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Adoptive T-Cell Therapy for Cancer: Boutique Therapy or Treatment Modality?

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Adoptive cellular therapy, involving the *ex vivo* enrichment and expansion of antigen-specific immune cells for adoptive transfer, has emerged as an increasingly effective modality for the treatment of patients with advanced cancer refractory to conventional therapy. *Clin Cancer Res; 19(17); 4550–2. ©2013 AACR.*

In this issue of *Clinical Cancer Research*, Besser and colleagues present an intent-to-treat (ITT) analysis of 80 patients enrolled in an adoptive therapy study using *ex vivo* expanded unselected tumor-infiltrating lymphocytes (TIL; 1). Among this cohort of patients with advanced disease, of the majority presenting with poor prognostic metastatic melanoma (stage M1c), 57 were eventually treated, with about half of those not receiving treatment due to nonclinical reasons (no TIL growth or refusal to further participate) and half clinically progressing too rapidly to receive therapy. The overall response rate and median survival were approximately 40% and 15 months, respectively, among the 57 treated patients, and 30% and 10 months for all patients enrolled. Considering that all patients had had at least one previous treatment for metastatic disease (often multiple prior lines of aggressive therapy), and the natural history of melanoma affecting visceral sites, these are very encouraging results for patients and for the field of immune-based therapies in general.

The development of immunotherapies for the treatment of refractory or recurrent disease has witnessed a renaissance of late in both cell-based and immunomodulatory approaches. Clinical trials using antibodies to establish immune checkpoint blockade against CTLA4 and the PD-1–PDL-1 axis report significant long-lasting responses via *in vivo* activation and expansion of the endogenous antitumor immune response (2). As a means of providing an exogenous source of *ex vivo* expanded effector cells, adoptive cellular therapy has also emerged as a highly effective modality capable of eliciting durable and complete responses.

Three forms of adoptive cellular therapy using T cells have been practiced: (i) TIL therapy, using lymphocytes expand-ed from a tumor biopsy sample (3); (ii) antigen-specific T-cell therapy, using endogenous T cells sourced from peripheral blood (4–6); and (iii) more recently, the use of gene-modified T cells engineered to express the desired T-cell receptor (TCR) or chimeric antigen receptor (CAR) with occasional remarkable results (ref. 7; Fig. 1).

When it became apparent that the duration of T-cell survival after adoptive transfer was correlated with clinical response, strategies to enhance *in vivo* persistence were implemented involving both extrinsic modification of the host environment, through the use of conditioning lymphodepletion, or intrinsic manipulation of the effector T cell itself, by enhancing cellular replicative potential via cytokine modulation (8), phenotype-based selection, or genetic engineering (7). By incorporating these approaches into the TIL therapy protocol, a significant increase in clinical response rates was achieved (>50% in select cases) as well as durable complete remissions in the setting of significant tumor burden (9).

In the field of adoptive T-cell therapy using TIL, two important milestones were attained, in large part through pioneering efforts of the Surgery Branch at the NCI, enabling its promulgation into the clinical arena as a feasible therapeutic option: One was a means of expanding the TIL population 1,000- to 5,000-fold based on methods originally established for antigen-specific T-cell expansion using a TCR trigger (anti-CD3) and irradiated feeder cells, and the second was inclusion of a lympho-depleting conditioning regimen for patients before TIL infusion. This regimen was initially nonmyeloablative, and later advanced to a total body irradiation–containing ablative regimen with not only a commensurate increase in serious adverse toxicities, but also dramatic and durable clinical responses (up to 40%). The nonmyeloablative regimen used in this study is the most established. Coupled with an expedited protocol to generate "young" TIL that was successfully expanded and infused in more than 90% of patients, this represented a potential "standardized" protocol with which to move forward to a randomized controlled clinical trial given the encouraging ITT results.

The impetus to develop improved and simpler TIL protocols arose from earlier work at the NCI and other centers involved in larger scale TIL trials such as those conducted at

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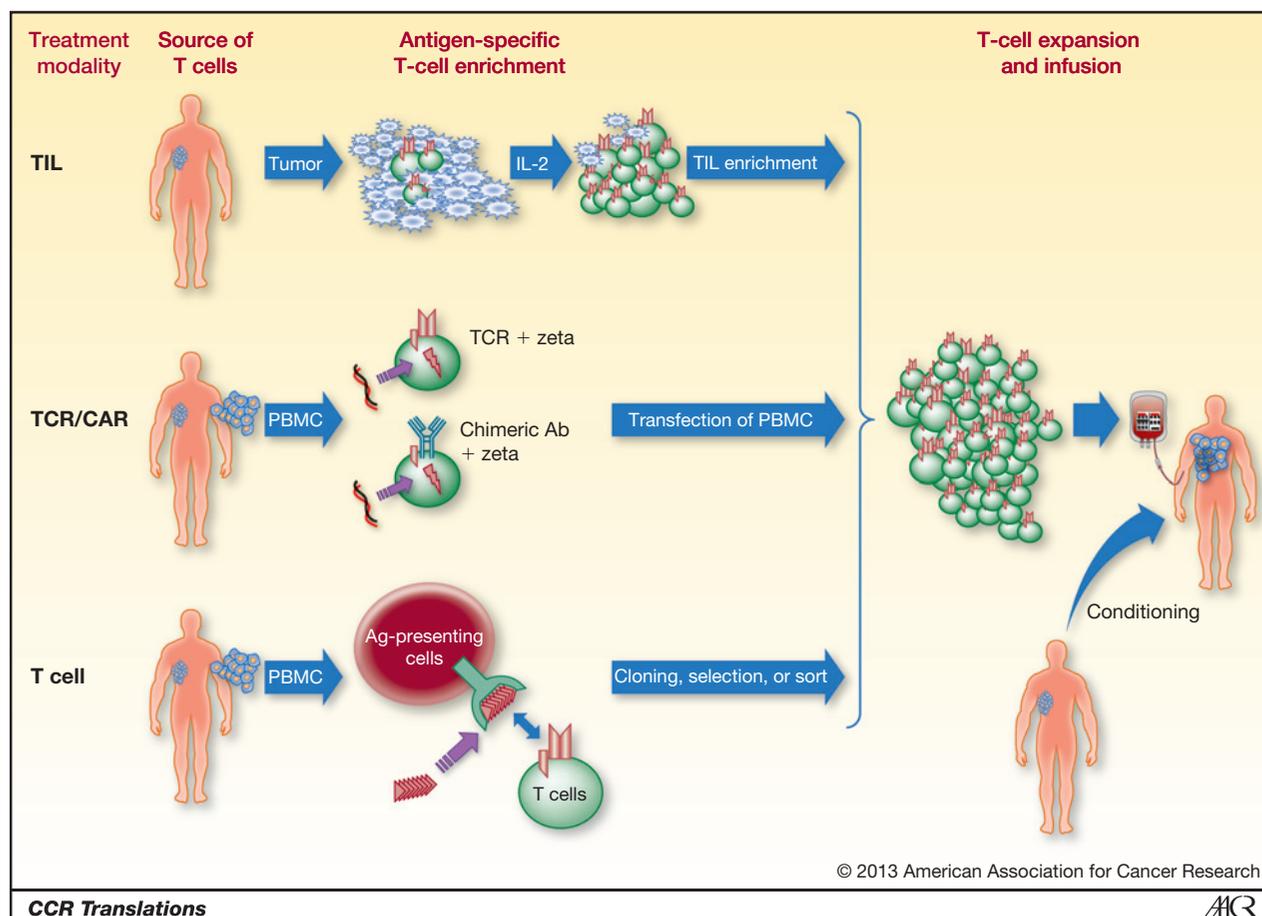*American Association for Cancer Research*

Figure 1. Adoptive cell therapy. Adoptive cell therapy is represented by three general approaches: (i) enrichment and expansion of TIL from a disaggregated tumor biopsy sample; (ii) genetic transfer of TCR-recognizing tumor antigen-derived peptide-MHC target or CAR-recognizing surface tumor protein; and (iii) enrichment of endogenous antigen-specific T cells from peripheral blood mononuclear cells (PBMC) by *in vitro* stimulation followed by cell selection or cloning. PBMCs are a source of both antigen-presenting cells and T cells. Following enrichment, the population of tumor-reactive T cells undergoes rapid expansion of 1,000- to 5,000-fold, achieving 10 to 100 billion cells for adoptive transfer. Patients often receive a lympho-depleting conditioning regimen before infusion followed by exogenous interleukin (IL)-2. In the case of adoptive TIL therapy, patients receive high-dose near-ablative or fully ablative conditioning before infusion and a course of high-dose IL-2 after infusion. In the study conducted by Besser and colleagues (1), "young" TIL were generated using a shortened preexpansion culture phase before rapid cell expansion, enabling production of an infusible T-cell product within 5 to 7 weeks from the time of tumor collection.

The MD Anderson Cancer Center at the University of Texas at Houston (10) and at the Sheba Medical Center in Israel (1), where response rates of 40% or more were consistently achieved among patients who eventually received treatment. Although these studies corroborated the original promising results, only 40% to as few as 27% of patients who underwent resection for TIL generation ultimately received TIL therapy (11); this attrition is due in part to disease progression, protocol-specific, and product-related exclusion criteria—features that could be addressed by a shortened time to therapy from enrollment and modification of product-release criteria. Although the original TIL protocol, commonly practiced at the NCI required 7 to 8 weeks from resection to TIL product, the young TIL protocol developed by Tran and colleagues shortened the pre-expansion phase, eliminated exclusion of TIL cultures on the basis of absent *in vitro* activity, and produced a TIL product in 4 weeks (12);

implementation of this protocol in the study presented by Besser and colleagues (1), led to more than 70% treatment: enrollment ratio, with response rates among treated patients at least as favorable as those shown in earlier studies. Only 10% of patients failed to yield a useable TIL product, and 14% were excluded due to clinical deterioration.

There remain, however, a number of issues yet to be resolved: Should ablative radiation therapy be added to the conditioning regimen, and which patients should be considered for this risk-intense but highly effective treatment? Can a superior TIL effector population be defined on the basis of *in vitro* phenotype selection or cytokine modulation? Is there a clinical or immunologic biomarker profile that can identify patients predicted to respond to therapy? Furthermore, the treatment landscape for patients with metastatic melanoma has changed in a very positive and dramatic fashion over the past 5 years. With the advent

of more and more positive data arising from the use of immune checkpoint inhibitors and targeted therapies, alone, in combination with each other, or in combination with conventional modalities, it is becoming less and less obvious which algorithmic endpoint cellular therapies will eventually find its niche; more than likely, combinational therapies involving the use of clinically approved immunomodulators together with adoptive cellular therapies will be established as the standard of practice for clinical trials and, one hopes, a standard of care.

In the parlance, then, of today's YouTube generation, is adoptive cellular therapy ready to go viral as in the case of a recently popularized Korean music video star, or is it limited still to an eclectic group of diehard believers? The answer lies somewhere in between. While there remains much to be addressed by taking a reductionist approach to adoptive cellular therapy—by isolating and expanding a uniform population of antigen-specific T cells, epigenetically modulating or genetically engineering an ideal central memory/stem cell effector population, limiting toxicities, and fine-tuning affinities—there is reason to believe that cellular therapy is now poised to make the leap from "boutique therapy" to treatment modality. The report presented here describes one significant step toward this goal, and now may just be the time for adoptive cellular therapy to go mainstream.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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