Total Marrow Irradiation (TMI) with Helical Tomotherapy and Peripheral Blood Progenitor Cell Rescue (PBPC) Following high-Dose Melphalan (Mel) and PBPC as Part of Tandem Autologous Transplant (TAT) for Patients with Multiple Myeloma.

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Abstract

Background: Ablative dose total body irradiation (TBI) of 800 cGy in combination with high-dose melphalan (MEL) was found to be too toxic. TMI, an image-guided targeted TBI using TomoTherapy intensity modulated radiotherapy , given as the sole ablative regimen for the second cycle (C) of tandem AT was tested in patients (pts) with stable (SD)/responsive MM, in a phase I-II trial. Here we provide long-term update on outcome.

Patients and Methods: We enrolled pts with Durie-Salmon stages (DS) I-III MM in response or with SD, who were ≤ 70 years old and ≤ 18 months from diagnosis. Pts received MEL 200 mg/m^2 and AT (C 1), and, after recovery, TMI (MTD : 1600 cGy) and AT (C 2) followed by maintenance with dexamethasone and an IMiD.

Results: 54 pts started treatment (23 F/31M). The median age was 54 years (31-67). DS stages were:I (N=4), II (N=18), III (N=32). 44 of the 54 pts received TMI (28 of 36 pts enrolled at the MTD received TMI). 10 pts did not receive TMI due to post-MEL toxicities or pt or doctor's choice. The median time between MEL and TMI was 65 days (range 47-125). All pts engrafted. 9/54 (17%) experienced febrile neutropenia (FN) following MEL, and 8/44 (18%) experienced FN after TMI; less frequent grade 3 or 4 non-hematologic toxicities were similar between MEL and TMI. Best responses included CR (N=22, of which 3 were in CR prior to MEL), very good partial response (VGPR, N=8, of which 2 were in VGPR prior to MEL) and PR or SD (N=14). Median follow-up of alive pts is 73 months (27-117). In intent-to-treat analysis median PFS for the 54 pts is 52 months (95% CI 34.4-NR), and median OS is not reached. PFS and OS at 5 years is 43% (95% CI 31-59) and 66% (95% CI 54-81), respectively. For pts enrolled at 1600cGy, the PFS and OS at 5 years were 48% (34-69) and 73% (59-90).

Conclusion: TMI of 1600 cGy is feasible following MEL in MM patients. The long-term safety and PFS/OS are encouraging, and further assessment of TMI is warranted.

Background

•While awaiting further confirmation, tandem cycle autologous transplant (TAT) has been found to yield improved progression-free survival in comparison to single AT in patients treated with older generations of induction therapies.

•Radiation therapy has been used primarily for palliation in pts with MM. Ablative dose total body irradiation (TBI) of 800 cGy in combination with high-dose melphalan (MEL) as part of single cycle autologous transplant was found to be too toxic, and therefore inferior, in comparison to MEL. TMI, a form of image-guided targeted TBI using intensity modulated helical tomotherapy, when given as the sole ablative regimen during the second cycle of TAT, may improve the efficacy of MEL without unacceptable toxicities.

Eligible Population

- Stage I-III multiple myeloma
- Responding or stable disease within < 18 mos from diagnosis
- Ability to lie supine in a full body cast for prolonged period
- Prior radiation < 2000 cGy to any area
- Karnofsky performance status of 60% or better
- Creatinine clearance > 50 mL/min
- Signed voluntary, IRB-approved, informed consent form

Treatment Regimen

Cyclophosphamide 1.5 gm/m^2 and G-CSF 10 µg/kg/day (d) to procure ≥ 4 x 10^6 CD34+ cells/kg

Cycle 1: Melphalan (Mel) 100 mg/m^2/day x 2 days and PBPC G-CSF 5 µg/kg/d starting on d 5

Cycle 2:TMI followed by PBPC and G-CSF 5 µg/kg/d starting on day 0

Day -5 cGy	Day -4	Day -3	Day -2	Day-1	TMI cGy	dose level	# of pts
200 am	200	200	200	200	1000	1	3
200 am 200 pm	200	200	200	200	1200	2	4*
200 am 200 pm	200 200	200	200	200	1400	3	3
200 am 200 pm	200 200	200 200	200	200	1600	4	6
200 am 200 pm	200 200	200 200	200 200	200	1800	5	7^
	200 am 200 pm	200 200	200 200	200 200	1600 MTD additional patients at phase II dose		22

* Patient was enrolled at 1400 cGy, but due to a machine problem she received 1200 cGy; ^ Patient did not receive TMI due to sepsis/CHF after Mel

Maintenance :Thalidomide (thal) 200 mg/d and Dexamethasone (dex) 40 mg/d x 4 days / q months for 12 months or 6 mos post CR

Statistical Methods

Phase I : No dose limiting toxicity (DLT) per cohorts of 3, or 1 DLT in 6 patients at each dose level during the escalation of TMI is allowed. No dose escalation to the next level until all patients treated at the previous dose level will have recovered. Once DLT is established, proceed to Phase II at a TMI dose of LTD – 1 (MTD). Phase II: A response rate of < 50% would not warrant further testing of the regimen; interim analysis for response is set; estimated accrual: 53-75 patients.

Characteristics and Results

•Age (years) 54 (31-67)

•Stage (N) I : 4 II : 18 III :32

•M protein IgG:40 IgA:8 non-secretory:5

•Cytogenetics/FISH del 13 n:4 t(11;14) n: 4 del 17, p53:n: 4 trisomy 5, 9 or 5, 11, or 5, 15 n:12; unkown:5

Induction Therapy

Thalidomide/lenalidomide:21/9 Bortezomib-containing regimens: 20 Anthracycline:9 Other: 9

Response (R) prior to High-dose Melphalan (n:44)

Complete R (CR):3 Very Good Partial R (VGPR): 12 PR: 22 Stable:7

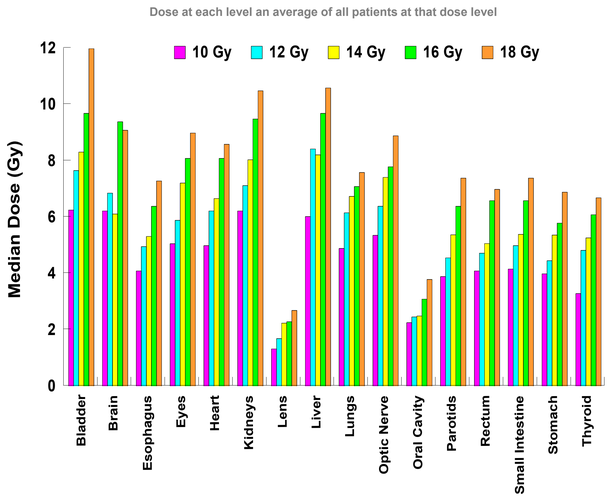
Median time between MEL and TMI was 65 days (range 47-125).

Best Response After Completion of Tandem Transplant

CR: 22 VGPR: 8 PR or stable: 14

. **Median follow-up** is 73 months (27-117) months for live patients

TMI D_{50} (Median) Organ Dose



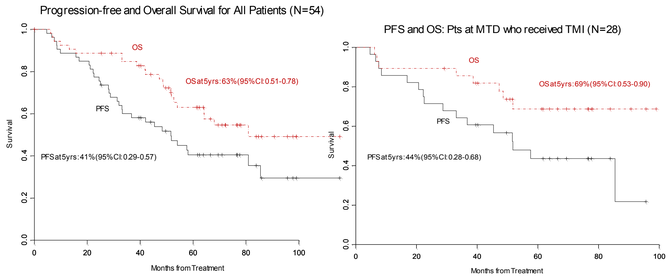
Toxicities

Grade 3/4 Non-Hematologic Toxicities

Treatment	Cycle 1 Mel (n:54)	Cycle 2 TMI (cGy; n:44)				
	200 mg/m2	1000	1200	1400	1600	1800
N	54	3	4	3	28	6
Febrile neutropenia	6	1	1	0	5	1
Fatigue/anorexia	5	1	0	0	4	2
Nausea/emesis	2	0	0	0	3	2
Enteritis/colitis	3	1	0	0	0	**2**
Engraftment syndrome	0	1	0	0	0	0
Pneumonitis	0	0	0	0	0	**1**
CHF/Hypotension	1	0	0	0	0	**1**
Metabolic/electrolyte	10	1	1	0	7	4

Second malignancies : 2 non-melanoma skin, 1 thyroid, and 1 beast cancer, 1 AML

Progression-Free (PFS) and Overall Survival (OS)



Conclusions

•Tandem cycle melphalan and TMI is feasible and can be safely delivered in ~80 % of carefully selected patients without an increase in long-term toxicities, including a low rate of secondary malignancies.

•CR and VGPR rates have doubled from 27% pre-transplant to 55% after tandem melphalan and TMI followed by maintenance by intent to treat analysis and resulted in an encouraging median PFS of 52 months.

• With recently developed novel induction regimens the CR and VGPR rates are likely to increase pre-transplant, and may allow for further improvement in post-PFS and OS with novel TMI-incorporating transplant strategies.

Supported by NCI Grant CA 33572