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Sustained Suppression of Involved Free Light Chain Predicts Long Term Outcomes in Multiple Myeloma after Allogeneic Hematopoietic Stem Cell Transplantation: A Multi-Institutional Study

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Background: Allogeneic stem cell transplantation (alloSCT) for multiple myeloma (MM) can offer prolonged remission and may have curative potential. Overproduction of the disease specific clonal serum free light chains by malignant plasma cells (*involved* free light chain, iFLC) is a marker of disease activity. Underproduction of the *uninvolved* serum free light chain (uFLC, from non-malignant plasma cells) is a marker of MM mediated immune suppression. Early prediction of relapse after allogeneic SCT remains a challenge, and is important for prognostic and therapeutic purposes. We hypothesized that sustained iFLC suppression at 12 months post-alloSCT would be associated with improved survival.

Methods: The primary cohort was 50 consecutive patients treated with allogeneic SCT from two institutions. This was selected from a total of 60 patients with patients excluded for death (n=6) or relapse (n=4) prior to one year. Data was collected retrospectively 2005-2010 and then prospectively from 2010-2012. Baseline and follow-up serum FLC (at 3 month intervals) were correlated with overall survival (OS). Patients were considered to have a "suppressed" FLC if the serum iFLC was reduced below the uninvolved FLC at 12 months post-alloSCT. OS was measured from 12 months post-alloSCT using Kaplan-Meier plots and the 2 groups were compared using log-rank test. A step-wise backward cox-proportional hazards model was used adjusting for age, $CD34^+$ stem cell dose, conditioning regimen (myeloablative vs. reduced intensity), graft versus host disease prior to one year, disease risk by FISH (standard vs. high risk), International Staging System (standard risk vs. high risk) and disease status prior to SCT (complete remission vs. no complete remission).

Results: Median follow-up time was 40.0 months from transplant (12-95.6 months). Longer duration of iFLC suppression was associated with superior outcomes. Patients without sustained iFLC suppression at one year post-SCT had worse OS (p=0.03, Figure 1). The 2-y OS in the sustained iFLC suppression cohort (95% [95% CI 86-NA]) was significantly superior to the non-sustained iFLC suppression cohort (70% [95% CI 57-99]) (P=0.03, Figure 1). By univariate analysis, there were no baseline characteristic differences. By multivariate analysis, lack of iFLC suppression at 1-year post-alloSCT was associated with significantly increased mortality (HR 7.01, 95% CI 1.21-40.8, p=0.03). Patients with iFLC recovery prior to one year had increased relapse risk compared to sustained iFLC suppression (HR 10.4, 95% CI 2.95-36.6, p=0.0003).

Conclusions: Sustained serum iFLC suppression at one year relative to the uFLC is a predictive marker of outcomes following alloSCT for MM. Early recovery of iFLC may be an indicator of disease progression following alloSCT, thus identifying patients who may benefit from preemptive interventions to prevent post-transplant relapse.

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High-Throughput Sequencing of Antibody Genes Successfully Identifies Clonal Ig Rearrangements in Multiple Myeloma Patients

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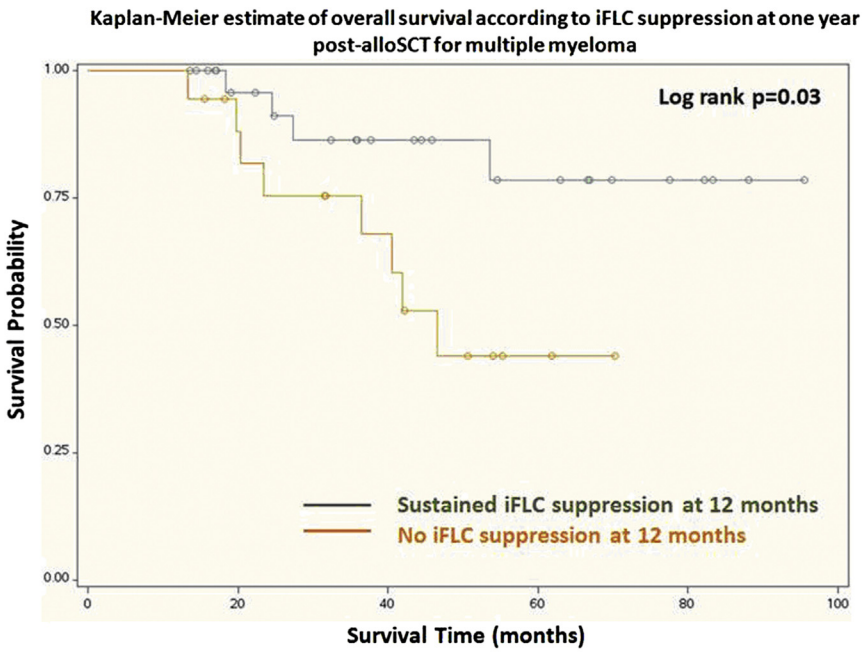

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Background: High-throughput sequencing (HTS) of antibody gene rearrangements is an emerging tool for minimal residual disease (MRD) monitoring in B cell malignancies in which the malignant clone harbors a monoclonal Ig heavy chain (IgH) and/or light chain (κ or λ) rearrangement. This approach has shown promise in B-ALL and CLL, but application of Ig HTS to clinical multiple myeloma (MM) samples has not been demonstrated previously.

Approach: We conducted HTS of PCR-amplified IgH (VDJ and DJ) and κ/λ (VJ) rearrangements from bone marrow aspirates (BMA) of patients with MM (n=9), MGUS (n=1), and lymphoplasmacytic lymphoma (n=1), and peripheral blood (PB) of a patient with plasma cell leukemia (n=1). In 9/12 samples, an aliquot was enriched for CD138+ cells by immunomagnetic separation and analyzed separately. Dominant clones from enriched and un-enriched aliquots were compared to verify the malignant clonotype sequence. Disease burden in un-enriched samples was also evaluated by microscopy (BMA/PB smear) and ranged from 0 (hemodilute) to 37%.

Results: In 11/12 samples, a clearly dominant IgH and/or κ/λ rearrangement (>2.7% of total sequences, range 2.7-99.9%) was identified with clear separation from background frequency (at least 2.7-fold higher frequency than next most common clone). One sample exhibited an oligoclonal repertoire with no clearly dominant sequence. In 9/9 cases with paired CD138-enriched samples, the dominant sequences in the enriched and un-enriched samples were identical, indicating successful identification of the malignant clonal Ig rearrangements in the un-enriched sample. Results were largely consonant with clinical data, though in one IgG-λ MM sample, no dominant, productive λ rearrangement was detected, and in one IgG-κ MM sample, no dominant, productive heavy chain rearrangement was detected. This may be due to mutations at primer-binding sites in these rearrangements. In both cases, alternative clone-tracking sequences were available from the other loci (i.e., IgH in the first case and κ in the second). In 7/12 cases, >1 dominant sequence among the IgH (VDJ and DJ), κ, and λ rearrangements was identified that would be suitable for longitudinally tracking the malignant clone.

Conclusion: HTS of Ig heavy and light chain rearrangements can successfully identify the MM clone in clinical specimens, including those with low MM burden. Application of this technique to MRD evaluation in MM warrants further development.

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Reduced Intensity Conditioning Allogeneic Stem Cell Transplantation for Adults with Relapsed and Refractory Mantle Cell Lymphoma: A Single Center Retrospective Analysis in the Rituximab Era

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Backgrounds: Despite recent improvements in the therapy of mantle cell lymphoma, relapsed and refractory disease still portends a dismal prognosis. Allogeneic stem cell transplantation (allo-SCT) represents the only potentially curative therapy in this setting. The aim of this report was to evaluate the results of reduced-intensity-conditioning (RIC) allo-SCT in a retrospective cohort of patients from a single institution.

Patients and Methods: Twenty-nine patients (median age 58 years, range 34-71) undergoing RIC allo-SCT from April 1999 to May 2013 are included in this retrospective analysis. The median number of previous lines of therapy was 5 (range 1-6) with 13 (45%) of patients having previously failed an autologous SCT. Twenty-six patients (90%) had chemosensitive disease at allo-SCT (CR=17, PR=9) and 3 (10%) had stable disease. The second line International Prognostic Index (sIPI) was 0 in 19 patients (65%) and ≥1 in 9 patients (31%). Data was missing in 1. RIC regimens included cyclophosphamide/ fludarabine/ TBI 200cGy with (n=17) or without (n=4) peri-allo-SCT rituximab and melphalan/ fludarabine with (n=6) or without (n=2) alemtuzumab. All patients received unmodified grafts from a matched related (n=12), matched unrelated (n=10) or mismatched unrelated (n=7) donor. Progression-free (PFS) and overall (OS) survival were calculated from the time of allo-SCT. Kaplan-Meier survival curves and a permutation-based logrank test were used to compare PFS and OS based on alemtuzumab use and the sIPI.

Results: All but one patient engrafted with full donor chimerism. The cumulative incidences (CI) of grade II-IV acute GVHD at days +100 and +180 were 36% (95%CI: 19-53%) and 46% (95%CI: 27-64%), respectively. The CI of chronic GVHD at 1 and 2 years was 20% (95%CI: 7-38%) and 29% (95% CI: 12-49%), respectively. The CI of progression of disease and non-relapse mortality at 2 years were 32% (95%CI: 15-51%) and 19% (95%CI: 7-37%), respectively. With a median follow-

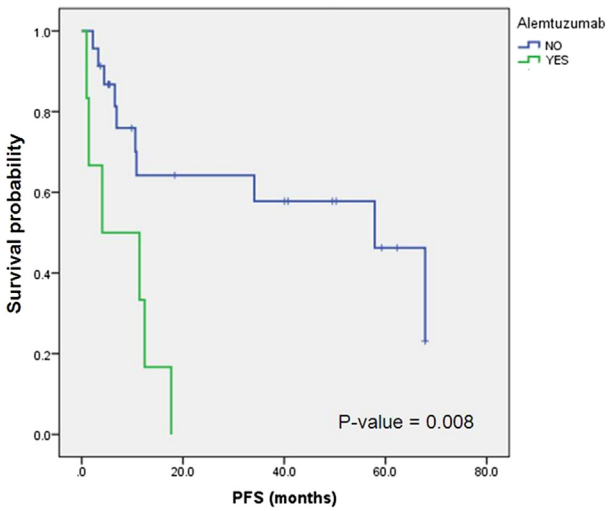

Figure 1. PFS is decreased in patients who receive alemtuzumab