Review

Medicine

Cytokine Immunotherapy for Neuroblastoma

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Neuroblastoma (NB) is an embryonal tumor originating from the sympathetic nervous system, which occurs during fetal period or early postnatal period, and is one of the most common extracranial solid malignant tumors in children. Cytokines are pleiotropic proteins that can effectively activate tumor immune cells and counteract immune suppression, thereby suppressing tumors. Cytokine immunotherapy provides more possibilities for the application of immunotherapy through its own induction and activation of the immune system and has also been extensively studied in NB immunotherapy. This article mainly introduces the research progress of several immunotherapies based on cytokines in the treatment of children with NB.

Keywords: Cytokines; Neuroblastoma; Immunotherapy; Outcomes

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NEUROBLASTOMA (NB) is an embryonal tumor originating from the sympathetic nervous system, which occurs in the fetus or early postnatal period, and is one of the most common extracranial solid malignant tumors in children (1). NB accounts for 6%-10% of all childhood cancer cases and 9%-15% of all childhood cancer-related deaths (2). The International Neuroblastoma Staging System (INSS) divides patients into low, intermediate, and high-risk groups according to prognostic factors, and different risk groups have different outcomes (3). The 5-year survival rates of NB patients in the low-risk group and high-risk group were 90% and 50%, respectively, and the prognosis of the high-risk group was poor (4).

Traditional treatments include chemotherapy, surgical debulking or resection of the primary tumor, radiotherapy, differentiation agent therapy (such as 13-cis retinoic acid), and autologous bone marrow transplantation (5). Most children with high-risk NB achieved remission shortly after induction chemotherapy, but children who received radiation to metastatic sites did not experience a significant improvement in 5-year survival compared with those who did not receive radiation (6). Many patients cannot avoid the possibility of recurrence with additional consolidation therapy (such as surgical resection) after radio/chemotherapy, and up to 20% of high-risk NB patients have no significant effect of induction therapy. Although surgical resection has certain advantages, it did not significantly improve the 5-year survival rate of patients (7). In patients with advanced NB who were 18 months or older at diagnosis, surgery at the primary tumor site had no effect on local control rate or prognosis (8, 9).

Although these traditional treatments have a certain effect on the treatment outcome, most high-risk NB patients are at risk of recurrence, and the metastases are resistant to multiple drugs, so it is very necessary to find alternative methods, such as im-

munotherapy. As a potential effective means of tumor treatment, tumor immunotherapy can control and kill tumor cells by stimulating or mobilizing the body's immune system and enhancing the anti-tumor immunity of the tumor microenvironment (10). The combination of immunotherapy and modern biotechnology has developed into the fourth tumor treatment method after surgery, chemotherapy, and radiotherapy.

The main immunotherapies associated with NB are cytokines, dendritic cell vaccines, anti-GD2 antibodies, and allogeneic hematopoietic stem cell transplantation. Anti-GD2 monoclonal antibody drugs are relatively the most mature means of immunotherapy of NB. GD2 is a unique type of carbohydrate antigen that does not depend on T cells (11). It is scattered outside the cell membrane in large quantities and exists in the form of oncoembryonic antigen. The current monoclonal antibody chimeric 14.18 (ch14.18) has shown good clinical efficacy, and cytokine-based immunotherapy, which can be used in conjunction with anti-GD2 monoclonal antibody drugs, also has good therapeutic prospects (12). Cytokine immunotherapy provides more possibilities for the application of immunotherapy through its own induction and activation of the immune system. This review discusses the application of several types of cytokine-based immunotherapy in children with NB.

Cytokine-Based Immunotherapy

Cytokines are polypeptides or glycoproteins with a relative molecular mass of less than 30,000, which provide growth, differentiation, and inflammatory or anti-inflammatory signals for different cell types, and can effectively activate tumor immune cells and/or counteract immune suppression, thereby inhibiting tumors (13, 14). Interleukin-2 (IL-2) can induce the proliferation of natural killer cells (natural kill cells, NK) and enhance their cytolytic ability, drive the proliferation and activation of CD8+ T cells, and promote the proliferation of B cells and antibody secretion (15). IL-21 gene transfer or recombination can trigger anti-tumor effects and induce NK and/or cytotoxic T lymphocyte (CTL) response (16, 17). Granulocyte-macrophage colony stimulating factor (GM-CSF) acts in a paracrine manner to recruit circulating neutrophils, monocytes, and lymphocytes to enhance their role in host defense function (18). Immunotherapy based on cytokines such as IL-2, IL-21 and GM-CSF has been widely studied in tumor immunotherapy.

IL-2

IL-2 is a monomeric secreted glycoprotein with a relative molecular mass of 15,000. It exists in a spherical structure and is folded into a typical type I cytokine by four α-helices (19). IL-2 is a growth-promoting active factor of bone marrow T lymphocytes and one of the earliest cytokines characterized at the molecular level (20). Experiments have shown that IL-2 is produced by cells stimulated by mitogens and is a soluble active substance present in the conditioned medium, which makes it possible to generate and cultivate T lymphocytes (21). IL-2 acts on many cell types, especially T lymphocytes. IL-2 is critical for regulating immune activation and homeostasis in CD4+ and CD8+ T cell proliferation (22).

A Spanish research team discovered that after autologous bone marrow transplantation (ABMT), the activation and response changes of NK could be observed during IL-2 treatment, which can be applied to improve the administration of IL-2 in immunotherapy (23). Timetable design of new immunotherapy regimens, provides hope for the treatment of stage IV NB (24). IL-2-targeted therapy combined with an anti-diisoganglioside antibody fusion protein was able to induce cell-mediated anti-tumor responses and effectively eradicate established syngeneic models of bone marrow and liver metastases in NB (25). Its mechanism is NK-dependent, and NK deficiency will destroy its anti-tumor effect. Targeting the tumor microenvironment to deliver cytokines induced an effective cellular immune response, and this NK-mediated immune response provided a new strategy for the treatment of metastatic NB (26, 27), with regard to T cell function after high-dose chemotherapy patients with suppressed but sufficient NK cells may have general clinical significance.

IL-2 has shown anti-tumor activity in many studies, it can activate and enhance the cytolytic activity of NK and T cells, and it has a partially overlapping effect with IL-12 on the process of activating various types of immune cells through IL-2 up-regulates IL-12 receptor and signal transducer and activator of transcription (STAT), thus playing a synergistic role in the process of activating NK cells (28). NK cells treated with a combination of IL-2 and IL-12 exhibited enhanced cytolytic activity in vitro, more efficiently lysed NB cells, and could reduce the dose of antibodies (such as anti-disialoganglioside antibodies) required, thereby reduce toxicity (29). The antitumor effect of autologous fibroblasts rather than tumor cells transfected ex vivo to express IL-2 and IL-12 was tested in a mouse model of NB (30). IL-2 and IL-12 can effectively fight the disease when co-transfected in tumor cells, which provides a promising immunotherapy approach for the treatment of NB, CD4+ and CD8+ T cells can mediate this reaction (31). Fibroblasts co-transfected with homologous IL-2 and IL-12 not only have therapeutic effects on diseases, but also can produce immune memory (32). Co-injection of IL-2 and IL-12 co-expressed fibroblasts and ex vivo transfected tumor cells with Neuro-2A tumor cells, which eliminated the tumorigenicity in patients with three intratumoral doses treatment with transfected fibroblasts has a significant curative effect, and the cure rate can reach 90% (33).

IL-21

IL-21 is a member of the IL-2 cytokine family. It is a cytokine closely related to IL-2 and IL-15, which promotes functional activity of T cells, B cells and NK cells (34). IL-21 also promotes the proliferation and cytotoxicity of CD8+ effector T cells and the production of interferon-γ (IFN-γ) and plays an important role in regulating B cell responses (35).

IL-21 is involved in the development of the autoimmune system, and unlike IL-2, IL-21 cannot promote the proliferation of anti-CD3 activated regulatory T cells (Treg cells) (36). Since Treg cells are involved in the suppression of anti-tumor immunity, IL-21 may be more suitable than IL-2 for inducing anti-tumor immunity. IL-21 gene transfer or recombination can trigger antitumor effects, thereby inducing NK and CTL responses (37). Studies have shown that gene delivery of IL-21 enhances the potency of antigen-specific vaccines in NB models. The therapeutic effect of IL-21 gene-modified cells

(neuro2a/IL-21) in the syngeneic transfer NB model and proved that NB cells secreting IL-21 passed the specific CTL with survivin as antigen (38). By administering the IL-21 gene-modified cell vaccine, the average disease-free survival rate was increased from 22-44 days to 75 days, and cure rate from 14% to 33% (39). This reveals the potential role of IL-21 in gene immunotherapy of NB.

IL-21 exerts anti-tumor activity without the assistance of CD4+ T cells, and as an auxiliary factor, it can directly stimulate the proliferation and functional activities of CD8+ T cells (40). In addition, IL-21 can inhibit helper T cell (helper T cell, Th) development and dendritic cell differentiation (41). Anti-CD4 monoclonal antibodies (mAbs) can also enhance IL-21-based immunotherapy by depleting Treg cells and their precursors and other potentially immunosuppressive CD4+ cell subsets, thereby allowing IL-21-driven CD8+ Development of T cell responses, mediating NB cell death (42, 43). Combination immunotherapy with anti-CD4 monoclonal antibody and recombinant IL-21 induces CD8+ T cell responses and reprograms CD4+ T cell immune regulation to anti-tumor functions, leading to tumor eradication and long-lasting immunity (44).

GM-CSF

GM-CSF is a hematopoietic growth factor and immunemodulator, mainly produced by activated T cells, B cells, macrophages, fibroblasts, epithelial cells, and some tumor cells, which can stimulate the proliferation and differentiation of bone marrow precursor cells into neutral granulocytes and macrophages can enhance the effective processing and expression of tumor-associated antigens, thereby enhancing the body's anti-tumor immune response and achieving anti-tumor effects (45, 46). Although produced locally, GM-CSF can recruit circulating neutrophils, monocytes, and lymphocytes in a paracrine manner, enhancing their function in host defense (47). Study suggested that GM-CSF can promote the maturation of dendritic cells and enhance the activity of macrophages (48). High expression of GM-CSF in tumor cells is closely related to the overall survival rate and disease-free survival rate of tumor patients, and the prognosis of tumor patients can be predicted according to TNM staging and distant metastasis (49).

Ganglioside sugar (GD2) is an abundant adhesion molecule in NB cells (50). It is rarely expressed in normal tissues except neurons, skin cells and pain fibers. Its high expression in NB cells and anti-GD2 monoclonal antibodies may be suitable for immunotherapy (51). When the anti-GD2 monoclonal antibody ch14.18 is used in combination with GM-CSF or IL-2, it can enhance antibody-dependent cell-mediated cytotoxicity, thereby improving the progression-free survival (PFS) and clinical data such as overall survival rate produced statistically significant changes (52). Immunotherapy with ch14.18, GM-CSF, and IL-2 significantly improved prognosis compared with standard treatment in high-risk NB patients (53). When used in combination with GM-CSF and IL-2 for the treatment of NB, anti-GD2 monoclonal antibodies were effective against NB in the presence of transgenic CSF (54). Compared with standard treatment, GM-CSF and IL-2 combined immunotherapy had a 2-year disease-free survival rate (46% vs. 66%) and overall survival rate (75% vs. 86%) is significantly higher (52). The addition of isotretinoin ch14.18 antibody immunotherapy combined with GM-CSF or IL-2 as consolidation therapy for high-risk NB patients had a significant effect (55).

Conclusion

Cytokines, as a special protein drug, can effectively activate tumor immune cells and counteract immune suppression, thereby suppressing tumors. In recent years, cytokine-based immunotherapy has also been continuously researched and developed in the treatment of children with NB. Manufacturing cytokine-based drugs is a daunting challenge that requires a solid understanding of cytokine biology and modern biotechnology to develop their antitumor activity while minimizing toxicity (30). Another key consideration is to limit the sites of action of cytokines to avoid systemic pro-inflammatory effects. Therefore, the combination of low-dose cytokines with gene therapy, cell therapy and monoclonal antibody-based therapy has become a research hotspot. In the future, cytokine-based immunotherapy will be more widely used in children with NB.■

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