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Adoptive cell therapy: a highly successful individualized therapy for melanoma with great potential for other malignancies

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Adoptive cell therapy (ACT) by infusion of autologous or redirected tumor-specific T-cells has had a major impact on the treatment of several metastasized malignancies that were until now hardly treatable. Recent findings provide a more profound knowledge on the underlying mechanisms of success and allow the optimization of the ACT protocol with respect to (1) the treatment related side-effects, (2) the quality and specificity of infused T-cells, and (3) the immunosuppressive phenotype of the tumor environment. In this review, the results and insights in the success of ACT as well as the possibilities to improve ACT and its exploitation as treatment option for various metastatic cancer types, will be discussed.

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Introduction

ACT, the *ex vivo* expansion of tumor-specific T-cells followed by reinfusion into the patient has been shown to be a very successful treatment option for late-stage metastatic melanoma. On average an objective response (OR) could be obtained in approximately 50% of the treated patients [1••,2]. More importantly, a substantial part of the observed responses are durable and 13% of the patients obtained a complete response (CR). For comparison, while OR rates of 57.6% were obtained with combined checkpoint blockade, CR percentages of 2.2%, 8.9% and 11.5% were recently reported after checkpoint-blocking immunotherapy of previously untreated metastasized melanoma patients with ipilimumab or nivolumab monotherapy, or the combination of both, respectively [3]. Currently used ACT protocols involve pre-conditioning of the patient with lymphodepleting chemotherapy and high dose interleukin-2 (IL-2) cytokine support after infusion, leading to clinical success but also to substantial treatment-related toxicity which limits the number of patients eligible for treatment and broad application of this ACT protocol.

Evolution of ACT as treatment for metastatic melanoma

Reduce treatment-related toxicity

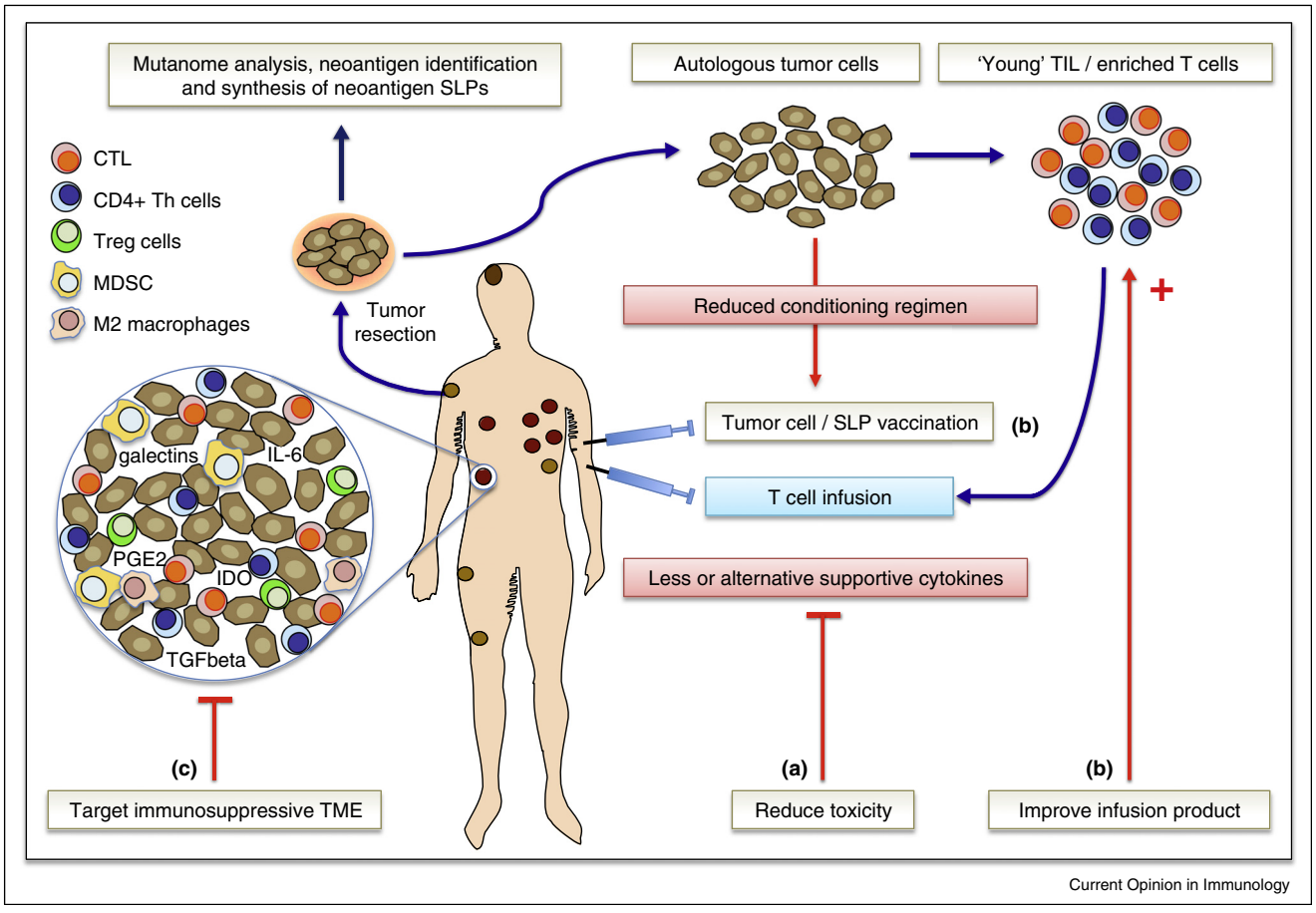
To minimize the patient burden caused by pre-conditioning-related and cytokine support-related toxicities several approaches were explored (Figure 1a). Although, patient conditioning is considered to be crucial to achieve tumor remission, this issue is not extensively addressed and there is only little evidence proving that it is indispensable. Notably, clinical effect of T cell transfer has been obtained without pre-conditioning, especially when lower doses of T cells enriched for tumor-specificity were infused [4•,5]. Our clinical trial showed that pretreatment with low dose IFN-alpha resulted in mild, but apparently sufficient leukopenia to achieve durable responses after transfer of autologous tumor stimulated T-cells [6•]. This mild conditioning allows administration of multiple T cell infusions with the benefit that higher frequencies of tumor-specific T-cells are present during a longer period of time, thus mimicking enhanced T cell persistence that is crucial for clinical benefit after ACT [1••,7,8•].

Similarly, low dose IFN-alpha [6•], reduced dose of IL-2 [9,10•] or a combination of both [11], were successfully used to support *in vivo* function and persistence of transferred T-cells while substantially diminishing toxicity caused by the IL-2 dose used in most other protocols (Figure 1a). Undesired on-target toxicity can be improved by increasing tumor-specificity of transferred T cells as will be addressed in the next paragraph.

Improve quality and specificity of infused T-cells

In order to improve clinical efficacy of ACT, effort has been made to identify parameters that define the optimal quality of TIL used for infusion (Figure 1b). Initially, individual TIL cultures were selected for further expansion based on *in vitro* recognition of shared melanoma antigens or allogeneic or autologous tumor cells (if available). However, this did not result in enhanced effectiveness, whereas as a consequence of selection, the overall culture time to obtain enough TIL for transfer increased. Detailed characterization of the infused TIL *versus* clinical outcome revealed that it was better to infuse so-called unselected 'young' TIL, that have longer telomeres [2,8•]

Figure 1



An optimized treatment protocol for ACT involves: **(a)** Reduction of treatment related toxicity that requires reducing lymphodepleting conditioning regimens and a less toxic cytokine supportive treatment following T cell infusion. **(b)** Improved quality of infusion product, comprising younger T cells, that have the ability to persist longer and have a better *in vivo* proliferative potential. Administration of a mix of CD8+ T cells (CTL), that can directly kill tumor cells, and CD4+ Th cells to enhance CTL recruitment and effector function and mediate antigen spreading via cross-presentation by dendritic cells. Furthermore, the infusion product can be highly enriched for tumor-specific T cells by two independent approaches that can be used in combination, that is, selecting them directly *ex vivo* based on activation marker expression and steering the culture towards more tumor-specific T cells by *in vitro* stimulation with whole autologous tumor cells or appropriate Ag, for example, synthetic long peptides (SLP) covering neoepitopes or viral Ag. Vaccination with these Ag/autologous whole tumor cells can subsequently boost the *in vivo* efficacy of infused T cells. **(c)** Combine ACT with modulators that change the immunosuppressive microenvironment within the tumor making it more susceptible for immune cells that can then effectively target the tumor.

and contain more CD27-expressing CD8+ T-cells, reflecting cells with a less differentiated phenotype and improved potential to persist *in vivo* [12]. Although improved response rate is claimed to correlate with transfer of higher absolute number of T-cells, and in particular CD8+ T-cells [13,14], lack of this correlation has also been reported [12]. Notably, substantial or complete tumor regression has been achieved after adoptive transfer of T-cells consisting only or mainly of CD4+ T-cells [4•,6•,15]. In these studies the clinical effect may be attributed to Ag-spreading; that is, antigen-specific CD4+ T-cells mediated cross-presentation of tumor Ag by dendritic cells to CD8+ T-cells. Indeed, transfer of clonal NY-ESO-1-specific CD4+ T-cells, resulted in tumor-response-related appearance of circulating MAGE-3-specific and MART-1-specific T-cells that were not detectable before treatment [4•]. Similarly, Ag-spreading is postulated to mediate the clinical efficacy of MHC class II neoepitope vaccination in several mouse models [16]. Additional mouse models showed that CD4+ T-cells mediate CD8+ recruitment and enhance their effector function at the tumor site [17•] probably via reducing CD8+ T cell exhaustion [18]. It is to be expected that for optimal clinical effect infusion of a combination of tumor-specific CD8+ and CD4+ T-cells is required.

Despite the apparent success of the infused TIL, the exact specificity of infused T-cells remained largely unknown.