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SIMPLE, BUT SIGNIFICANT FACTORS FOR SURVIVAL AFTER AUTOLOGOUS TRANSPLANTATION IN 181 MULTIPLE MYELOMA PATIENTS: A SINGLE CENTRE EXPERIENCE

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Background. Autologous stem cell transplantation (ASCT) has an established role in the treatment of symptomatic multiple myeloma (MM). Reliable and simple staging of MM is important for accurate prognostic evaluation and for the comparison of data from different clinical trials. Attempts to improve the widely accepted Durie-Salmon (DS) staging system have led to the development of numerous new prognostic systems, that have not been universally accepted. Recently new International Staging System (ISS) was presented. It has shown promise in patients (pts) treated by conventional as well as high-dose chemotherapy and is based on a simple combination of serum β2microglobulin (B2M) and albumin (alb) values (stage 1 = B2M under 3.5 mg/L and alb above 3.5 g/dL; stage 2 = B2M under 3.5 mg/L and alb under 3.5 g/dL, or B2M from 3.5 mg/L to 5.5 mg/L; stage 3 = B2M above 5.5 mg/L). *Aims.* The aim of our analysis was to evaluate the impact of selected clinically significant parameters for the survival of MM pts after ASCT including both ISS and DS systems in our set of pts. *Methods.* We have retrospectively evaluated 181 pts with MM undergoing autologous transplant (ASCT) in our centre between 1995-2004, median follow up from ASCT is 59 months, range 8-107 months. All pts had the same pretransplant therapy and were transplanted to one year after diagnosis. *Results.* Following ASCT, 52 pts (29%) were in complete remission (CR) and 113 pts (62%) in partial remission (PR). The median progression-free (PFS) and overall (OS) survival from transplant were 26.7 and 72.6 months, respectively. Seventeen pts (9%) are in CR and disease free over 5 years after ASCT (median follow up of this subgroup is 87 months, range 63-112). Differences in survival among pts with clinical stages according to DS system were not statistically significant (p=0.214). Patients with clinical stages according to ISS were significant differences in survival (p under 0.001): stage I (71 pts) ' median was not yet reached, stage II (70 pts) - median 72 months, stage III (25 pts) median 26.0 months. Significant prognostic parameters for poor survival were: age at transplant over 60 years (p under 0.001), IgA typ of monoclonal immunoglobulin (p=0.036), renal impairment with serum creatinine at diagnosis over 2 mg/dL (p=0.007), no achievement of CR after ASCT (p under 0.001). The status of disease before ASCT and type of maintenance therapy after transplant (alone interferon (IFN), IFN + dexamethasone, 4 cycles of chemotherapy CED and after it IFN) did not significantly affect OS after ASCT. *Conclusion.* In our group of patients the survival after ASCT correlated with the stage according to ISS, age, clinical response after transplant, type of paraprotein and renal impairment at diagnosis. The most significant parameters for better survival of MM pts after transplant are: age under 60 years at transplant, no ISS stage III at diagnosis and achievement of CR after transplantation.

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IDENTIFICATION OF NOVEL GENE EXPRESSION SUBGROUPS IN MULTIPLE MYELOMA USING UNSUPERVISED CLUSTER ANALYSIS

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Background. Accumulation of malignant plasma cells in the bone marrow is a hematological malignancy referred to as multiple myeloma (MM). Heterogeneity in clinical presentation and molecular markers strongly suggest that MM is a conglomerate of diseases with different molecular mechanisms. This is the most likely explanation for heterogeneous response of myeloma patients to therapeutic approaches such as high-dose therapy, conventional chemotherapy or the new agents bortezomib and thalidomide/Imids. Future development of effective therapies and specific strategies to overcome therapy-resistance will only be possible if we are able to recognize and understand the biological subtypes of myeloma. Therefore, there is a continuous need to improve the molecular classification of MM. *Aims.* Our hypothesis is that unsupervised cluster analysis of gene expression profiles will provide an improved molecular classification of myeloma patients compared to cytogenetics alone. The aim of this study is to test this hypothesis. *Methods.* Expression data of 173 newly diagnosed, untreated myeloma patients previously reported by Tian *et al.* (NEJM 2003,349:2483-2494) were downloaded from the Gene Expression Omnibus (www.ncbi.nlm.nih.gov/geo), accession number GDS531. The dataset contains expression data that were obtained using Affymetrix U95Av2 arrays and were normalized using the method of global scaling, provided in the Affymetrix MAS5.0 software. Unsupervised hierarchical cluster analysis was performed with complete linkage and Euclidean distance as similarity metric, using the Omniviz package. Supervised analyses were performed with the use of SAM software. Cluster-specific gene lists obtained using the SAM method were imported in EASE v2.0. Based on available annotations in Gene Ontology and the GenMAPP database we determined which pathways or processes were statistically overrepresented in the cluster-specific gene lists. Correction for multiple testing was performed using the Benjamini-Hochberg method in EASE v2.0. *Results.* Unsupervised cluster analysis defined ten clusters based on overall correlation. Clusters displayed unique, non-overlapping gene expression signatures. Six of these clusters have not been described before. Three clusters corresponded to recurrent 14q32 translocations: t(4;14), t(11;14) and t(14;16)/t(14;20). One cluster appears to represent polyclonal plasma cell preparations. One of the novel clusters displayed specific expression of WNT10B, BIK and CST6 combined with STAT1 downregulation. A novel subgroup of t(11;14) patients was identified as a particularly distinct cluster lacking expression of TNFRSF7/CD27 and specifically expressing RBP1 and RAB33A. Samples from patients lacking myeloma-related bone lesions mainly grouped together in only three clusters. FRZB downregulation was specifically associated with these three clusters. Analysis of cluster specific gene signatures identified expression of WNT10B, bone morphogenetic protein 4, and osteopontin as specific events in subgroups with low bone-disease frequencies. *Summary/Conclusion.* Using gene expression profiling we have identified a novel subgroup of t(11;14) myeloma patients and a new genetic cluster in which only 37% of the patients were diagnosed with bone disease. The unsupervised nature of our analysis has proven a powerful method for the classification of MM patients, showing improved discriminating capacity.

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EFFICACY OF SINGLE-AGENT BORTEZOMIB VERSUS THALIDOMIDE IN PATIENTS WITH RELAPSED OR REFRACTORY MULTIPLE MYELOMA: A SYSTEMATIC REVIEW

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Aim. To perform a systematic review of the efficacy of monotherapy with bortezomib versus thalidomide in patients with relapsed or refractory multiple myeloma. *Methods.* Scientific literature published in English from 1966 to June 2005 (MEDLINE, EMBASE, Cochrane library), publication reference lists, Janssen-Cilag Pty Ltd data-on-file, and abstracts from recent multiple myeloma conferences were reviewed. Prospective studies containing at least a single arm of either treatment group with n ≥30 and using continuing or variable thalidomide dosing were included. Studies adding dexamethasone for non-responders were excluded. Outcomes were analysed on an intent-to-treat basis. Statistical pooling was performed where possible for the primary outcome of response rate, defined by a serum M-protein reduction ≥50% (A) and by strict (e.g. European Bone Marrow Transplant, EBMT) criteria (B), and for the secondary outcomes of overall survival and progression-free survival. *Results.* One bortezomib (n=333, APEX, NEJM 2005, 352; 2487-98) and 15 thalidomide (n=1007) studies were included. Patient baseline characteristics including age, gender, IgG:IgA, disease duration and β-2 microglobulin (β2M) were well matched, except that 48% of bortezomib patients had received prior thalidomide. On an intent-to-treat basis, the overall estimate for response rate (A) was 53% for patients receiving bortezomib versus 32% for thalidomide (p<0.001, n=10 studies). For response rate (B) the estimate was 36% for patients receiving bortezomib versus 22% for thalidomide (p<0.001, n=4 studies). One-year overall survival was 80% for patients receiving bortezomib versus 63% for thalidomide (p<0.001, n=6 studies). Due to differences in disease monitoring and definitions of progression, it was not possible to compare results for progression-free survival. *Conclusion.* Bortezomib was associated with a significantly higher response rate and a greater proportion of patients achieving one-year overall survival than thalidomide in patients with relapsed or refractory multiple myeloma, despite 48% of bortezomib treated patients having received prior thalidomide.