cell infiltration. In contrast, no WT1 expression was observed when disease was absent.

Our findings suggest an association between the emergence of WT1-specific T cells and graft-versus-myeloma effect in pts being treated for relapsed MM.

In conclusion, overall survival after salvage from 2nd autologous stem cell transplant is longer than after a 2nd allogeneic transplant. Upfront, planned tandem autologous stem cell transplant is superior to both salvage strategies. Larger, randomized trials are needed to confirm these results.

246

UPFRONT TANDEM AUTOLOGOUS STEM CELL TRANSPLANT IS SUPERIOR THAN AUTOLOGOUS OR ALLOGENEIC STEM CELL TRANSPLANT AFTER FAILURE OF 1ST AUTOLOGOUS TRANSPLANT IN PATIENTS WITH MULTIPLE MYELOMA

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Disease progression remains the main cause of treatment failure after autologous stem cell transplant (SCT) in patients with multiple myeloma (MM). It is unclear what is the best salvage therapy after failure of a 1st autologous SCT in MM.

We performed a retrospective study comparing 2nd autologous (auto-auto) versus 2nd allogeneic (auto-allo) SCT in patients progressing or relapsing after their 1st autologous SCT and compare their outcomes with patients receiving sequential planned double autologous (tandem) SCT as part of their upfront therapy for MM.

The data was collected from CIBMTR reports and medical records at Texas Transplant Institute from 2001 to 2010. Patient's characteristics and outcomes are described in table. Response to 1st and 2nd SCT was determined at 100 days post transplant and classified as good (stringent complete remission [sCR], complete remission [CR], very good partial remission [VGPR]) or poor (partial remission [PR], stable disease [SD] or progressive disease [PD]). All patients in the auto-allo group received a reduced intensity regimen. The overall survival was calculated from the date of the 2nd transplant to the known date of death in all groups. Patients in the auto-allo group (15.9 months) had a worse median survival than in the auto-auto group (39 months) with both of them having a worse survival compared to patients undergoing tandem transplants (64.3) (p value = 0.003).

Forward stepwise Cox regression analysis was used to measure factors affecting overall survival. Factors used for analysis included age, cytogenetics (high risk = mutated p53, t(14;16), t(4;14), del 13), International Staging System (ISS) before 1st and 2nd SCT, use of maintenance therapy after 1st SCT, days from diagnosis to 1st SCT and days from 1st to 2nd SCT, CD34+ cells infused at 1st and 2nd SCT. Age and ISS of III at 2nd transplant were identified as factors affecting survival in the auto-auto group (hazard ration of 1.081 and 5.700, respectively).

247

RETROSPECTIVE REVIEW OF DPACE THERAPY AS A SALVAGE REGIMEN IN PATIENTS WITH RELAPSED MULTIPLE MYELOMA PRIOR TO AUTOLOGOUS STEM CELL TRANSPLANT

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Background: The landscape of multiple myeloma (MM) treatment has improved substantially since the introduction of novel agents thalidomide, bortezomib and lenolidomide. However, it is not always clear what therapy would be effective in patients after they progress with these novel agents. To identify effective salvage therapy, we performed a retrospective review of DPACE (dexamethasone, cisplatin, doxorubicin, cyclophosphamide, and etoposide) chemotherapy in pretreated MM patients who were candidates for autologous stem cell transplant (ASCT).

Methods: Review of electronic medical records at our institution from January 1, 2005 to July 31, 2011 was performed. Eligible subjects were ≥18 years old with a diagnosis of MM that received DPACE after their disease had progressed with chemotherapy including a novel agent and were transplant candidates. Data collected included ISS stage at diagnosis, response to therapy, safety data, time to transplant, and time to progression and death.

Results: We evaluated 24 patients who had received a median number of 2 (range 1-4) prior therapies, excluding single agent dexamethasone.Prior to DPACE, 38% (n = 9) had undergone at least one ASCT. The median number of DPACE cycles was 2 (range 1-5). Median age was 57 (range 46 - 75); 75 % (n = 18) were African-American and 25% (n = 6) were Caucasian. Partial response or greater was achieved in 79% (n = 19), stable disease in 13% (n = 3), and 8% had progressive disease (n = 2). Dose reduction occurred in 25% (n = 6) of patients with dose reductions ranging from 20 to 50%. Sixteen patients (67%) proceeded to ASCT including five of the 9 (55%) who had prior ASCT. Median time to transplant was 3 months (range 2 -11) from first DPACE cycle. Six patients experienced CTCAE v4.0 grade 3/4 neutropenia with only 16% (n = 4) febrile neutropenia. All patients received growth factor support. Grade 3/4 thrombocytopenia (n = 2), anemia (n = 2), and mucositis (n = 2)

Table. Patient Characteristics and Outcomes

	Tandem (n = 29)	Auto-Auto (n = 32)	Auto-Allo (n = 10)
Median age, years (range)	62 (41-78)	62.5 (45-81)	54 (43-63)
Median days from diagnosis to 1st transplant	224.5 (93-1344)	226 (117-1074)	254.5 (101-416)
Median days from 1st to 2nd transplant	149 (99-189)	847 (210-4158)	350 (88-1281)
Median total CD34+ cell infused 1st transplant	3.29 (2-12)	5.87 (2-28)	6.03 (2-14)
Median total CD34+ cell infused 2nd transplant	3.22 (2-9)	4.47 (2-19)	5.25 (3-11)
Median WBC engraftment	11 (9-13)	11 (9-47)	N/A
Median Platelet engraftment	16 (10-19)	15 (10-23)	N/A
Cytogenetics-High Risk	17%	3%	10%
ISS at 1st transplant I	31%	41%	40%
ISS at 1st transplant II	34%	12%	0
ISS at 1st transplant III	14%	6%	10%
ISS at 2nd transplant I	48%	53%	40%
ISS at 2nd transplant II	17%	9%	0
ISS at 2nd transplant III	10%	13%	10%
Response to 1st transplant Good	10%	63%	70%
Response to 1st transplant Poor	80%	25%	20%
Response to 2nd transplant Good	52%	47%	30%
Response to 2nd transplant Poor	80%	25%	20%
Median Followup (months)	57.1 (3.4-76.7)	24.6 (10.5-87.8)	48.0 (31.9-64.0)

where the next most common toxicities. Solitary cases of cardiotoxicity, renal dysfunction, and orthostatic hypotension were observed.
Conclusion: Based on this small cohort of relapsed, transplant eligible MM patients, DPACE appears to be safe and effective salvage therapy that may serve as a bridge to ASCT. Ongoing work is being performed to compare the effectiveness of this regimen with other salvage therapies used in a similar population of MM patients and to measure progression free and overall survival after treatment.

248

BI-MODAL AGE DISTRIBUTION OF PATIENTS WITH RELAPSED HODGKIN LYMPHOMA UNDERGOING AUTOLOGOUS STEM CELL TRANSPLANTATION CORRELATES WITH MARKEDLY INFERIOR SURVIVAL AMONG PATIENTS AGE 35 YEARS AND OLDER

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Background: About 1/3 of advanced Hodgkin lymphoma (HL) patients fail first line therapy and are candidates for autologous stem cell transplantation (ASCT). Surveillance, Epidemiology and End Results (SEER) data indicates a bi-modal age distribution and superior survival among children/adolescents with HL (Bazzeh 2010). The aim of this study was to analyze the impact of age on overall survival (OS) among patients with relapsed/refractory HL undergoing ASCT. We hypothesized that 1) HL patients undergoing ASCT have a bi-modal age distribution; 2) the older age cohort has inferior OS after ASCT.
Patients and Methods: We performed an IRB approved, retrospective analysis of a combined cohort of 131 adult and pediatric HL patients undergoing ASCT at Emory University from 1995 to 2011. The cohort included 54% male, 65% Caucasians, and 26% African American patients. OS was compared using Kaplan Meier estimates for the time-to-event analysis and log rank test. Univariate and multivariate Cox proportional hazards models were used to test our hypotheses.
Results: Hypothesis 1: Two age cohorts of HSCT patients were identified: younger (≤35 years, n = 96) and older (>35 years old, n = 35), based on a bimodal distribution similar to SEER incidence. Hypothesis 2: Univariate analysis showed a significantly higher post-transplant mortality (p = 0.004) for patients >35 compared to those ≤35 years. Multivariate analysis, adjusting for gender, race, histology, disease status at transplant and stage, showed a hazard ratio of 2.4 for patients >35 years compared to those ≤35 years of age. Histology was similar across the age groups, with 75% patients having nodular sclerosing histology.
Conclusions: Our analysis shows markedly inferior OS among older patients with undergoing ASCT. The age related differences in post-transplant survival were not explained by the decreased actuarial life expectancy of older subjects based upon life-table projections of survival for the general population. While there were differences in supportive care, toxicity from treatments, and co-morbid diseases among older HL patients undergoing ASCT compared with younger HL patients, the inferior survival of older HL patients undergoing ASCT suggests that there may be differences in the biology of the disease based upon the age at which HL is diagnosed. Alternative strategies for autologous transplantation of older patients with relapsed/refractory HL are needed.

249

EPIGENETIC CHANGES ENHANCE THE CYTOTOXICITY OF COMBINED NUCLEOSIDE ANALOG-DNA ALKYLATING AGENTS IN LYMPHOMA CELLS

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Lymphomas are heterogeneous diseases that require combination therapy for an effective control. A sizable fraction of patients still fail to respond, or suffer progressive disease, after initially responding to treatment. In this setting, hematopoietic stem cell transplantation (HSCT) has been effective particularly in patients who respond to salvage chemotherapy. In an attempt to design more efficacious and safe pre-HSCT conditioning treatment, we expanded our previous observation on the synergistic cytotoxicity of nucleoside-analog-(NA) and DNA alkylating agent (AA) and investigated the interactions between AAs busulfan (Bu) and melphalan (Mel) and NA gemcitabine (Gem) in human lymphoma cell line J45.01. We used ~IC_{10} drug concentrations (57 μM Bu, 1 μM Mel and 0.02 μM Gem) which individually did not have significant effects on cell proliferation. However, their combination resulted in 50% inhibition of proliferation. Reduction to almost half (20 μM Bu, 0.7 μM Mel and 0.01 μM Gem) did not result in inhibition of cell proliferation. Addition of 0.6 μM suberoylanilide hydroxamic acid (SAHA) to the latter combination resulted in 65% inhibition of proliferation. The synergistic cytotoxicity of [Bu+Mel+Gem+SAHA] combinations correlates with the activation of the ATM-CHK2 pathway, phosphorylaton of KAP1, epigenetic changes such as methylation and acetylation of histone 3, and activation of apoptosis. We deduce that chromatin alterations mediated by Gem and SAHA may make genomic DNA more accessible to DNA alkylation by Bu and Mel resulting in increased DNA lesions and commitment of cells to apoptosis. The relevance of epigenetic changes in this drug exposure is further shown by the induction of expression of DNA methyltransferases in lymphoma (and leukemia) cells, which have low constitutive levels of DNMT3A and DNMT3B proteins. The addition of 5-aza-2'-deoxycytidine (DAC) to [Bu+Mel+Gem+SAHA] further enhances cell killing. Our results suggest that epigenetic changes mediated by Gem, SAHA and DAC alter chromatin structure and enhance DNA alkylation with Bu and Mel. Such effects are further aggravated by the ability of Gem to inhibit ribonucleotide reductase and DNA repair. In summary, this study expands our previous observation of NA-mediated synergistic toxicity mediated by AAs, and provides a basis to justify future mechanism-based clinical trials using [Bu+Mel+Gem+SAHA] as pre-HSCT conditioning for patients with chemotherapy-refractory lymphoma.

250

IMPROVED OUTCOME OF AFRICAN AMERICAN MULTIPLE MYELOMA PATIENTS WITH NOVEL AGENTS AND AUTOLOGOUS STEM CELL TRANSPLANT

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African Americans (AA) have twice the risk of developing multiple myeloma (MM) and, in prior studies, a higher mortality rate when compared to non-African Americans (non-AA). Novel agents, such as thalidomide, lenalidomide and bortezomib have improved the outcome of MM patients but the impact of these new therapies in AA patients has not been evaluated. In this study, 53 consecutive patients (23 AA, 30 non-AA) with newly diagnosed MM were retrospectively analyzed after induction treatment incorporating a novel agent. AA and non-AA patients were comparable for age, immunoglobulin isotype, stage of disease, serum albumin level, and cytogenetic abnormalities including del13 (27% vs. 38%, respectively, p = NS). Median serum level of â2 microglobulin at diagnosis was higher in AA than non-AA (5.9 mg/L vs. 3.5 mg/L, p = 0.024). Using the international uniform criteria, response rates to induction therapy were not statistically different between AA and non-AA: overall response rate (ORR, 91% vs. 77%), complete remission (CR, 22% vs. 27%), very good partial remission (VGPR, 26% vs. 20%), or partial remission (PR, 43% vs. 30%). However, rate of progressive disease was significantly higher in non-AA patients (p = 0.03). Of 53 patients, 46 (20 AA, 26 non-AA) received standard high-dose chemotherapy followed by autologous stem cell transplant (ASCT). With a median follow-up of 47 months, the ORR to ASCT was 89% in AA and 85% in non-AA, CR+VGPR rates were 61% in AA and 45% in non-AA (p = NS). Disease-free survival