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Review of the Targeted Therapy for Advanced/Aggressive Neuroblastoma as Adjuncts to Standard Therapy

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ABSTRACT

Neuroblastoma is an aggressive paediatric malignancy originating from neural crest cells. It typically presents as an abdominal mass with associated symptoms such as fever, weight loss, and bone pain. It primarily affects children below 5 years; also, it is categorised based on clinical and genetic features. Likewise, staging systems like the International Neuroblastoma Risk Group (INRG), which guides prognosis and treatment decisions, are investigated. Managing advanced or aggressive neuroblastoma remains a significant challenge due to high-risk features like MYCN (myelocytomatosis-neuroblastoma) amplification and Anaplastic Lymphoma Kinase (ALK) mutations despite advancements in treatment. Standard therapies, including surgery, chemotherapy, radiotherapy, and in some instances, immunotherapy, are available. Yet, these therapies often fail to provide a long-term cure for high-risk patients, necessitating new therapeutic approaches. Still, emerging targeted therapies offer promising adjuncts to standard treatments, focusing on molecular targets to improve outcomes. Thus, this review explores the pathophysiology of neuroblastoma, highlighting critical therapeutic targets, such as MYCN, ALK, the Paired-like Homeobox 2B gene (PHOX2B), and epigenetic alterations that drive tumorigenesis. Understanding these molecular mechanisms provides the foundation for developing targeted treatments, including ALK inhibitors, MYCN-targeted therapies, and strategies to modulate rat sarcoma (Ras) Mitogen-Activated Protein Kinase (MAPK), cell cycle regulators, and apoptotic pathways. Immunotherapies, such as monoclonal antibodies and immune checkpoint inhibitors, also show potential in combination with conventional therapies.

Keywords: Neuroblastoma, Targeted Therapy, MYCN Amplification, ALK Mutations, Epigenetic Modifications, Immunotherapy, Multi-modality Therapy, and Paediatric Oncology

1. Introduction

Neuroblastoma embodies both scientific fascination and clinical imperative as a juvenile cancer characterised by its biological unpredictability and varied clinical manifestations. In contrast to other paediatric malignancies, it possesses a notable ability to either regress spontaneously or develop into an unyielding, treatment-resistant condition. This tumour, derived from immature nerve cells of the sympathetic nervous system, can develop at any location along the neural axis, resulting in unpredictable presentations. Neuroblastoma serves as a paradigm of heterogeneity for physicians and researchers, since age, genetic composition, and cancer biology intersect to influence outcomes. In recent years, profound genomic findings and focused therapies have started to alter the narrative, providing new optimism in what has historically been one of the most formidable paediatric cancers.

1.1 OVERVIEW OF NEUROBLASTOMA

A sympathetic nervous system tumour originating from neural crest cells during foetal or early postnatal development is termed neuroblastoma. It is the most common extracranial solid tumour in children, and it can also lead to malignancy in infants. It represents 8% to 10% of every paediatric malignancy along with contributing to 15% of cancer-related deaths in this population[1]. The annual incidence is approximately one case per 100,000 children in the United States [2]. Likewise, there are over 700 newly diagnosed cases each year. This accounts for nearly 8% of paediatric cancers in individuals under 15 years yet disproportionately contributes to 15% of paediatric cancer mortality rates; the presentation of neuroblastoma is highly variable [3]. Over 90% of cases are diagnosed before the age of five, with 30% occurring within the first year. The average age at diagnosis is 22 months [4]. Neuroblastoma hardly occurs in adulthood, but these cases can be associated with poor outcomes. The disease displays slight male predominance, with the male-to-female ratio being 1.2:1[1]. The familial connection related to autosomal dominant inheritance has been identified in one to two percent of cases. Familial neuroblastoma is diagnosed at the average age of nine months, and these patients show multiple primary tumours. Also, neuroblastoma could happen in association with congenital disorders, including Hirschsprung's disease and congenital hypoventilation syndrome, together with neurofibromatosis type 1, though these associations may reflect coincidental rather than causal links [5].

Tumours may spontaneously progress or differentiate into benign forms without intervention, while others exhibit aggressive, poorly responsive phenotypes that challenge even intensive multimodal therapies. Heterogeneity of the neuroblastoma identifies biological and molecular markers that can predict the clinical behaviour of the tumour. These markers help in risk assessment and make personalized treatment plans possible[6]. High-risk patients commonly receive aggressive multimodal treatments mainly for curing tumours; however, the low-risk patients are treated conservatively to minimize the therapy-related toxicity while maintaining high Survival Rates (SR) [7].

In the past 3 decades, there has been a key augmentation in survival rates for neuroblastoma. The five-year SR has increased from 52% to 74%; this has been made possible by advances in the treatment of lower-risk cases, as the survival rates in these types of cases have increased by 90%. Yet, high-risk patients face an aggressive prognosis that has a relapse rate of 50 to 60%, and the five-year SR is, on average, over 20% [8,9]. The average time to relapse is 13.2 months, and most relapse occurs in children 18 months or older [9].

1.1.1 Clinical Presentation

Neuroblastoma's clinical presentation is variable; also, it is influenced by factors like tumour location, size, extent of invasion, catecholamine secretion, and paraneoplastic syndromes. The abdomen, which accounts for approximately 65% of cases, is the most common site, with half of these localised to the adrenal medulla. Other primary sites include the neck (5%), chest (20%), and pelvis (5%), while over one percent of patients present without any detectable primary tumour [10]. Patients are primarily asymptomatic, but also constitutional symptoms, such as fevers, malaise, weight loss, or any localised symptoms like abdominal distension, respiratory distress, and lymphadenopathy, may occur [11]. Pelvic tumours can cause urinary symptoms or gastrointestinal symptoms. The thoracic tumours may cause issues in the respiratory system or rarely cause thoracic outlet syndrome. Cervical tumours may present along with Horner's Syndrome, and over 15% of the cases show epidural extension. This may cause neurological deficiency, such as progressive paralysis [11].

During diagnosis, patients (over 50%) show localized disease, but 35% of patients have regional lymph node involvement. It commonly affects the bone marrow, liver, and bone, and it has some distinctive features like periorbital swelling, also known as raccoon eyes, and blue subcutaneous nodules, also termed blueberry muffin syndrome. The blueberry muffin syndrome is related to favourable outcomes and potential tumour regression. Catecholamine secretion can result in hypertension and tachycardia, while paraneoplastic syndromes like intractable diarrhoea (owing to vasoactive intestinal peptide) along with opsoclonus-myoclonus syndrome (OMS) are rare manifestations [12]. OMS, characterized by rapid eye movements, limb spasms, and diarrhoea cases often involves less aggressive neuroblastomas. With all these different presentations, symptomatic paraneoplastic syndrome occurs in less than 0.01 percent of cancers [13]. Figure 1 explains the MRI scan images (A, B) of abdominal neuroblastoma patients.

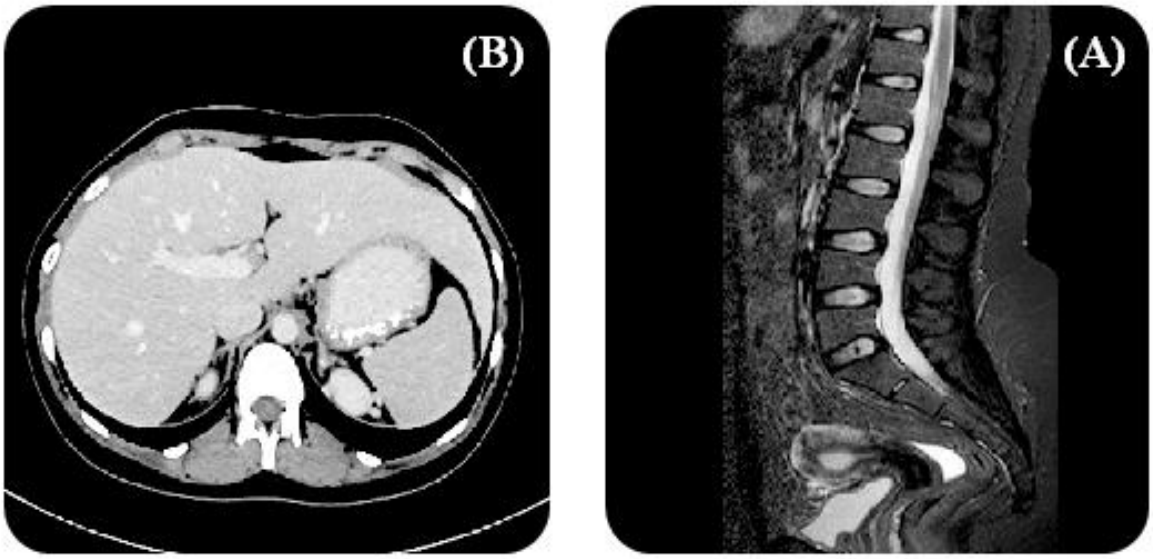

Figure 1: *MRI scan images (A, B) of a patient with abdominal neuroblastoma, demonstrating distinct tumour characteristics. Image A highlights the tumour's irregular shape and size, while Image B emphasizes the extent of invasion into surrounding tissues.*

1.1.2 Classification and Staging

Neuroblastoma is classified within the peripheral neuroblastic tumours that include ganglion neuroblastoma and ganglion neuroma, further classified by neuroblastic differentiations, such as undifferentiated, poorly differentiated, or differentiated. Also, the mitosis karyorrhexis index is low, intermediate, or else high [14]. As per international neuroblastoma pathology classification, prognosis is mainly based on histopathology and age. It also helps in the identification of unfavourable outcomes for undifferentiated tumours with high MKI or older patients with intermediate to high MKI tumours [15]. The (A-B) Histopathological images from patients are elucidated in Figure 2 [16].

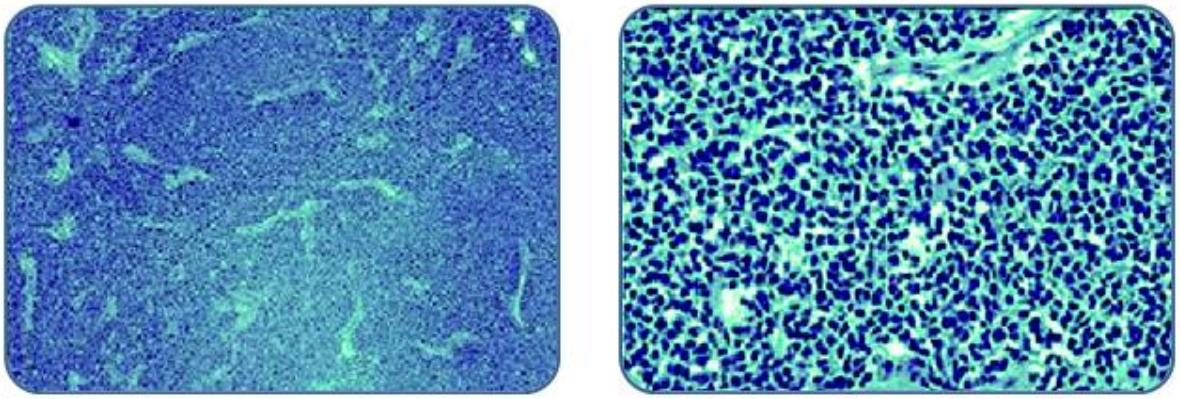

Figure 2: (A-B) *Histopathological images from the patient (Alexander et al., 2021). The images highlight neuroblastic differentiation and mitosis karyorrhexis index variations, key to prognosis and classification in neuroblastoma pathology.*

Staging mainly uses the International Neuroblastoma Staging System along with the new International Neuroblastoma Risk Group Staging System. It classifies the stages as L1, L2, M, or MS and stratifies the patients during pre-treatment based on the imaging and clinical criteria. This helps to refine risk-based treatment strategies [17,18]. The International Neuroblastoma Risk Group staging is explored in Table 1.

Table 1: International Neuroblastoma Risk group staging

Stages	***Report***	***Stage Indicators***
Stage 1	Localised, completely resected tumour	- Tumour confined to one area - complete surgical resection - No regional LN involvement
Stage 2A	Unilateral tumour with incomplete resection	-a single-sided tumour with positive margins -Involvement of the same side's regional LNs
Stage 2B	Unilateral tumour with regional LN involvement	-Tumour confined to one side -not resectable -Regional LN involvement on the same side

Stages	*Report*	*Stage Indicators*
Stage 3	Unresectable tumour with bilateral LN involvement or crossing midline	- LNs on both sides or span the midline
Stage 4	Distant metastasis	The tumour has spread to distant organs like the liver, bone marrow, or distant LNs.
Stage 4S	Special Stage for infants under 1 year with localised primary tumour	-Localised primary tumour with limited regional or distant metastasis (e.g., liver, skin)

Table 1: *The table provides a comprehensive classification of neuroblastoma, detailing tumour localisation, resectability, regional lymph node involvement, and metastatic status.*

The tumour is fully removed and restricted to a single location with no involvement of nearby LNs or distant metastases in stage 1. Single-sided, imperfectly excised tumours that include regional LNs on the similar side but don't have distant metastases are referred to as unilateral tumours with incomplete resection (stage 2A). The tumour cannot be removed and stays localised to one side without spreading to other areas even though a unilateral tumour with regional LN involvement is present in stage 2B. Stage 3 is an incurable tumour that lacks distant metastases and involves bilateral LNs or crosses the midline. The tumour may include LNs on both sides. Stage 4 denotes distant metastasis, where the tumour has migrated to distant organs like the liver, bone marrow, or distant LNs. The last stage, Stage 4S, is exclusive to children under one year old and is characterised by a confined original tumour with limited regional or distant metastases, such as to the skin or liver. Every stage is identified by a unique number [19,20,21,22,23], which offers comprehensive details regarding the location of the tumour, its resectability, the involvement of regional LNs, and the availability or unavailability of distant metastases. The table helps with diagnosis, therapy planning, and determining the degree of disease dissemination by offering a thorough summary of tumour progression and classification.

1.1.3 Challenges in treating advanced/aggressive neuroblastoma

Treatment for advanced or aggressive neuroblastoma is challenging, as its biological complexity and heterogeneity are complex. Aggressive genetic alterations and resistance to established treatment methods typically define this malignancy. This makes it necessary to provide new innovative treatment methods. Neuroblastoma shows genetic variability with poor prognostic indicators like MYCN amplification and 11q deletion, which are particularly noticeable [24,25]. Likewise, the laws of critical gene isoforms like DLG2 isoform 7/8 are related to advanced disease progression and reduced SRs [26]. Resistance to conventional treatments like chemotherapy and radiotherapy is a significant challenge that needs to be addressed for advanced neuroblastoma. Resistance is mainly because of mechanisms like tumour hypoxia and improved DNA repair capacities [25,27]. Emerging techniques like low-dose pulse to radiotherapy also show some potential in reducing the radioresistance in neuroblastoma [17]. Conventional treatment methods have only resulted in marginal survival benefits; this states the need for targets that can use non-oncogene dependencies. Research focusing on metabolic pathways involving serine and arginine can provide promising results for future interventions [24,28].

1.1.4 Role of standard therapies (surgery, chemotherapy, and radiotherapy)

In cancer management, the role of standard therapies like surgery, chemotherapy, and radiotherapy is significant, and they are primarily used in combination to improve the efficacy of the treatment. These treatment modalities aim to remove the cancer cells and improve patient outcomes by using integrated methods. Surgery is one of the most common curative treatment methods. Approximately 80% of cancer patients undergo surgical interventions [29]. It plays a key role in solid tumour removal and allows for maximum safe resection that can improve the SR significantly [30]. The other method is chemotherapy, which uses different drugs to target the cancer cells. Commonly used drug regimens are 5-FU and cisplatin for specific cancers like oesophageal squamous cell carcinoma. [31]. When the surgical options are limited, combining chemotherapy with radiotherapy can improve the treatment's efficacy[32]. Radiotherapy is used in approximately 39 percent of cancer cases. This makes it an important treatment method for incompletely resected or recurrent malignancies. It induces damage to the DNA in tumour cells, helps to facilitate apoptosis, and improves the immune responses when integrated with the immunotherapy approaches[32,33].

1.1.5 Emerging importance of targeted therapies as adjunctive options

The limitations caused by the standard therapy surgery, chemotherapy, and radiotherapy in advanced management of high-risk neuroblastoma have made it necessary for the development of targeted therapy. These treatment methods provide molecular and genetic information in tumour biology and give a personalised approach to fight against the aggressive nature of neuroblastoma. Targeted therapy, such as monoclonal antibodies, kinase inhibitors, and immune-based treatment, mainly aims to disturb the oncological signalling pathways selectively or improve the immune mediator tumour destruction. For instance, by targeting Disialoganglioside GD2, a molecule that is overexpressed in neuroblastoma cells, anti-GD2 antibodies have shown improvement in survival outcomes in high respirations [34]. Gene mutations in inhibitors like ALK are also observed in familial and sporadic neuroblastomas. These targeted therapies have emerged as adjuncts for standard treatment methods [35].

The combination of the therapies into the treatment not only addresses chemotherapy resistance but can also

help in minimising toxicity in the system. These are the critical considerations for paediatric patients. Ongoing research in metabolic reprogramming and non-oncogenic dependency can highlight the potential of novel interventions that target specific tumours and provide a way to improve the outcomes in aggressive neuroblastoma cases.

1.1.6 Objective and scope of the review

The aim is to evaluate targeted therapies as adjuncts to standard treatments for advanced neuroblastoma. This review examines therapies like ALK inhibitors, MYCN-targeted treatments, and epigenetic modulators alongside conventional methods such as surgery and chemotherapy. It highlights recent findings on combining these strategies to overcome treatment limitations and improve outcomes in high-risk neuroblastoma.

2. Pathophysiology of Neuroblastoma and Therapeutic Targets

A paediatric malignancy initiated from neural crest progenitor cells, exhibiting considerable heterogeneity that complicates treatment approaches, is termed neuroblastoma. Its pathophysiology is driven by genetic and epigenetic alterations, contributing to the tumour's aggressive behaviour and resistance to conventional therapies. Because of the rapid progression and therapeutic resistance, high-risk neuroblastoma is commonly presented as abdominal masses that are related to poor prognosis [36]. Some changes are demonstrated in the cellular plasticity in adrenergic (ADRN) and mesenchymal (MES) subtypes, showing responses to therapy and different immunotherapeutic target expressions [37]. In neuroblastoma cases, no uniform genetic alteration is observed after sequencing DNA and RNA over 1000 times. This accounts for the complete spectrum of the disease [38].

Also, structural genomic changes like 1p deletion, MYCN amplification, or addition of 17q are related to distinctions of types of neuroblastomas; also, this might influence patients' SRs [39,40]. There is no consistency in specific genomic alterations in neuroblastoma, loss of heterozygosity (LOH), or genetic translocation. This is related to high-risk neuroblastoma tumours. This molecular complexity indicates that the neuroblastoma represents a diverse spectrum of the disease. Clinically, the heterogeneity is a challenge, as tumours exhibiting the same phenotype and morphological features can respond to the treatment differently. Therefore, the research has investigated the transcriptomes and oncological pathways active in the most aggressive together with fatal subtypes of neuroblastoma [41]. This can help in identifying genetic as well as epigenetic origins of neuroblastoma along with the aim of identifying potential therapeutic target for this cancer.

Various therapeutic targets have been researched, including ferroptosis and cuproptosis pathways, to overcome the resistance mechanism [42,43]. BMX kinase is identified as a high-risk virus neuroblastoma along with MYCN non-amplified neuroblastoma. This correlates with poor outcomes and chemoresistance [44]. A broad spectrum of treatment options is provided by immunotherapeutic targets like CD276 (B7-H3) and L1CAM [37]. However, tumour inherent heterogeneity is a significant challenge that makes it necessary to research various emerging targets.

Neuroblastoma, a complex paediatric malignancy, involves several genes and their corresponding epigenetic alterations that influence tumour behaviour and progression. High-risk neuroblastomas frequently have increased transcription factor MYCN levels, which is linked to changes in DNA methylation and histone modification patterns that promote carcinogenesis [45]. Neuroblastoma frequently has ALK mutations, which result in abnormal signalling pathways in a similar vein. These mutations affect ALK expression and encourage aggressive tumour behaviour when combined with DNA methylation and histone alterations [46]. Neuroblastoma cells' differentiation and proliferation are impacted by PHOX2B, a crucial regulator that is commonly altered. The expression of PHOX2B is controlled by epigenetic modifications like DNA methylation along with histone acetylation [47]. The activity of stem cells depends on TET2, which encodes an enzyme involved in DNA demethylation. Mutations or lack of function in TET2 result in aberrant DNA methylation patterns, which aid in the formation of neuroblastoma [48]. Aggressive neuroblastomas are linked to DNMT3A, which oversees de novo methylation of DNA. When this gene is overexpressed, it causes aberrant DNA methylation and silences tumour suppressor genes, which accelerates the growth of tumours [49]. Histone H3K27 methylation is caused by overexpression of the histone methyltransferase EZH2, which is implicated in the silencing of tumour suppressor genes. And EZH2 represses important genes that stop the evolution of neuroblastoma [50]. A transcriptional repressor called REST is frequently dysregulated, which results in histone changes and the silence of genes involved in neural development, thus fostering the formation of tumours [51]. Last but not least, KDM5C is a histone demethylase that controls gene expression as neuroblastoma develops. Mutations or deletions in KDM5C cause abnormal patterns of histone modification, which have a major impact on tumour behaviour [52]. Lastly, the complex web of genetic and epigenetic changes in neuroblastoma emphasises the disease's intricacy and suggests possible treatment targets.

2.1 THE ROLE OF MYCN IN NEUROBLASTOMA DEVELOPMENT

MYCN is an important cause of tumorigenesis in neuroblastoma. This makes it a particularly aggressive subset of tumours. MYCN amplification is present in over ten gene copies in over 20% of neuroblastoma cases; also, it is related to poor prognosis. Transgenic mouse models have robustly demonstrated that aberrant expression of MYCN, explicitly targeting the neural crest, is adequate to induce neuroblastoma with higher penetrance, solidifying MYCN's critical role in disease initiation [53].

MYCN is a transcription factor that exerts oncogenic effects via direct DNA binding and indirect protein-protein interactions. It helps to control different genetic targets, including mRNA, microRNAs (miRNAs), and long non-coding RNAs (lncRNAs). They influence cellular processes like proliferation, differentiation, together with

survival[54]. MYCN and its paralog MYCC (C-MYC) have the same key function as anti-p53 activity and promotion of cell proliferation that leads to Epithelial-to-Mesenchymal Transition (EMT) [55].

MYCN is expressed in the neural crest cells destined to form the sympathetic ganglia during normal embryogenesis [56]. Therefore, it is unsurprising that MYCN overexpression is frequently observed in poorly differentiated, aggressive neuroblastomas [57]. This has spurred clinical efforts to target MYCN as well as its downstream pathways like MDM2, ODC1, and mTOR, with agents like RG3788, Difluoromethylornithine (DFMO), and Temozolomide [58].

2.2 THE ROLE OF ALK MUTATIONS IN NEUROBLASTOMA

In neuroblastoma pathogenesis, ALK mutations are important. This is mainly in high-risk cases, and it leads to poor prognosis and resistance to treatment. These mutations are present in approximately 10% of freshly diagnosed neuroblastoma. This states the importance of genomic profiling for making informed, targeted therapy strategies. During diagnosis, over 10.5% of cases of neuroblastoma have identified ALK mutations. Prevalence increases in stage four patients below 18 months [59]. During relapse, the ALK mutation increases by 70 percent and is frequently driven by de novo mutations like R1275Q that show sensitivity to ALK inhibitors [59,60]. In the ALK gene, activating mutations also significantly affect neuroblastoma pathogenesis. ALK mutations are found in approximately 6-10% of spontaneous neuroblastoma cases and are nearly ubiquitous in familial cases, although these represent less than 1% of total neuroblastoma cases[61]. ALK is a receptor tyrosine kinase (RTK) that is well recognised as an oncogene in various malignancies, including lymphomas along with lung cancers, where it is associated with translocations, such as the ALK-NPM fusion[62,63]. Recently, a study has linked ALK with sympathetic neuron development along with the survival of migrating neural crest cell processes essential for neurogenesis and the formation of the sympathetic nervous system [51]. ALK inhibitors like Lorlatinib have shown some significant potential in treating neuroblastomas. Some studies have observed that integrating these inhibitors with other therapies can improve efficacy by 28.57% of relapsed or refractory cases with ALK mutations. This shows the clinical improvements after following targeted therapies [60,64,65]. Resistance to ALK inhibitors frequently arises due to secondary mutations in the RAS-MAPK pathways. [64]. This states the need for integrated approaches to fight against the resistance and optimise the outcomes.

2.3 THE ROLE OF PHOX2B IN NEUROBLASTOMA

The differentiation of neural lineage and Congenital Central Hypoventilation Syndrome (CCHS) are encompassed in PHOX2B. In PHOX2B, the non-polyalanine repeat mutations (NPARMs) are associated with neuroblastoma. This states the influence of genes in neural crest-derived tumours' phenotype [66,67]. The mutational landscape of PHOX2B encompasses both polyalanine repeat mutations (PARMs) and NPARMs, with the latter frequently implicated in syndromic presentations, including neuroblastoma [67]. Familial cases further highlight this genetic variability; for instance, a recent case report described a toddler with neuroblastoma whose diagnosis revealed a familial NPARM, demonstrating the diverse phenotypic expressivity of identical mutations within the same lineage [66]. In neuroblastoma, the expression levels of PHOX2B is an important prognostic indicator. This overexpression is correlated with low SRs [68]. Also, to detect PHOX2B-positive cells, the RT-qPCR application is used, making it sensitive, along with a specific method for identifying minimal residual disease that helps to monitor and assess the disease progression [69]. Even if PHOX2B is integrated with neuroblastoma, its involvement in CCHS shows a complex genetic component influencing the clinical outcomes and therapeutic methods.

2.4 EPIGENETIC MODIFICATIONS IN NEUROBLASTOMA

Epigenetic modifications are significant in neuroblastoma's pathogenesis and therapeutic responses, particularly in high-risk groups. Changes like DNA methylation along with histone modifications could result in the dysregulation of transcriptional programs and evasion of immune system mechanisms. DNA methylation profiles are identified as key classifiers for neuroblastoma subgroups. This is particularly true for patients with MYCN amplification. These patterns are related to the different prognostic outcomes. This states the utilisation of risk stratification [70]. The interaction between the Polycomb Repressive Complex 2 (PRC2) activity and DNA methylation silences tumour-suppressive differentiation pathways in high-risk neuroblastoma. These pathways can be reactivated with the help of epigenetic therapies, and it has shown some potential to induce differentiation and suppress tumour growth. Characteristics of enhancers in genes encompassed in epithelial-to-mesenchymal transition (EMT), like SNAIL, SOX10, and FOXD3 are specific histone modifications like H3K27ac and H3K4me1, along with p300 [71].

Also, specific neural crest-specific promoters exhibit "bivalent" histone marks, namely H3K27me3/H3K4me3, which are associated with poised promoters found in pluripotent embryonic stem cells. This shows the complex regulation mechanism of neural crest differentiation that is necessary for neuroblastoma development [72]. Epigenetic modulators like DNMT and HDAC inhibitors are observed to be able to restore MHC class I and II expressions. This transformation of immunologically "cold" tumours into "hot" ones improves the visibility of tumours to immune cells, helping to provide an immune-modulated response [73,74].

In high-risk neuroblastoma, the presence of bivalent genes that help regulate differentiation is expressed. This can correlate with poor outcomes. These genes may act as prognostic biomarkers and provide details regarding the progression of tumours and their response to the treatment [72].

2.5 THE ROLE OF ATRX IN NEUROBLASTOMA TUMOUR DEVELOPMENT

Mutations in the ATRX gene, specifically Multi-Exon Deletions (MEDs), are frequently associated with neuroblastoma and contribute to a poorer prognosis. These changes can impact gene expression patterns,

tumours' behaviours, and therapeutics. Approximately over 68% of the ATRX mutations in neuroblastomas is MEDs involved. In this, 75% of them are predicted to be able to generate in-frame fusion proteins. This makes it possible to gain a functional effect and contributes to the aggressive nature of the ATRX-mutated neuroblastoma. Distinct gene expression patterns have been identified in ATRX-mutated neuroblastomas [75]. These alterations influence processes, such as ribosome biogenesis and metabolic regulation, which may necessitate tailored therapeutic approaches [75,76]. ATRX mutations and MYCN amplification may also rarely coexist. The loss of ATRX and MYCN overexpression can lead to lethality in neuroblastoma [77]. With their association with high-risk diseases, ATRX mutations offer information regarding developing targeted therapies, which aim to improve the outcomes in this aggressive cancer subtype [78].

2.6 NON-CODING RNAs

In regulating stem cell biology, development, as well as neural crest differentiation, a key role is played by microRNAs (miRNAs), long non-coding RNAs (lncRNAs), and piRNAs. Those non-coding RNAs in neuroblastoma are dysregulated, contributing to tumorigenesis by inhibiting p53 activity and promoting Epithelial-Mesenchymal Transition (EMT) and metastasis [79]. microRNA processing's key regulator, LIN28, can augment neuroblastoma tumorigenesis by suppressing the tumour-suppressive effects of Let7a miRNA [80]. Also, miRNAs, such as (i) miR-9, (ii) miR-17-92a, and (iii) miR-25-106b cluster, are implicated in tumour progression, metastasis, and differentiation regulation in neuroblastoma and other malignancies[81,82]. Despite the complexity of non-coding RNA biology, integrating transcriptomic along with epigenetic data (e.g., ChIP-seq as well as methylome analyses) from neuroblastoma models and neural crest development is advancing, offering new avenues for identifying therapeutic targets together with pathways critical to various neuroblastoma subtypes.

3. Current Standard Treatments for Advanced/Aggressive Neuroblastoma

The treatment of advanced or high-risk neuroblastoma makes it necessary to take a multimodal approach that can combine chemotherapy, surgical intervention, radiotherapy, and immunotherapy. This can help in addressing the aggressiveness of the disease along with heterogeneity.

3.1 MULTI-MODALITY THERAPY

Multimodal treatment is the key factor of high-risk neuroblastoma (high-risk neuroblastoma) treatment. This method aims to achieve initial disease remission and sustain long-term control. The treatment starts with the initiation of chemotherapy, which helps reduce the tumour's burden; then, surgery will be initiated. Higher doses of chemotherapy and autologous stem cell transplantation are encompassed in consolidation therapy. Next, it will be supplemented with radiotherapy to remove residual disease. Post consolidation, anti-GD2-based immunotherapy and isotretinoin target the minimal residual disease. Even after this rigorous procedure, only over 20% of patients have achieved complete remission after induction therapy [83,84,85].

3.2 CHEMOTHERAPY REGIMENS

In managing the high-risk neuroblastoma, chemotherapy is a backbone. The induction regimen mainly uses platinum-based agents, topoisomerase inhibitors, and alkylators. Standardised protocols like the five-cycle COG regimen and the rapid COJEC protocol in Europe are established by the Children's Oncology Group (COG) along with the Society of Paediatric Oncology Europe Neuroblastoma Group (SIOPEN). Both regimen methods showed comparable rates of survival outcomes, but their toxicity varies, as a compressed COJEC regimen potentially increases myelosuppressive complications [86]. The stem cells are integral to subsequent ASCT during the induction process. This makes removing the residual malignant cells necessary to prevent them from reinducing tumour cells. Nevertheless, studies have shown no significant survival differences between purged and unpurged stem cells, and the latter has become standard practice [87]. Emerging therapies like targeted agents and immunomodulatory drugs are being integrated into induction regimens to improve response rates [88 89].

3.3 SURGICAL APPROACHES

After induction chemotherapy, the primary tumour's surgical resection is performed. Tumour removal's extent influences patient outcomes. Studies show that gross total resection correlates with improved event-free survival along with reduced local progression rates [84,86]. The aggressive surgical approaches may increase the risk of intraoperative complications in anatomically challenging locations. Image-defined risk factors are a valuable predictor of surgical difficulty and potential morbidity [90].

3.4 RADIOTHERAPY

Radiotherapy is critical in consolidation therapy, particularly in addressing residual or microscopic disease. Standard practice involves delivering 21.6 Gy to the preoperative tumour bed and metastatic sites. However, intensifying radiation has not yielded superior outcomes and may exacerbate long-term toxicities. For instance, the addition of boost radiotherapy failed to show improved survival in patients with residual tumours following induction [91,92]. Current studies focus on reducing radiation doses to minimise late effects without compromising local control [93].

3.5 IMMUNOTHERAPY

In high-risk neuroblastoma treatment, the introduction of anti-GD2 antibodies, such as Dinutuximab, has marked a significant advancement. These antibodies target the GD2 glycolipid, which is highly expressed in neuroblastoma cells. Clinical trials have demonstrated improved survival outcomes with Dinutuximab-based regimens compared to isotretinoin alone [34,94]. Despite its efficacy, anti-GD2 therapy is associated with notable toxicities, including neuropathic pain, fever, and capillary leak syndrome. Modifications, such as omitting interleukin-2 (IL-2) from the regimen, have reduced toxicity without compromising efficacy [95].

Novel approaches to GD2 targeting are under investigation, including humanised antibodies like nixtamal and vaccine strategies to enhance immune responses. These innovations aim to improve outcomes

while mitigating the adverse effects associated with current immunotherapies [96,97].

3.6 OUTCOMES AND PROGNOSIS

Despite advancements, the prognosis for high-risk neuroblastoma remains guarded, with 5-year Overall Survival (OS) rates ranging between 40% and 60% for high-risk patients. The end-of-induction response is a critical predictor of long-term outcomes, emphasising the need for enhanced induction strategies [98]. While multimodal therapy has improved survival, relapsed or refractory high-risk neuroblastoma continues to present a significant therapeutic challenge. Emerging therapies, including targeted agents and combination regimens, offer hope for improving outcomes in this population [99,100].

The standard treatment of advanced or aggressive neuroblastoma integrates a complex interplay of modalities that are aimed at achieving disease remission and prolonging survival. Nevertheless, substantial limitations remain, particularly in treatment-related toxicity and suboptimal response rates [101].

4. Targeted Therapies in Advanced/ Aggressive Neuroblastoma

4.1 ANAPLASTIC LYMPHOMA KINASE INHIBITORS

In genes like F1174, F1248, and R1275, ALK mutations commonly occur. This results in constitutive kinase activation and oncogenesis in neuroblastoma. Some studies have come from ALK mutations that independently induce the neuroblastoma in preclinical models. They can also synergise the MYCL overexpression to increase the disease progression [35,102,103]. Crizotinib is the 1st-generation ALK inhibitor that has depicted efficiency in tumours with ALK mutation. It is limited in patients with the ALK1174 mutation because of the intrinsic resistance [104,105].

To overcome these limitations, ensuing-generation inhibitors like Lorlatinib are developed. Lorlatinib shows an improved ALK binding affinity in mutational variants, providing good therapeutic outcomes. This compound is evaluated in clinical trials like the NANT study (NCT03107988) [106]. Also, other ALK inhibitors, such as ceritinib and Entrectinib, are in paediatric Phase 1 trials that help to assess their safety and efficiency (NCT01742286, NCT02650401). Entrectinib shows additional inhibitory effects on rkB, a receptor associated with poor neuroblastoma prognosis [107,108]. Integrating ALK inhibitors with traditional chemotherapy or novel agents has shown synergistic effects in preclinical settings, marking a significant step forward in combating high-risk neuroblastoma [109,110].

4.2 ROLE OF MYCN-TARGETED THERAPIES

Amplification of the MYCN oncogene remains a hallmark of poor prognosis in neuroblastoma [111]. Direct targeting of MYCN is challenging unlike ALK owing to its lack of defined binding pockets suitable for small-molecule inhibitors [112,113]. Thus, therapeutic strategies have focused on indirect mechanisms to modulate MYCN activity. BET inhibitors like JQ-1, OTX015, and I-BET726 disrupt the MYCN transcription by targeting bromodomain proteins. This causes apoptosis and reduced tumour growth in MYCN-amplified models [114,115]. These agents are in clinical trials for various malignancies; also, they have potential applications in MYCN-driven neuroblastoma [116]. Likewise, MYCN degradation is improved by small-molecule inhibitors targeting Aurora A kinase (AURKA). In preclinical studies along with early-phase clinical trials, Alisertib, an AURKA inhibitor, has shown significant antitumor activity [117,118].

Also, MYCN proteasomal degradation is promoted by inhibitors targeting the PI3K/AKT/mTOR pathway and has shown promise in both in vitro as well as in vivo studies [119]. In phase I/Ib trials, perifosine, a PI3K/AKT inhibitor, shows better outcomes, extending progression-free survival in patients with relapsed neuroblastoma [120]. Lastly, MYCN downstream molecules, such as ornithine decarboxylase (ODC1), have emerged as alternative targets. DFMO, an ODC1 inhibitor, reduces MYCN levels and inhibits tumour growth in preclinical models [121]. Clinical trials are ongoing to evaluate DFMO's efficacy in neuroblastoma [103].

4.3 TARGETING RAS/MAPK PATHWAYS IN NEUROBLASTOMA

Mutations within the Ras/mitogen-activated protein kinase (RAS/MAPK) signalling cascade, including genes such as NRAS, KRAS, HRAS, BRAF, NF1, and PTPN11, are present in approximately 3% to 6% of primary neuroblastoma cases. However, these mutations become markedly enriched in relapsed or refractory tumours, where they are detected in up to 78% of cases [38,122]. This shift likely reflects selective pressure from prior therapy and highlights the pathway's central role in treatment resistance and disease progression. In addition to genetic mutations, aberrant activation of upstream tyrosine kinase receptors such as anaplastic lymphoma kinase (ALK), epidermal growth factor receptor (EGFR), and ERBB2—often in the absence of mutations—further drives RAS/MAPK pathway activity, underscoring the rationale for targeted therapies in this context.

MEK inhibitors, including trametinib and binimetinib, have demonstrated efficacy in preclinical models of neuroblastoma by inhibiting downstream ERK signalling, inducing apoptosis, and reducing tumour proliferation [123,124]. Nonetheless, MEK inhibitor monotherapy with trametinib has shown limited durability in clinical settings due to compensatory activation of alternate survival pathways, such as PI3K/AKT [125]. As a result, combination approaches are under active investigation. Promising strategies include pairing MEK inhibitors with agents targeting BCL2, IGF1R, or CDK4/6—such as ribociclib—with preclinical data indicating enhanced tumour suppression [126]. Clinical trials such as NCT02780128 and NCT02124772 are currently evaluating the efficacy of ALK and MEK inhibitor combinations in relapsed neuroblastoma with defined molecular alterations. In parallel, the ongoing Phase I/II trial NCT06933394 is assessing arsenic trioxide combined with trametinib and chemotherapy in patients with high-risk or relapsed disease. This regimen aims to exploit oxidative stress and MAPK modulation to enhance cytotoxicity and prevent resistance [127].

Altogether, targeting the RAS/MAPK axis—particularly through rational combination regimens—represents a promising precision medicine approach in neuroblastoma.

As comprehensive molecular profiling becomes increasingly integrated into clinical practice, such targeted strategies may provide improved outcomes for patients with relapsed or genetically defined high-risk neuroblastoma.

4.4 TARGETING ACTIVATED SIGNALING PATHWAYS IN NEUROBLASTOMA

In neuroblastoma biology, the neurotrophin receptors, TrkA as well as TrkB, play contrasting roles. TrkB expression correlates with aggressive disease and poor prognosis, while TrkA is associated with favourable outcomes. Pan-Trk inhibitors like GNF-4256 as well as AZD6918, have shown promise in preclinical models by enhancing chemotherapy efficacy [103,111,128]. Likewise, Entrectinib is targeting both ALK and TrkB and has shown potent antitumour effects in xenograft models, making it a promising candidate in ongoing clinical trials (NCT02097810, NCT02650401)[129,130]. Nevertheless, inhibitors targeting EGFR have shown limited efficacy, as seen with agents like erlotinib and gefitinib in preclinical and clinical settings, indicating a need for alternative approaches [108].

Neurotrophin receptors of the Trk family (TrkA, TrkB, and TrkC), encoded by the NTRK genes, influence the progression of neuroblastoma. Through the BDNF/TrkB signalling pathway, TrkB overexpression, which is commonly associated with high-risk disease, promotes tumour survival and metastasis. Preclinical evidence shows that in xenograft models, Trk inhibition by drugs such as entrectinib and GNF-4256 significantly slows tumour growth and increases the efficacy of chemotherapy[103,111]. Entrectinib is being studied in clinical trials (e.g., STARTRK-NG, NCT02650401) for paediatric patients with NTRK gene fusions and shows notable anti-tumor efficacy in Trk-driven neuroblastomas[108,129].

In vitro and in vivo, pan-Trk inhibitors like GNF-4256 and AZD6918 have demonstrated effectiveness in overcoming chemoresistance by increasing tumour sensitivity to etoposide[130]. Thus, it makes it easier to include them in combination treatments for neuroblastoma that is at high risk.

Anaplastic lymphoma kinase is an important target, especially when neuroblastoma is familial or has relapsed. ALK amplifications and mutations are linked to a poor prognosis and aid in the activation of the MAPK pathway. Co-targeting the ALK/MET axis has been shown to be therapeutically significant in Ewing sarcoma research, suggesting possible cross-applicability. These results lend credence to the creation of multi-targeted treatment plans for aggressive neuroblastoma variants that include Trk and ALK inhibitors[128].

4.5 TARGETING EMBRYONAL SIGNALING PATHWAYS

The Hedgehog (Hh) signalling system, essential for embryogenesis and stem cell control, is inappropriately activated in neuroblastoma, facilitating tumour growth and survival. Focussing on this route downstream at the GLI transcription factor level has demonstrated superior therapeutic potential compared to upstream Smoothened (SMO) inhibition, especially in tumours exhibiting non-canonical activation. GANT61, a small-molecule GLI inhibitor, has exhibited substantial anti-tumor efficacy by inhibiting neuroblastoma cell growth and inducing apoptosis in vitro, in addition to diminishing tumour burden in xenograft models[131]. These outcomes underscore the therapeutic potential of directly manipulating terminal effectors of the Hh circuit. Complementary findings underscore the importance of targeting oncogenic drivers in neuroblastoma—specifically Trk receptors, ALK, and GLI—to disrupt critical survival pathways and mitigate resistance to conventional therapies. Integrating GLI inhibition with drugs such as GANT61 into multimodal therapies may offer novel strategies for addressing aggressive, treatment-resistant neuroblastoma[103].

4.6 TARGETING CELL CYCLE AND APOPTOTIC REGULATORS

In neuroblastoma, apoptotic resistance is frequently facilitated by the overexpression of BCL-2 and impaired DNA damage response mechanisms. The selective BCL-2 inhibitor venetoclax (ABT-199) has demonstrated significant preclinical efficacy and is currently being assessed in clinical trial NCT03236857. Moreover, prexasertib (LY2606368), a CHK1 inhibitor, impairs cell cycle checkpoints and promotes tumour regression in neuroblastoma models, with clinical safety assessed in NCT02808650. These drugs offer promising components for targeted therapy in high-risk neuroblastoma.[103].

4.7 MODULATING p53 ACTIVITY

Approximately 50% of relapsed neuroblastomas exhibit impaired p53 function through various mechanisms, including MDM2 overexpression and TP53 missense mutations, while p53 mutations are rare at diagnosis. The p53 tumour suppressor pathway is often inactivated in neuroblastoma via non-mutational mechanisms[132,133]. MicroRNA miR-380-5p and histone methyltransferase SETD8 inhibit p53 expression, especially in MYCN-amplified tumours, thereby facilitating chemoresistance and leading to unfavourable prognosis. Reactivation of p53 represents a promising approach in neuroblastomas with wild-type p53. Nutlin-3, an MDM2 antagonist, demonstrates significant anti-tumor efficacy through the stabilisation of p53 and the induction of apoptosis, particularly in chemoresistant scenarios. Simultaneous inhibition of MDM2 and BCL-2 has shown synergistic effects in preclinical models[135]. The clinical development of MDM2 inhibitors, such as idasanutlin (trial NCT02633010), is currently in progress, presenting opportunities for the targeted reactivation of p53 in neuroblastoma[134].

4.8 CDK4/CDK6 INHIBITION

Neuroblastomas exhibit distinct genetic profiles that are associated with tumour characteristics and therapeutic results. Dysregulation of the cell cycle is a hallmark in high-risk cases, making CDK4/CDK6 attractive targets. Preclinical investigations demonstrate that ribociclib, a selective CDK4/6 inhibitor, successfully promotes cell-cycle arrest and senescence in neuroblastoma cells[136]. The clinical trial NCT04238819 is presently examining ribociclib in paediatric solid tumours, such as neuroblastoma, thereby endorsing its potential as a component of precision medicine in genetically stratified patient populations[137].

4.9 TARGETING ANTI-APOPTOTIC PROTEINS IN NEUROBLASTOMA

The overexpression of proteins such as BCL2 and Survivin is particularly notable in neuroblastoma, where elevated levels are associated with poorer prognoses [103,138]. While initial studies with the BCL2 inhibitor ABT263 demonstrated limited efficacy in neuroblastoma models, subsequent analyses revealed that the majority of neuroblastoma cell lines exhibit low BCL2 expression. Yet, they have heightened sensitivity to anti-BCL2 treatments in BCL2-expressing cells both in vitro and in vivo [134]. Likewise, neuroblastoma cell growth is inhibited by targeting BIRC5 (Survivin) using the antisense molecule EZN3042 or else the suppressant YM155 [37,103]. Survivin's role in promoting glycolysis and resistance to treatment is further evidenced by its influence on mitochondrial dynamics; inhibitors like lonidamine and 2-deoxy-d-glucose successfully induce autophagy in cells with aberrant Survivin expression [140]. These therapies remain untested in paediatric populations despite promising preclinical results [103].

4.10 TARGETING EPIGENETIC CHANGES IN NEUROBLASTOMA

In neuroblastoma, epigenetic dysregulation has prompted the development of agents targeting DNA methylases, histone deacetylases (HDACs), and other epigenetic modulators [141]. Among these, HDAC inhibitors like panobinostat as well as vorinostat depicted efficacy in preclinical studies [142]. Although vorinostat monotherapy yields no significant responses in clinical trials, its combination with 13-cis-retinoic acid demonstrates some success, warranting further investigation (NCT01208454) [143,144]. Vorinostat has also shown potential in enhancing the efficacy of 131 I-MIBG radiotherapy through upregulation of norepinephrine transporter expression, currently being assessed in clinical trials [145]. The false complete response after 131-I-mIBG therapy is elucidated in Figure 3[145].

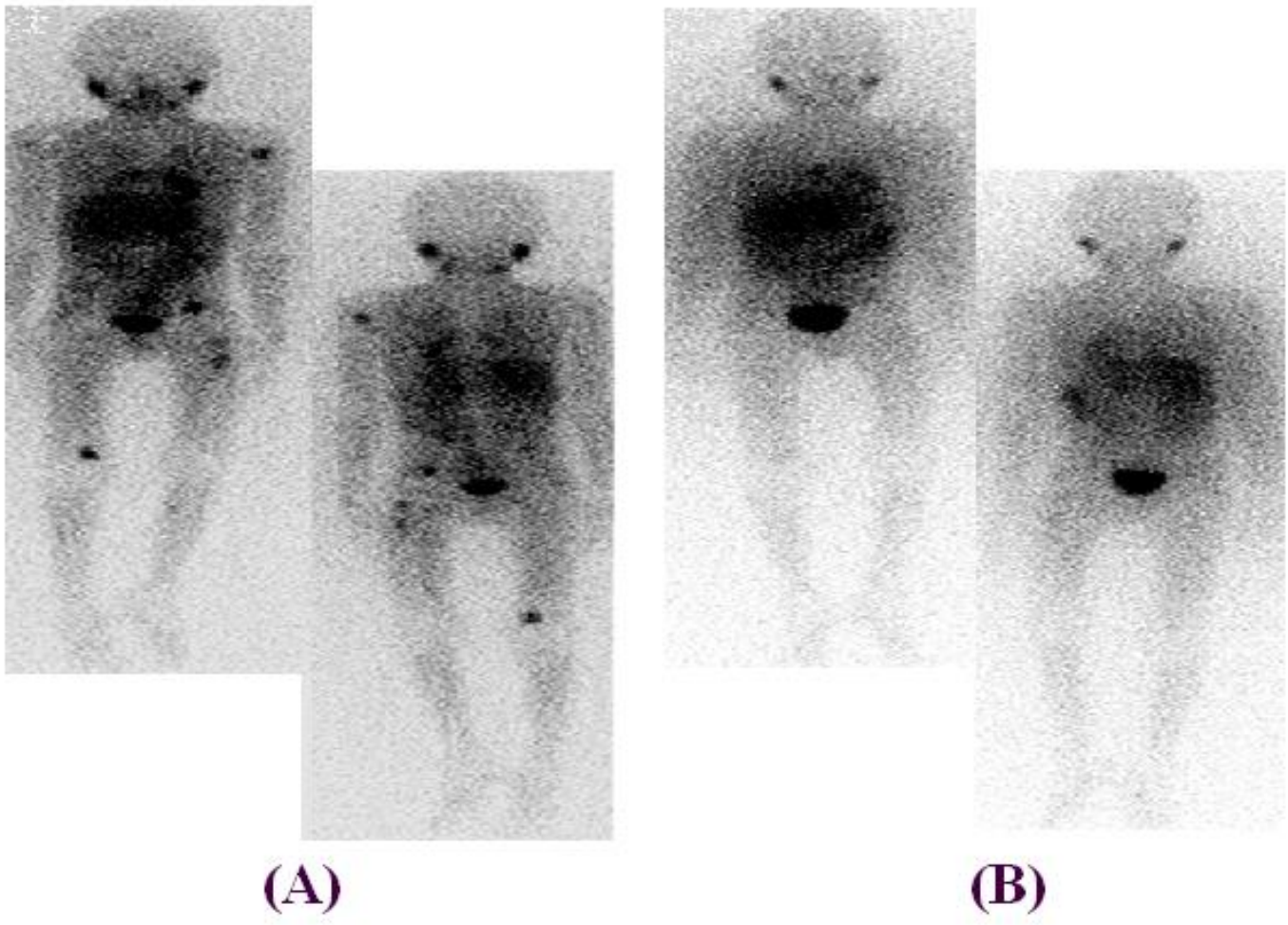

Figure 3: *The phenomenon of "false complete response" following 131-I-mIBG therapy, as detailed by Rubio et al. (2020), highlights the challenges in accurately assessing treatment outcomes in neuroblastoma.*

4.11 Immunotherapy for Neuroblastoma

Apoptotic resistance in neuroblastoma can be addressed via targeted and immunotherapeutic approaches. Venetoclax (ABT-199), a BCL-2 inhibitor, promotes apoptosis in high-risk tumours and is now being studied in NCT03236857[103]. Immunotherapy with the anti-GD2 antibody ch14.18/CHO, along with GM-CSF and IL-2, has markedly enhanced survival rates in clinical studies by augmenting antibody-dependent cellular cytotoxicity. PD-1 inhibition enhances this immune response, presenting synergistic potential[147]. Furthermore, CAR T-cell treatment, utilising virus-specific T cells modified with tumor-specific receptors, has exhibited durability and sustained anti-tumor efficacy in patients with recurrent neuroblastoma[148]. Complementary treatments, like low-dose aspirin, retard inflammatory tumour growth in vivo, whilst cyclooxygenase inhibitors augment chemotherapy-induced apoptosis through p53/HDM2 regulation. These multimodal strategies addressing apoptotic pathways and immune evasion highlight a developing treatment

framework in neuroblastoma, especially for relapsed or refractory cases, combining molecular precision with immunological activation to improve long-term results[149,150].

5. Challenges and Future Directions in Targeted Therapy for Neuroblastoma

Multiple challenges remain despite significant advancements in targeted therapies for neuroblastoma, necessitating innovative approaches to improve clinical outcomes. Resistance mechanisms are one critical issue. Tumours often adapt to evade the effects of targeted agents through genetic mutations, bypassed signalling pathways, or activation of compensatory mechanisms. These adaptations significantly diminish therapeutic efficacy, requiring combination therapies or novel inhibitors to address resistance effectively. Another challenge is tumour heterogeneity. Neuroblastoma exhibits high inter- and intra-tumour variability, both genetically and phenotypically, complicating the identification of universally effective therapeutic targets. This heterogeneity underscores the necessity for strategies tailored to individual tumour profiles. Paediatric-specific pharmacokinetics and pharmacodynamics further complicate treatment. Children's physiological differences from adults affect drug absorption, distribution, and metabolism, along with elimination, necessitating precise dosing regimens to maximise efficacy while minimising toxicity. The emergence of personalised medicine offers promising solutions, but it requires advancements in biomarker discovery and genomic profiling to enable patient-specific therapeutic approaches. Similarly, emerging technologies, such as artificial intelligence and organoid models, hold the potential to revolutionize drug discovery and preclinical evaluation. Despite these advances, gaps in clinical trial data persist. Many trials lack sufficient paediatric representation or fail to include long-term follow-up, limiting insights into efficacy and late toxicities. Expanding robust clinical trial frameworks with multicenter collaborations is essential. Addressing these challenges will demand multidisciplinary efforts, integrating innovative technologies, precision approaches, and comprehensive clinical evaluations to transform neuroblastoma management.

6. Conclusion

Here, the growing evidence supporting the integration of targeted therapies in treating advanced and aggressive neuroblastoma is highlighted in this review. Current approaches have significantly improved patient outcomes, but the prognosis for high-risk cases remains unclear. In improving the efficacy of conventional treatment regimens, emerging therapies, such as ALK inhibitors, MYCN modulators, and agents targeting Ras/MAPK pathways, show promise. These targeted therapies address critical molecular and genetic abnormalities underlying neuroblastoma's pathogenesis and provide more personalised treatment options. Adjunctive-targeted therapies provide a substantial potential to improve SRs and reduce treatment-associated toxicities when combined with standard multimodal strategies. ALK inhibitors like Lorlatinib and MYCN-targeted therapies, including BET inhibitors and AURKA inhibitors, show synergistic effects when used alongside chemotherapy and immunotherapy. Likewise, for overcoming resistance in refractory cases, epigenetic modulators and apoptotic regulators present opportunities. While promising, these novel therapies require careful evaluation to balance efficacy and potential long-term adverse effects. In the future, research must prioritise large-scale, randomised clinical trials to validate these findings in broader patient populations. Also, new therapeutic avenues could be unlocked by exploring combinations of existing and emerging therapies. Advances in genomics and proteomics might enable novel biomarkers' identification, guiding patient stratification and treatment customisation. The journey toward improving outcomes in high-risk neuroblastoma is ongoing. Likewise, sustained collaborative efforts between clinicians, researchers, and pharmaceutical innovators will be crucial in shaping the future of this challenging domain.

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