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THE "SIDE-POPULATION" OF HUMAN LYMPHOMA CELLS HAVE INCREASED CHEMO-RESISTANCE, STEM-CELL LIKE PROPERTIES AND ARE POTENTIAL TARGETS FOR IMMUNOTHERAPY

Shafer, J.A.[1,2], Leen, A.M.[1,2], Cruz, R.[1,2], Craddock, J.A.[1,2], Heslop, H.E.[1,2], Rooney, C.M.[1,2], Brenner, M.K.[1,2], Bollard, C.M.[1,2], Foster, A.E.[1,2] [1] Baylor College of Medicine, Houston, TX; [2] Baylor College of Medicine, Houston, TX

We have previously demonstrated that hematological malignancies contain a distinct "side-population" (SP), which is characterized by the active transport of Hoechst fluorescent dye. The mechanisms responsible for Hoechst efflux contribute to SP resistance to chemotherapy and SP have been shown to be enriched for tumor initiating cells in several human cancer models. We hypothesize that targeting the cancer "SP" cells using immunotherapy may prevent relapse by eliminating the cell population that is chemoresistant and has tumor repopulating potential. We characterized SP cells in 11 human lymphoma cell lines. 5/11 lymphoma cell lines had a distinct SP ranging from 0.8–2% of total cells. We subsequently found SP cells with tumor associated antigens (TAAs) in biopsy samples from patients with Hodgkin's Lymphoma, T-cell Lymphoma, and Follicular lymphoma. Culture of the sorted cell lines show that SP but not the non-SP cells produced progeny that were both SP and non-SP cells. Gene expression analysis of the SP showed increased expression of ABC transporters that mediate transport of some chemotherapeutic agents out of the cell. We evaluated whether lymphoma cell lines with a SP are resistant to the chemotherapeutic drug gemcitabine. The viability of lymphoma lines containing SP cells was markedly higher (mean 59.8%; range 37.4–87.8) than the viability of lines without a SP (mean 9.3% range 3.0%–12.2) when cultured with 10nM gemcitabine for 3 days. The SP component of the lymphoma cells became enriched 10-fold when cultured with gemcitabine. Moreover, when equal numbers of SP and non-SP cells were grown in separate fractions with gemcitabine, there was reduced viability of the non-SP (mean 2,247 ± 294 cpm) by thymidine assay. In contrast, the viability of the SP was preserved (mean 13,200 ± 7500 cpm). Although lymphoma SP cells are resistant to chemotherapeutic agents, they also express higher levels of TAAs that are known targets for cytotoxic T-cells. RT-PCR and immunohistochemistry both show that SP cells are HLA positive and have increased expression of TAAs (e.g. MAGEA, SSX, PRAME) transcripts and protein compared to non-SP cells from the same tumor. We have generated T-cells that recognize these TAAs and have shown they can recognize and kill SP targets. Hence, lymphoma cell lines and primary lymphoma tissue contain chemotherapy-resistant SP cells which express tumor associated antigens and may be targeted by specific T cells.

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REDUCED-INTENSITY ALLOGENEIC VERSUS AUTOLOGOUS PERIPHERAL BLOOD STEM CELL TRANSPLANTATION IN PATIENTS WITH HODGKIN'S AND NON-HODGKIN'S LYMPHOMA

Gutierrez-Aguirre, C.H.[1], Cantu-Rodriguez, O.G.[1], Gonzalez-Llano, O.[1], Jaime-Perez, J.C.[1], Salazar-Riojas, R.[1], Martinez-Gonzalez, O.L.[1], Gutierrez-Riverol, K.I.[2], Ruiz-Delgado, G.J.[2], Ruiz-Arguelles, G.J.[2], Gomez-Almaguer, D.[1] [1] Hospital Universitario de La U.A.N.L., Monterrey, Nuevo Leon, Mexico; [2] Centro de Hematologia y Medicina Interna de Puebla, Puebla, Mexico

Introduction: The role of reduced-intensity conditioning allogeneic stem cell transplantation (allo- RICSCT) compared with high-dose chemotherapy followed by autologous stem cell transplantation (auto-SCT) in Hodgkin's disease (HD) and in non Hodgkin's lymphoma (NHL) patients remains poorly defined. We retrospectively analyzed the outcome of 71 patients with advanced disease who received one of both treatments, 39 patients with NHL and 32 with HD. Twenty three NHL patients and 14 HD patients received an allo-RICSCT using fludarabine-cyclophosphamide-low dose busulfan as conditioning regimen. Sixteen NHL patients and 18 HD patients received auto-SCT using cyclophosphamide and etoposide as conditioning regimen.

Results: (see table 1).

Table 1

	NHL + Allo	NHL + Auto	HD + Allo	HD + Auto
Age (median) years	47	56	26	26
Disease stage before SCT				
1st remission	0	7 (44%)	1 (7%)	3 (17%)
2nd remission	8 (35%)	2 (12%)	0	3 (17%)
Refractory	16 (65%)	7 (44%)	13 (93%)	12 (66%)
Ann Arbor I-II	5 (22%)	7 (44%)	0	6 (33%)
Ann Arbor III-IV	18 (78%)	9 (56%)	14 (100%)	12 (67%)
B symptoms	65%	75%	85%	89%
CD34+ cells infused	5 × 106	2.2 × 106	4.5 × 106	3 × 106
aEICH / cEICH	39% / 31%	—	14% / 7%	—
Overall survival	69%	81%	36%	65%
Death	7 (31%)	3 (19%)	9 (64%)	7 (35%)
Relapse	4 (17%)	5 (31%)	7 (50%)	11 (61%)
Relapse as cause of death	3(42%)	1(33%)	7 (78%)	7 (100%)
n=	23	16	14	18

Characteristics of the patients included and results. **Conclusions:** We found significant difference in overall survival between allo-RICSCT recipients and auto-SCT recipients and also a higher mortality in HD patients and in NHL patients who received an allo-RICSCT. The relapse rate was higher in autografted patients, both in NHL an HD, even in patients in first remission. We conclude that both therapeutic modalities may be useful in refractory NHL patients and seems that in refractory HD the results were better using autologous grafts.

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PRE-MOBILIZATION BONE MARROW PLASMACYTOSIS PREDICTS SUCCESSFUL STEM CELL MOBILIZATION IN PATIENTS WITH MULTIPLE MYELOMA RECEIVING LENALIDOMIDE-BASED INDUCTION REGIMENS

Benson, D.M.[1], Hofmeister, C.C.[1], Hamadani, M.[1], Panzner, K.[1], Smith, M.K.[3], Penza, S.L.[1], Elder, P.[2], Krugh, D.[2], O'Donnell, L.[2], Devine, S.M.[1] [1] The Ohio State University, Columbus, OH; [2] The Ohio State University, Columbus, OH; [3] The Ohio State University, Columbus, OH

High-dose chemotherapy (HDC) with autologous stem cell transplant (ASCT) remains a crucial therapeutic option for many patients with multiple myeloma (MM). Although thalidomide, lenalidomide and bortezomib may be associated with improved outcomes compared with traditional therapies, how to best integrate novel agents into a treatment plan incorporating HDC/ASCT remains unknown. Moreover, recent studies have suggested that the use of lenalidomide, in particular, may impair subsequent ability to harvest stem cells for ASCT. We examined our institutional experience in 287 sequential patients with MM who underwent HDC/ASCT from 1992 to 2008 stratified by the type of induction regimen received prior to HDC/ASCT: chemotherapy-based (e.g., VAD, DVD) or novel agent-based (thalidomide, lenalidomide, or bortezomib). Patients were similar in age, Durie Salmon and ISS stage, high-risk karyotype/FISH status, and other variables. Time from diagnosis to mobilization was similar and no differences were seen in remission status at time of stem cell mobilization. However, successfully mobilized patients who received induction regimens containing a novel agent had lower pre-mobilization marrow plasmacytosis (mean 12.9% ± SD 16) than patients who received chemotherapy-based inductions (mean 22% ± 27, p = 0.001), yet total marrow cellularity was similar between groups. Controlling for other variables (e.g., use of cyclophosphamide for mobilization and prior radiation exposure), pre-mobilization marrow plasmacytosis predicted the chances of successful stem cell mobilization in patients who received induction with lenalidomide: successfully mobilized patients had less marrow plasma cells pre-mobilization (5% ± 8) than patients who failed mobilization (21% ± 1.2, Table 1, p = 0.001). Patients with prior lenalidomide or bortezomib exposure collected fewer CD34(+) stem cells than patients receiving chemotherapy or thalidomide based inductions (p = 0.0001). Patients who received prior lenalidomide also engrafted slower than patients who received other induction regimens following HDC/ASCT, independent of