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Immunotherapy for the Treatment of Pediatric Cancers: What is the Best Option?

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Abstract

Cancer is the leading cause of death by disease in the pediatric population in the United States. The current standard of care for treating pediatric cancer is traditional: chemotherapy, radiation, and surgery. However, these conventional approaches have many unpleasant short-term and long-term side effects and do not offer a genuine cure. Immunotherapy as a cancer treatment is a new approach that has produced very promising results in the pediatric population. Four leading therapies for pediatric cancers are CAR T-cell therapy, oncolytic virotherapy, monoclonal antibody treatments, and cancer vaccines. Some of the therapies have more promising results than others, and different cancers respond differently to immunotherapies. This review critically analyzes, discusses, and compares some of the available and emerging cancer immunotherapies for pediatric patients.

Introduction

The leading cause of death by disease in the pediatric population in the United States of America is cancer. In the USA, approximately 1 in every 285 children will be diagnosed with cancer before age 20 (American Childhood Cancer Organization [ACCO]). In 2021, it was estimated that 15,590 pediatric patients (up to 20 years) would be diagnosed with cancer, and 1,780 of them would die (National Cancer Institute, 2021). The standard of care for treating pediatric cancers is chemotherapy, surgery, and radiation.

Although these may sound like good options, these conventional approaches have many pitfalls and downsides. The immediate side effects of chemotherapy and radiation can be incredibly distressing and cause significant harm to the body, especially for pediatric patients. Aside from nausea, vomiting, and fatigue, patients may also lose their hair, develop anemia, and develop painful mouth sores. Children going through chemotherapy are often in pain and are very prone to infections (Bryant, 2003). A cytotoxic approach can often have long-term effects on pediatric patients, as many parts of development can be damaged by chemotherapy and radiation. Radiation can harm the thyroid, causing hormone problems. It can also damage bones and stunt growth. Additionally, radiation aimed toward the brain can cause cognitive impairment and a whole host of brain-related problems (American Cancer Society [ACS], 2017). Chemotherapy can damage future male and female fertility, cause long-lasting damage to the lungs and heart, and induce tooth decay and other dental-related problems (ACS, 2017). Another problem with cytotoxic approaches is that often the cancer returns, and chemotherapy and other modalities have a much lower chance of being effective. An additional issue with a standard cytotoxic approach is that it often is simply not enough to fully eliminate cancer from the patient's body.

Immunotherapy is a new and emerging science to treat cancer. Immunotherapy involves stimulating the immune response to recognize and carry out an attack on cancer cells. Immunotherapy modalities could rid a body of cancer without long-term side effects and have the potential for curing cancers rather than just stopping the progression (Wedekind et al., 2018). Although immunotherapy was formally discovered in the 19th century, until around 50 years ago, immunotherapy research was practically nil, apart from a few doctors who used bacterial infections to treat cancers (Dobosz & Dzieciatkowski, 2019). There are currently many immunotherapies in various stages of development and implementation, some of which have had very positive and promising outcomes thus far.

Some of the leading immunotherapies in terms of positive results include: CAR T-cell therapy (chimeric antigen receptor T-cell therapy), oncolytic virotherapy, various antibody treatments, and cancer vaccines. CAR T-cell therapy involves collecting T-cells from a patient and altering them to express CARs on their surfaces making the T-cells much more effective at destroying cancer cells (Boettcher et al., 2022). Oncolytic virotherapy uses viruses that are genetically engineered to target cancer cells while leaving healthy cells alone (Cockle & Scott, 2018). Antibody treatments and specific monoclonal antibody treatments work by killing cancer cells in a variety of ways and in some cases altering tumor cells to be more responsive to treatment. Monoclonal antibody treatments have been used for adult cancers for a while and are beginning to be used for pediatric cancers (Furman, 2021). A new, incredible treatment is anticancer vaccines, which are used to elicit antitumor responses in the body and are best used in addition to other treatments (Kopp & Katsanis, 2015). These immunotherapies along with many emerging therapies appear to be the future of cancer treatments.

Methods

The literature referenced in this paper helped provide an understanding of pediatric cancer and different treatment methods. Articles were accessed mainly through databases such as PubMed, ProQuest, and the National Institute of Health via Touro College's Online Library. Searches used key terms including: "immunotherapy for pediatric cancer", "pediatric cancer treatments", and "clinical trials for pediatric cancer treatments".

CAR T-Cell Therapy

Chimeric Antigen Receptor (CAR) T-cell therapy is an adoptive T-cell therapy (ACT) where T-cells are engineered to express a chimeric antigen receptor against a

specific tumor antigen (TA), allowing for the identification and killing of cancer cells. CARs consist of a recognition domain, single-chain antibody, and T-cell stimulatory domain. These CARs can then be transferred into T-cells using plasmids, RNA, or viral vector transduction to display on the cell surface (Lin et al., 2022). The structure of the CAR has evolved over the last three decades to help improve efficacy, endurance, and safety (Boettcher et al, 2022). CAR T-cells perform MHC I-unrestricted tumor cell killing by enabling the binding of T-cells to target T-cell surface antigens. Once engaged, CAR T-cells form a non-classical immune synapse (IS) which is imperative for effector function. CAR T-cells can then mediate anti-tumoral effects in several pathways, including the Fas and Fas ligand axis, cytokine release, and the perforin and granzyme axis (Benmebarek et al., 2019).

Many studies have been conducted on CAR T-cell therapy specifically for treating hematologic cancers like leukemias and lymphomas. The results of the initial studies led to adjustments and modifications in the therapy that led to improvements. One of the pioneering CAR T-cell therapies, tisagenlecleucel-T targets CD19 (a surface protein on B-lymphocytes). It ascertained efficacy in early results from the phase-2 ELIANA trial. In August 2017, it became the first FDA-approved CAR T-cell therapy for the treatment of B-cell acute lymphoblastic leukemia (ALL). This study of 75 children and adolescents had a positive outcome with a 60% complete remission rate and 81% overall response rate. It was reported that 80% of the patients were relapse-free at 6 months, a result attributed to prolonged detection of CAR T-cells in blood samples (Lin et al., 2022). Soon after this initial study, the FDA approved two more therapies. One was axicabtagene ciloleucel from the ZUMA-1 trial, and its results were very similar to the ELIANA trial with an 88% overall response rate and a 58% complete remission in the study of 108 patients (Huang et al., 2020). Toxicity was less in this trial than in the previous one, resulting in less severe side effects. The success of the ELIANA trial led to the approval of JULIET, which utilized the same therapy, tisagenlecleucel, for the treatment of relapsed and refractory lymphoma. The JULIET trial demonstrated a 40% complete recovery and a 100% durable response at its 29-month follow-up of the 93 participants. The toxicity reported in this study was like that of ELIANA. The positive results from these trials have led to the authorization of three therapies: Yescarta, Kymriah, and Brexucel. Numerous trials are being conducted, primarily aimed at reducing the toxicity of CAR T-cell therapy, improving response rate, longevity of CAR T-cells, and endurance of remission (Lin et al., 2022).

Thus far, researchers have established clear guidelines for the creation and implementation of the treatment. T-cells are removed from the patient's body via apheresis: a process where blood is drawn from one arm, spun in a centrifuge, and then all blood products except white blood cells (WBC) are returned to the body. The white blood cell products are then sent to a laboratory, where only the T-cells are extracted. CARs are then transfected into each T-cell using a variety of methods, either viral vector transduction, plasmids, or RNA techniques. The modified T-cells go through a multiplication process to ensure that a large amount of CAR T-cells are available for transfusion back into the patient. The modified T-cells are shipped back to the hospital where they are administered to the patient via a single transfusion (Kew, 2021). Patients remain in the hospital for monitoring.

CAR T-cell therapy has shown remarkable success; however, one of its drawbacks is its toxicities which produce adverse effects. The two main sources of toxicities are cytokine release syndrome (CRS), and Immune effector Cell-Associated Neurotoxicity Syndrome (ICANS). Interestingly, both syndromes have been reported at much higher rates in patients treated with CAR T-cell therapy for acute lymphocytic/lymphoblastic leukemia (ALL), than any other cancer (Sheth & Gauthier, 2020). The American Society for Transplantation and Cell Therapy (ASTCT) defines CRS as a "supraphysiologic response following any immune therapy that results in the activation or engagement of endogenous or infused T-cells and/or other immune effector cells." (Lee et al., 2018). Symptoms of CRS may include fever at the onset which may be accompanied by constitutional symptoms like fatigue, nausea, and headaches. Other symptoms of CRS are hypotension, hypoxia, and end-organ dysfunction. Bloodwork may indicate elevated D-Dimer levels and hypofibrinogenemia. The onset of CRS is typically 1-2 weeks after product administration but may occur up to 8 weeks post-administration (Baumeister et al., 2022). Often, but not always, ICANS or neurotoxicity will occur following the onset of CRS. ICANS symptoms may vary, but are typically temporary and mild, particularly in pediatric patients. Symptoms may include headaches, word retrieval difficulties, dysphasia, mental status changes (hallucinations and confusion), and possible seizures (Baumeister et al., 2022).

Typically, and especially in pediatric patients, the therapy is administered in an in-patient setting with patients remaining under close observation for around a month to monitor them and watch for any signs of CRS or any other toxicity so it can be treated efficiently and effectively. Initial treatment for patients with CRS involves infusions of IV fluids. Following this, Tocilizumab is

administered through IV. Tocilizumab is a monoclonal antibody that inhibits IL6 receptors, thereby inhibiting the IL6 pathway; it plays a crucial role in intervening with the inflammatory pathway of CRS without impacting CAR T efficacy (Maude et al., 2014). Originally, Tocilizumab was reserved for patients with Grade 3 or higher organ toxicity but, with experience, it was learned that earlier administration of Tocilizumab can offset high-grade CRS and is now employed much earlier on in the progression of CRS (Baumeister et al., 2022). In the rare event that the earlier methods do not work, third-line agents such as Siltuximab or Anakinra may be utilized.

Throughout the risk period, patients should undergo neurological assessments twice daily. The ICE (Immune Effector-Cell associated Encephalopathy) score should be used for patients over age 12, and the CAPD (Cornell Assessment of Pediatric Delirium) score should be used for patients under age 12 or those developmentally unable to use ICE score. A baseline evaluation should be conducted before the administration of therapy. The neurological assessments will be used to access ICANS and its grade. In the event of high-grade ICANS and lower-grade CRS, the patient may be placed on corticosteroids to manage the neurotoxicity. There are concerns about Tocilizumab causing increased neurotoxicity. In cases of high-grade CRS and ICANS, the patient will be treated both for the neurotoxicity with corticosteroids and for the cytokine storm with Tocilizumab (Baumeister et al., 2022). In such instances patients will be closely monitored in the PICU and treated on a case-by-case basis.

Most of the above research is great news for those with hematologic cancers. However, for those with solid tumors, brain tumors, or tumors of the central nervous system (CNS), this therapy has not shown many positive results. Several breakthroughs have been made in treating adult brain tumors. For example, there is a case of a patient with glioblastoma who was treated with IL13Rα2-specific CAR T-cells and is now in remission. There are unique problems when it comes to treating pediatric brain tumors (PBT) including the developing brain as a tumor site, the complexities of the blood-brain barrier, and the wide variety of types of brain tumors, but the small number of patients with each tumor type (Thomas et al., 2021). A large part of the problem with using CAR T-cell therapy for brain tumors is the associated side effects, CRS, and specifically ICANS. For patients with brain tumors, doctors don't want to take the risk of a treatment with a high likelihood of causing neurotoxicity and an even higher chance of neurotoxicity in those with existing brain tumors. Another large obstacle to overcome is the difficulty in finding target antigens for CARs on solid tumors that are absent on healthy tissue (Thomas et al., 2021). A small study was conducted on CNS solid tumors in patients diagnosed before turning 18. In a phase-1 study of a CAR T vaccine, three participants were treated with CAR T-cells designed to target HER2+ CNS tumors. The vaccine was injected intratumorally/intraventricularly, and no major toxicities were reported. This study demonstrated the feasibility of creating CAR T-cell therapy to target CNS tumors (Shalita et al., 2022). As demonstrated, there are many problems with CAR T-cell therapy for solid tumors. Researchers hope, that with additional measures to lessen the frequency of CRS occurring with treatment and by conducting more research on target antigens, treating solid tumors with CAR T is in our future.

Oncolytic Virotherapy

Oncolytic virotherapy is a cancer therapy that uses viruses to treat cancer. Since the mid-1800s, there have been many documented cases where patients entered remission following severe viral infections. In the last three decades medical professionals and researchers have begun genetically engineering viruses to target, infect, and lyse cancer cells, while leaving normal cells untouched (Cockle & Scott, 2018). Due to their many biological assets, oncolytic viruses are good tools for combating solid tumors. These (advantages) include the selective replication of oncolytic viruses (OVs) without harming healthy cells, and the lack of a resistance mechanism in targeted cells. The biological advantages of OVs include the high capacity of the oncolytic virus to spread throughout the tumor effectively and efficiently once only a few cells are infected, and its capacity to trigger an immune response against the tumor (Varela-Guruceaga et al., 2018). There have been many trials with a wide variety of DNA viruses, such as enveloped herpes simplex virus and poxvirus, unenveloped adenovirus and parvovirus, and RNA viruses, both enveloped and unenveloped (de la Nava et al., 2022).

Oncolytic viruses work by eliciting antitumor responses in the body without requiring defined antigens to be included in the vector. OVs initiate antitumor activity through two distinct modes of action: selective replication in neoplastic cells which leads to direct lysis of tumor cells, and induction of systemic antitumor immunity. The actual contribution of these mechanisms depends on the nature of both the cancer cell and viral vector, and the interactions between the virus, tumor microenvironment, and the host immune system. The response of the immune system to OVs yields mixed outcomes. On one hand, these viruses can promote an antitumor immune response by allowing for tumor antigen presentation in an active viral infection. However, antiviral responses can

block viral replication and infection in tumor cells so the immune system response may come in too early before all tumor cells are marked. The therapeutic outcome is a delicate balance that depends on the interplay between these two elements. In many cases, however, once systemic immunity is engaged, therapeutic responses have been observed both in locally injected tumors and in sites of uninfected tumor growth (Kaufman et al., 2015).

The methods through which OVs elicit antitumor responses work through a long chain of signaling pathways. These pathways are typically stimulated by local IFN (interferon) release or intracellular Toll-like Receptors (TLR). TLRs are pattern recognition receptors that are activated in response to pathogen-associated molecular pathways (PAMPs), which are typical in pathogenic bacteria and viruses. TLR signaling induces host-cell antiviral activity and systemic innate immunity. The TLR-associated factors trigger the JAK-STAT (Janus kinase–signal transducer and activator of transcription) pathway, coordinating the antiviral machinery in infected cells. The antiviral machinery activates the release of various IFNs, which leads to the termination of cell protein synthesis, the promotion of rapid cell death, and viral clearance (Kaufman et al., 2015).

Adenoviruses have demonstrated great responses in a variety of pediatric solid tumor cancers, including CNS tumors, neuroblastomas, and sarcomas. There are many different adenoviruses used in a various studies, but all adenoviruses have a similar structure. Adenoviruses are non-enveloped viruses with an icosahedral capsid containing up to seven different proteins. The most important protein is fiber, a trimeric protein that contributes to virus tropism and protrudes from the virus, like an antenna (Garcia-Moure et al., 2016). A study was conducted using an adenovirus called Delta-24-RGD to treat adult and pediatric brain tumors. Delta-24-RGD demonstrated a good antiglioma effect in preclinical and clinical studies on adult patients with recurrent gliomas. It also triggered immune-mediated responses, with many immune populations within the tumors. The same group also studied this virus in the context of high-risk pediatric brain tumors. Treatment with Delta-24-RGD resulted in increased survival in both human xenografts and in syngeneic mouse models with pediatric high-grade gliomas (pHGGs) and diffuse midline gliomas (DMGs). Delta-24-RGD was also studied in atypical teratoid/rhabdoid tumors (AT/RTs) and CNS embryonal tumors with a survival time of 6-12 months. Delta-24-RGD demonstrated positive results, with long-term survival rate increasing up to 70% (de la Nava et al., 2022). In a different study, oncolytic adenoviruses were used specifically for the treatment of osteosarcomas. This study utilized Delta-24-RGD therapy, and antitumor efficacy was observed in lung and tibial osteosarcomas. Thus far, this study has shown encouraging results but was conducted only in immunodeficient mice, so changes to the therapy must be made for immuno-virotherapy to consider immune system responses (Garcia-Moure, 2016).

Another virus that has gained popularity due to positive outcomes is the use of engineered oncolytic herpes simplex virus (HSV). HSV is an attractive candidate for oncolytic virotherapy due to its unique properties. The two major properties of the large double-stranded DNA are that HSV-1 replication occurs in the nucleus but does not cause insertional mutagenesis (DNA mutations by the addition of one or more base pairs), and that HSV-1 has a very large genome (152 kb), with 30 kb encode genes that are not essential for viral replication (Kaufman et al., 2015). Neuroblastoma, a tumor of the neural crest derivatives, constitutes 8-10% of pediatric cancers. It has a very poor prognosis and is responsible for over 15% of pediatric cancer deaths. A study published in 2013 discusses the use of oncolytic virotherapy as a treatment for pediatric neuroblastoma. M002, the engineered HSV used in this study, has deletions of the γ134.5 gene and enables replication in tumor cells while preventing infection of normal cells. In vitro, M002 produced cell death in neuroblastoma cell lines, and in vivo, it reduced tumor growth of neuroblastomas. This study found that the best results were acheived with the addition of multiple doses of ionizing radiation (Gillory, 2013). In a study involving HSV-1 for Ewing sarcoma, the second most common bone tumor in the pediatric population, and very difficult-to-treat cancer, HSV-1 rRp450 was combined with either of two macrophage-reducing drugs: Clodrosome and Trabectedin. Both drugs demonstrated good results in xenografts in mice, with trabectedin producing slightly better results (Denton et al., 2018). There is still room for a lot of work in this field, but encouraging results are there.

Currently, three oncolytic virotherapies have received regulatory approval for cancer treatment. In the United States the only oncolytic virus that has received approval is Talimogene laherparepvec (T-vec), an HSV-1 virus that encodes for GMCSF (granulocyte-macrophage colony-stimulating factor) and provides an immunological boost. In a phase 3 trial in patients with unresectable melanoma, patients receiving T-vec intratumorally had a durable response rate of 19.3%, and 80% of those were complete responses. The results demonstrated slight efficacy, leading to approval by the FDA in 2015 (Hemminki et al., 2020). Another OV that has received approval is RIGVIR, an ECHO-7 virus, a picornavirus with innate

tumor selectivity. Although it is not approved in the USA, RIGVIR was approved by Latvia and several other countries in 2004 (Alberts et al., 2018). The third OV is an adenovirus called Oncorine (H101), which has been approved in China for the treatment of solid tumors since 2005 (Hemminki et al., 2020).

There is not much data available discussing the side effects of oncolytic virotherapy in patients. This may be because there aren't too many side effects, but the more likely reason is the fact that most studies on OV are still in the early phases and have been done in immunodeficient mice and not humans.

Monoclonal Antibody Therapy

Monoclonal antibodies are antibodies that are synthesized in a laboratory for the treatment or detection of cancer cells. Monoclonal antibodies work by binding to antigens on the tumor cell surface and facilitating an immune response. They have a great advantage over cell-based approaches because they can be stored in clinics and hospital pharmacies and advanced cell-based expertise is not needed, therefore, they are more readily available than other therapies (Huang et al., 2015). Monoclonal antibodies (mAbs) can essentially be designed to behave in one of three ways: they can block the growth of cancer cells, flag cancer cells for immune system-mediated destruction, or deliver harmful substances that destroy cancer cells (National Cancer Institute, 2019). Monoclonal antibodies can be classified into three different groups based on their construction and mechanism. Naked antibodies bind to cell surface antigens and mediate cell lysis through antibody-dependent-cellular cytotoxicity (ADCC), complement-mediated cytotoxicity (CDC), and by inducing apoptosis. Conjugated antibodies link a monoclonal antibody to a potent cytotoxin or radioisotope. They are absorbed immediately after binding to the surface cell marker, and lead to cell death by releasing toxins. Bispecific or bifunctional antibodies engage two target domains simultaneously, consisting of variable domains linked together to form a single-chain antibody (such as a BiTE: Bispecific T-cell engager antibody), dual-affinity re-targeting antibodies, and tandem single-chain variable fragments (Guerra et al., 2019).

There are a few monoclonal antibody therapies that have received federal approval in the USA and even more that are in various phases of trials. Scientists generally approach mAb therapies in two ways; either by finding receptors that are specific to distinct types of cancers and creating a therapy targeting those specific receptors, or they develop a treatment directed toward a specific target and assess its efficacy in treating various types of cancers. One therapy, Rituximab, has received approval for clinical use in the USA since 1997. It is designed to target CD20, an antigen expressed specifically in B-cell lymphomas. It was first approved for use in non-Hodgkin lymphoma, Burkitt lymphoma, and chronic lymphocytic leukemia. In a phase II trial for lymphocyte-predominant Hodgkin lymphoma, Rituximab demonstrated a 96% overall response rate and 75% 1-year event-free survival (EFS) (Huang et al., 2015). In a study conducted in 2014 on adults with B-lineage CD20-positive ALL (acute lymphoblastic/lymphocytic leukemia), treatment with Rituximab resulted in longer EFS than those in the control group (Maury et al., 2016). Following this study, the University of Texas MD Anderson Cancer Center adopted a new standard of care, which involved incorporating an anti-CD20 antibody, such as Rituximab, to the chemotherapy regimen for all patients under age 60 with positive B-cell ALL (Guerra et al., 2019). There are other treatments targeting CD20, such as Ofatumumab, which is currently less popular than Rituximab, but studies are being conducted to see if Ofatumumab has better long-term outcomes than Rituximab. Another naked mAb therapy was approved in 2011 by the FDA for the treatment of Relapsing/Refractory HL (Hodhkin lymphoma) and ALCL (anaplastic large cell leukemia) (Huang et al., 2015). This anti-CD30 mAb, brentuximab vedotin was administered to pediatric patients who had previously received chemotherapy, and 47-64% had positive overall response rates to this treatment (Younes et al., 2010).

An emerging class of mAbs with highly promising results is known as bispecific antibodies. This new therapy is called Blinatumomab, which is a bispecific T-cell engager (BiTE) targeting two different antigens on the tumor cell surface, Blinatumomab targets CD19 positive cells and simultaneously binds to CD3 receptors on T-cells. T-cells are designed to recognize and eliminate cancer cells through cytotoxic mediator release, however, neoplastic cells evade detection by T-cells by modifying recognition signals between cells. Blinatumomab acts as a bridge between cells by binding CD19 and CD3, and thus, stimulates the immune system to recognize and kill cancer cells by bypassing the MHC class I restriction (Huang et al., 2015). This therapy is currently used for the treatment of Recurrent/Refractory (R/R) ALL and B-cell lymphoma. In an interesting development, in 2021, Australian researchers used Blinatumomab to treat pediatric patients suffering from R/R ALL with. Blinatumomab caused a large expression of CD19 in patients, and subsequently, patients were able to be treated with CAR T-cell therapy due to the retention of CD19. This study had very promising results (Mejstrikova et al., 2021).

Monoclonal antibody therapy has demonstrated positive results in the treatment of pediatric neuroblastomas. In the 1980s, researchers discovered that almost all neuroblasts express disialoganglioside (GD2) on their surfaces. There are currently two FDA-approved mAb therapies that target GD2. The major anti-tumor mechanism of anti-GD2 mAbs is ADCC (antibody-dependent-cell-mediated cytotoxicity) mediated mostly by NK cells and partially by neutrophils and macrophages (Perez Horta et al., 2016). The first FDA-approved anti-GD2 therapy is Dinutuximab (Ch14.18). It consists of human Fc constant regions of an IgG1 immunoglobulin fused with the Fab portion of a murine antibody to produce this chimeric mouse/human antibody against GD2. Children over the age of one year received Dinutuximab following myeloablative chemotherapy which resulted in a dramatic improvement in the 2-year EFS (event free survival) at 66% as opposed to 46% (Furman, 2021). Ongoing studies are investigating the use of Dinutuximab as a monotherapy or in combination with other treatments to improve antitumor efficacy (Perez Horta et al., 2016). The other FDA-approved mAb for neuroblastoma treatment uses humanized anti-GD2 antibodies and is called naxitamab. Humanizing murine mAbs makes them less immunogenic and are tolerated better by patients (Harding et al., 2010). They are made from fully human amino acid sequences for the IgG1 form of the murine anti-GD2 mAb 3F8. The trials had very positive results which led to the approval of naxitamab for use in patients older than 12 months with persistent refractory disease. Other studies of mAbs for neuroblastoma include anti-Anaplastic Lymphoma Kinase (ALK) antibodies to target the 8% of neuroblastomas that express ALK antibodies (though not yet available for testing), bispecific mAbs, and PD-1/PD-L1 (programmed cell death-1/programmed death-ligand-1) mAbs (Furman, 2021). Many of these studies are in the very early stages of testing but look promising.

Monoclonal antibody therapies do induce some side effects, but in comparison to chemotherapy, their side effects are generally milder. There is some variation of side effects amongst different therapies, but most of the side effects are similar across the board. Brentuximab vedotin, which is used in pediatric patients for the treatment of R/R HL and ALCL, produces moderate adverse effects in patients. Most of the adverse reactions are grade 1 or 2 and are typically managed with basic supportive care. The cytotoxic component of the drug can sometimes cause peripheral neuropathy and associated adverse events. In many cases, the symptoms had already resolved on their own by the time of follow-up appointments (Younes et al., 2010). In trials, Dinutuximab displayed serious toxic effects including pain, hypersensitivity reactions, capillary leak, and hypotension. As a result, humanized antibodies were used instead (Naxitamab) to improve tolerability and lessen toxicity, resulting in improvements, but without any breakthroughs. It appears to be a step in the right direction (Furman, 2021). The FDA's review of Naxitamab states that it can cause infusion-related reactions and neurotoxicity, including neuropathic pain and transverse myelitis. Adverse reactions to the drug itself are usually grade 1 or 2, with symptoms like pain, vomiting, nausea, fatigue, headaches, and similar symptoms. Approximately 5 percent of patients experience grade 3 or 4 blood laboratory abnormalities, such as decreased lymphocytes, neutrophils, hemoglobin, potassium, and platelet count (FDA, 2020). No major long-term effects have been determined yet, but in truth, the mAbs have not been used for that many years, resulting in limited long-term data.

Cancer Vaccines

Monoclonal antibody therapy is a form of passive immunization which often does not create long-term immunologic memory. In contrast, cancer vaccines initiate an active immune response. They can be tumor or immune cells, peptides or proteins, or genetic vaccines. Active cancer vaccines initiate a local inflammatory response against cancer antigens, mediating an antigen-specific T-cell response. The activated T-cells can then become effector cells or central memory cells, which can survey and initiate protection against residual tumors or minimal disease states (Dyson et al., 2019). Every vaccine directed against tumor cells must have a high concentration of antigen delivery to the cells it is directed against to combat an immune system that has already developed tolerance. Whereas preventative vaccination is not combating an activated immune system, and therefore does not need as high a concentration of antigen delivery (Shiqi Wang et al., 2019). One of the most common vaccine approaches is the use of dendritic cell (DC) vaccines. These vaccines utilize DCs to recognize and respond to tumor antigens, resulting in the destruction of the tumor in situ. Another less common vaccine approach involves autologous tumor cell vaccines which seek to initiate DC responses in vivo. The most recent cancer vaccines are non-cell-based vaccines, which also deliver antigens to DCs in vivo (Dyson et al., 2019).

An important aspect of cancer vaccines is the selection of the appropriate antigen. An ideal tumor antigen is highly expressed and has a strong attraction for binding with MHC molecules. These are important factors for ensuring that the antigen is properly presented to elicit immune cell recognition and lysis. The antigen must also

be able to handle the magnitude of CD8+ and CD4+ T-cell responses for antigen recognition. The CD8+ T-cells recognize the amino acids associated with MHC-I, while the CD4+ T-cells recognize the amino acids of MHC-II (Olsen et al., 2021). One antigen used is tumor-associated antigens (TAAs), native proteins that are overexpressed by tumor cells, which makes them a good option. TAAs do have limitations, including the possible risk of damage to healthy tissue and that central tolerance can cause the removal of TAA-reactive T-cells, leaving behind only low-affinity T-cells. The other antigen commonly used is tumor-specific antigens (TSAs) or neoantigens. TSAs are mutated proteins that stem from the genetic instability of the tumor. TSAs are advantageous because they are only expressed by unhealthy cells and therefore unaffected by central tolerance. The T-cells generated by TSAs are more targeted and effective than those of TAAs while maintaining a low risk of autoimmunity. Their disadvantage is that TSAs vary greatly from tumor to tumor and often need to be highly personalized, making them quite inconvenient (Sampson & Mitchell, 2015).

The first cancer vaccine to receive approval from the FDA is a DC vaccine called Provenge (sipuleucel-T) for the therapeutic treatment of prostate cancer. To create this drug, and all DC vaccines, autologous DCs are isolated via apheresis, matured with immunostimulatory agents, and loaded with an antigen before injection into the patient (Olsen et al., 2021). The DCs can be engineered using CRISPR, RNA interference, and viral transduction (Perez & De Palma, 2019). DC vaccines do have many downsides including labor and cost problems, potentially weak response due to insufficient cell numbers and activation, as well as T-cell inactivation due to immunosuppression. Despite the limitations, DC vaccines have been utilized in a variety of pediatric trials, with encouraging results. In one such phase II trial, pediatric patients with metastatic or relapsed sarcomas were treated with an autologous tumor lysate-pulsed DC vaccine. Compared to patients undergoing standard chemotherapy treatments, these children demonstrated a 12% increase in overall survival (OS). Five-year overall survival rate of patients with Ewing sarcoma was 77% compared to the standard 30-50%. Additional trials with DC vaccines achieved similar results (Olsen et al., 2021).

There are cancer vaccines that employ different techniques and methods, although DC vaccines are the most common. Peptide vaccines use peptide antigens that are processed and presented by DCs and other antigen-presenting cells (APCs) to prime T-cell immunity at the vaccination site. Peptide vaccines include synthetic peptides of tumor antigens combined with adjuvants (immunostimulants). Peptide antigens, both TSAs, and TAAs, are selected for their length to maximize the range of T-cell responses and include almost all the amino acids in CD8+ and CD4+ T-cell epitopes (Olsen et al., 2021). Peptide vaccines are a good option because production is relatively fast and inexpensive, and they have hardly any innate immunostimulatory properties, which can be determined by the adjuvant. The trials conducted with peptide vaccines on children, however, did not produce very satisfactory results overall. In an early phase trial of five patients with Wilms' Tumor gene WT-1, one patient achieved complete remission, while the other four patients experienced disease progression and/or death. Other peptide vaccine trials had some better results, but there is still significant work required for peptide vaccines before they become a viable option. Additional cancer vaccine strategies include nucleic acid vaccines which utilize plasmid DNA or mRNA to express tumor antigens, and viral vector vaccines which utilize potent vaccine technologies to induce T-cell immunity (Olsen et al., 2021).

Cancer vaccines appear to have significant potential, but they require extensive further research and refinement before they are a viable and reliable option for cancer treatment. Combination immunotherapies that include combining vaccines with other methods like chemotherapies and oncolytic viruses are beginning to be viewed as effective approaches for reversing immunosuppression and intensifying vaccine efficacy. It is important to note that most cancer vaccine trials have been with adults specifically, and afterward, some have been tested in pediatric patients. It is possible that trials that were not effective in adults can induce a positive response in pediatric patients, because pediatric patients generally respond better to immunotherapies and specifically vaccines, more so than adults (Olsen et al., 2021).

Conclusion

The use of immunotherapy for the treatment of pediatric cancers is an important technique for a variety of reasons and for the future of cancer treatment. Immunotherapy has a significant advantage over traditional cancer treatment approaches, especially for pediatric cancers because they cause much less long-term negative side effects. Traditional cancer treatment can cause great harm to the developing bodies and body systems of young patients by stunting growth, development, and maturation in all aspects. Most immunotherapies are new treatments that have not been in use for more than ten years, so we do not know the long-term effects, but research is promising, and the thought is that by inducing a self-mediated immune response the patient's body will not be so damaged

to maintain long term damage and side effects.

Many immunotherapies have been explored as potential cancer treatments for pediatric patients, including those previously discussed in detail: CAR T-cell therapy, oncolytic virotherapy, monoclonal antibody therapy, and cancer vaccine therapy. Research has demonstrated that the most effective immunotherapy for treating pediatric hematologic cancers is CAR T-cell therapy. Although CAR T-cell therapy often has many side effects, they are typically short-term and there are established methods for treating the side effects. This treatment has also shown no long-term effects in patients who received this treatment as children and are now adolescents or young adults. CAR T-cell therapy has not, however, produced positive results when used as a treatment for solid tumors. CAR T-cell therapy has typically been used as a last resort treatment for pediatric patients but as it continues to demonstrate positive results it is likely to soon become a treatment option earlier in pediatric hematologic cancer care with the hope of eventually replacing traditional cancer approaches.

Currently, the therapy that seems most promising for the treatment of pediatric solid tumors is monoclonal antibody therapy. There are currently several mAbs on the market that have demonstrated good results when used as a treatment for solid tumors, such as lymphomas and neuroblastomas. A drawback of mAb therapy is that it currently is used and investigated as an option to employ alongside traditional cancer treatments instead of as a replacement for traditional cancer treatments.

Other potential immunotherapies show promise in the treatment of brain tumors and other pediatric cancers but are not developed enough to be viable treatment options just yet. The science of utilizing immunotherapy as an essential treatment for pediatric cancer is a very promising and hopeful field with a lot of potential research and options. Considerable research remains to be conducted, including the study of long-term effects and therapies independent of traditional cancer care. Although the hope is for cancer therapy with as few long-term side effects as possible, at the end of the day, what parents want is an effective treatment for their children that will cure them of this terrible disease, without thinking about long-term effects. The future is bright and with more research every day we are closer to reaching an effective cure for cancer.

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