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REVIEWS

Cellular immunotherapy for pediatric solid tumors

MEENAKSHI HEGDE[1,2,3], ALEXANDER J. MOLL[1], TIARA T. BYRD[1,2], CHRYSTAL U. LOUIS[1,2,3] & NABIL AHMED[1,2,3]

[1]*Center for Cell and Gene Therapy,* [2]*Texas Children's Cancer Center and* [3]*Department of Pediatrics, Baylor College of Medicine, Houston, Texas, USA*

Abstract

Substantial progress has been made in the treatment of pediatric solid tumors over the past 4 decades. However, children with metastatic and or recurrent disease continue to do poorly despite the aggressive multi-modality conventional therapies. The increasing understanding of the tumor biology and the interaction between the tumor and the immune system over the recent years have led to the development of novel immune-based therapies as alternative options for some of these high-risk malignancies. The safety and anti-tumor efficacy of various tumor vaccines and tumor-antigen specific immune cells are currently being investigated for various solid tumors. In early clinical trials, most of these cellular therapies have been well tolerated and have shown promising clinical responses. Although substantial work is being done in this field, the available knowledge for pediatric tumors remains limited. We review the contemporary early phase cell-based immunotherapy efforts for pediatric solid tumors and discuss the rationale and the challenges thereof.

Key Words: *cell therapy, pediatric solid tumor, T cell, vaccine*

Introduction

Outcomes for the majority of childhood cancers have improved substantially over the past 40 years. This was achieved because of the systematic consortium efforts largely focused on dose-intense multimodality and multi-agent interventions as well as improvements in the supportive measures needed. Despite this progress, the prognosis for children with refractory and relapsed malignancies remains dismal. Furthermore, long-term toxicities of the intense chemotherapy/radiation therapy regimens are now becoming more evident with improving survival, highlighting the need for a qualitative change in our approach. Targeted therapies are being explored to overcome these toxic effects and to further improve survival. In this review, we discuss the various cellular immunotherapeutic approaches that are currently being investigated for some of the difficult-to-treat pediatric solid tumors.

For targeted cellular therapy of cancer, ideal candidate antigens are those that have high levels of expression on malignant cells with no or very low expression on normal cells. This would eliminate or minimize the systemic toxicities from on-target off-tumor effects [1]. Cellular immunotherapy for cancers can be either active or passive. Active immunotherapy involves *in vivo* activation of the innate and adaptive immune system to induce a more sustained anti-tumor response. Autologous dendritic cells (DCs) loaded with tumor antigens *ex vivo* are most commonly used as antigen presenting cells (APCs). They evoke active specific anti-tumor responses by the host immune system. DCs are the most efficient APCs because they are able to present and cross-present antigenic peptides by both major histocompatibility complex (MHC) I and MHC II pathways, thereby stimulating both CD4+ and CD8+ lymphocytes [2]. Although tumor vaccines have been largely well tolerated and shown encouraging results in early clinical trials, these studies have also highlighted some of the limitations of DC vaccines such as low frequency of antigen-specific T cells after vaccination [3]. Furthermore, although

Correspondence: **Meenakshi Hegde**, MD, or **Nabil Ahmed**, MD, MSc, Center for Cell and Gene Therapy, Baylor College of Medicine, 1102 Bates Street MC 3-3320, Houston, TX 77030, USA. E-mail: mghegde@bcm.edu or nahmed@bcm.edu

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the use of tumor vaccines for various adult malignancies has been investigated extensively over the past decade, the experience in the pediatric population has been limited.

For passive immunotherapy, immune cells such as tumor infiltrating lymphocytes (TILs), cytotoxic T lymphocytes (CTLs), natural killer cells (NK cells) and natural killer T cells (NKTs) can be generated *ex vivo*, expanded and infused in to the patient. Autologous or donor-derived T cells, NK and NKT cells can also be genetically engineered to express chimeric antigen receptors (CARs) that can specifically recognize and kill target antigen–positive tumor cells [4]. CAR molecules consist of an extracellular antigen binding domain traditionally derived from the heavy and light chain variable regions of a monoclonal antibody and an intracellular signaling domain derived from the CD3-ζ chain. Co-stimulatory molecules such as CD28, 4-1BB or OX-40 can be incorporated to the signaling domain to enhance their performance [5,6]. Hence, CAR-redirected T cells combine the specificity of monoclonal antibodies with the cytolytic activity, potential for expansion and persistence ability of T cells. They induce tumor cell killing in a MHC-independent manner, thereby overcoming some of the mechanisms tumors employ to evade the host's immune system, such as down-regulation of MHC class I molecules or components of the antigen processing machinery.

Tumors of the central nervous system

Conventional therapies using debulking surgery, radiation and chemotherapy have not been effective in preventing tumor progression in high-grade glioma, as evidenced by the poor survival rates [7,8]. Brain tumors in general are significantly less responsive to systemic chemotherapy due, in part, to the presence of a blood–brain barrier that often limits the drug penetration into the central nervous system. Treatment failures are also often secondary to the development of primary or acquired drug resistance [9,10]. However, although improvements have been seen in some brain tumors such medulloblastoma (MB; 60–80% overall survival at 5 years), treatment-associated morbidities continue to be substantial [11]. Targeted immunotherapies have the potential to improve such outcomes while minimizing the treatment-related toxicities affecting the normal developing brain in children.

Cellular immune responses in glioma patients have long been known to be deficient as shown by lack of T-cell proliferation in response to phytohemagglutinin [12,13]. Other factors, such as the down-regulation of MHC class I and class II expression, along with lack of co-stimulatory molecules on glioma cells [14,15], secretion of transforming growth factor-beta (TGF-β) and inhibitory prostaglandins by tumor cells [16–19] and infiltration of the tumor with regulatory T cells (T_{regs}) [20,21], have been implicated in glioma-induced immunosuppression. These represent major hurdles to developing effective immunotherapeutic approaches for glioma patients. The mechanisms of immune-evasion in MB are not yet clearly understood [22,23]. Although it has been shown that the MHC class I antigen processing machinery components are down-regulated in MB cells, whether this contributes to the failure of immune surveillance is not well delineated. Despite the altered MHC expression, most brain tumors preserve some degree of antigen presentation to CTLs [24].

Most of the progress made in brain tumor immunotherapy can be attributed to the use of vaccines to induce an active cellular immunity against glioma. To generate glioma-specific DCs, the peripheral blood monocyte–derived DCs are pulsed *ex vivo* with tumor cell antigens in the form of tumor lysates, acid-eluted membrane peptides or by fusing the DCs with tumor cells [25–29]. Single antigen–based vaccines have been shown to result in target antigen–negative tumor cell variants, a phenomenon seen less frequently with whole tumor cell–derived vaccines [30]. Most investigators have used an intradermal approach to inject the DC vaccines, although the subcutaneous and the intravenous approaches have been tried as well. From either of these injection sites, DCs then migrate to the draining lymph nodes to activate CTLs [31,32].

Results of multiple phase I/II clinical trials have now established the feasibility and safety of DC vaccines for brain tumors. Some of these studies in adults with malignant glioma have demonstrated objective clinical responses [29,33–35]. Although research groups have administered DC vaccines according to different schedules, the total duration of vaccine therapy needed to maintain an anti-tumor immune response remains unknown. In recent years, investigators have pursued the use of adjuvant DC vaccines for children with high-grade glioma and other aggressive/recurrent brain tumors [25,36,37]. In a clinical trial of 45 children with malignant brain tumors including high-grade glioma (HGG; $n = 33$), MB/primitive neuro-ectodermal tumor ($n = 5$), ependymoma ($n = 4$) and atypical rhabdoid teratoid tumor (ATRT; $n = 3$), tumor lysate–loaded DC vaccines were well tolerated with no severe adverse events, and more favorable responses were noted in patients with HGG and ATRT than with those with MB/primitive neuro-ectodermal tumor [36]. At a median follow-up of 35.7 months, 7 patients with HGG were alive (median overall survival 13.5

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