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Mini Review

Neuroblastoma: New Insights

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Received: December 23, 2024; **Published:** January 11, 2024

Abstract

Neuroblastoma is a pediatric malignancy of sympathetic origin that presents significant clinical challenges due to its heterogeneous nature. Recent advancements in immunotherapy, such as GD2-targeting specific antibodies and CAR T-cell therapies, offer promising approaches to improve outcomes in high-risk cases. Moreover, molecular-targeted therapies, including ALK inhibitors, are being refined to overcome resistance and enhance treatment efficacy. Liquid biopsy and precision diagnostics play a key role in early detection and personalized treatment. However, the field faces ongoing challenges, including tumor resistance and the need for more reliable biomarkers, underscoring the importance of continued research to optimize therapeutic strategies and improve survival rates. This review aims to integrate recent advancements in the diagnosis and treatment of this complex malignancy.

Keywords: *Neuroblastoma; Biomarkers; Immunotherapy; Molecular Targeted Therapy*

Abbreviations

ALK: Anaplastic Lymphoma Kinase; ASCT: Autologous Stem Cell Transplantation; CAF: Cancer-Associated Fibroblasts; CAR T-Cell: Chimeric Antigen Receptor T-Cell; CT: Computed Tomography; DNA: Deoxyribonucleic Acid; EBRT: External Beam Radiotherapy; GD2: Disialoganglioside 2; HVA: Homovanillic Acid; INRG: International Neuroblastoma Risk Group; IHC: Immunohistochemistry; MIBG: Metaiodobenzylguanidine; MRI: Magnetic Resonance Imaging; MYCN: MYCN Proto-Oncogene, Basic Helix-Loop-Helix Transcription Factor; NGS: Next-Generation Sequencing; PD-1: Programmed Death-1; PET: Positron Emission Tomography; TAMs: Tumor-Associated Macrophages; TME: Tumor Microenvironment; VMA: Vanillylmandelic Acid

Introduction

Neuroblastoma is a malignancy arising from neural crest-derived cells and can develop at any site within the sympathetic nervous system. It is the most common extracranial solid tumor in children. Most patients are diagnosed under the age of 5 years, with a median age at diagnosis of 17 months. Clinical symptoms vary based on the location of the primary tumor, and may include abdominal mass, abdominal pain, respiratory distress, or neurological symptoms from spinal cord involvement. In rare cases of neuroblastoma, lesions may regress spontaneously, while in others, the disease can behave aggressively, leading to recurrent and refractory metastatic disease. Contemporary treatment protocols, including multiagent chemotherapy, surgical resection, high-dose chemotherapy with autologous stem

cell transplantation (ASCT), external beam radiotherapy (EBRT), and immunotherapy, have improved outcomes, with 3-year survival rates now exceeding 60% [1].

Advances in pathogenesis and biology

MYCN amplification and *ALK* mutations

The *ALK* gene and corresponding protein are important players in embryonic neural development. The discovery of activating mutations in the tyrosine kinase domain of ALK as the primary cause of hereditary neuroblastoma represents the first example of a pediatric cancer arising from germline mutations in an oncogene. The role of *MYCN* in neuroblastoma is well established, and the evaluation of *MYCN* amplification in tissue samples plays a crucial role in current risk stratification protocols. Interestingly, both genes are located just 13.2 megabases apart on chromosome 2p. As a therapeutic target in primary neuroblastoma, ALK represents a major research advance in neuroblastoma. A recent cohort study of 60 patients with neuroblastoma demonstrated notable clinical and pathological characteristics. The cohort exhibited a slight male predominance, older age distribution, and advanced stage at diagnosis. Histological analysis revealed poorly differentiated neuroblastoma as the most prevalent subtype (55%), followed by undifferentiated neuroblastoma (42%), with no cases of differentiating neuroblastoma observed. Evaluation of *MYCN* amplification across 46 cases revealed its presence in nearly half (48%), aligning with its established role as a hallmark of high-risk neuroblastoma. Risk stratification using the International Neuroblastoma Risk Group (INRG) system revealed a predominance of high-risk cases (60%), reflecting the aggressive clinical profile of this cohort. This underscores the critical prognostic value of integrating *MYCN* amplification with histological and genetic data for personalized risk assessment. ALK protein expression, assessed through immunohistochemistry (IHC), was observed in 65% of cases, exhibiting heterogeneous cytoplasmic and membranous staining. This expression, while not correlated with patient outcomes independently, was particularly noted in poorly differentiated neuroblastomas with *MYCN* amplification. Targeted next-generation sequencing (NGS) highlighted mutations in the *ALK* gene, including missense mutations at exon 23 (e.g. p.Phe1174Leu), associated with poor prognosis. A novel *IDH1* mutation (p.Arg119Gln) was identified in a patient with a favorable clinical outcome, emphasizing the complex interplay between genetic alterations and tumor behavior [2].

Tumor microenvironment and immunology

Recent advances in understanding the tumor microenvironment (TME) of neuroblastoma have provided crucial insights into its influence on tumor progression and response to therapies. Notably, the composition of the TME varies between MYCN-amplified ("cold" tumors with low immune infiltration) and non-amplified ("hot" tumors with higher immune activity) neuroblastomas. These differences have significant implications for therapeutic strategies. Immune cells, including tumor-associated macrophages (TAMs), dendritic cells, and lymphocytes, are key players in shaping the immune landscape of neuroblastoma. TAMs, for example, are known to promote immunosuppressive environments, aiding in tumor escape from immune surveillance. Extracellular vesicles and their cargo, such as microRNAs, facilitate communication between tumor cells and the TME, contributing to immunosuppression and metastasis. Meanwhile, non-immune cells like cancer-associated fibroblasts (CAF) and Schwann cells also contribute to inflammation and extracellular matrix remodeling, promoting tumor progression. Therapeutic strategies are increasingly targeting TME components. For example, efforts to remodel the immunosuppressive environment include the use of checkpoint inhibitors and tumor vaccines. Biomarker integration, such as assessing the inflammatory status of the TME, holds promise for designing precision immunotherapies tailored to neuroblastoma subtypes [3].

Innovations in diagnosis - Advances in imaging and biomarkers

Advancements in the diagnosis of neuroblastoma have focused on enhancing imaging techniques and identifying novel biomarkers to improve early detection, prognosis, and treatment monitoring. Imaging modalities such as positron emission tomography (PET) with radiotracers have significantly improved the detection of neuroblastoma, particularly in metastatic cases, providing higher sensitivity. Multiparametric magnetic resonance imaging (MRI) has emerged as another key diagnostic tool, offering detailed anatomical and functional

information with no radiation exposure, which is particularly advantageous for pediatric age. This approach can improve the differentiation of tumor types and allow for non-invasive monitoring of treatment responses [4]. Additionally, ^123I-metaiodobenzylguanidine (MIBG) scintigraphy remains a critical tool for staging and assessing therapeutic response, although newer PET tracers are gaining prominence in clinical practice. In parallel, the development of biomarkers has revolutionized neuroblastoma diagnosis. Urinary catecholamine metabolites, including vanillylmandelic acid (VMA) and homovanillic acid (HVA), remain important for initial diagnosis and monitoring; however, newer techniques like liquid biopsy are gaining ground. These include the use of circulating tumor DNA (ctDNA) and tumor-derived exosomes to track disease progression, predict relapse, and evaluate treatment efficacy [5]. Together, these innovations in imaging and biomarker development are paving the way for more accurate, non-invasive diagnostic methods, enabling improved risk stratification, personalized treatment strategies, and better overall patient outcomes.

Treatment strategies

New approaches in chemotherapy, radiotherapy, and surgery

In recent years, advances in the treatment of neuroblastoma, particularly in high-risk cases, have focused on refining existing therapies such as chemotherapy, radiotherapy, and surgery, while integrating newer, more targeted approaches. For chemotherapy, improvements include the use of combination regimens, which have demonstrated enhanced efficacy in overcoming resistance mechanisms observed in relapsed or refractory neuroblastoma. For instance, combinations of irinotecan, temozolomide, and immunotherapies, such as dinutuximab, have shown promising results in both frontline and relapsed settings. Moreover, while ASCT following high-dose chemotherapy has been a cornerstone of treatment for high-risk neuroblastoma, its necessity is being reevaluated in light of new treatments such as immunotherapy and targeted agents, which may offer less toxic alternatives [7]. Radiotherapy remains crucial for localized disease and for sites of persistent metastases after induction therapy. However, ongoing studies are exploring the optimal radiation doses and modalities, particularly in metastatic disease, to minimize long-term morbidity [8]. These developments highlight the continued evolution of treatment strategies, aiming to balance efficacy with reduced side effects and improve long-term outcomes for patients with neuroblastoma.

Emerging therapies: Immunotherapy, CAR T-cells, and molecular-targeted drugs

Emerging therapies for neuroblastoma have advanced significantly in recent years, with promising approaches such as immunotherapy, CAR T-cell therapy, and molecular-targeted drugs being explored to improve treatment outcomes. Immunotherapy, particularly the use of monoclonal antibodies targeting GD2 (such as dinutuximab), has shown effectiveness in pediatric neuroblastoma, especially when combined with other modalities like cytokine therapy. The use of immune checkpoint inhibitors, such as nivolumab and pembrolizumab, is also under investigation to enhance T-cell response and overcome immune evasion mechanisms employed by tumor cells [9]. CAR T-cell therapy involves genetically modifying T-cells to express a receptor specific for neuroblastoma antigens. Clinical trials have demonstrated the feasibility of using CAR T-cells targeting GD2, with early results indicating robust anti-tumor responses, although challenges remain in terms of durability and potential side effects [10]. Molecular-targeted therapies, including ALK inhibitors such as crizotinib and lorlatinib, are being tested for their efficacy in neuroblastoma patients with *ALK* mutations or amplifications. Recent studies show that these agents, when used in combination with chemotherapy, might improve survival, particularly in patients with high-risk, relapsed neuroblastoma [11].

Ongoing research and potential breakthroughs

Advances in bispecific antibodies, such as dinutuximab, targeting the GD2 antigen, show promising potential by enhancing the immune system's ability to attack neuroblastoma cells. When combined with immune checkpoint inhibitors like anti-PD1/PDL1 agents, these antibodies are currently under investigation to improve efficacy in high-risk case [2]. CAR T-cell therapies are being refined to address challenges such as tumor antigen heterogeneity and resistance. Newer-generation CAR T-cells are being engineered with dual-targeting capabilities or cytokine support systems to improve their persistence and anti-tumor activity. Molecular-targeted drugs, particularly ALK inhibitors like lorlatinib, are also a critical area of research, showing activity against ALK-mutated neuroblastomas. Combining ALK

inhibitors with epigenetic drugs or microenvironment-modulating agents is being explored to enhance treatment durability [11]. Efforts are also underway to incorporate liquid biopsies for real-time monitoring of tumor evolution, enabling earlier detection of resistance mechanisms and guiding therapy adjustments. These advances, coupled with a deeper understanding of tumor biology and immunology, pave the way for personalized, more effective treatment approaches that could revolutionize neuroblastoma care in the coming years.

Conclusion

Neuroblastoma research has made significant advances in areas such as liquid biopsy, targeted therapies, and immunotherapies like CAR-T cell treatments, offering new hope for patients. Despite these breakthroughs, challenges related to tumor heterogeneity, resistance mechanisms, and the identification of reliable biomarkers persist, hindering optimal therapeutic outcomes. Continued innovation, particularly in refining combination therapies, improving early detection, and overcoming resistance mechanisms, remains crucial. Future research must focus on addressing these barriers to provide more effective, personalized treatment strategies, ultimately improving survival rates and patient quality of life.

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Volume 14 Issue 2 February 2025