85

CT7/MAGE-C1 Expression and Immune Responses Following Allogeneic Transplant for Multiple Myeloma

Eleanor M. Tyler[1,2], Achim A. Jungbluth[3], Sacha Gnjatic[3], Richard O'Reilly[4], Guenther Koehne[5]. [1] Immunology and Microbial Pathogenesis Program, Weill Cornell Graduate School of Medical Sciences, New York, NY; [2] Sloan-Kettering Institute, New York, NY; [3] Ludwig Institute for Cancer Research, New York Branch, New York, NY; [4] Department of Pediatrics, Pediatric Bone Marrow Transplant Service, Memorial Sloan-Kettering Cancer Center, New York, NY; [5] Department of Medicine, Adult Bone Marrow Transplant Service, Memorial Sloan-Kettering Cancer Center, New York, NY

Cancer-testis antigen 7 (CT7, or melanoma-associated antigen (MAGE)-C1) is the most frequently and consistently expressed MAGE antigen in multiple myeloma (MM). CT7 is an independent negative prognostic factor for MM, exhibits a tissue-restricted expression pattern, and is highly expressed during all stages of disease. Consequently, CT7 is regarded as a potential target for immunotherapeutic strategies in MM.

We sought to characterize CT7 protein expression in the bone marrow (BM) of MM patients (pts) following allogeneic T cell-depleted (TCD)-HSCT, and to examine the significance of CT7-specific cellular and humoral immune responses in these pts. We further aimed to determine CT7-derived immunogenic epitopes and their associated allelic restrictions.

Expression of CT7 in neoplastic $CD138^+$ plasma cells was evaluated by immunohistochemistry double staining in BM biopsies from 15 pts. CT7 expression was present in 13/15 pts. Longitudinal analyses conducted in 10 of these pts showed that low levels of CT7 protein were associated with better outcomes. Conversely, the presence of CT7 protein in a high percentage of myeloma cells was associated with a poorer prognosis.

The nonamer FLAMLKNTV was predicted to have the highest binding indices for HLA-A*0201 by reverse immunology. Indeed, we confirmed epitope-specific reactivity by measuring intracellular IFN-γ production to this peptide in PBMC and BMMC from HLA-A*0201-expressing pts. The tetramer HLA-A*0201-$CT7_{1087\text{-}1095}$ was generated to permit longitudinal monitoring of CT7-specific T cell frequencies.

CT7-specific T cell frequencies were quantified by tetramer staining in PBMC from 4 HLA-A^*0201^+ MM pts. Two pts who developed marked $tetramer^+$ T cell responses (up to 17.7 $CD8^+$T cells/μL PB) entered CR. In contrast, 2 pts who failed to develop prominent $tetramer^+$ T cell responses exhibited progressive disease. Phenotypic analyses revealed the predominant presence of central memory CT7-specific T cells in the BM, while effector memory cells dominated in the PB. These initial clinical results suggest a potential relationship between CT7-specific T cell frequencies and disease course.

Humoral responses to a panel of tumor antigens, including CT7, were examined longitudinally in 10 pts. Analyses of CT7-specific antibody titers in one pt revealed a response to a single CT7-derived peptide ($CT7_{1029\text{-}1048}$). This response developed at a later time point than T cell responses occurring in the same pt.

Finally, we report CT7-specific cytotoxic activity against the CT7-expressing HLA-A^*0201^+ MM cell line U266 by T cells expanded from a donor-reconstituted HLA-A^*0201^+ MM pt. Together, these results provide evidence of CT7-specific T and B-cell responses that are able to target MM cells in treatment responsive patients. Adoptive immunotherapeutic approaches targeting CT7 may therefore prove useful in pts with MM post allogeneic TCD-HSCT.

86

Clinical Outcomes of Hematopoietic Cell Transplantation in Patients with Diffuse Large B Cell Lymphoma Transformed From Follicular Lymphoma

Baldeep Wirk[1], Linda Burns[2], Timothy Fenske[3], Zhenhuan Hu[4], Ginna G. Laport[5], Silvia Montoto[6], David G. Maloney[7], Wael Saber[8]. [1] Hematology/Oncology, University of Florida, Gainesville, FL; [2] Medicine, University of Minnesota, Minneapolis, MN; [3] Hematology/Oncology, Medical College of Wisconsin, Milwaukee, WI; [4] CIBMTR, Milwaukee, WI; [5] Division of BMT, Stanford University Medical Center, Stanford, CA; [6] Centre for Medical Oncology /Institute of Cancer, QMUL/Barts and The London School of Medicine and Dentistry, London, United Kingdom; [7] Data Abstraction Department - Clinical Research, Fred Hutchinson Cancer Research Center, Seattle, WA; [8] Medical College of Wisconsin/CIBMTR, Milwaukee, WI

Background: Transformation of follicular lymphoma (FL) to diffuse large B cell lymphoma (DLBCL) occurs in 30% of cases at 10 years. Historically, survival with chemotherapy is poor. Limited data are available on the role of autologous or allogeneic hematopoietic cell transplantation (autoHCT or alloHCT) for DLBCL transformed from FL.

Methods: Descriptive analysis of 155 patients (age>18 years) from 89 centers with transformation of FL to DLBCL reported to the CIBMTR who had autoHCT or alloHCT from 1990-2009. Pathology reports were reviewed in all cases to confirm transformation of FL to DLBCL. This is the largest epidemiologic series analyzing outcomes of HCT in transformed DLBCL.

Results: Patients were classified into 3 groups consisting of autoHCT (N=108), alloHCT (N=33), alloHCT (N=14) after prior autoHCT (performed for FL) with median ages of 56, 49, 51 years (yr) who received median of 3, 4, 5 lines of chemotherapy prior to HCT, respectively. AutoHCT, alloHCT, and alloHCT with prior autoHCT groups had 5 yr relapse rates 54% (95% confidence intervals [CI] 45-64%), 33% (95% CI 17-50%), 38% (95% CI 15-65%); 1 yr treatment related mortality 8% (95% CI 3-14%), 41% (95% CI 25-58%), 62% (95% CI 35-85%); 5 yr progression free survival (PFS) 36% (95% CI 27-46%), 18% (95% CI 6-35%), 0%; 5 yr overall survival (OS) 50% (95% CI 40-60%), 22% (95% CI 8-41%), 7% (95% CI 0-26%) respectively. The size of the cohort did not allow multivariate analysis. Univariate survival analysis of associations between risk factors and post autoHCT and alloHCT outcomes showed age, Karnofsky performance status, rituxan use, extranodal disease and disease status at HCT (complete remission versus primary induction failure) were not significant factors. Use of HLA identical sibling vs unrelated donors, ATG/campath vs none, did not impact PFS/ OS after alloHCT. Chemotherapy vs total body irradiation-based conditioning for autoHCT had improved 3 yr PFS (46% [95% CI 35-57%] vs 24% [95% CI 9-43%]; $P = .04$); but 3 yr OS was not significantly different. Transformation >1 yr vs <1yr from diagnosis (dx) yielded improvement in 1 yr PFS for the autoHCT (61% [95% CI 51-71%] vs 29% [95% CI 11-53%]; $P = .01$) and alloHCT groups (44% [95% CI 24-64%] vs 11% [95% CI 0-38%]; $P = .03$). Transformation > 1 yr vs <1 yr from dx also had better 2 yr OS in the alloHCT group (43% [95% CI 24-64%] vs 11% [95% CI 0-38%]; $P = .03$). Time from dx to transformation was not associated with OS after autoHCT. The Kaplan Meier graph for PFS/ OS showed a plateau after 40 months only for autoHCT group.

Conclusions: Both autoHCT and alloHCT are feasible and provide durable PFS and OS in this high risk cohort. Transformation to DLBCL > 1 year after dx of FL is associated with improved 1 yr PFS in both autoHCT and alloHCT groups, and superior 2 yr OS in the alloHCT group compared to those cases with transformation< 1year from dx of FL. Patients with primary induction failure also benefit from consolidation with HCT.

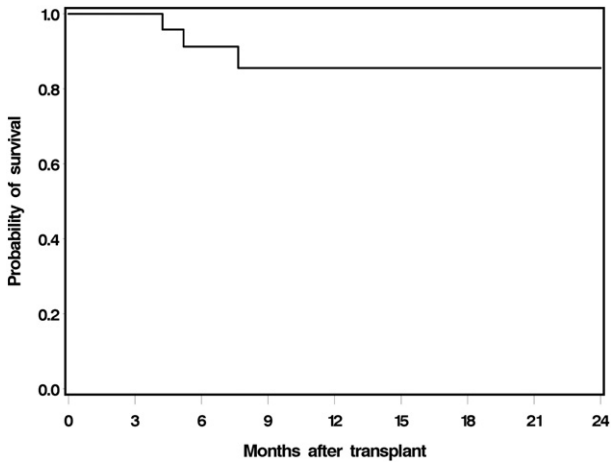
PEDIATRIC DISORDERS ORAL

87

Treosulfan Based Conditioning Followed by Allogeneic Hematopoietic Cell Transplantation for Treatment of Patients with Non-Malignant Diseases: Preliminary Results of a Phase II Study

Lauri Burroughs [1,2], Eneida Nemecek [3], Troy Torgerson [2], Katherine A. Guthrie [4], Julie-An Talano [5], Jennifer Domm [6], Akiko Shimamura [1,2], Paul A. Carpenter [1,2], Suzanne Skoda-Smith [2], Janet A. Englund [2], K. Scott Baker [1,2], Rainer F. Storb [1,2], Ann Woolfrey [1,2]. [1] Fred Hutchinson Cancer Research Center; [2] University of Washington School of Medicine; [3] Oregon Health & Science University; [4] Clinical Oncology, Fred Hutchinson Cancer Research Center, Seattle, WA; [5] Medical College of Wisconsin; [6] Vanderbilt University

Treosulfan has several characteristics that make it appealing for use in conditioning, including bypass of hepatic enzyme activation, a highly predictable pharmacokinetic profile, and sufficient immunosuppressive activity to allow for engraftment of donor cells across histocompatibility barriers. Here we report the preliminary results of a phase II multi-center clinical trial for 25 patients with non-malignant diseases [primary immune deficiency diseases (PIDD, n=12), hemophagocytic lymphohistiocytosis (HLH; n=5), inherited bone marrow failure syndromes (n=4), and other non-malignant diseases (n=4)] who received allogeneic hematopoietic cell transplantation (HCT) from October 2009 to July 2012. Patients were given HLA-matched related (n=2) or unrelated (n=23) marrow (n=23) or G-CSF mobilized peripheral blood stem cell (n=2) grafts following conditioning with treosulfan (total dose: 42 grams/m^2), fludarabine (total dose: 150 mg/m^2), +/- thymoglobulin (rabbit ATG, n=16; total dose: 6 mg/kg). All patients received tacrolimus and methotrexate for GVHD prevention. Median age at HCT was 8.3 (range, 0.4-30.5) years. Three patients had received a previous allogeneic HCT. Median time to neutrophil engraftment was 22 days. Of the 25 evaluable patients, all had full (>95%; n=19) or mixed (50-94%, n=3; 6-49%, n=3) donor CD3+ T-cell chimerism. One patient with sickle cell disease who received a very low total nucleated cell dose required a stem cell boost due to poor graft function. With a median follow-up for survivors of 12 (range, 2-35) months, the 1-year survival was 86%. Three patients died; one died from GVHD 5 months after HCT, one died at 4 months from an unrelated surgical complication, and one died at 8 months from recurrent CNS HLH. None of the patients developed sinusoidal obstructive syndrome. One patient was intubated for airway protection in the setting of herpes stomatitis. The cumulative incidence of grades III-IV acute GVHD at 100 days and 1-year chronic GVHD were 12% and 25%, respectively. Patients who received ATG had a significantly lower incidence of grade III-IV acute GVHD (0% compared to 33%; $P = .02$). Our results to date indicate that the combination of treosulfan, fludarabine, and rabbit ATG is effective at establishing donor engraftment with a low toxicity profile. These results suggest that the reduction of regimen-related toxicities will translate into improved survival outcomes in patients with PIDD and other non-malignant diseases, and support the need for future disease-specific clinical trials.



88

HLA Allele Matched Unrelated Donor Stem Cell Transplant As First Line Therapy for Children with Acquired Severe Aplastic Anemia

Jing Chen [1], Vincent Lee [2], Chengjuan Luo [3], Alan Kwok-Shing Chiang [4], Suradej Hongeng [5], Poh-Lin Tan [6], Ah-Moy Tan [7], Sanpakit Sanpakit [8], Chun Fu Li [9], Anselm Chi-wai Lee [10], Hsin Chieh [11]. [1] shanghai children's medical center; [2] Prince of Wales Hospital, Hong Kong; [3] shanghai children's medical center, shanghai; [4] Queen Mary Hospital, the University of Hong Kong; [5] Pediatrics, Ramathibodi Hospital, Mahidol University, Bangkok, Thailand; [6] Paediatrics, National University Health System, Singapore, Singapore, Singapore; [7] Paediatric Medicine, KK Women's and Children's Hospital, Singapore, Singapore; [8] Department of Pediatrics Faculty of Medicine Siriraj hospital Mahidol University; [9] Nanfang Hospital Southern Medical University; [10] Children's Haematology and Cancer Centre Mount Elizabeth Hospital; [11] National University Health System and Yasuhiro Okamoto, Kagoshima University Medical and Dental Hospital

From August 2000 to November 2011, 127 children under the age of 18 years with acquired severe aplastic anemia (SAA) received hematopoietic stem cell transplantation (HSCT) in one of the 10 Asia Pacific institutions of the VABMT Consortium, including 53 with matched sibling donor (MSD) and 74 with alternative donor (AD). Among these 74 AD, 22 were matched unrelated donor (MUD), 32 were mismatched unrelated donor (MMUD) and 20 were mismatched related donor (MMRD). Although the MSD group developed less grade II-IV acute GVHD compared to the AD group (14.3% vs 32.8%, $P = .029$), there was no significant difference in grade III-IV GVHD (10.2% vs 12.5%, $P = .774$) or chronic GVHD (19.6% vs 35.0%, $P = .088$). After a median follow-up of 33.5 months, the incidence of graft failure and 3-year overall survival were