Society for Immunotherapy of Cancer

White Paper on Adoptive Cell Therapy for Cancer with Tumor-Infiltrating Lymphocytes: A Report of the CTEP Subcommittee on Adoptive Cell Therapy

Jeffrey Weber, Michael Atkins, Patrick Hwu, Laszlo Radvanyi, Mario Sznol and Cassian; on behalf of the Immunotherapy Task Force of the NCI Investigational Drug Steering Committee. *Clin Cancer Res. 2011; 17(7); 1664–73.*

SITC leaders played a key role in developing a *Special Report* on adoptive cell therapy (ACT) using tumor-infiltrating lymphocytes (TIL) for cancer treatment. The authors describe the state-of-the art in ACT for melanoma using expanded TIL. The report reviews current clinical and preclinical data that support development of adoptive immunotherapy with "young" TIL. Results with various strategies for lymphoid depletion and the selection and expansion of TIL cultures are reviewed. The authors summarize several studies in which antigen-specific $CD8^+$ T cells were isolated and expanded for ACT. These studies employed different types and duration of preconditioning with varying results, pointing to the need for further efforts to refine and standardize regimens for optimal function and persistence of the transferred T cells. $CD4^+$ T cell therapy is also highlighted in the report, with these cells playing an important role in mediating direct or indirect killing of class II^+ and class II^- tumor targets, respectively. Not only do $CD4^+$ T cells support the survival and function of transferred $CD8^+$ effector cells *in vivo*, ACT with NY-ESO or tyrosinase-specific Th1-type $CD4^+$ T cells led to PR or disease stabilization in 4/9 patients with refractory metastatic melanoma, and durable CR >3 years in one patient. ACT with these $CD4^+$ T cells was associated with antigen spreading, broadening the anti-tumor response in some of the patients. The report also reviews promising results with the use of antigen-specific T cell therapy of leukemia recurrence following hematopoietic stem cell transplantation.

The authors identify important, unanswered questions that must be addressed to advance adoptive cancer immunotherapies with TIL. These pivotal questions are directed towards building consensus around key issues including, optimal type of effector cells for ACT of cancer, rapid expansion of effector cells, and identification of an optimal preconditioning regimen for ACT.

In an effort to define a proof of concept trial for ACT using TIL for cancer treatment the authors suggest two possible randomized trial designs for studies that could significantly advance the field. In the first trial design, patients' lesions would be harvested, and TIL initially expanded for subsequent large-scale, rapid expansion. Patients would be randomized to two treatment arms: 1) TIL (preceded by lymphodepletion) followed by high-dose IL-2, or 2) high-dose IL-2 alone at the time point *when TIL would be available*. This could be a constructed as a crossover study with response rate and time to progression as the endpoint (rather than overall survival). This trial design would determine the benefit of TIL compared to IL-2, eliminating bias by starting with the ability to grow TIL as a baseline.

In a second trial design, patients would be randomized to receive TIL-based treatment when available or to immediately receive high-dose IL-2. This intent-to-treat design would help determine if there are disadvantages to waiting for TIL expansion.

The report also reviews practical considerations for establishment of ACT as a standard-of-care cancer treatment modality, including development of the appropriate institutional infrastructure and standardization of SOPs surrounding tumor harvesting, preservation, shipping, and TIL preparation. The authors outline potential benefits of using a centralized facility for growing TIL and employing immune-related response criteria for assessment of clinical responses to ACT to identify patients most likely to benefit from continuing ACT, despite disease progression by standard RECIST response criteria. The authors present a promising scenario for ACT and point to practical steps to increase clinical application of ACT with TIL for cancer treatment. The full report appeared in the April 2011 issue of *Clinical Cancer Research.*