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POSTER ABSTRACTS

637.MYELODYSPLASTIC SYNDROMES - CLINICAL AND EPIDEMIOLOGICAL

Checkpoint Immunotherapy Is Associated with Preferential Activation of Tumor-Antigen Specific CD4 + T Cells in MDS

Elizabeth A. Griffiths, MD[1], Pragya Srivastava, PhD[2], Eduardo Cortes Gomez[3], Junko Matsuzaki, PhD[4,5], Kunle Odunsi, MD PhD[5,4], Laura W Dillon, PhD[6], Devdeep Mukherjee, PhD[6], Christopher S. Hourigan, DM, DPhil[6], Jacqueline Peng[7], Shovik Bandyopadhyay[8], Kai Tan, PhD[9], Krista Belko, PhD[10], Amanda C. Przespolewski, DO[2], Eunice S. Wang, MD[2], Prashant Singh, PhD[11], Jianmin Wang, PhD[3], Michael J. Nemeth, PhD[12]

[1] Leukemia Service, Department of Medicine, Roswell Park Comprehensive Cancer Center, Buffalo, NY
[2] Department of Medicine, Roswell Park Comprehensive Cancer Center, Buffalo, NY
[3] Department of Biostatistics and Bioinformatics, Roswell Park Comprehensive Cancer Center, Buffalo, NY
[4] Center for Immunotherapy, Roswell Park Comprehensive Cancer Center, Buffalo, NY
[5] Department of Obstetrics and Gynecology, University of Chicago Medicine Comprehensive Cancer Center, Chicago, IL
[6] Laboratory of Myeloid Malignancies, Hematology Branch, National Heart, Lung, and Blood Institute, Bethesda, MD
[7] Cellular and Molecular Biology Graduate Group, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA
[8] Cellular and Molecular Biology Graduate Group, Perelman School of Medicine, University of Pennsylvania, EUREKA, MO
[9] Department of Pediatrics, Children's Hospital of Philadelphia, University of Pennsylvania Perelman School of Medicine, Philadelphia, PA
[10] Clinical Research Services, Roswell Park Comprehensive Cancer Center, Buffalo, NY
[11] Department of Cancer Genetics and Genomics, Roswell Park Comprehensive Cancer Center, Buffalo, NY
[12] Department of Immunology, Roswell Park Comprehensive Cancer Center, Buffalo, NY

Background: Patients with intermediate and higher-risk MDS are generally treated with the DNA hypomethylating agents (HMAs) azacytidine and decitabine. These agents improve survival and cytopenias in ~50% of those treated; but only responders derive clinical benefit, and no pre-treatment response prediction has proven efficacy. There is thus an urgent need to develop new approaches to complement or enhance the response to standard-of-care HMA therapies. Studies suggest that HMAs might act in part via activation of anti-tumor immune mechanisms. Based upon this hypothesis a series of early phase trials combining immune checkpoint inhibitors (ICI: both anti-PD1/PDL1 and CTLA4) with azacitidine in MDS/AML patients were undertaken but clinical and immunological efficacy have proven disappointing. In these studies, the lack of antigen specificity made systematic assessment of the anti-MDS immune response and *milieu* challenging. Antigen specific assessments are particularly important in MDS patients treated with ICIs because distinct from solid tumors, myeloid stem cell cancers involve the populations of antigen presenting cells that modify the capacity for T-cell response, such as dendritic cells. Our group has shown that MDS/AML patients treated with decitabine show increased expression of NY-ESO-1, a well-characterized tumor antigen whose expression is normally suppressed through dense promoter hypermethylation. In our prior Phase I study, MDS patients received vaccination against NY-ESO-1 in combination with standard decitabine. This combination was not only safe, but it also induced NY-ESO-1 specific CD4 + and CD8 + T cell responses in most patients. We hypothesized that combining anti-NY-ESO-1 vaccination (an antigen specific approach) with decitabine and an ICI would allow us to understand the immune synapse in patients with MDS. *Methods*: We developed an investigator-initiated Phase 1 trial in transplant-ineligible patients with MDS/low blast count AML adding an anti-PD-1 ICI to our established combination of decitabine + NY-ESO-1 vaccination (#NCT 0335871). This open-label, non-randomized single center Phase 1 study used an HLA unrestricted NY-ESO-1 vaccine (CDX-1401 (1 mg) + poly-ICLC (1.8 mg)) in combination with standard dose decitabine (20mg/m2/d x 5 days) and nivolumab (3 mg/kg every 2 weeks), 4 cycles of combination therapy were planned on study; patients deriving clinical benefit could continue treatment at the discretion of the treating physician. The study was conducted in accordance with the Declaration of Helsinki and approved by the Roswell Park Cancer Institute (RPCI) Internal Review Board. Six patients were enrolled, treated, and completed > 4 cycles of decitabine; serial bone marrow and peripheral blood samples were collected for analysis. The combination was safe. *Results*: Two patients developed CR and the remainder had stable disease as the best response to

therapy (Table 1). The majority of patients mounted NY-ESO-1 specific CD4 $^{+}$ T cell responses associated with up-regulation of anti-PD-1 immunotherapy gene signatures in the CD4 $^{+}$ memory T cell compartment. No responses in CD8 $^{+}$ T cells were seen. In seeking explanation for the disparate findings in CD4 $^{+}$ and CD8 $^{+}$ T-cell compartments, we examined conventional dendritic cell populations associated with activation of CD8 $^{+}$ T cells and identified that our patients had markedly reduced numbers of conventional dendritic cells marked by high expression of CD141 (cDC1). This population is critical for a successful response to immunotherapy. cDC1 from MDS patients also showed reduced expression of genes that are key for optimal T-cell activation and expansion. *Conclusions*: These results suggest that the use of immunotherapy to induce effective, cytotoxic anti-tumor T cell responses depends upon the myeloid immunologic *milieu* in MDS patients. The critical importance of cDC1 function has recently been described and appreciated in the context of solid tumor immunotherapy. The observation of both numerical and functional defects of this cell population in patients with myeloid neoplasia provides a possible explanation for the disappointing efficacy of immunotherapies in this disease state. Approaches to augment the number and function of specific cDC1 populations in myeloid disease might overcome this defect and thereby enhance the efficacy of immunotherapy for patients with MDS.

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Patient	IPSS-R	Best Response	CD4 Response		CD8 Response	
			Pre	EOS	Pre	EOS
1	Int	CR	- (0)	+++ (8)	- (0)	- (0)
2	Int	CR	- (0)	+++ (2)	- (0)	- (0)
3	High	SD	- (0)	+ (2)	- (0)	- (0)
4	V. High	SD	- (0)	- (0)	- (0)	- (0)
5	Int	SD	- (0)	+++ (3)	- (0)	- (0)
6	V. High	SD	- (0)	NA	- (0)	- (0)

Table 1. Characteristics and Responses of Patients Enrolled on NCT 0335871. Patients are marked by an ID number. IPSS-R scores are based on the criteria described in Greenberg, *et al.*, Blood, 2012. Best responses were annotated using modified Cheson criteria for AML. Frequencies of NY-ESO-1 antigen specific T cells were measured using ELISPOT assays prior to start of treatment (Pre) and at the EOS. Number of IFN-γ spots/50,000 cells: < 25 spots (-); 25-99 spots (+); 100-199 spots (++); 200-499 spots (+++); >500 spots (++++). Numbers in parentheses indicate number of epitopes recognized by T cells. CR = complete remission; SD = stable disease; EOS = end of study; NA = not available.

Figure 1

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