Patient #	Age/sex	Involvement	Pretreatment	Status at alloSCT	Conditioning	Donor	Outcome
1	64/m	Skin	ALL-like, HD-Mtx	CR2	Flu-Bu-Cy-ATG	MMUD 8/10	Chronic GVHD, alive in CR, 44+ mo
2	67/m	Skin, BM	ALL-like, Gemcitabine	Refractory	Flu-Bu-Cy-ATG	MMUD 9/10	Dead (REL 7+ mo)
3	69/m	Skin, BM	AML-like	Refractory	Flu-Treosulfan-ATG	MUD 10/10	Alive in CR 7+ mo
4	55/f	Skin	ALL-like	CR1	Flu-Bu-Cy-ATG	MUD 10/10	Alive in CR 5+ mo

Six consecutive patients with BPDC have been treated at our institution between 2004 and 2008. All patients responded to acute leukemia-like induction therapy. Whereas two patients were ineligible for alloSCT due to comorbidity and experienced rapid relapse, 4 patients proceeded to RIC alloSCT as part of first-line (n = 1) or salvage treatment (n = 3) (**Table**). Median age was 66 (55-69) years. Two patients had active disease at the time of alloSCT. Conditioning was based on submyeloablative doses of busulfan or treosulfan with fludarabine and ATG, followed by transplantation of unmanipulated peripheral blood stem cell grafts obtained from matched or mismatched unrelated donors. Three patients live progression-free 44, 7 and 5 months post alloSCT, one patient relapsed 7 months after SCT and died soon thereafter.

We conclude that RIC SCT from unrelated donors is feasible in elderly patients with BPDC and might provide curative potential in this otherwise incurable disease. Prospective analyses of RIC alloSCT in BPDC are warranted.

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OUTCOME OF ELDERLY PATIENTS WITH ACUTE LYMPHOBLASTIC LEUKEMIA (EALL) WITH CHEMOTHERAPY: THE VANCOUVER EXPERIENCE

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Introduction: Age remains probably the most important prognostic factor in acute lymphoblastic leukemia (ALL). Adults with ALL have poor outcome with chemotherapy when compared to children; as age increases overall survival (OS) continuously declines. Elderly ALL (EALL) patients (pts) have the worst outcome with chemotherapy. Despite good initial response to induction chemotherapy, relapse rate (RR) is high and most pts will succumb to their disease. Few studies have addressed the outcome of EALL with chemotherapy.

Patients and Methods: Retrospective analysis of 32 EALL pts treated with chemotherapy at the L/BMT program of BC, Canada between 1989-2008. EALL was defined by age ≥60 years. Cytogenetics was available on 28(87.5%) pts. All pts received a consistent induction/consolidation and maintenance chemotherapy as per our modified ALL89-01 protocol. Complete remission (CR), Event free survival (EFS) and OS were analyzed.

Results: Betwen1989-2008, 32 pts (8.7% of adult ALL) were EALL, median age 66.0(60.1-76.1) years, 50% males. Median wbc count was 7.4(0.8-43) $x10^9$/L. 7/32(28%) were Ph+. Only one pt had CNS involvement. All pts received a consistent induction with daunorubicin, vincristine and prednisone. 27/32(84.4%) achieved CR. 18/27(66.7%) of pts. who achieved CR received phase II induction consisting of cyclophosphamide, cytarabine, and mercaptopurine. Consolidation chemotherapy was given in 17/27 (62.9%), in 15/17(88.2%) consisted of 1-2 cycle of cytarabine and tenoposide. 6 pts also received modified intensification with vincristine, daunorubicin, cyclophosphamide. 4 pts received tyrosine kinase inhibitor (TKI) with consolidation. 2 pts received other chemotherapy. Maintenance with methotrexate and mercaptopurine were given in 20 pts which include 4 pts who did not receive consolidation. 23/27(85.2%) pts who achieved CR had relapse. Median time to relapse from diagnosis is 240(112-1317) days. Median EFS and OS are 313(0-1317) and 489(38-1770) days, respectively. Cause of death was disease progression in 25/27 (92.6%). 6/7(85%) of Ph+ pts received combination chemotherapy with TKI. 3-year OS for the whole group was 26%, 36% for Ph+ pts and 23% for Ph- ALL.

Conclusions: EALL have poor outcome with chemotherapy. Despite the excellent CR rate with chemotherapy (84.4%), RR remains high (85.2%) and most patients (96.2%) die secondary to DP. In the TKI's era, EALL with Ph+ disease relatively fair better than Ph- EALL.

3-year disease free survival and over all survival

	All Patient	Ph+ group	Ph- group	P value
Number	32	7	25	
3-year DFS	15%	0%	19%	0.20
3-year-OS	26%	36%	23%	0.81

LYMPHOMA/MULTIPLE MYELOMA

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ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION WITH REDUCED-INTENSITY CONDITIONING IN PATIENTS WITH REFRACTORY AND RELAPSING MULTIPLE MYELOMA: LONG-TERM FOLLOW-UP

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Allogeneic SCT with myeloablative conditioning is potentially curative therapy for multiple myeloma (MM), but is associated with excessively high rates of non-relapse mortality (NRM). Reduced-intensity conditioning (RIC) allows reduction of NRM but relapse rate is increased. The role and timing of allogeneic SCT during the disease course are controversial. There is only limited data on the long-term outcome of RIC in the relapsing/refractory setting. We retrospective analyzed SCT outcomes in 50 patients (pts) given RIC for relapsing/refractory MM, between the years 2000-2004, from related (n = 27) or unrelated (n = 23) donors. The median age was 53 years (32-64). This was a relatively heavily pretreated group, a median of 3 years from diagnosis (0.5-14 years). Forty-seven pts failed one (n = 31) or two (n = 16) prior autologous SCT. Thirty pts were in PR (n = 26) or CR (n = 4) at the time of SCT and 20 pts had stable or progressive disease. RIC consisted of fludarabine and melphalan (100-140 mg/m^2). Disease response was assessed at day +100; 23 pts achieved CR; 17 PR, 7 died and 3 have already progressed by day +100. With a median follow-up of 6.4 years (range, 5-7.9 years), 16 pts are alive and 34 have died; 13 had NRM (cumulative incidence 26%) and 21 died of relapse. The median survival is 2.3 years and the estimated 7-year overall and progression-free survival (PFS) rates were 34% (95 C.I. 21-47%) and 26% (95 C.I. 14-38%), respectively. The PFS curve showed an apparent plateau after 3 years, with no later relapses, suggesting a potential cure. In multivariate analysis, adverse prognostic factors for survival included SCT not in remission, long duration of disease and SCT from a female donor to a male recipient. Related and unrelated donor SCT had a similar outcome. The 7 year PFS in 19 pts with none of these adverse factors was 47%. Chronic GVHD and achievement of CR after SCT were associated with improved outcome. In conclusion, allogeneic SCT can result in long-term PFS in a subset of MM pts failing prior therapy and should be considered early after failure and preferably after achieving a response with salvage therapy. The treatment goal is to achieve a CR as this is associated with better outcome.

Relapsing disease is still the major cause of treatment failure. Additional strategies, such as maintenance therapy with novel agents or judicious use of donor lymphocyte infusions merit further investigation for converting PR to CR and reducing relapse risk.

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THE GRAFT-VERSUS-MYELOMA EFFECT USING NON-MYELOABLATIVE OR REDUCED INTENSITY ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION (HSCT)

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Following myeloablative conditioning due to high treatment-related mortality (TRM), some studies have shown an inferior outcome using allogeneic HSCT compared to autologous transplant. More recently, non-myeloablative (NMA) and reduced intensity conditioning (RIC) for allogeneic HSCT was introduced. A prerequisite for this approach is a significant graft-versus-myeloma effect, which has not clearly been demonstrated. Between 1997 and 2005, 177 patients were reported to the CIBMTR following NMA (n = 120) or RIC (n = 57) and an allogeneic HSCT from an HLA-identical sibling donor. Median age was 50 years (range 24-69). Planned tandem autologous transplant followed by allogeneic HSCT was given to 105 of these patients. Most patients were given peripheral blood stem cells (98%). Outcomes, with a median follow-up of 55 months (range 3-98) and 25 months (range 3-76) respectively for allogeneic HSCT and autologous transplant followed by allogeneic HSCT, see Table below.

The following variables were significant in univariate outcomes analyses and were therefore used in the multivariate modelling: age, sex, performance status, IgG vs. non IgG myeloma, disease status and chemosensitivity, prior lines of chemotherapy, donor-recipient sex match, NMA vs. RIC, year of transplant and GVHD as the time dependent covariate. The only factor on multivariate analysis that increased the risk of TRM was acute GVHD (RR 2.38, p = 0.018). Only chronic GVHD decreased the probability of relapse on multivariate (RR 0.43, p = 0.012), but this effect was not seen in patients with IgG myeloma (n = 97, RR 0.7, p = 0.3) in comparison to all other types of myeloma (n = 80, RR 0.11, p = 0.004). Improved PFS was associated with autologous + allogeneic HSCT (RR 3.6, p = 0.001) and absence of acute GVHD (p = 0.001), but not chronic GVHD (RR 0.9, p = 0.7). In conclusion, patients receiving allogeneic HCT for myeloma, chronic GVHD decreased the probability of relapse, but only in patients with non-IgG myeloma. PFS was improved in patients receiving autologous + allogeneic HCT and was decreased in those with acute GVHD.

Outcomes	Allo only	Auto + Allo
Number of patients	72	105
Acute GVHD at 100 days, grades (1-4)	47 (37-60)%	37 (28-46)%
Chronic GVHD at 3 years	55 (43-67)%	58 (43-72)%
Treatment Related Mortality (TRM) at 3 years	27 (17-38)%	16 (10-25)%
Relapse at 3 years	48 (36-60)%	41 (29-54)%
Progression-free survival (PFS) at 3 years	25 (15-37)%	42 (20-43)%
Overall Survival at 3 years	45 (33-58)%	64 (53-75)%

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PHENOTYPIC ANALYSIS OF MULTIPLE MYELOMA CELL PROGENITORS

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The lack of specific molecules to define the multiple myeloma (MM) malignant cells responsible for disease development and relapse has hampered the evaluation of minimal residual disease (MRD) in MM. PC development compromises an array of subpopulations with distinctive phenotypes. Syndecan (CD138) is expressed in plasma cells (PC) and studies using CD138+ selected cells may be problematic since earlier progenitors may be excluded. To define myeloma bone marrow (BM) progenitor phenotype we developed a multicolor flow cytometry assay to study them. We have identified a CD138- subset that co-express CD19+, CD27+ and identical kappa or lambda light chain restriction as the abnormal plasma cells, as previously shown by others. Further characterization has shown that this subset co-expresses the c-Kit (CD117) (20%) and Notch-1 receptors (90%) as the hematopoietic stem cells (HSC) CD34+ counterpart. A small percentage of this BM cells show aldehyde dehydrogenase (ALDH) activity. Flow sorting of CD138- was feasible with 99% purity. Isolated populations were grown in methylcellulose with 5% PHA-leukocyte conditioned medium. CD138+ cells did not exhibit colony formation, and neither did the CD138-/CD38+/CD19-/CD34- cells. Instead, CD138-/CD38+/CD19+/CD34- cells were able to grow cell colonies (>100 cells) although their efficiency was low (1 in 15,000). CD34+ cells (HSC) also were able to grow cell colonies but with a significant lesser efficiency compared to SCF, IL-3 and GM-CSF cytokine stimulation. Cells harvested at day 14 from CD34+ and CD138-/CD38+/CD19+/CD34- generated colonies showed a lympho-plasmacytoid appearance. We showed that only CD138-/CD38+/CD19+/CD34- cells, but not CD34 + HSC, differentiated into a more mature syndecan (CD138+) expressing cell as determined by flow cytometry. Isolated CD138-/CD38+/CD19+/CD34- cells shown to be relatively bortezomib-resistant when compared to CD138+ plasma cells. The lacking expression of mature PC markers in this MM sub-population makes us hypothesize that they represent a progenitor B cells that differentiate into the malignant PC. Surrogate assays for stem cell activity (long term culture-initiating cell (LTC-IC), cobblestone-area forming cells (CAFC) and xenotransplant models should determine cancer stem cell activity of these cells. Research studies of these CD138- MM putative progenitor cells may lead to develop novel treatments to target MM subpopulations that may constitute the MRD reservoir.

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EFFICACY AND SAFETY OF CHEMOMOBLIZATION WITH VP-16 AND G-CSF IN PATIENTS (PTS) UNDERGOING AUTOLOGOUS STEM CELL TRANSPLANTATION (ASCT) FOR MULTIPLE MYELOMA (MM)

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Introduction: Although the number of ASCTs performed for MM continues to increase, the optimal mobilization strategy remains unclear. Additionally, concern has arisen about the impact of age and prior lenalidomide exposure on mobilization efficacy. High dose etoposide has been previously shown to have antitumor activity and efficacy in progenitor cell mobilization, and has a favorable safety profile when cytokine is also given (Gianni et al., JCO 1992). Here, we report on the efficacy and safety of mid-dose etoposide and G-CSF as a mobilization regimen for pts with MM.

Methods: Between May 2004 and June 2009, 152 pts with MM underwent ASCT following the use of VP-16 (375 mg/m2 on D#1 and D#2) and G-CSF (5mcg/kg twice daily from D#3 through the final day of collection) for mobilization. 65 pts were female, 87 were male, and median age was 56 yrs (range 17-72). Collection was