IJRAR.ORG E-ISSN: 2348-1269, P-ISSN: 2349-5138

INTERNATIONAL JOURNAL OF RESEARCH AND ANALYTICAL REVIEWS (IJRAR) | IJRAR.ORG

An International Open Access, Peer-reviewed, Refereed Journal

OPTIMIZING PHARMACOTHERAPY IN PAEDIATRIC NEUROBLASTOMA AND WILMS TUMOR: CURRENT EVIDENCE AND FUTURE DIRECTIONS

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ABSTRACT: Neuroblastoma and Wilms tumor are the most common extracranial solid malignancies in children, representing significant challenges in paediatric oncology due to their heterogeneous biology, complex clinical presentations and varied therapeutic responses.[1-3] Recent advances in molecular biology, imaging and pharmacotherapy have substantially improved survival outcomes, yet high-risk disease continues to be associated with poor prognosis.[4-6] This narrative review synthesizes current evidence on the pharmacological management of paediatric neuroblastoma and Wilms tumor, drawing from clinical practice guidelines, global trials, and translational research.[7,8] Emphasis is placed on risk-adapted strategies, novel targeted therapies, immunotherapeutic approaches and supportive care optimization. [9,10] Comparative evaluation of treatment algorithms between Children's Oncology Group (COG), International Society of Paediatric Oncology (SIOP) and other cooperative groups is presented. [7,8] Furthermore, emerging therapeutic innovations, including MIBG radiotherapy, ALK inhibitors, immune checkpoint blockade, and epigenetic modifiers, are explored as potential game-changers. [9,10] Challenges in drug resistance, toxicity mitigation, and survivorship care are highlighted, underscoring the need for precision medicine approaches. [11,12] Future directions involve integration of molecular diagnostics, adaptive clinical trial designs, and global collaborations to optimize outcomes.[13,14] The review provides a comprehensive resource for clinicians, researchers and policy makers aiming to refine pharmacotherapy and advance care in paediatric neuroblastoma and Wilms tumor. [15]

Keywords: *Neuroblastoma, Wilms tumor, pharmacotherapy, paediatrics, ALK inhibitors, Dinutuximab*

INTRODUCTION

Paediatric solid tumors constitute a major health burden worldwide, with neuroblastoma and Wilms tumor (nephroblastoma) being among the most prevalent [1,2]. Neuroblastoma, derived from neural crest cells, accounts for 8–10% of all childhood cancers and contributes disproportionately to cancer-related mortality in children under five years of age [3,4]. In contrast, Wilms tumor, an embryonal renal malignancy, accounts for approximately 6% of childhood cancers and has benefitted from remarkable improvements in prognosis due to multimodal therapy [5,6]. Despite advances in multimodality treatment; combining surgery, chemotherapy, radiotherapy and in selected cases, hematopoietic stem cell transplantation—challenges remain in high-risk neuroblastoma and anaplastic Wilms tumor subtypes.[7,8]

From a global health perspective, significant disparities exist in the burden and outcomes of paediatric cancers. Although Wilms tumor survival surpasses 90% in high-income nations, it drops to 40–50% in several low- and middle-income countries (LMICs) because of delayed presentation, inadequate resources, treatment abandonment and restricted access to high-cost chemotherapeutics and supportive care [7,9]. Similarly, children with neuroblastoma in LMICs often present with advanced-stage disease, limiting the effectiveness of available interventions. [9,10] These inequities highlight the urgent need for context-specific strategies to improve access to essential drugs, reduce costs of targeted agents, and strengthen supportive care systems globally. [7,9] Over the past three decades, international cooperative trials have refined risk stratification, enabling tailored pharmacotherapeutic regimens that balance efficacy with long-term toxicity [7,8]. Advances in genomics and molecular biology have provided insights into tumor heterogeneity, leading to targeted therapeutic interventions [9,10]. However, resistance to standard chemotherapeutics, relapse in high-risk groups and treatment-related morbidities necessitate further innovation. [11,12] Furthermore, as survival rates improve, long-term toxicities such as cardiomyopathy, renal insufficiency, secondary malignancies and infertility have gained increasing attention in the paediatric oncology community. [13,14]

A central rationale for focusing this review on pharmacotherapy arises from the fact that drug treatment forms the cornerstone of both neuroblastoma and Wilms tumor management. Even in patients who undergo surgical resection, chemotherapy remains essential for eradication of micro metastatic disease and risk-adapted intensification [1][5]. Moreover, the use of high-dose regimens in neuroblastoma, coupled with autologous stem cell transplantation, underscores the critical role of optimized drug dosing and scheduling[7][9]. Pharmacokinetics and pharmacodynamics (PK/PD) in children differ substantially from adults due to developmental physiology, affecting drug absorption, metabolism and excretion [9,11]. This has direct implications for dosing strategies and toxicity management in paediatric oncology. Drug-related toxicities remain a limiting factor in treatment delivery. Cisplatin-associated nephrotoxicity and ototoxicity, doxorubicin-induced cardiomyopathy, vincristine-related neuropathy and actinomycin-D hepatotoxicity illustrate the delicate balance between cure and morbidity. [9][12] Supportive care strategies such as mesna for cyclophosphamide-induced cystitis or dexrazoxane for anthracycline cardio protection exemplify how pharmacotherapy optimization can reduce long-term harm.[12,13]

In addition, drug resistance continues to be a major obstacle. For example, multidrug resistance mediated by P-glycoprotein overexpression, alterations in DNA repair pathways and tumor microenvironment factors contribute to relapse in high-risk neuroblastoma [10,11]. Similarly, diffuse anaplastic Wilms tumor often displays intrinsic chemoresistance and requires intensified regimens with greater toxicity [7,8]. Addressing these mechanisms through novel targeted therapies and immunotherapies is therefore a research priority.

This review provides a detailed, evidence-based narrative on optimizing pharmacotherapy in paediatric neuroblastoma and Wilms tumor. [15] By evaluating existing drug regimens, emerging targeted therapies, PK/PD considerations, adverse drug reactions and supportive care strategies, this article aims to provide clinicians, researchers and policy-makers with a comprehensive understanding of current evidence and future directions. The ultimate goal is to inform risk-adapted, precision-driven approaches that maximize cure while minimizing toxicity and addressing global inequities in care.

Pathophysiology

Neuroblastoma: Peak incidence occurs before 2 years of age [3][4]. Tumor biology is diverse, ranging from spontaneous regression (stage 4S disease) to aggressive metastatic spread [4][6]. Molecular hallmarks include MYCN amplification, ALK mutations, ATRX deletions and chromosomal aberrations (1p, 11q deletions) [6][9]. Tumor heterogeneity drives variability in clinical outcomes and treatment[10][11]

Wilms Tumor: Represents the most common paediatric renal malignancy, with peak incidence between 2–5 years [2][5]. Genetic predisposition syndromes such as WAGR, Beckwith-Wiedemann, Frasier syndrome and Denys-Drash increase risk [5][7]. Mutations in WT1, WT2 and epigenetic regulators such as IGF2 contribute to tumorigenesis [7,8]. Tumor histology is stratified into favourable and unfavourable (diffuse anaplasia) categories, which are strongly predictive of outcome [9,10].

Risk stratification systems:

- Neuroblastoma: International Neuroblastoma Risk Group (INRG), COG (Children's Oncology Group), and SIOPEN (International Society of Paediatric Oncology Europe Neuroblastoma Research Network) classifications incorporate clinical stage, age, histology, MYCN status, ploidy and chromosomal aberrations.
- Wilms Tumor: NWTS (National Wilms Tumor Study)/COG and SIOP (International Society of Paediatric Oncology) staging systems guide therapy, distinguishing favourable from unfavourable histology.

Global Protocol Differences (COG vs. SIOP)

One major distinction in Wilms tumor management lies in the differing philosophies between COG and SIOP [7,8]. The COG approach favours upfront nephrectomy followed by adjuvant chemotherapy tailored to stage and histology [7]. This allows accurate staging based on untreated tumor histology but may increase risk of surgical complications [8]. In contrast, SIOP advocates preoperative chemotherapy, which shrinks tumors, reduces intraoperative rupture risk, and permits nephron-sparing surgery but complicates precise histological assessment [9]. In neuroblastoma, COG protocols often employ dose-intensive chemotherapy and early autologous stem cell rescue, while SIOPEN trials emphasize immunotherapy integration and stratified dose tailoring [10,11].

Current Pharmacotherapy in Neuroblastoma

- Low- and Intermediate-Risk Disease*:* Often treated with surgery alone or surgery plus reduced-intensity chemotherapy (vincristine, cyclophosphamide, doxorubicin, cisplatin, etoposide) [6,7]. Outcomes exceed 90% event-free survival [7].
- High-Risk Disease: Multimodal regimens include induction chemotherapy, surgical resection, consolidation with high-dose chemotherapy and autologous stem cell rescue, radiotherapy and maintenance with immunotherapy [8,9].
- Induction chemotherapy: Commonly cisplatin, carboplatin, etoposide, cyclophosphamide and doxorubicin [7,9].
- Myeloablative consolidation: Busulfan/melphalan conditioning is widely used [9].
- Immunotherapy: Anti-GD2 monoclonal antibodies (dinutuximab) with cytokines (GM-CSF, IL-2) and isotretinoin improve survival. [9,10]
- MIBG (Metaiodobenzylguanidine) therapy: Utilized in relapsed/refractory cases, with ongoing trials for earlier incorporation. [11,12] MIBG therapy uses radioactive iodine-labelled metaiodobenzylguanidine (^{131}I-MIBG) to deliver targeted radiation to neuroblastoma cells. The radioisotope concentrates in neuroblastoma cells → emits beta radiation → kills tumour cells with minimal effect on surrounding tissues.

Novel Agents:

- ALK inhibitors (crizotinib, lorlatinib) in ALK-mutant disease [12,13].
- Checkpoint inhibitors (nivolumab, pembrolizumab) under investigation [13,14].
- Epigenetic therapies and CAR T-cell therapy targeting GD2 show early promise. [14,15]
- Nanoparticle-based delivery systems aim to reduce systemic toxicity. [15,16]
- MYCN-directed strategies: Since MYCN amplification is the strongest poor prognostic marker in neuroblastoma, approaches such as BET inhibitors (JQ1, OTX015) to suppress transcription, Aurora kinase A inhibitors (Alisertib) to destabilize the protein, and siRNA/antisense oligonucleotides to silence MYCN are being explored, though these remain largely in preclinical and early-phase trials.

Table 1. Pharmacology of Commonly Used Drugs in Neuroblastoma

Drug	Paediatric Dose (Typical Protocols)	Major Adverse Drug Reactions (ADRs)
Vincristine (VCR)	1.5 mg/m² IV weekly (max 2 mg)	Peripheral neuropathy (dose-limiting), constipation, SIADH, jaw pain, alopecia
Cyclophosphamide (CPM)	250–1,200 mg/m² IV per cycle (protocol-dependent)	Myelosuppression, haemorrhagic cystitis (prevented with Mesna), infertility, SIADH
Cisplatin (CDDP)	60–120 mg/m² IV every 3–4 weeks	Nephrotoxicity, ototoxicity, neurotoxicity, electrolyte wasting, nausea/vomiting
Carboplatin (CBDCA)	Dosed by Calvert formula (AUC 5–6)	Myelosuppression, nephrotoxicity (less than cisplatin), ototoxicity
Etoposide (VP-16)	100–200 mg/m² IV daily × 3–5 days	Myelosuppression, secondary AML, mucositis, alopecia
Doxorubicin (DOX)	30–60 mg/m² IV every 3–4 weeks (cumulative max ~450–550 mg/m²)	Cardiotoxicity (dose-dependent), myelosuppression, mucositis, alopecia
Dinutuximab (Anti-GD2 mAb)	17.5 mg/m²/day IV for 4 days per cycle (with GM-CSF or IL-2)	Neuropathic pain, capillary leak syndrome, hypersensitivity, hypotension
Naxitamab-gqgk	(≥1 yr): 3 mg/kg/day IV (max 150 mg) on Days 1, 3, 5 of each 4-wk cycle + GM-CSF (250 mcg/m² SQ Days –4–0; 500 mcg/m²	Neuropathic pain, allergic reactions, hypotension or hypertension, fever, chills

	SQ Days 1–5). Premeds: gabapentin, opioids, ±ketamine, steroids, antihistamine, H2 blocker, acetaminophen, antiemetic. Continue q4wk until response + 5 cycles; may extend q8wk.	

Current Pharmacotherapy in Wilms Tumor

Wilms tumour (WT) is mainly driven by tumour suppressor gene mutations (WT1, WT2/IGF2, CTNNB1, TP53). Current therapies are mostly surgery + chemotherapy (vincristine, actinomycin D, doxorubicin) ± radiotherapy.

Standard Therapy:

- *COG approach:* Upfront nephrectomy followed by risk-adapted chemotherapy (vincristine, actinomycin-D, doxorubicin) [6,7]. Radiotherapy is reserved for advanced disease [8].
- *SIOP approach:* Preoperative chemotherapy (vincristine, actinomycin-D ± doxorubicin) to reduce tumor burden prior to surgery [7,8].
- *Relapsed/Refractory Disease:* Novel regimens with cyclophosphamide, etoposide, irinotecan, and targeted agents (mTOR inhibitors, IGF-1R inhibitors) are being studied [12,13].
- *Histology-Specific Considerations:* Anaplastic Wilms tumors have poor prognosis and require intensified therapy [9,13].

Table 2. Pharmacology of Commonly Used Drugs in Wilms Tumor

Drug	Paediatric Dose (Typical Protocols)	Major Adverse Drug Reactions (ADRs)
Vincristine (VCR)	1.5 mg/m² IV weekly (max 2 mg)	Peripheral neuropathy, constipation, SIADH, alopecia
Actinomycin-D (Dactinomycin)	15 mcg/kg IV daily × 5 days OR 45 mcg/kg every 3 weeks	Hepatic veno-occlusive disease, myelosuppression, mucositis, alopecia
Doxorubicin (DOX)	30–60 mg/m² IV every 3–4 weeks (cumulative max ~450–550 mg/m²)	Cardiotoxicity, myelosuppression, alopecia, mucositis
Ifosfamide (relapsed)	1,500 mg/m² IV daily × 5 days (with Mesna)	Haemorrhagic cystitis, encephalopathy, nephrotoxicity, myelosuppression
Irinotecan (relapsed)	50 mg/m² IV daily × 5 days OR oral formulations	Severe diarrhoea (early cholinergic & late secretory), myelosuppression
Cyclophosphamide (CPM)	250–1,200 mg/m² IV per cycle	Myelosuppression, haemorrhagic cystitis, infertility, SIADH

Novel treatments:

Genetic Treatments in Wilms Tumour:

i. IGF2 Pathway Targeting - WT2 locus (11p15) → loss of imprinting/overexpression of IGF2 drives tumour growth. IGF1R inhibitors (e.g, linsitinib/OSI-906) being tested preclinically.

ii. TP53 Mutation (Anaplastic Wilms Tumour) - TP53 alterations are associated with poor prognosis, chemoresistance MDM2 inhibitors (like idasanutlin) are being explored to restore p53 activity.

Monoclonal Antibodies:

Currently, no monoclonal antibody is approved for standard WT treatment, but research is ongoing.

Anti-VEGF Therapy: Bevacizumab (anti-VEGF mAb) has been tested in relapsed/refractory WT (small studies, limited activity).

Immune Checkpoint Inhibitors: PD-1/PD-L1 inhibitors (e.g, nivolumab, pembrolizumab) being tested in early-phase trials for refractory paediatric solid tumours including Wilms Tumour.

Table 3: Pharmacotherapy in Neuroblastoma by Risk Group

Risk Group	**Standard Chemotherapy**	**Consolidation**	**Maintenance**	**Novel/ Adjuncts**
Low-risk	Surgery ± VCR, ACT-D	None	None	None
Intermediate	VCR, ACT-D, DOX, CDDP, VP-16	Surgery	None	None
High-risk	CDDP, CBDCA, VP-16, DOX, CPM	Myeloablative + stem cell rescue	Anti-GD2 (dinutuximab) + isotretinoin	ALK inhibitors, checkpoint blockade, MIBG

Table 4. Pharmacotherapy in Wilms Tumor by Risk Group

Histology & Stage	**Standard Chemotherapy**	**Radiotherapy**	**Relapse/Novel Approaches**
Stage I-II, favourable	VCR, ACT-D	None	Rarely needed
Stage III-IV, favourable	VCR, ACT-D, DOX	Local RT, whole-lung RT (if pulmonary mets)	Cyclophosphamide, irinotecan
Anaplastic histology	VCR, ACT-D, DOX + intensified therapy	Yes (local + lung if needed)	mTOR inhibitors, IGF-1R blockade

Future Directions

Biology-driven risk stratification in Wilms tumor is increasingly incorporating 1q gain, TP53 status in anaplastic disease and emerging biomarkers to tailor anthracycline and radiotherapy (RT) exposure [7,8,28]. Response-adapted therapy is being refined through harmonized COG and SIOP trials, which are evaluating RT omission or dose reduction in cases of low-burden pulmonary metastases with rapid complete response, while escalating therapy for slow responders [6–8,26,27]. Although targeted and immune-based approaches, including inhibitors of the mTOR/IGF-1R axis, WT1-directed strategies and PD-1/PD-L1 blockade, are under early-phase exploration, none have yet replaced conventional chemotherapy; therefore, enrolment into carefully designed clinical trials remains essential [12,13,26,27]. To mitigate late effects, protocols aim to minimize cumulative anthracycline exposure and reduce lung and abdominal RT in favourable histology, supported by structured survivorship programs addressing long-term risks such as cardiotoxicity, renal impairment and infertility [6–8,26,27]. Looking ahead, precision medicine through genomic sequencing holds promise for individualized therapy selection, while immunotherapy continues to expand with next-generation CAR T cells, bispecific antibodies, and tumor vaccines. Targeted agents exploiting ALK, ATRX, TP53, and WT1 pathways are under investigation, alongside toxicity mitigation strategies such as cardio protectants, nephron protectants and advanced supportive care. Finally, global collaboration through harmonization of protocols across COG, SIOP, SIOPEN and Asian paediatric oncology groups remains vital for optimizing outcomes worldwide.

CONCLUSION

The management of paediatric neuroblastoma and Wilms tumor has undergone remarkable evolution, with risk-adapted pharmacotherapy significantly improving outcomes. While low- and intermediate-risk cases enjoy excellent survival, high-risk neuroblastoma and anaplastic Wilms tumor remain therapeutic challenges. Integration of molecular diagnostics, immunotherapy and targeted agents represents the future of paediatric oncology. Multidisciplinary care, international collaboration and precision medicine will be pivotal in optimizing pharmacotherapy, reducing toxicities and enhancing survival outcomes.

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