Is there a future for adoptive cell transfer in melanoma patients?

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Abbreviations: ACT, adoptive cell transfer; IL-2, interleukin-2; OR, objective response; TIL, tumor-infiltrating lymphocytes

The adoptive transfer of tumor-infiltrating lymphocytes (TILs) can yield durable responses in patients affected by metastatic melanoma. In particular, we have recently reported an 80% 3 year survival rate among patients who responded to this immunotherapeutic regimen. Of note, overall response rates were equal among ipilimumab-naive and ipilimumab-refractory patients. Thus, the adoptive transfer of TILs, as a standalone therapeutic intervention or combined with other treatment modalities, bears a high clinical potential that must be optimally employed.

Tumor-infiltrating lymphocytes (TIL) are a heterogeneous cell population found within neoplastic lesions and mainly composed of T cells. A fraction of TILs expresses T-cell receptors directed against unique or shared tumor-associated antigens and exert cytotoxic effects against malignant cells. The adoptive transfer of TILs to cancer patients involves the large-scale expansion of autologous TILs (which are obtained from resected tumors) ex vivo and their reinfusion, which normally ensues a pre-conditioning regimen and is combined with the administration of interleukin-2 (IL-2).1,2 Lymphodepleting pre-conditioning transiently removes immunosuppressive cells from the patient, whereas IL-2 supports the survival of adoptively transferred cells.3

In the past few years, several groups published the results of Phase II clinical trials testing TIL-based adoptive cell transfer (ACT) in patients with metastatic melanoma.1–4 These studies differed from each other with regard to lymphodepleting regimen (i.e., myeloablative vs. non-myeloablative protocols)2 and TIL production protocol (e.g., CD8+ T cell-enriched vs. non-enriched TILs, the latter of which also contains CD4+ T cells).1,3,4 The use of myeloablative pre-conditioning has yielded the highest objective response (OR) rate ever reported for TIL-based ACT (i.e., 72%),2 whereas the use of CD8+ T cell-enriched TILs (in a non-myeloablative setting) was associated with the lowest one (i.e., 20%).3 Since myeloablative pre-conditioning is associated with severe toxicities, the use of non-enriched TILs in conjunction with non-myeloablative regimens nowadays stands out as the most feasible approach in clinical terms, resulting in 38–50% OR rates, as demonstrated in multiple independent studies.1–4

The major benefit of TIL-based ACT is the duration of responses, which in many patients last for years. Moreover, 10–20% of patients experience complete remission. In a previous study, 19 of 20 patients who completely responded to TIL-based ACT were in remission 4–8 y after treatment,3 and also in our cohort, none of such patients (n = 5) has relapsed after a median follow-up of 39 mo (as of August 2013).

We have recently published clinical results as well as long-term follow-up data regarding 80 metastatic melanoma patients who were allocated to receive adoptively transferred non-enriched TILs upon non-myeloablative lymphodepletion.6 This report provides data on the intent-to-treat analysis, with a special focus on the efficacy of TILs in ipilimumab-refractory patients.

Patients were enrolled regardless of disease burden or tumor progression. 80% of them had multiple metastases in visceral organs and all patients were refractory to prior therapies. TIL cultures were successfully established for 72 (90%) patients. Altogether 23 (29%) patients discontinued the study, including 3 patients who chose to resign and 11 patients who clinically deteriorated in the course of TIL production.

Such a drop-out rate is relatively low, especially when compared with that of other anticancer regimens that also require biotopic or surgical material for the assessment of eligibility. For example, only approximately 50% of melanoma patients bear a mutation at BRAF codon 600, which justifies the use of the BRAF inhibitor vemurafenib.7 Along similar lines, just about 20% of breast carcinomas exhibit high expression levels of v-erb-b2 avian erythroblastic leukemia viral oncogene homolog 2 (ERBB2, also known as HER2 or neu), justifying the administration of ERBB2-targeting agents such as trastuzumab or lapatinib. Of note, clinical data on the efficacy of antineoplastic
medications (if not of medications in general) usually refer to treated patients only, and not to the intent-to-treat population. Moreover, survival data are generally measured from the day of treatment, rather than from the day in which biopsy was collected, which should not be any different in the context of ACT-based immunotherapy.

Of 57 patients receiving TIL-based ACT in our cohort, 18 experienced partial and 5 complete remission, corresponding to an objective response rate of 40% (Fig. 1A). The disease control rate, including patients who manifested disease stabilization, was 65%. TIL-based immunotherapy was applied to a population of patients bearing very advanced tumors. 79% of treated patients exhibited indeed multiple sites of disease and were staged M1c, including 11 (19%) patients with brain metastases. The median overall survival (OS) of this cohort was 15.2 mo. Objective responses were significantly associated with a survival benefit, as patients who responded to therapy did not reach the median OS after a median follow-up time of 28 mo, whereas patients who failed to do so had a median OS of 6.1 mo. Noteworthy, 78% of patients who experienced ORs to TIL-based ACT are alive 3 y after therapy. Moreover, as mentioned above, all 5 complete responders, including one patient who had brain metastases at enrollment, have no evidence of disease 2 to > 5 y after treatment.

Interestingly, TIL-based ACT was as effective in ipilimumab-refractory patients as in ipilimumab-naïve ones, and the toxicity profile of treatment did not differ between these 2 patient subsets. There was no correlation between the type of response to prior ipilimumab- or IL-2-based immunotherapy and the response to the adoptive transfer of TILs (Fig. 1B). Therefore TIL-based ACT stands out as an optional treatment modality for melanoma patients progressing on standard anticancer regimens.

TIL-based ACT is an individualized treatment that requires specialized laboratories, and thus is more complex to perform than most conventional antineoplastic interventions. Still, the clinical results obtained with TIL-based ACT might to be superior even to those observed in response to vemurafenib (both these treatments induce high response rates, but the responses to TIL-based ACT seem to be more durable) or ipilimumab (higher OR rates have been obtained with adoptively transferred TILs than with ipilimumab). Clearly, properly designed, randomized clinical trials are required to formally demonstrate the advantages of TIL-based ACT over other treatment modalities. In addition, TIL expansion protocols have been substantially simplified over the years, increasing the number of centers that may be able to provide this therapeutic option to patients.

Figure 1. Overall response rate and median overall survival of melanoma patients subjected to TIL-based ACT. (A–C) Best overall response rates (according to RECIST v. 1.1) in all patients treated with tumor-infiltrating lymphocyte (TIL)-based adoptive cell transfer (ACT) (n = 57) (A), in ipilimumab (IPI)-refractory patients treated with TIL-based ACT (n = 13) (B), and ACT-refractory patients treated with ipilimumab (n = 19) (C). Ipilimumab was employed at a dose of 3 mg/kg. In panels (B) and (C), lines indicate individual patients and their best overall response to each treatment. Median overall survival (OS) was measured from the initiation of second-line therapy. CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease.
ligand (CD274, also known as PD-L1), are rapidly approaching regulatory approval, combinatorial immunotherapy might provide the landmark in the treatment of melanoma patients. Preliminary studies combining inhibitors of PDCD1-dependent and cytotoxic T lymphocyte-associated protein 4 (CTLA4)-dependent immunological checkpoints (i.e., nivolumab and ipilimumab, respectively) show promising results. Combinatorial regimens involving TIL-based ACT and checkpoint inhibitors will definitively be of great interest. In our very small patient cohort, 3 of 19 (16%) ACT-refractory patients experienced durable complete remission in response to ipilimumab (Fig. 1C), which as single agent yielded < 1% complete responses.

Ongoing research efforts focusing on the discovery of highly reactive TIL subsets and the genetic engineering of TILs prior to reinfusion can further improve the clinical efficacy of this immunotherapeutic regime. TIL-based ACT has a substantial clinical potential, both as a standalone therapeutic intervention and in combination with other treatment modalities.

Disclosure of Potential Conflicts of Interest
No potential conflicts of interest were disclosed.

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