to RIC regimen has resulted in unacceptable toxicities in adults (Petropoulos et al. 2006). At City of Hope a pilot trial evaluated the feasibility of combining TMLI with the established RIC regimen of fludarabine and melphalan. The hypothesis was that given the targeted nature of the radiotherapy it would be better tolerated than standard TBI in combination with Flu-Mel. The target structures for TMLI included bone, as well as major lymph node regions (TLI) and spleen to optimize the immunosuppression needed for

allogeneic HCT and since these regions potentially harbored disease. Brain and testes were included as target regions in patients with ALL.

TMLI at 12 Gy (1.5 Gy BID) was combined with Flu (25 mg/m^2/d × 5 days) and Mel (140 mg/m^2) followed by allogeneic HCT in patients with advanced hematologic malignancies and who were older than age 50 or with co-morbidities and were ineligible for standard TBI myeloablative regimens. At study entry marrow blasts had to be <10% or reduced by over 50% after induction chemotherapy. The initial results of the first 33 patients have been reported (Rosenthal et al. 2011). Nineteen patients had AML and 3 ALL. Twenty-two were felt to be at very high risk having disease in induction failure, relapse, second or third remission or with a history of prior HCT. The TRM rate at 1 and 2 years was 19% and 25% respectively, which compared favorably to the 30-40% rates reported for Flu and Mel alone in a similar patient population (Giralt et al. 2001, 2002; Ritchie et al. 2003; de Lima et al. 2004). With a median follow-up for living patients of 14.7 months, 1-year overall survival, event free survival, and non–relapse-related mortality were 75, 65, and 19%, respectively. The authors concluded that the addition of TMLI to RIC is feasible and safe and could be offered to patients with advanced hematologic malignancies who might not otherwise be candidates for RIC. A recent updated analysis of 60 patients on this trial with a median follow-up of 5 years demonstrates similar TRM, relapse, event-free survival and overall survival rates (unpublished data). Further studies are needed to determine whether the addition of TMLI to an RIC regimen provides additional benefit compared to RIC regimens alone.

5.3.3 TMLI as an Alternative to TBI as Part of a Radiation Containing Myeloablative Conditioning Regimen in Allogeneic HCT

A previous trial at City of Hope demonstrated the feasibility of combining 12 Gy TBI, Bu and VP-16 as a conditioning regimen for poor risk acute leukemia patients undergoing allogeneic HCT (Stein et al. 2011). This led to two successor phase I trials evaluating the feasibility and defining the MTD of dose escalated TMLI with either Bu/VP-16 or Cy/VP-16 in poor risk acute leukemia. In both trials dose to the target structures bone, major lymph node chains, and spleen were escalated per standard phase I trial design. Target structures also included liver and brain which were kept at 12 Gy for all dose levels. Fraction schedule was 1.5–2 Gy BID over 4–5 days.

For the TMLI/Bu/VP-16 phase I trial the conditioning regimen was Bu days −12 to −8 (800 uM min), TMLI days −8 to −4, and VP-16 day −3 (30 mg/kg). TMI dose (Gy) was 12 (n = 18) and 13.5 (n = 2) at 1.5 Gy BID. Twenty patients with advanced acute leukemia were treated; 13 with induction failure, 5 in first relapse and 2 in second relapse. Nineteen patients still had detectable blasts in marrow prior to HCT with involvement ranging for 3 to 100% and 13 had circulating blasts prior to HCT ranging from 6–63%. Grade 4 dose limiting toxicities of stomatitis and sinusoidal obstructive syndrome (SOS) were seen at 13.5 Gy (Wong et al. 2013).

Hepatotoxicity was likely due the combination of Bu and a liver dose of 12 Gy, each of which has been associated with a risk of SOS.

TMLI dose escalation was also evaluated in combination with Cy and VP-16 (Stein et al. 2015). A phase I trial in 51 patients (age: median 34, range 16–57 years) with relapsed or refractory AML and ALL undergoing HCT with active disease and therefore conventionally ineligible for transplant, underwent a conditioning regimen of escalating doses of TMLI (range 12–20 Gy, days −10 to −6) with Cy (100 mg/kg day −3) and VP-16 (60 mg/kg day −5). Thirty-four were in induction failure, 14 in first relapse and 3 in second relapse. Fifty patients still had detectable blasts in marrow with involvement ranging form 5 to 98% and 27 had circulating blasts ranging from 6–85% prior to HCT. One patient at the 15 Gy level experienced Bearman scale (Bearman et al. 1988) grade 3 mucositis, but no other grade 3 dose limiting toxicities were observed up to 20 Gy. The maximum tolerated dose was declared at 20 Gy since as noted earlier TMLI planning indicated that prescribed target doses >20 Gy might deliver D_{80} doses to lung comparable to 12 TBI resulting in pneumonitis risks comparable to standard TBI. The post-transplant non-relapse mortality rate was 3.9% (95% CI: 0.7–12.0) at day 100 and 8.1% (95% CI: 2.5–18.0) at one year. The day +30 complete remission rate for all patients was 88 and 100% at 20 Gy. With a median follow-up if 24.6 months (3.3–72.0) of surviving patients, the overall one-year survival was 55.5% (95% CI: 40.7–68.1) and progression free survival 40.0% (95% CI: 26.4–53.2). Eleven patients are alive and in continuous complete remission at 1.6 to 6 + years. The authors concluded that TMLI/CY/VP16 conditioning regimen was feasible with acceptable toxicity at TMLI doses up to 20 Gy and with encouraging results for disease control for a very poor risk population not eligible for standard-of-care HCT regimens. A phase II trial is currently ongoing with the primary endpoint of 2 year progression free survival.

Figure 5 shows median (D_{50}) organ doses averaged for each dose level in the 51 patients undergoing TMLI combined with Cy and VP-16 and allogeneic HCT. Table 9 shows organ doses as a percentage of the prescribed target dose. Dose escalation to target structures up to 20 Gy was not associated with a proportionate increase in median organ doses for most critical organs. Median organ doses ranged from approximately 16–60% of the prescribed marrow dose with lung 44%, esophagus 33%, and oral cavity 28%. Lung D_{80} doses have been below 7.0 Gy even at the 20 Gy dose level. Figure 6 shows the level of dose uniformity within the target structure bone.

5.3.4 TMI Clinical Trials Performed at Other Institutions

Recently, other groups have evaluated TMI and TMLI containing conditioning regimens although the published experience to date is limited. Hui and colleagues at the University of Minnesota (Hui et al. 2007) reported on the first patient treated as part of a phase I autologous HCT trial in Ewing's sarcoma using TMI to 6 Gy (2 Gy per day), followed by Bu (targeted, 4 mg/kg days −8 to −6), Mel (50 mg/m^2 days −5 and −4) and thiotepa (250 mg/m^2 days −3 and −2). The regimen was well tolerated with only nausea and vomiting observed. Sheung et al. (2009) reported on

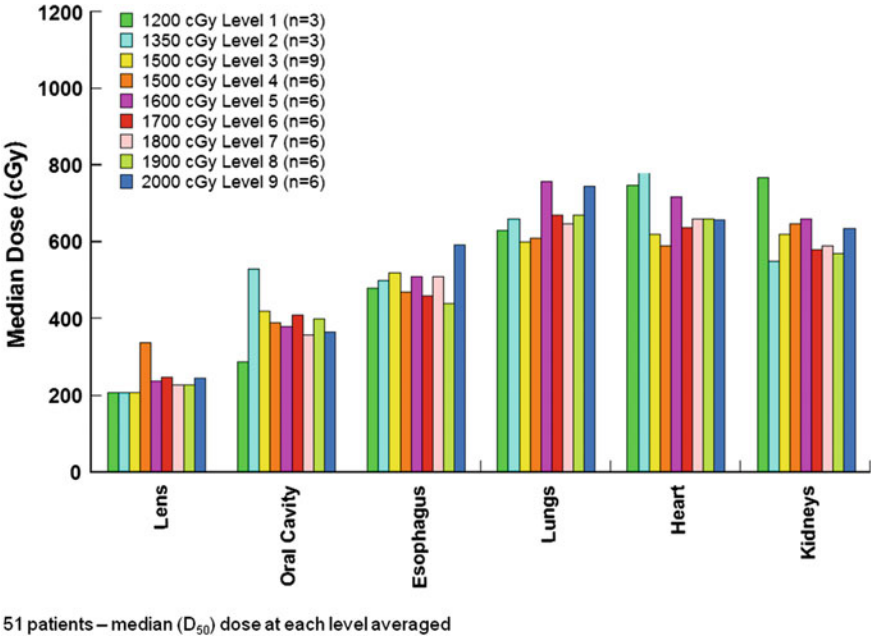

Fig. 5 Median (D_{50}) organ doses averaged for each dose level in 51 patients undergoing TMLI combined with Cy and VP-16 and allogeneic HCT. Dose escalation to target structures up to 20 Gy was not associated with a proportionate increase in median organ doses for most critical organs. Median organ doses ranged from approximately 16 to 60% of the prescribed marrow dose with lung 44%, esophagus 33%, and oral cavity 28%

Table 9 Median (D_{50}) organ dose as a percent of the prescribed target dose (n = 51)

Organs	Mean ± 1 SD	Range
Lens	15.0 ± 4.3	10.0–34.0
Oral cavity	24.3 ± 8.4	14.0–51.3
Rectum	33.1 ± 8.2	17.9–54.1
Esophagus	30.8 ± 5.8	16.3–44.2
Eyes	28.4 ± 13.0	13.1–71.9
Stomach	39.7 ± 7.4	27.1–58.3
Thyroid	44.6 ± 12.7	15.3–88.9
Parotids	39.6 ± 7.5	26.0–60.0
Lungs	41.5 ± 6.3	32.0–55.0
Heart	42.2 ± 10.3	28.8–69.2
Kidneys	37.9 ± 9.2	21.8–67.5
Small intestine	45.4 ± 6.9	26.8–61.1
Bladder	54.5 ± 12.5	25.3–89.2

SD standard deviation

Target Organs	D80	D50	D10
Bone (n = 51)	101 % (97-106)	105 % (102-115)	109 % (104-119)

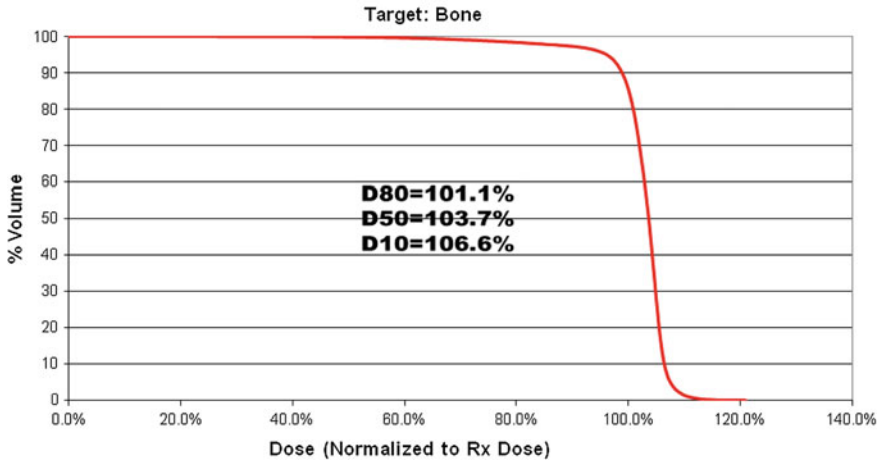

Fig. 6 Average D_{80}, D_{50} D_{10} Target Doses (as a percent of prescribed dose) in 51 Patients. DVH plot is a representative plot from one patient. This demonstrates the level of uniformity of dose to the bone compartment

3 patients conditioned with 8 Gy TMI at 2 Gy per day (days −6 to −3) combined with Mel at 140 mg/m^2 (day −2) prior to autologous HCT and observed only a single event of grade 3 toxicity (mucositis). Corvo et al. (2011) demonstrated the feasibility of adding a 2 Gy TMI boost to bone marrow and spleen after standard TBI 12 Gy (2 Gy BID) and Cy in 15 patients with AML and ALL undergoing allogeneic HCT and, with a median follow-up of 310 days, reported a cumulative TRM rate of 20%, relapse rate of 13% and disease free survival rate of 67%. Patel et al. (2014) were the first the deliver TMI using a VMAT approach with Flu and Bu. They reported on 14 patients most with advanced acute leukemia and established an MTD of 9 Gy (1.5 Gy BID). With a median follow-up of 1126 days TRM was 29%, RFS 43% and OS 50%.

Other centers in Europe, North America and Asia have also initiated similar trials but the early experience to date remains unpublished. Tables 10 and 11 list select TMI trials in multiple myeloma and leukemia that are ongoing. Most are pilot or phase I TMI dose escalation trials in patients with advanced, poor risk disease and are combined with RIC or myeloablative conditioning regimens. Most TMI schedules use 1.5 to 2 Gy fractions twice a day although some plan on using 3 to 4 Gy daily fractions.

5.3.5 High Dose-Rate and Organ Sparing

Clinical results have addressed initial concerns of TMI approaches. One concern was that the higher dose-rate with TMI (approximately $\geq$400 cGy/minute)

Table 10 Select TMI and TMLI trials currently open for accrual of patients with leukemia[a]

Institution	Type of trial	Type of HCT	Disease type	Age	Targets	TMI dose (Gy)	Fraction and schedule	Chemo therapy
City of Hope NCT02446964	Phase I	Allogeneic Haplo-identical	AML, ALL CR1 high risk, CR2, CR3, refractory	12–60	bone, spleen nodes	12, 14, 16, 18 20	1.5-2 Gy BID	Flu, Cy and post transplant Cy
City of Hope NCT02094794	Phase II	Allogeneic	AML or ALL, IF, relapsed or > CR2	18–60	bone, spleen, node, liver, brain	20 (12 to liver, brain)	2 Gy BID	Cy, VP16
U. Chicago NCT02333162	Phase I	Allogeneic	recurrent AML, ALL, MDS undergoing second HCT	18–75	Not Stated	NS	BID over 2-5 days	Flu, Mel
Case Comprehensive Cancer Center NCT02129582	Phase I	Allogeneic	ineligible for full myeloablative regimen AML, ALL, NHL, HL, MM, MDS, CLL, CML.	18–75	Not Stated	NS	BID over 4 days	Flu, Bu
U. Minnesota NCT00686556	Phase I	Allogeneic	ALL, AML CR2, CR3, Relapse, IF	pediatrics and adults	bone	15, 18, 21, 24	3 Gy QD	Flu, Cy
Ohio State NCT02122081	Pilot	Allogeneic	AML, ALL, MDS > 50 or comorbidities unable to undergo TBI based regimens;	18–75	bone, brain, testes	12	2 Gy BID	Cy

[a]Listed at www.cliniclatrials.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; *Flu* fludarabine; *Mel* melphalan; *VP-16* etoposide; *Gy* Gray

Table 11 Current TMI trials for patients with multiple myeloma[a]

Institution NCT trial no.	Type of trial	Type of HCT	Disease type	Age	Target	TMI dose levels (Gy)	Fraction and Schedule	Chemotherapy
City of Hope 01163357	Phase I	Allogeneic	MM refractory, relapsed prior auto HCT allowed	18–70	bone	12, then de-escalated to 9	1.5 Gy BID	Flu Mel Bortezomib
France multi-center 01794572	Phase I/II	Autologous	MM first relapse	18–65	bone	8, 10, 12, 14, 16	1–2 Gy BID over 4 d	Mel 140
Ottawa Regional 00800059	Phase I/II	Autologous	MM relapsed	18–60	bone	14, 16, 18 completed plan to go to 28	2 Gy BID	none
Marie Sklodowska- Curie Cancer Center, Poland 01665014	Pilot	Autologous tandem	MM in CR, VGPR, or PR	18–65	bone	12 Gy	4 Gy QD	Mel 200 second auto HCT
U. Illinois at Chicago 020243860	Phase I	autologous	MM with high or intermediate risk of progression	18–75	bone	3, 6, 9, and 12	3 Gy QD	Mel 200
U. Illinois at Chicago 02043847	Phase I	Autologous	MM relapsed or refractory	18-75	bone	3, 6, and 9	3 Gy QD	Mel 200
U Rochester 01182233	Phase I	Autologous	MM	$\leq$70	bone	10–20	2–4 Gy QD	Mel 200

[a]Listed at www.cliniclatrials.gov

HCT hematopoietic cell transplantation; *MM* multiple myeloma; *TMI* total marrow irradiation; *CR* complete remission; *VGPR* very good partial response; *PR* partial response; *QD* once per day; *BID* twice per day; *Mel* melphalan; *Gy* Gray

compared to the low dose-rate with TBI (5–30 cGy/minute) would result in greater toxicity. The available toxicity data summarized earlier show that this is not the case. In addition, to the authors' knowledge there has not been a single reported case of non-engraftment. Finally, pre-clinical studies have demonstrated that dose-rate effects are not seen at dose-rates higher than approximately 25 cGy/minute and are significantly mitigated the more the TBI dose is fractionated (Travis et al. 1985; Tarbell et al. 1987). This may explain the lack of any dose-rate effect seen in the clinical trials to date.

Organ sparing has raised concerns of sparing of cancer cells. For example, in a study of 14 patients with refractory anemia undergoing allogeneic HCT and treated with Cy and TBI utilizing 95% attenuation lung and right hepatic lobe blocks, there was an increase in relapse rate (34% vs. 2%, $p = 0.0004$) and decrease in disease free survival (38% vs. 61%, $p = 0.16$) when compared to historical controls (Anderson et al. 2001). The authors hypothesized that 95% shielding of lung and liver may have shielded malignant cells or reduced immunosuppression and graft versus leukemia effect.

We have continued to monitor the rate and sites of extramedullary recurrences in patients treated with TMI regimens undergoing allogeneic HCT. Of 101 patients with a median follow-up of 12.8 months, 13 developed extramedullary relapses at 19 sites. The site of relapse was not dose-dependent, with 9 relapses occurring in the target region ($\geq$12 Gy), 5 relapses in regions receiving 10.1 to 11.4 Gy and 5 relapses in regions receiving 3.6 to 9.1 Gy (Kim et al. 2014). The risk of extramedullary relapse was comparable to that of standard TBI. In multivariate analysis extramedullary disease prior to HCT was the only predictor of extramedullary relapse. The use of TMI does not appear to increase the risk of relapse in non-target regions.

5.4 Future Directions

Ways to optimize dose delivery continue to be explored. Optimum dose schedules, fraction sizes, and chemotherapy regimens need to be defined. Larger fraction sizes of 3–4 Gy are being evaluated. Although this may be more time efficient, it diminishes the organ sparing effects of fractionation and hyperfractionation. Reduced fractionation combined with higher dose rates of TMI may increase the potential for organ toxicity particularly to the lungs, liver and kidneys.

The most appropriate target regions and target doses for a given patient population needs to be defined. The feasibility and benefit of dose escalation needs to be demonstrated in more trials. Other areas that need to be addressed are what patient population are TMI strategies most appropriate for and are TMI based regimens best used in patients who are poor risk and would do poorly with current regimens or in standard risk patients as a replacement for current TBI or on-TBI based regimens.

5.4.1 Multimodal and Functional Imaging for TMI Dose Painting and Response Assessment

An established principle in radiation oncology is that increased dose is needed to regions of higher tumor burden. Currently with TMI and other forms of image guided systemic radiotherapy dose escalation is to a CT based anatomic region such as bone and bone marrow. The assumption that the greater tumor burden is in the marrow and uniformly distributed throughout the bone and body for leukemia, multiple myeloma and other hematopoietic malignancies may not be the case. Future trials will explore the use of multi-modality and functional imaging to refine targeting and response assessment. ^{18}FDG- PET imaging and MRI including multi-parametric MRI are being actively being investigated to define areas of greater tumor burden, to define extramedullary disease and to assess response (Valls et al. 2016; Rubini et al. 2016). [^{18}F]-fluorothymidine, a DNA precursor which targets areas of greater DNA synthesis and cell proliferation, has demonstrated promise in detecting intramedullary distribution of acute leukemia and early recurrence (Vanderhoek et al. 2011).

Hematologic disease (especially leukemia) is assumed to be systemic, distributed homogeneously in the skeletal system and thus the iliac crest biopsy is the standard way to assess disease and to determine treatment management. In addition, the skeletal system micorenvironment and its compositional, structural, physiological, and functional units are assumed to be invariant. However, a small percentage of cells can become resistant and proliferate. As a result there have been new treatment strategies focusing in several areas: (1) the evolution of intrinsic cellular changes including stem cell clonogens, genetic mutations and various other ways to develop resistance to treatment and (2) the bone marrow (BM) "environment" which is beginning to be recognized as key contributing biological factor in hematological malignancies. The skeletal system is perhaps the largest and most complex physiological system. Pre-clinical studies indicate the important role the local BM environment plays in survival of leukemia cells or leukemia resistance after treatment (Kode et al. 2014; Konopleva and Jordan 2011; Raaijmakers 2011; Schepers et al. 2013). Recent pre-clinical studies with advanced imaging suggest structural and functional heterogeneity of BM (Lassailly et al. 2013; Naveiras et al. 2009).

The term functional total marrow irradiation or "fTMI" is coined to develop targeted radiation that incorporate functional information of the cancer, bone and marrow system, and interaction of cancer cells with BM macro- and the microenvironment. The path to develop and implement fTMI is complex and will develop over the next decades as the complex relation of hematologic cancers and its interaction with the BM environment and bone marrow hematopoiesis is better understood.

Hui and colleagues presented the concept of differential radiation targeting based on differences in bone marrow composition, namely active red marrow (RM), and yellow marrow (YM) or bone marrow adipose tissue or BMAT) as their functions are distinct. 3D mapping of marrow composition was developed using newly developed whole body DECT. In this framework, differential radiation to RM or YM was proposed (Fig. 7) (Magome et al. 2016). The radiation exposure was

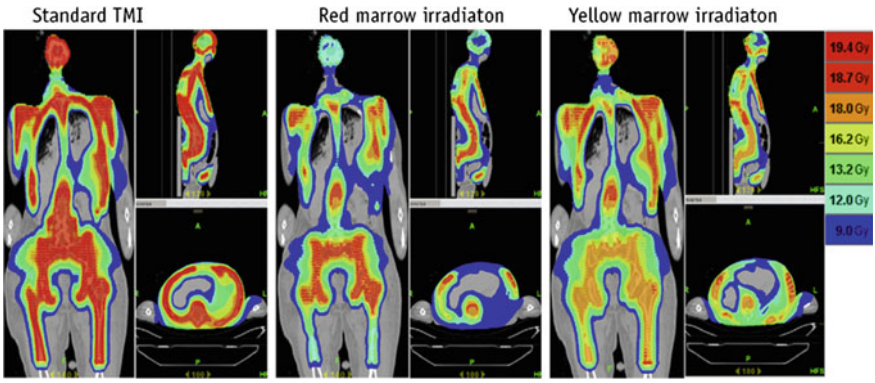

Fig. 7 Comparison of standard total marrow irradiation (TMI), *red marrow irradiation* (RMI), and *yellow marrow irradiation* (YMI). (A) Dose distributions of standard TMI, RMI, and YMI

significantly reduced to organs at risk (OARs) in RM and YM irradiation compared with standard total marrow irradiation (TMI). Although leukemia is prevalent in the vascularized marrow niche, regions of lower vascularity and higher hypoxia such as YM may function to enhance cancer resistance to systemic chemotherapy and radiation (Conklin 2004). Because cancer treatment changes marrow fat composition (Hui et al. 2015) individual factors including age and prior treatment may influence the distribution of marrow composition in different sites and possibly the distribution of viable tumor burden within the skeletal system.

A hybrid whole-body PET/DECT (3′-deoxy-3′[^{18}F]-fluorothymidine) imaging system, which is functional-anatomical-physiologic based imaging, offers the possibility of identifying spatial distribution of leukemia. Hui et al. observed highly heterogeneous distribution (systemic and focal lesions) of leukemia throughout the skeletal system. The majority of cells were systemic and uniformly distributed, but with additional regions of localized leukemia, that was associated with cortical bone in spine, proximal and distal femur, and pre-dominantly in RM regions. These data are hypothesis generating and raise the interesting possibility that heterogeneous distribution of leukemia could be associated with differences in the local marrow environment and possibly associated with different response characteristics to therapy.

Hui and colleagues simulated different TMI dose painting scenarios utilizing standard CT based imaging, FLT-PET based imaging and DCET based imaging (unpublished data). The full dose target region or planning tumor volume (PTV) for FLT or DECT based planning was dramatically reduced compared to the PTV of conventional TMI plan. Figure 8 shows color wash dose distributions of conventional, FLT, and DECT based TMI plans. With reduction in the volume of the target region, doses to critical organs could be reduced in FLT and DECT based TMI plans compared with the conventional TMI. In summary, multimodality image guided "fTMI" would allow for differential irradiation of regions with higher burden of chemo-resistant leukemia cells and the potential to more selectively increase dose and improve outcomes.

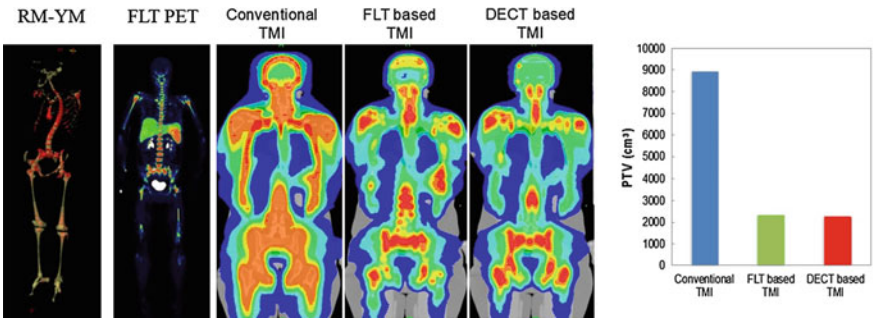

Fig. 8 Functional total marrow irradiation development (from *left* to *right*): 3D mapping BM composition using DECT (verified using water-fat MRI), FLT PET with DECT (not shown), dose painting comparison between conventional (CT based) total marrow irradiation (TMI), FLT imaging-based TMI, and DECT imaging-based TMI, and dose volume histograms of conventional (*blue*), FLT-based (*green*), DECT-based (*red*) TMI plans

6 Conclusions

In summary, strategies to deliver a more targeted form of TBI continue to be actively investigated in this emerging area through the use of newer image guided IMRT radiotherapy delivery systems. Although the follow-up has been short and the number of patients treated has been limited, initial results with TMI have been encouraging and demonstrate feasibility, acceptable toxicities, TRM rates that compare favorably to standard conditioning regimens, and encouraging response and survival rates in advanced disease. Dose escalation is possible when combined with certain drug combinations such as Cy/VP-16. TMI can now be delivered on more than one technology platform, through helical tomographic or VMAT based image guided IMRT delivery. The number of centers and trials continue to increase. Today TMI and TMLI trials are being performed or planned in centers in North America, Central America, Europe, Asia and Australia which demonstrates that this approach is exportable and reproducible at other centers. This emerging area will soon be positioned to carry out multicenter trials to answer important clinical questions that remain.

A potential advantage of TMI and TMLI is the ability to reduce doses to normal organs, thereby reducing toxicities and broadening the spectrum of patients able to tolerate radiation conditioning regimens, such as older patients or those with co-morbidities. As a result TMI and TMLI can be combined with established RIC regimens in an effort to improve outcomes. Another potential advantage is the ability to escalate target dose with acceptable toxicities. Although, TMI is represents a paradigm shift from standard TBI, its full clinical benefit needs to be validated through well-designed clinical trials. Ultimately trials need to demonstrate that TMI based conditioning regimens offer advantages over already established TBI and non-TBI containing conditioning regimens.

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