The overall and CR rates were: Gem/Bu/Mel: 91% and 81%; BEAM: 93% and 66%; Bu/Mel: both 64%. Despite its worse prognostic features Gem/Bu/Mel pts had improved EFS (63% v 42% v 38%, P = 0.002) and OS (85% v 63% v 62%, P = 0.02) compared to BEAM or Bu/Mel. Gem/Bu/Mel was superior in both PET- and PET+ subsets. Cox regression models identified the use of a regimen other than GemBuMel [risk ratio 2.1 (95% CI, 1.3-3.5, P = 0.002)], PET+ tumors at HDC [RR 1.9 (1.2-3.3), P = 0.002] and >1 prior relapse [RR 1.8 (1.1-2.9), P = 0.01] as independent adverse predictors of EFS.

Conclusions: Despite its markedly worse prognostic features, refractory HL pts treated with the novel regimen Gem/Bu/Mel show superior outcome than contemporaneous pts receiving BEAM or Bu/Mel. A randomized trial of Gem/Bu/Mel vs BEAM is warranted.

# 13 HIGHER MELPHALAN EXPOSURE IS ASSOCIATED WITH IMPROVED OVERALL SURVIVAL FOR MYELOMA PATIENTS UNDERGOING AUTOLOGOUS TRANSPANT

**Shae, P.J.1, 2, Nath, C.E.1, Nixon-Smith, I.1, Joshua, D.E.1, Kerridge, I.H.1, 2, Presgrave, P.K., Tiley, C.R., Kuan, Y.L.1, Trotman, J.1, 2 Children’s Hospital at Westmead, Sydney, NSW, Australia; 3 St Vincent’s Hospital, Sydney; 4 Royal Prince Alfred Hospital, Sydney; 5 Royal North Shore Hospital, Sydney; 6 Wellington Hospital, Wellington; 7 Gold Coast Hospital, Gold Coast; 8 Concord Hospital, Sydney**

**Introduction and Aims:** High dose melphalan (HDM) followed by autologous stem cell transplantation (ASCT) has a central role in the treatment of myeloma. We have already shown that patients given the same dose of HDM are exposed to a 5 fold variation in total exposure, as measured by area-under-the-concentration-versus-time curve (AUC) (1). It may be possible to improve outcomes by modifying the individual patient dose to optimize their exposure to melphalan. The aim of this study was to investigate if exposure to HDM was a significant determinant of outcome in myeloma patients.

**Methods:** This study included myeloma patients undergoing ASCT at six hematology centres, from 2004-2010. Melphalan concentrations were measured in 6-11 plasma samples collected after a median dose of 192mg/m² (range: 136-450 mg). This data was used to develop a population pharmacokinetic model for melphalan (1) and to determine total exposure to melphalan (AUC) for each patient. In this pharmacodynamic analysis, we report the relationship between exposure to various levels of melphalan and clinical outcome.

**Transplant toxicities were recorded using the Common Toxicity Criteria. Factors affecting transplant toxicity and disease outcomes were analysed by Cox regression analysis.**

**Results:** A total of 115 patients (66 males, 49 females) aged 35-73 years (median 58 years) were studied, with a median follow-up of 3.1 years. Myeloma type was IgG (n = 72), IgA (n = 26), biclonal (n = 1), Light chain only (n = 14) and non-secretory (n = 2). Melphalan AUC ranged from 4.9-24.6 mg/L.h, median 12.85 mg/L h. Risk factors for mucositis of ≥Grade 3 were higher melphalan exposure (HR 1.17, p = 0.08) and higher pre-transplant β2-microglobulin (HR 4.39, p = 0.007). Patients with AUC above the median were associated with the following: (1) improved Time to Progression (TTP), HR 0.56, p<0.02, (2) improved overall survival (OS) at both 2 years (91% versus 78%) and 4 years (82% versus 55%), HR 0.35, (p = 0.006). Progression free survival was not statistically significant, HR 0.64, (p = 0.08).

**Conclusions:** Detailed pharmacokinetic data following administration of HDM confirms that high exposure is associated with more mucositis, but an improved outcome, as measured by TTP and OS. These results suggest targeting a higher AUC is warranted in patients receiving HDM.


# 14 INCIDENCE OF CARDIAC ARRHYTHMIAS FOLLOWING AUTOLOGOUS PERIPHERAL BLOOD STEM CELL TRANSPLANTATION

**Singla, A.1, Hogan, W.H.1, Ansell, S.M.2, Buadi, F.K.2, Dingli, D.3, Dispenzieri, A.2, Gastineau, D.A.4, Gertz, M.A.1, Hayman, S.R.1, Irizards, D.J.1, Johnston, P.B.2, Lacy, M.Q.2, Lizov, M.R.2, Micalef, J.N.2, Porrata, L.E.2,5, Kamar, S.K.1,4 Creighton University Medical Center, Omaha, NE; 5 Mayo Clinic, Rochester, MN**

**Background:** Arrhythmias, especially supraventricular arrhythmias (SVA), often complicate autologous stem cell transplantation (ASCT). While easily treatable, they result in prolongation of hospital stay and increased rate of intensive care admissions. We undertook this study to determine the incidence and risk factors for cardiac arrhythmias during ASCT.

**Methods:** We examined the medical records of 983 patients who underwent ASCT for various hematological malignancies between Aug 2006 and Dec 2010. The underlying disease included plasma cell disorders in 573 (58%) patients and lymphoma or leukemia in the remaining. The rhythm had normalized in 81 (88%) patients at the time of dismissal post transplant, with a median duration of arrhythmia of <1 day (range <1 to 17 days). We then examined various pre and peri-transplant clinical and laboratory parameters to identify risk factors for SVA. In a univariate analysis, older age, presence of supraventricular complexes or AV conduction delays on pre-transplant ECG, presence of any valvular abnormality, increased atrial size, any prior history of arrhythmia, or being on a beta blocker or an antiarrhythmic agent, all increased the risk. In a multivariate analysis, only age > 65 years, presence of supraventricular complexes or AV conduction delays on pre-transplant ECG, and history of any prior arrhythmia increased the risk of arrhythmia during transplant. Among the patients with age > 65 years, presence of supraventricular complexes or AV conduction delays on pre-transplant ECG, and history of any prior arrhythmia, 20%, 26% and 23% respectively developed an arrhythmia compared to 4%, 8% and 8% among those without the risk factors, respectively (P = 0.001 for all three comparisons).

**Conclusions:** Among patients undergoing ASCT, 9% develop supraventricular arrhythmias. The risk is elevated among the older patients, those with a prior history of arrhythmias, and those with AV conduction delay or prematurity supraventricular complexes on ECG. Identification of patients at a higher risk may allow development of specific interventions.

**ALLOGENEIC TRANSPLANTS**

# 15 B CELLS FROM PATIENTS WITH CHRONIC GVHD SIGNAL VIA THE AKT-DRIVEN SURVIVAL AND METABOLIC FITNESS PATHWAY

**Allen, J.L.1, Wooten, T.1, Fore, M.2, Bhuva, N.S.3, Armitstead, P.1, Coghill, J.M.1, 2, Gabriel, D.1, Roehrs, P.A.2, Sharif, A.1, Irons, R.N.1, Hoffert, T.1, Richards, K.,2, Sesh, T.C.,3, Baldwin, A.S.1, Serody, J.1,3, Sarantopoulos, S.1,3 1 University of North Carolina, Chapel Hill, NC; 2 Cambridge Health Alliance, Boston, MA; 3 UNC School of Medicine, Chapel Hill, NC; 6 UNC School of Medicine, Chapel Hill, NC; 7 UNC School of Medicine, Chapel Hill, NC**

**Allogeneic hematopoietic stem cell transplant patients (HSCT) who develop chronic GVHD (cGVHD) have delayed B cell reconstitution**