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Review Article

Adoptive cell transfer using autologous tumor infiltrating lymphocytes in gynecologic malignancies

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HIGHLIGHTS

- Modern T cell therapies are rapidly changing the landscape of tumor treatment.
- TIL-based ACT is a highly personalized cancer treatment with impressive clinical response rate.
- TIL-based ACT has been used to successfully treat a few patients with ovarian and cervical cancer.
- Several TIL-based ACT trials are actively recruiting patients with gynecologic malignancies.

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ABSTRACT

During the last decade, the field of cancer immunotherapy has been entirely transformed by the development of new and more effective treatment modalities with impressive response rates and the prospect of long survival. One of the major breakthroughs is adoptive cell transfer (ACT) based on autologous T cells derived from tumor-infiltrating lymphocytes (TILs). TIL-based ACT is a highly personalized cancer treatment. T cells are harvested from autologous fresh tumor tissues, and after ex vivo activation and extensive expansion, are reinfused to patients. TIL-based therapies have only been offered in small phase I/II studies in a few centers given the highly specialized care required, the complexity of TIL production and the very intensive nature of the three-step treatment protocol. The treatment includes high-dose lymphodepleting chemotherapy, the infusion of the expanded and activated T cells and interleukin-2 (IL-2) injections to increase survival of the T cells. Despite the limited data on ACT, the small published studies consistently confirm an impressive clinical response rate of up to 50% in metastatic melanoma patients, including a significant proportion of patients with durable complete response. These remarkable results justify the need for larger clinical trials in other solid tumors, including gynecologic malignancies. In this review we provide an overview of the current clinical results, future applications of TIL-based ACT in gynecologic malignancies, and on risks and challenges associated with modern T cell therapy.

Contents

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1. Introduction

Traditional cancer treatments, surgery, chemotherapy and radiation, have demonstrated limited efficacy for patients with late-stage and recurrent gynecological malignancies and often cause substantial and long-lasting adverse effects. In the past decade cancer immunotherapy has shown remarkable promise, especially for disease refractory to standard of care approaches. Cancer immunotherapy encompasses a wide range of methods, spanning from active immunization to immune stimulatory methods to enhance tumor immunogenicity and improve immune cell trafficking, and cell based approaches using adoptive cell transfer (ACT). Among these strategies, ACT has been demonstrated to be the most effective immunotherapy method that can result in long-term remission (>5 years) and low recurrence rate.

Successful immunotherapy requires the activation, expansion and efficient trafficking of cancer-specific T cells to the tumor microenvironment. T cell-mediated anticancer responses in vivo include three basic steps. First antigen-presenting cells capture and process cancer antigens into antigenic peptides and present these in combination with human leukocyte antigen (HLA) molecules for T cell receptor (TCR) recognition on T cells. The second step is T cell activation, which requires the binding of the costimulatory surface molecules B7 and CD28 on antigen-presenting cells and T cells. T cell activation is then followed by trafficking to tumor microenvironment and tumor cell recognition and elimination. In cancer patients this complex system fails to function properly as T cells are often unable to recognize cancer antigens, are unable to traffic into the tumor, and/or become disabled locally by the suppressive tumor microenvironment.

Not surprisingly several studies have demonstrated a clear association between the number of tumor infiltrating lymphocytes (TILs) and patient outcomes. The quantity of TILs and TIL phenotype, especially CD8+ cytotoxic T lymphocytes, predict increased progression-free survival (PFS) and overall survival (OS) in many tumor types including melanoma [1], head and neck squamous cancer [2,3], colon [4,5], gastric [6], pancreatic [7,8], lung [9,10], breast [11,12] and ovarian cancer [13,14]. Although TILs are capable of accessing tumor tissue and recognizing tumor-specific antigens, they are often at low numbers and fail to control tumor growth due to the highly immunosuppressive environment.

Therefore, alongside novel immune therapeutics being developed by the pharmaceutical industry, a huge effort from non-commercial research groups around the world has been made to develop highly individualized cellular cancer therapies, particularly those based on transfer of autologous T cells. These treatments are now becoming more accessible to patients with advanced gynecologic malignancies. In this review we will focus on the role of tumor infiltrating lymphocytes (TILs) in antitumor immune responses and their therapeutic implications in the three main tumor types in gynecologic cancer: ovarian, cervical and endometrial cancers. We will discuss the basic concepts in ACT utilizing autologous TILs and review established protocols and the unique toxicities associated with ACT and their management. Other techniques for adoptive cell transfer exist, including genetically modified T cell receptor and chimeric antigen receptor (CAR) T cell therapy; however this review will focus specifically on adoptive T cell therapy using autologous TILs.

2. Historical perspective on adoptive T cell therapy

Adoptive cell therapy for the treatment of cancer is a concept that began over 30 years ago. The possibility of utilizing of lymphocytes in cancer immunotherapy was first investigated in animal tumor models, where donor lymphocytes from infiltrating tumors were capable of inducing tumor regression in recipient animals [15,16]. The commercial production of IL-2 in the 1970s allowed researchers to expand TILs in vitro while maintaining their effector function. Rosenberg and colleagues at the National Cancer Institute (NCI) pioneered the use of TILs as a source of tumor-specific T-cells that could be expanded ex vivo in the 1980s [17]. Subsequently, human trials were initiated using TILs and IL-2. Rosenberg et al. published the first trial using adoptive T cell transfer in humans in 1988. They treated 20 patients with metastatic melanoma with tumor infiltrating lymphocytes that were expanded ex vivo and re-infused in combination with IL-2 after a single dose of cyclophosphamide. There was 55% objective response by RECIST criteria [18]. This study laid the groundwork for ACT in cancer treatment, although, the duration of response was usually short and a follow-up study demonstrated a response rate of 34% [19]. A significant breakthrough in ACT was the addition of a lymphocyte-depleting chemotherapy regimen prior to TIL transfusion [20,21], which improved the rates and duration of response and the persistence of tumor-specific T-cells in the circulation [22]. Several similar trials of TIL infusion in metastatic melanoma have been reported, with variation of the lymphocyte-depletion regimen, and objective responses ranging from 38% to 56% [20,23,24]. Parameters that correlated with response include number of TILs infused, number and percentage of CD8+ TILs, CD8+ phenotype [24], and telomere length [25]. Most of the pioneering work in TIL ACT was done in melanoma patients. Although less accessible than checkpoint blockade, autologous TIL therapy in recurrent/metastatic melanoma is arguably the most effective therapy with response rates >50% and durable complete response rates of >20% [20] and thus holds a promise for other intractable solid tumors.

3. Adoptive T cell transfer: concepts and strategies for this treatment modality

ACT is defined as the infusion of T cells extracted from autologous tumor tissue, after ex vivo activation and multiple rounds of expansion. ACT takes advantage of the presence of enriched tumor-specific T cells found in tumors and aids these cells in completing their antitumor immune function. ACT allows T cell activation and expansion to bypasses the normal host immune regulatory responses, which would prevent rapid and massive expansion of the effector T cells with tumor antigen specificity. Final TIL infusion products consist of CD8+ and CD4+ T cells at highly variable ratios, as well as a very small fraction of γδ T cells [26]. The efficacy of TIL therapy was traditionally primarily attributed to CD8+ T cells; however, newer studies suggest that tumor-reactive CD4+ T cells can also be identified in TILs preparations [26], and many of the patients achieving long-lasting complete remission, were actually treated with TIL products largely dominated by CD4+ T cells [24].

TIL manufacturing is a complex and labor-intensive process, thus it needs to be carried out in a Good Medical Practices (GMP) compliant specialized laboratory. In earlier protocols selected TIL manufacturing took 5–8 weeks, which often led to high patient drop out due to clinical deterioration. New modified protocols thus abandoned culture selection and use single bulk TILs extracted from the resected specimen. Unselected TILs first undergo expansion using IL-2 to yield at least 40–50 million total cells, which takes 2–4 weeks [27]. At this point cryopreservation of the cells is possible for future use, which allows more flexibility and also to save cell product for non-progressing patients for later use. During the final 2 weeks using rapid expansion protocols (REP) T cells are cultured with anti-CD3 antibody and IL-2 resulting in a 1000-fold to 3000-fold expansion of the T cells to generate clinical grade TIL products from about 90% of tumor samples [27]. This whole process of "young TIL" generation takes 4–6 weeks, and typically a total of 2–20 $\times$ 10^{10} TILs can be produced and infused [27]. Besides the shortened preparation time the final infusion product contains younger cells with high expression of co-stimulatory receptor molecules (such as CD27), longer telomere length and great diversity in anti-tumor recognition, thus future clinical trials on ACT with TIL are unlikely to require T cell selection based on antitumor reactivity.

In order to enhance the efficacy of ACT, infusion of the final product is preceded by lymphodepleting cytoxan and fludarabine treatment.

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