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Perspective

Various Immunotherapies to Treat Childhood Cancer

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DESCRIPTION

Pediatric malignancies continue to remain the largest cause of cancer death in people under the age of 20 despite improvements in chemotherapy and radiation over the past few decades, which have had a significant impact on the overall survival of children with cancer. Additionally, a lot of patients who make it through adolescence and beyond frequently do so with a variety of incapacitating treatment-related side effects that may have a long-term negative influence on their quality of life. Emerging therapies called immunotherapies aim to reduce many of the unfavorable side effects of current treatments while assisting the patient's immune system in eliminating malignant cells. Numerous types of immunotherapy have demonstrated encouraging outcomes in treating adult cancers, opening the door for their use in treating different types of childhood cancers.

Bispecific antibodies are a group of novel-targeted antibodies, and blinatiumomab is one of their first-in-class members (BsAbs). Usually, a flexible linker connects two single-chain variable fragments (scFv) to form these molecules. While there is potential for variety, the majority of BsAbs currently available have a similar architecture in that one scFv is targeted to the CD3 component of the T cell receptor and the other is specific for a tumour antigen that has been verified. By physically connecting T cells to tumour cells, BsAbs aid in the development of an immunological synapse that triggers T cell degranulation and ultimately results in the death of the attached tumour cell. Since almost all B-lineage lymphoblastic leukemias and lymphomas exhibit the B lymphocyte antigen CD19, the tumor-targeting component of blinatumomab is a scFv. By demonstrating that this design significantly increased cytotoxicity in CD19+ lymphoma cells co-cultured with unstimulated T lymphocytes at doses of 10–100 pg/mL and effector to target cell ratios as low as 2:1, Löffler and colleagues introduced blinatumomab for the first time in 2000.

Disialoganglioside (GD2), a glycolipid antigen that is highly expressed on the surface of neuroblastoma and a variety of other embryonal tumours such as rhabdomyosarcoma, Ewing sarcoma, retinoblastoma, osteosarcoma, and some paediatric brain tumours, is the target of the chimeric human-mouse antibody known as dinutuximab. Dinutuximab, formerly known as "ch14.18," was developed in the 1980s along with a number of other clinical-grade anti-GD2 antibodies as a neuroblastoma therapy. By attaching to GD2 on the tumour cell surface, these antibodies because the corresponding Fc sections of monocytes, macrophages, neutrophils, and natural killer cells to connect to receptors on the tumour cells. Following this contact, the tumour cell is killed by Complement-Dependent Cytotoxicity (CDC) or Antibody-Dependent Cell-mediated Cytotoxicity (ADCC). Dinutuximab is made up of the constant sections of human IgG1 and the variable parts of the murine IgG3 anti-GD2 monoclonal antibody 14.G2a. This design decision was made as a preventative strategy to reduce the likelihood that the patient would experience a Human Anti-Mouse Antibody (HAMA) response after injection, which could impair the anticancer drug's effectiveness.

Two of the most well-known immunotherapeutics in a class known as immune modulators or immune checkpoint inhibitors are pembrolizumab and ipilimumab. Even though the two antibodies' targets differ, they both work by preventing inhibitory signals from T cell activation, which in turn helps these cells generate a more potent antitumor response.

Tisagenlecleucel is a CAR-T cell therapy for B cell malignancies that have relapsed or are resistant to treatment. CAR-T cells are created by genetically modifying a patient's own T cells to join an antibody's extracellular antigen recognition domain with the T Cell Receptor's (TCR) intracellular signalling domain. This antigen recognition domain on tisagenlecleucel was generated from the mouse monoclonal antibody FMC63, which binds human CD19 in its natural conformation. Transmembrane and spacer domains connect this domain to the TCR domain, giving it extra flexibility to optimally interact with cancer cells that express CD19. Tisagenlecleucel has also been created as a "second-generation" CAR-T treatment to express a 4-1BB (CD137) costimulatory domain to support T cell proliferation and persistence in the patient after injection. Because they can interact with tumor cells without relying on the Major Histocompatibility Complex (MHC), which is frequently down regulated or missing in many tumors as a protection against immune-mediated destruction, CAR-T cells are an appealing method of immunotherapy.

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