Targeted therapy for neuroblastoma: applications and future possibilities

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Abstract

Background : Neuroblastoma is a highly lethal childhood malignancy. Existing treatment modalities for advanced or recurring cases are restricted, and efficacy stays disappointing. A variety of targeted therapies for neuroblastoma have emerged as our knowledge of neuroblastoma's molecular biology has improved and clinical trials of targeted drug therapy have progressed.

Data sources : All new literatures on neuroblastoma targeted therapies on PubMed were searched and reviewed.

Results : This article reviewed neuroblastoma targeted therapies in clinical trials and got preliminary findings. The characteristics, benefits, and drawbacks of targeted radiation therapy, immunotherapy, gene and pathway molecular inhibitors, and angiogenesis inhibitors were all addressed.

Conclusion : This study offers references for a greater understanding of the current progress of neuroblastoma targeted therapies.

Introduction

Neuroblastoma is a highly malignant and aggressive childhood growth that can spread to other parts of the body. Despite advances in multimodal treatment regimens such as induction chemotherapy and surgery, intensive consolidation chemotherapy, irradiation, and autologous hematopoietic stem-cell rescue, the outcome for children with advanced or recurrent diseases has only been slightly improved. With the promotion of neuroblastoma molecular biological research, a variety of targeted therapies for clinical trials have been developed, offering promising intervention therapies for high-risk neuroblastoma, particularly relapsed/refractory disease. In this review, we presented the current status and prospects of neuroblastoma targeted therapies in clinical trials, as well as early findings.

The Importance of Neuroblastoma Targeted Therapy

At the time of diagnosis, approximately half of all infants with neuroblastoma have distant metastasis. To date, the standard-of-care treatment plan for high-risk neuroblastoma is a multimodal approach that includes induction chemotherapy and surgery, consolidation chemotherapy with autologous hematopoietic stem-cell rescue, radiation therapy, and immunotherapy. [1] More than half of high-risk neuroblastoma patients were either resistant to conventional chemotherapies or relapsed after therapy. According to an analysis of large registry-based findings, patients with recurrent or refractory neuroblastoma had especially low survival rates. [2] [3] According to a study from the International Neuroblastoma Risk Group project, the 5-year overall survival (OS) postrelapse was 20%, and the 5-year OS was only 8% for patients in stage 4 with postrelapse.[3] The 4-year OS was found to be 20%2% in 35 phase I/II clinical trials for recurrent/refractory neuroblastoma carried out by Children's Oncology Group (COG) between August 2002 and January 2014.[4] The analysis of these studies revealed that the majority of high-risk neuroblastoma patients stopped receiving other treatments after starting chemotherapy due to the drug's inadequate effect. For instance, 51.5% of the high-risk patients dropped out of a randomized phase III study run by HR-NBL1/SIOPEN after completing induction therapy.[5] [6] Therefore, it is crucial to create new actors.

When compared to primary tumours, recurrent neuroblastomas have a higher mutational load but less subclonal heterogeneity. A retrospective analysis of 138 patients whose tumours had been sequenced at diagnosis showed significant mutational evolution

during treatment and progression. A wide range of mutated genes are both targetable and hopeful. 7 Surprisingly, anaplastic lymphoma kinase (ALK) was the most frequently mutated gene at diagnosis and had a higher incidence of mutations in recurrent tumours. Activating mutations in the RAS-MAPK pathway were also found to be more prevalent in tumours after chemotherapy or during recurrence. 7 8 As a result, targeted therapies have emerged as a hopeful strategy for treating patients with neuroblastoma (particularly relapsed and refractory cases) and increasing prognosis.

More and more targeted drugs have been launched as a result of intensive research into the aetiology of neuroblastoma. Several new drugs, including targeted radiation therapy, targeted immunotherapy, gene and pathway molecular inhibitors, and angiogenesis inhibitors, have been tried in clinical trials or are presently being tested. The sections that follow go into great depth about these drugs.

Approaches to targeted therapies for neuroblastoma
Targeted radiation therapy
MIBG is a compound that, when combined with radioactive iodine (131I), can be used to administer targeted radiation therapy. It is a norepinephrine analogue that was first used as a radioactive tracer for visualising the adrenal medulla. Tumor cells derived from sympathetic nervous system tissues, such as neuroblastoma, express the SLC6A2 gene-encoded norepinephrine transporter, which is believed to have high specificity and sensitivity to MIBG. 9 MIBG labelled with 131I could render it radioactive, achieving the treatment goal of killing tumour cells. 10 Several clinical trials have shown that progressively increasing the frequency and cumulative dose of 131I-MIBG in neuroblastoma can result in a 37% response rate, and the MIBG therapy also demonstrated high efficacy and tolerability.

Targeted immunotherapy
Anti-GD2 antibodies
Disialoganglioside (GD2) is a b-series ganglioside that is required for embryonic growth. 14 GD2 is heavily expressed on the surface of neuroblastoma tumour cells, but it is not found in normal tissues. Furthermore, inhibiting GD2 expression has a significant antitumor impact, making this surface glycolipid antigen an ideal target for neuroblastoma immunotherapy. 15 There are three types of GD2 antibodies presently in clinical use: mouse monoclonal antibodies (mAb), human-mouse chimeric antibodies, and humanised antibodies.

Active immunotherapy
Neuroblastoma cells can escape being attacked by T and NK cells by downregulating human leukocyte antigen and adhesion molecules. Simultaneously, its cell surface contains an abundance of gangliosides and sialic acid-containing carbohydrates and proteins, making it immunosuppressive. 16 As a result, aggressive immunotherapy for neuroblastoma is required, with anti-idiotype vaccine and bivalent ganglioside vaccine being the most prominent examples.

Adoptive T- cell therapy
Adoptive cell therapy is the process of isolating and re-injecting a significant number of tumor-specific lymphocytes (e.g., T-lymphocytes) into a patient after genetic modification and in vitro culture. 16 The treatment of high-risk neuroblastoma primarily centres on chimeric antigen receptor (CAR)-T-cell therapy. CAR-T cell treatment is the mainstay of adoptive cell therapies for high-risk neuroblastoma. CAR is made up of a single-chain variable segment (anti-GD2), a transmembrane domain, and an inner domain's extracellular domain. CAR connects tumour cell surface antigens and sends co-stimulatory signals to T cells, allowing T cells to directly identify and kill tumour cells that are not presented by the major histocompatibility complex.

Gene and pathway molecular inhibitor
ALK inhibitors
ALK is an oncogene in human tumours and belongs to the insulin receptor protein-tyrosine kinase superfamily. Copy number variation (CNV), increase, and mutation are all examples of ALK mutations in neuroblastoma. ALK copy number increase occurs in 15%-25% of neuroblastoma cases, amplification occurs in 4% of high-risk cases, and mutation occurs in 6%-10% of cases. The most prevalent ALK point mutations are R1275Q (43%), F1174L (30%), and F1245C (12%), which can cause autophosphorylation of the tyrosine kinase domain and abnormal ALK receptor activation. 16 18 19 Preclinical studies showed that ALK was a promising therapeutic target with the following benefits and characteristics. First, ALK abnormalities can be blocked by small-molecule blockers, which are simple to make and use.Second, ALK inhibition was efficacious in both wild-type and mutated neuroblastoma cells. 20 Finally, ALK mutations are frequently linked with MYCN amplification. ALK is a transcriptional target of MYCN, and it stimulates MYCN transcription in neuroblastoma cell lines. 21 As a result, ALK inhibitors can be used to treat neuroblastoma in high-risk patients with MYCN amplification.

Targeting MYCN-dependent transcription and N-Myc protein stability

MYCN is a transcription factor in the MYC family that regulates cell proliferation, development, differentiation, and survival in embryonic central nervous system cells. The MYCN gene amplification is the most prevalent focal gene mutation in sporadic neuroblastoma, and it is also a significant predictor of poor prognosis. However, it is still challenging to use the MYCN gene as a direct therapeutic target. MYCN can be suppressed by inhibiting MYCN transcription and decreasing the stability of the N-Myc protein. 16 For example, a bromodomain and extra terminal (BET) inhibitor can block BET family proteins, which are transcription factors that bind to the MYCN promoter and suppress MYCN transcription.

Pathway inhibitors

Gene pathways that are abnormally activated play an essential role in the malignant progression of neuroblastoma. ALK mutations also activate numerous downstream signalling pathways, including phosphatidylinositol 3-kinase/protein kinase B/mammalian target (PI3K/AKT/mTOR) and Ras/ mitogen-activated protein kinase (RAS-MAPK). 24 The PI3K/AKT/ mTOR signalling system is important in tumorigenesis because it promotes cell growth, proliferation, metastasis, angiogenesis, and glucose metabolism. 25 This route is frequently activated abnormally in high-risk neuroblastoma. 26 Several novel agents have been discovered in recent years to inhibit the occurrence and progression of neuroblastoma by blocking various targets in the PI3K/AKT/mTOR pathway.

Angiogenesis inhibitor

Angiogenesis is a critical step in the progression of neuroblastoma growth and metastasis. A significant number of pro-angiogenic factors have been identified to date, including vascular endothelial growth factor (VEGF), interleukin 8 (IL-8), fibroblast growth factor 2 (FGF-2), transforming growth factor-, platelet-derived growth factor A (PDGF-A), erythropoietin, and angiopoietins. 27 The expression of VEGF and the VEGF receptor (VEGFR) was linked to high-risk and advanced neuroblastoma, and these factors were responsive to antiangiogenic therapy. 28 29 Single-pathway inhibitors and multipathway inhibitors are examples of antiangiogenic drugs. Bevacizumab, for example, is a VEGF antiangiogenic antibody that blocks VEGF binding to the receptors Flt-1 (VEGFR-1) and KDR (VEGFR-2). 30 Ponatinib and imatinib are new angiogenesis-inhibiting tyrosine kinases inhibitors.

Advantages and disadvantages of currently applied targeted agents

Advantages of targeted therapies

High specificity

Drugs with greater specificity typically focus on a specific target of neuroblastoma tumour cells. 3F8 was the first mouse mAb used to treat neuroblastoma; it is an IgG3 antibody with a strong affinity for GD2. 32 Hu3F8 is a humanised 3F8 mAb with increased stability on the GD2-positive cell surface. Furthermore, GD2-specific humoral immune reaction against gangliosides on the surface of neuroblastoma cells was induced in mice and specifically killed neuroblastoma cells. In the phase I trial of the anti-idiotype vaccine racotumomab, 11 of 13 infants had an IgM and/or IgG antibody response against NeuGcGM3. JQ1 is a BET inhibitor that targets BRD4 from the MYCN promoter, resulting in MYCN transcription34 inhibition and cell cycle halt and apoptosis.

Great antitumor activity

Several targeted drugs demonstrated significant antitumor action. A study of 39 individuals with recurrent or refractory neuroblastoma who were treated with 131I-MIGB monotherapy revealed a 46% objective response rate (ORR). 13 When compared to mouse mAb 14G2a, the human-murine chimeric anti-GD2 antibody ch14.18 (dinutuximab) had the same complement-mediated cytotoxicity (CMC) potency and 50- to 100-fold greater antibody-dependent cell-mediated cytotoxicity (ADCC). 35 When combined with chemotherapy, IL-2, granulocyte-macrophage colony-stimulating factor (GM-CSF), and NK cell infusion, the humanised anti-GD2 mAb hu14.18 increased ADCC and decreased CMC compared to mouse mAb, with a high ORR of 61.5%. 36 Phase I study of third-generation CAR-T GD2-CAR3 cells revealed an increase in circulating IL-15 levels as GD2-CAR3T cell expansion.

Improved prognosis

A range of targeted drugs, particularly targeted immunotherapies, improved the prognosis of people with high-risk neuroblastoma. In the novel approaches to neuroblastoma therapy phase II trial, a comprehensive therapy including 131I-MIGB improved the prognosis of refractory neuroblastoma, with a 3-year OS of 62%8%. 38 Anti-GD2 mAb ch14.18 combined with GM-CSF plus IL-2 and RA substantially improved 2-year progression-free survival (PFS) (66%5% vs 465%, p=0.01) and overall survival (OS) (86%4% vs 755%, p=0.02). 39 The results of a phase I study of a bivalent gangliosides vaccine combined with

immunological adjuvant OPT-821 and -glucan demonstrated remarkable antitumor activity, with a 2-year event-free survival. In a phase I study, the combination of Aurora A kinase inhibitor MLN8237, irinotecan, and temozolomide demonstrated an ORR of 31.8% and a 2-year PFS of 52.4%. 41 The phase II trial found that the combination had antitumor activity (1-year PFS 34%), especially in children with MYCN non-amplified neuroblastoma. 42 Perifosine, an AKT inhibitor, demonstrated a 3-year PFS rate of 36% in patients with relapsed/refractory neuroblastoma in a phase I study, and 9 of 27 children without MYCN amplification had a median PFS of 54 months. Imatinib, a multikinase angiogenesis inhibitor, demonstrated a complete remission (CR) rate of 21% at the time of the first report and a 10-year OS of 12.5% in a long-term phase II trial, indicating that imatinib is effective in some patients with relapsed/refractory neuroblastoma.

Less side effects

Targeted drugs typically have fewer side effects, resulting in higher compliance and therapeutic use. Hu14.18K322A is a humanised anti-GD2 mAb to 14G2a with a single point mutation (K322A) to prevent complement cascade activation, thereby reducing complement-mediated pain and the chance of allergic reaction. 44 Sensory neuropathy, serum sickness, and posterior reversible encephalopathy syndrome have all been reported as dose-limiting grade 3 or 4 effects. Most patients experienced discomfort of grade 3 or 4. 44 When compared to anti-GD2 mAbs, the regimen containing the bivalent gangliosides vaccine had the benefit of not causing neuropathic pain. 40 MIBG's most frequent side effects were myelosuppression and diarrhoea, indicating a promising application. 45 The ALK inhibitor crizotinib was well taken, with no signs of cumulative toxicity.

Disadvantages of targeted therapies
Limited antitumor activity

Although anti-GD2 immunotherapies demonstrated excellent cytotoxicity against neuroblastoma, early phase clinical trials of several targeted drugs, such as gene and pathway inhibitors, revealed limited antitumor activity. A phase I trial of crizotinib in children with refractory neuroblastoma was designed by COG. Only one of the 11 children in this trial with an ALK translocation had CR, two stayed SD, and the remaining cases had progressive disease. 47 The phase II trials of the mTOR inhibitor temsirolimus demonstrated that the 1-year PFS rate of patients with relapsed/ refractory neuroblastoma with temsirolimus plus irinotecan/ temozolomide was only 24.7%, which was significantly lower than the efficacy of ch14.18 plus irinotecan/temozolomide with

a 1-year PFS rate of 76.5%. Furthermore, the combination of the angiogenesis inhibitor bevacizumab with irinotecan and temozolomide did not enhance the response rate of refractory neuroblastoma.

Drug resistance

Because of drug resistance and disease progression, the usefulness of some targeted drugs has been restricted. An example is an ALK inhibitor, and early phase clinical trials of the ALK inhibitor crizotinib revealed a significant disease progression rate. 47 48 In vitro studies showed that neuroblastoma cell lines with F1174 and F1245 mutated ALK had increased ATP-binding affinity but a decreased ability to competitively inhibit ATP, resulting in resistance. 49 Another study discovered no new mutations or CNV in ALK, but the level of tyrosine kinase receptor activation changed, with substantially increased EGFR phosphorylation in a crizotinib-resistant neuroblastoma cell line. 50 Furthermore, activation of receptor tyrosine kinases and PI3K signalling increased BET inhibitor drug resistance in neuroblastoma, implying efficacious synergistic therapies.

Immunogenicity

Although several targeted immunotherapies have shown promising curative benefits, they all share some flaws, one of which is immunogenicity. Previous research discovered that the incidence of antidrug antibody was 70%-80% for human antimouse antibody (m3F8), 19%-21% for human antichimeric antibody (ch14.18), and 40% for human antihuman antibody (hu14.18K322A), resulting in faster elimination of antibodies from the body due to neutralising antibodies and affecting the half-life of antibodies in the body. 52 Surek and Ektomab are also anti-GD2 trifunctional bispecific full-length antibodies that comprise Fab fragments from the GD2/GD3-specific antibody ME361 and the T cell-specific CD3 antigen, which attract cytotoxic lymphocytes and direct them to GD2-positive tumours.

Difficult to penetrate tumor tissue

The first barrier to adoptive cell therapy for neuroblastoma is the trouble in penetrating the tumour to discharge their cytotoxic function. Unlike CAR-T cells, which have a high degree of migrating effectiveness against haematological malignancies, solid tumours such as neuroblastoma secrete chemokines such as CXCL12 and CXCL5, which inhibit T-cell migration into tumour regions. 54 Furthermore, abnormal vasculature impedes effective infiltration, and immunosuppressive bone marrow cells can be drawn to the tumour microenvironment via the surrounding matrix and physical barrier, stopping T-cell

infiltration. Solving these issues is a significant task for CAR-T therapy.

CONCLUSION

Several clinical trials of novel targeted agents have been performed over the last decade. Targeted immunotherapy has played a significant part. Anti-GD2 chimeric mAb ch14.18 was the first drug authorised by the US Food and Drug Administration (FDA) for first-line treatment of high-risk neuroblastoma in nearly 30 years, marking a milestone in neuroblastoma treatment. Anti-GD2 mAb has shown extraordinary antitumor efficacy, has significantly improved the survival rate of children with neuroblastoma, and is currently the most promising drug in the treatment of neuroblastoma. The combination of cytokines and anti-GD2 mAbs increased synergy, resulting in greater cytotoxicity effectiveness. CAR-T therapy for neuroblastoma is still in its early stages of research.

Due to the relatively high mutant frequency of recurrent neuroblastoma, therapies targeting actionable mutations and abnormally activated signalling pathways are also a hot subject of current research. Several novel agents and small molecular inhibitor combinations have been tried in preclinical and early phase clinical trials. However, the majority of clinical trial findings were underwhelming, with limited antitumor activity and low rates of objective response. Furthermore, when children were involved in clinical trials, it was often impossible to acquire tumour tissues at the time of relapse in order to learn more about mutations and abnormal pathways. The drugs' effectiveness may be limited due to a lack of understanding of molecular pathways.

Despite a plethora of potential targets, the number of high-risk neuroblastomas available for randomised clinical trials is restricted. Early identification of patients with neuroblastoma who are at high risk of treatment failure has become a trend for novel agent intervention to prevent patients becoming refractory or relapsed cases. 6 This necessitates a better knowledge of the molecular biology of neuroblastoma's relapsing process and resistant mechanism, as well as an early predictive model that includes molecular biomarkers.

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