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Immunotherapy for Pediatric Central Nervous System Tumors

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INTRODUCTION

Despite significant advances in surgical techniques, irradiation, and chemotherapy, central nervous system (CNS) tumors are the second-leading cancer-related cause of death in children [1]. Many of those fortunate enough to survive their CNS tumors are left with life-long deficits resulting from their treatments [2]. Thus, investigators are exploring new therapeutic approaches more specifically targeted against the tumors, resulting in better tumor kills with fewer long-term side effects.

Immunotherapeutic approaches to treating CNS tumors are currently of significant interest. These approaches include passive immunotherapy through the use of monoclonal antibodies (mAbs), adoptive immunotherapy through the use of ex vivo expanded tumor-specific T cells, and active immunotherapy through the use of tumor lysate and peptide vaccines.

PASSIVE IMMUNOTHERAPY (SHARON L. GARDNER)

mAbs offer the advantage of attaching specifically to tumor antigens causing cell death through antibody-dependent cell-mediated cytotoxicity, complement-dependent lysis, and possibly tumor antigen inhibition [3]. In addition, mAbs can be used as vehicles to deliver cytotoxic agents, such as irradiation and toxins directly to the tumor cells.

Several mAbs, including rituximab (anti-CD20), myelotarg (anti-CD33), and alemtuzumab (anti-CD52), are used to treat leukemia and lymphoma [4]. mAbs also have produced responses in children with metastatic neuroblastoma [5]. Although several trials incorporating monoclonal antibodies are underway, the role of these antibodies in treating pediatric CNS tumors has not yet been definitively established.

Similar to other malignancies, CNS tumors offer the challenge of identifying unique antigens for the antibodies to target. Epidermal growth factor receptor (EGFR) is a target that has been studied in both adult and pediatric brain tumors. Studies have shown that EGFR is overexpressed, amplified, or mutated in a significant proportion of high-grade gliomas [6]. Nimotuzumab, a humanized IgG_1 antibody directed against the extracellular ligand-binding domain of EGFR, is one of several mAbs developed to target abnormal signaling through EGFR. In a phase II study of nimotuzumab in children and adolescents with refractory high-grade gliomas, 12 of 34 patients had a partial response or stable disease after 2 months of therapy, including 9 of 14 patients with diffuse intrinsic brainstem gliomas [7].

mAbs have been used to deliver toxins and irradiation directly to tumor cells. The use of toxin or irradiation-conjugated mAbs precludes the need for complement-mediated lysis, which can be difficult in the CNS. Radiation-conjugated mAbs can be used for diagnostic purposes as well as to deliver radiation therapy.

Tenascin is one of the most widely used targets for radioimmunotherapy. Tenacin-C, an extracellular matrix glycoprotein, is expressed several-fold greater in high-grade gliomas than in normal brain tissue [8]. In a phase II trial of I^{131}-labeled anti-tenacin antibody,

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median survival in patients with newly diagnosed high-grade glioma exceeded that exceeded in historical controls treated with irradiation and chemotherapy [9].

Radiolabeled mAbs also have been used to treat patients with refractory primitive neuroectodermal tumors (PNETs) with leptomeningeal dissemination. in 19 patients with refractory PNET with measurable disease, mAbs labeled with I^{131} were chosen from a panel of antibodies based on binding with each individual tumor and absence of binding on normal CNS tissue. The overall response rate was 64% (complete response [CR], 37%; partial response [PR], 16%; stable disease [SD], 11%) [10].

Targeted therapy also has been explored through the use of toxins conjugated to ligands, such as transforming growth factor (TGF)-α and transferrin, which bind to receptors overexpressed on brain tumors. Pseudomonas exotoxin conjugated with TGF-α enables delivery of the exotoxin to glioma cells through binding to EGFRs [11]. A diphtheria-transferrin conjugate has been used to treat glioma by exploiting the enhanced expression of transferrin receptors on glioma cells [12].

Along with directly targeting tumor cells, many investigators are examining the environment surrounding the tumors as well. More than 30 years ago, Judah Folkman hypothesized that tumors could be contained with drugs that prevent the development of new blood vessels to feed the tumors [13]. Bevacizumab is a monoclonal antibody that targets vascular endothelial growth factor [14]. Investigators at Duke combined bevacizumab with irinotecan in adults with recurrent malignant glioma, and found an objective response rate of 57% and a 6-month progression-free survival (PFS) of 46% [15]. Although some small preliminary studies in children with refractory high-grade gliomas have not shown a benefit with bevacizumab, there is a suggestion that it may be efficacious in children with low-grade gliomas. In a small pilot study of 10 children with low-grade gliomas with refractory disease after exhausting all conventional treatments, 7 of 9 evaluable patients had a minor, partial, or complete radiographic response, as well as clinical improvement, following 2 courses of bevacizumab and irinotecan [16]. At the time of the report, 6 children remained on therapy for between 3 and 22 months, and 8 children were progression-free survivors. The therapy was well tolerated; only 2 patients suffered a dose-limiting toxicity, with transient leukoencephalopathy in one and grade 3 proteinuria in the other.

ADOPTIVE CELLULAR THERAPIES FOR BRAIN TUMORS (NABIL AHMED)

Immunotherapy with T cells has been most successful in hematopoietic stem cell transplantation (HSCT) recipients, in whom the T cell source is normal marrow donors. Adoptive immunotherapy with donor lymphocyte infusion (DLI) has been used to effectively augment the graft-versus-leukemia (GVL) response and to treat Epstein-Barr virus (EBV)-associated lymphoproliferative disease after HSCT; however, DLI is associated with a high risk of graft-versus-host disease (GVHD) and is not always effective [17-20]. Selectively activated and/or expanded cytomegalovirus (CMV)- or EBV-specific cytotoxic T lymphocytes (CTLs) have been successful in restoring immune response and preventing diseases associated with these viruses without causing GVHD [21].

Factors Limiting the Application of Antigen-Specific T Cell Therapy

The broader use of antigen-specific CTLs for tumor therapy is currently limited by several factors, including (1) the reliable generation of tumor-specific T cells; (2) decreased major histocompatibility (MHC) class I expression on tumor cells or defects in the antigen-processing machinery; (3) the presence of inhibitory T cells, such as T helper type 2 (Th2) cells and/or T regulatory cells (Tregs), at the tumor site; and (4) limited in vivo expansion of adoptively transferred T cells. One strategy for overcoming many of these limitations is the genetic modification of T cells to express chimeric antigen receptors (CARs). CARs are synthetic molecules consisting of an extracellular receptor domain (ectodomain) that contains the heavy-chain and light-chain variable regions of an mAb joined to a transmembrane and a cytoplasmic-signaling domain (endodomain) derived from the CD3-ξ chain and costimulatory molecules such as CD28, OX40, and 4-1BB (Figure 1) [22,23]. CARs provide T cell activation in a non-MHC-restricted manner and thereby circumvent some of the major mechanisms by which tumors avoid MHC-restricted T cell recognition, such as downregulation of HLA class I molecules and defects in antigen processing. Moreover, expressing CARs with multiple signaling domains in T cells renders them resistant to the inhibitory effects of regulatory Tregs [24]. Finally, CAR-expressing T cells can be readily prepared in large quantities ex vivo for clinical applications. Indeed, our preliminary results indicate that T cells expressing CARs specific for the human epidermal growth factor receptor 2 (HER2) could overcome several of the current limitations of malignant glioma-specific T cell therapies.

Human epidermal growth factor receptor 2 (Her2) has been used as a T cell therapy target in malignant gliomas. The ideal target for biological therapies is one that distinguishes tumor cells from normal surrounding tissue, thereby avoiding unwanted bystander effects. In addition, the therapeutic target should be essential to the malignant phenotype of cancer cells,