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Pediatric onconeurology; mechanisms of renal involvement, treatment toxicity, and mitigation strategies

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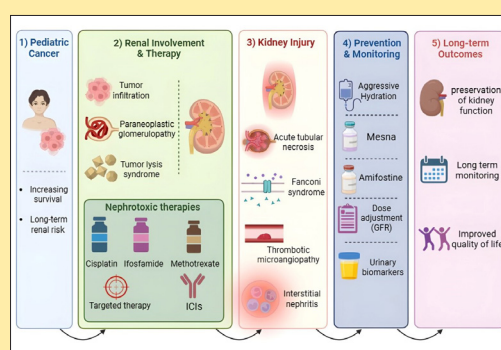
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ABSTRACT

Pediatric onconeurology has emerged as a critical subspecialty at the intersection of pediatric oncology and nephrology, driven by the remarkable increase in childhood cancer survival rates and the subsequent recognition of long-term renal morbidity. Understanding the complex interplay between oncological disease and renal pathophysiology is necessary. Renal involvement in pediatric malignancies arises through diverse mechanisms, including direct neoplastic infiltration, paraneoplastic glomerulopathies, and metabolic emergencies such as spontaneous or treatment-induced tumor lysis syndrome. Furthermore, the therapeutic armamentarium for childhood cancers is frequently nephrotoxic. Conventional chemotherapeutic agents, notably cisplatin, ifosfamide, and high-dose methotrexate, predominantly cause acute tubular necrosis and Fanconi syndrome, while novel targeted therapies and immune checkpoint inhibitors introduce new patterns of injury, including thrombotic microangiopathy and immune-mediated interstitial nephritis. These insults can lead to irreversible chronic kidney disease, hypertension, and electrolyte wasting, profoundly impacting long-term survivorship. Mitigation strategies require a proactive, multilayer approach encompassing risk stratification, aggressive peri-treatment hydration, and the judicious use of pharmacological protectants such as mesna and amifostine. Dose modulation based on real-time glomerular filtration rate assessments and the emerging utilization of novel urinary biomarkers for early subclinical tubular injury detection are necessary for timely intervention. In severe cases, temporary or permanent renal replacement therapy may be necessitated. Finally, optimizing outcomes in pediatric onconeurology demands rigorous long-term monitoring and comprehensive survivorship care plans to preserve renal function, minimize late effects, and ensure the highest possible quality of life for childhood cancer survivors.



Review

Implication for health policy/practice/research/medical education:

Pediatric onconeurology addresses the complex intersection of childhood cancers and kidney health, highlighting significant implications for both immediate survival and long-term well-being. The mechanisms of renal involvement are multifactorial, arising from direct tumor infiltration, systemic paraneoplastic syndromes, or metabolic emergencies like tumor lysis syndrome, which can rapidly precipitate acute kidney injury. Furthermore, treatment toxicity poses a substantial threat, as essential chemotherapeutic agents such as cisplatin, ifosfamide, and high-dose methotrexate regimens, alongside abdominal radiation, frequently induce nephrotoxicity, potentially resulting in irreversible chronic kidney disease. To combat these adverse effects, critical mitigation strategies must be implemented. These modalities include aggressive intravenous hydration, meticulous dose adjustments based on renal function, and the administration of nephroprotective agents like amifostine, mesna, or rasburicase. Finally, proactive, multidisciplinary monitoring is absolutely essential to balance optimal oncologic efficacy with the preservation of renal function, ensuring improved quality of life for pediatric cancer survivors and minimizing severe late-effect morbidities.

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Introduction

Pediatric onconeurology has arisen as a critical and rapidly expanding subspecialty at the intersection of pediatric oncology and pediatric nephrology, driven by the remarkable advancements of modern cancer therapy (1). Over the past few decades, the survival rates for childhood malignancies have improved dramatically, with overall five-year survival rates now exceeding eighty percent for many common pediatric cancers (2). However, this unprecedented success has unmasked a significant long-term health burden, as a growing population of adult survivors faces with the late effects of their disease and its treatment (2). Among these late effects, renal impairment is particularly prominent, as the kidneys are highly susceptible to both the direct infiltrative effects of malignancies and the profound toxicities of chemotherapeutic agents, radiation, and surgical interventions (3). The pediatric kidney is uniquely vulnerable to these insults. In contrast to the fully mature adult kidney, the pediatric kidney undergoes prolonged postnatal development (4). Nephrogenesis is generally complete by approximately 37 weeks of gestation, but tubular transport functions continue to mature throughout early childhood (5). Furthermore, children have a higher renal blood flow relative to their body mass and a higher metabolic rate, which increases their exposure to circulating toxins and reactive metabolites (6). Understanding the interacted mechanisms of renal involvement, the specific toxicities of cancer therapies, and the implementation of robust mitigation strategies is therefore necessary for optimizing both the immediate survival and the long-term quality of life for pediatric cancer patients (7).

Search strategy

For this review, we searched PubMed, Web of Science, EBSCO, Scopus, Google Scholar, Directory of Open Access Journals (DOAJ) and Embase, using different keywords such as chronic kidney disease, nephrotoxicity, childhood cancer, tumor lysis syndrome, acute tubular necrosis, thrombotic microangiopathy, biomarkers, acute kidney injury, paraneoplastic syndrome, minimal change disease, Fanconi syndrome and end-stage renal disease.

Renal involvement in pediatric oncology

The direct involvement of the kidney in pediatric oncology can occur through several primary mechanisms, beginning with direct tumor infiltration and mechanical obstruction (8). Hematologic malignancies, such as acute lymphoblastic leukemia and non-Hodgkin lymphoma, frequently infiltrate the renal parenchyma (9). This infiltration can lead to bilateral nephromegaly, disruption of the normal renal architecture, and subsequent acute

kidney injury, often manifesting as a decline in glomerular filtration rate and mild proteinuria (10). In contrast, solid tumors such as Wilms tumor, neuroblastoma, and various retroperitoneal or pelvic sarcomas can cause renal injury through mechanical compression and obstructive uropathy (11,12). Obstruction of the ureters or the urethra leads to hydronephrosis, increased intratubular pressure, and a subsequent drop in the glomerular filtration gradient, culminating in post-renal acute kidney injury (13). If left unresolved, chronic obstruction can induce irreversible tubular atrophy and interstitial fibrosis. Beyond direct physical effects, malignancies can also induce renal injury through paraneoplastic syndromes (14, 15). Although less common in children than in adults, glomerular diseases such as membranous nephropathy or minimal change disease can occur secondary to solid tumors or Hodgkin lymphoma, driven by the deposition of circulating immune complexes or the secretion of cytokines that alter podocyte function (16). Additionally, the rapid turnover and spontaneous necrosis of highly proliferative tumors can precipitate spontaneous tumor lysis syndrome. This oncologic emergency involves the massive release of intracellular contents into the systemic circulation, leading to hyperuricemia, hyperkalemia, and hyperphosphatemia (17). The subsequent precipitation of uric acid crystals and calcium phosphate in the renal tubules causes severe intratubular obstruction, direct tubular toxicity, and profound acute kidney injury, necessitating immediate and aggressive medical intervention (18).

Chemotherapy-induced nephrotoxicity

Though the direct effects of the tumor are significant, the iatrogenic renal toxicities associated with cancer treatment represent the most important challenge in pediatric onconeurology (3). Chemotherapy-induced nephrotoxicity is a major cause of both acute kidney injury and chronic kidney disease in this population (19). Notably, cisplatin, a platinum-based antineoplastic agent, is a cornerstone in the treatment of numerous pediatric solid tumors, including osteosarcoma, hepatoblastoma, and medulloblastoma (20). However, its efficacy is severely limited by its potent nephrotoxicity (21). Cisplatin is freely filtered by the glomerulus and subsequently concentrated in the proximal tubular cells by specific transporters, notably organic cation transporter 2 and copper transporter 1 (22). Once inside the cell, cisplatin forms DNA adducts, triggers oxidative stress, and induces mitochondrial dysfunction, leading to apoptotic cell death predominantly in the S3 segment of the proximal tubule (23). Clinically, this manifests as acute kidney injury, but it also causes chronic, often irreversible, electrolyte wasting, particularly of magnesium and potassium, due to the loss of tubular reabsorptive capacity (24). Over time, repeated cycles of

cisplatin can lead to chronic tubulointerstitial nephritis and a progressive decline in the glomerular filtration rate (25). Similarly, ifosfamide, an alkylating agent used in the treatment of sarcomas and various relapsed solid tumors, is notorious for causing proximal tubular toxicity (26,27). The nephrotoxicity of ifosfamide is primarily mediated by its metabolite, chloroacetaldehyde, which accumulates in the proximal tubule and depletes intracellular glutathione. This depletion impairs the cell's antioxidant defenses and inhibits mitochondrial oxidative phosphorylation (28,29). The resulting cellular energy failure leads to Fanconi syndrome, a generalized dysfunction of the proximal tubule characterized by the urinary wasting of glucose, amino acids, uric acid, phosphate, and bicarbonate (30). In children, the profound phosphaturia and bicarbonate loss can result in severe hypophosphatemic rickets, growth failure, and metabolic acidosis, complicating the child's overall development and recovery (31). Other chemotherapeutic agents also pose significant risks to the developing kidney. Methotrexate, a folate antagonist used in leukemia and osteosarcoma protocols, is primarily excreted by the kidneys (32). In acidic environments, methotrexate and its metabolites have low solubility and can precipitate within the renal tubules, causing crystal nephropathy and direct tubular toxicity. This risk is exacerbated by high-dose regimens and concurrent volume depletion (33). In the context of hematopoietic stem cell transplantation, which is frequently utilized for high-risk or relapsed pediatric leukemias, the conditioning regimens and subsequent immunosuppression introduce unique renal challenges (34). Likewise, calcineurin inhibitors, such as cyclosporine and tacrolimus, are mainstays of graft-versus-host disease prophylaxis but are highly nephrotoxic (35). They induce intense vasoconstriction of the afferent arterioles by altering the balance of vasoactive mediators, leading to ischemic injury to the tubules and a reversible or sometimes irreversible decline in the glomerular filtration rate (36). Furthermore, these agents, along with certain conditioning chemotherapies, can damage the renal microvasculature, precipitating transplant-associated thrombotic microangiopathy (37). This severe condition is characterized by endothelial injury, microvascular thrombosis, hemolytic anemia, thrombocytopenia, and progressive renal failure. The advent of targeted therapies and immunotherapies has added new dimensions to onconeurology (38,39). Remarkably, vascular endothelial growth factor inhibitors, used in certain refractory solid tumors, disrupt the critical crosstalk between podocytes and glomerular endothelial cells, frequently resulting in new-onset hypertension, heavy proteinuria, and thrombotic microangiopathy (40). Similarly, immune checkpoint inhibitors, which are increasingly being investigated in pediatric oncology,

can unleash autoreactive T-cells that infiltrate the renal interstitium, causing acute tubulointerstitial nephritis that often requires prolonged courses of systemic corticosteroids (41,42).

Focus on radiation therapy

Beyond pharmacological toxicities, radiation therapy and surgical interventions contribute significantly to the renal morbidity in pediatric cancer survivors (43). Radiation nephropathy is a delayed, dose-dependent complication that typically manifests months to years after exposure to abdominal, flank, or total body irradiation (44). The primary target of radiation injury is the renal microvasculature, particularly the glomerular capillary endothelium. Radiation induces endothelial cell swelling, apoptosis, and the subsequent rarefaction of the peritubular capillary network (45). This ischemic environment triggers the activation of the renin-angiotensin-aldosterone system, leading to malignant hypertension, which further exacerbates vascular injury (46). Over time, the glomerular basement membrane thickens, mesangial matrix expands, and the kidney progresses to global glomerulosclerosis and tubular atrophy (44). The pediatric kidney is particularly sensitive to radiation, and the threshold for clinically significant injury is lower in children than in adults. Surgical management of renal tumors also carries long-term nephrological consequences (3). The standard of care for unilateral Wilms tumor often involves a radical nephrectomy. While the remaining contralateral kidney undergoes compensatory hypertrophy and hyperfiltration to maintain normal overall renal function in the short term, this chronic hyperfiltration state places immense mechanical stress on the remaining nephrons (47,48). According to the hyperfiltration hypothesis, this sustained intraglomerular hypertension eventually leads to secondary focal segmental glomerulosclerosis, proteinuria, and a progressive decline in renal function over the ensuing decades (49). Children who undergo bilateral nephrectomies, partial nephrectomies for bilateral disease, or nephron-sparing surgeries for complex anatomical reasons are at an even higher risk for early-onset chronic kidney disease (50).

Mitigative modalities in pediatric onconeurology

Given the profound and multifaceted risks to renal function, the implementation of comprehensive mitigation strategies is a cornerstone of modern pediatric onconeurology (1). These strategies span the entire continuum of care, from pre-treatment risk stratification to intra-treatment nephroprotection and long-term survivorship monitoring (51,52). Prior to the initiation of any potentially nephrotoxic therapy, a meticulous baseline assessment of renal function is mandatory. In children,

relying solely on serum creatinine can be misleading due to variations in muscle mass, particularly in those with cancer cachexia or neuromuscular complications (53). Therefore, the use of cystatin C-based equations or formal exogenous clearance studies is increasingly recommended to obtain an accurate baseline glomerular filtration rate (54). Baseline urinalysis, urine protein-to-creatinine ratios, and comprehensive electrolyte panels are also essential to identify pre-existing renal vulnerabilities (55). Once treatment begins, aggressive preventative measures are employed to mitigate toxicity (56). For cisplatin, vigorous intravenous hydration with isotonic saline is the most effective strategy to maintain high urine flow rates and minimize the concentration of the drug in the renal tubules (57,58). Concurrent magnesium supplementation is routinely administered to counteract the predictable tubular wasting (59). Since, the cytoprotective agent amifostine has been shown to reduce cisplatin-induced nephrotoxicity by scavenging free radicals, its clinical use in pediatrics is often limited by severe side effects, including profound hypotension and emesis. Consequently, dose modification remains a critical tool (60,61). Oncologists may opt for continuous infusions rather than bolus dosing, split the total dose over several days, or substitute carboplatin, which is significantly less nephrotoxic, when clinically appropriate (62). For patients receiving ifosfamide, mitigation focuses on preventing the accumulation of toxic metabolites (63). Although mesna is universally administered to bind acrolein in the bladder and prevent hemorrhagic cystitis, it does not protect the proximal tubule from chloroacetaldehyde (64). Therefore, the primary mitigation strategies for ifosfamide-induced Fanconi syndrome include maintaining high urine output, avoiding concurrent use of other nephrotoxins, and closely monitoring urinary markers of tubular damage, such as alpha-1-microglobulin or retinol-binding protein, which can detect tubular injury before it becomes clinically apparent (63,65). If early signs of tubular dysfunction emerge, the ifosfamide dose should be promptly reduced or discontinued to prevent irreversible damage (66). When administering high-dose methotrexate, urinary alkalization is paramount (66). Intravenous sodium bicarbonate is given to increase the solubility of methotrexate and prevents intratubular crystallization (67). Aggressive hydration and the timely administration of leucovorin rescue are also critical components of the protocol to protect the renal tubules (68). In the setting of hematopoietic stem cell transplantation, minimizing the use of calcineurin inhibitors, utilizing alternative immunosuppressants like sirolimus when feasible, and maintaining strict blood pressure control are vital strategies to prevent endothelial injury and thrombotic microangiopathy (69). For patients undergoing radiation

therapy, advanced techniques such as intensity-modulated radiation therapy and proton beam therapy are utilized to sculpt the radiation dose, thereby sparing as much of the normal renal parenchyma as possible and keeping the mean kidney dose below the established toxicity thresholds (70).

Lifelong monitoring in pediatric cancer survivors

The mitigation of renal injury does not end with the completion of cancer therapy; rather, it transitions into a lifelong commitment to survivorship care (7). Pediatric cancer survivors, particularly those who received nephrotoxic chemotherapy, abdominal radiation, or underwent nephrectomy, require lifelong monitoring in specialized late-effects clinics (43). The goal of long-term surveillance is the early detection of chronic kidney disease, hypertension, and electrolyte imbalances (71). Annual screening should include blood pressure measurements, serum electrolytes, blood urea nitrogen, creatinine, and cystatin C, as well as a urinalysis and a urine albumin-to-creatinine ratio (71). The early identification of proteinuria or a declining glomerular filtration rate allows for the timely initiation of renoprotective therapies. Angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers are the first-line agents for managing hypertension and reducing proteinuria in these patients, as they reduce intraglomerular pressure and slow the progression of glomerulosclerosis (72,73). However, their administration requires careful monitoring, particularly in patients with underlying tubular dysfunction who may already be prone to hyperkalemia (74). For survivors who develop Fanconi syndrome or chronic electrolyte wasting, lifelong oral supplementation with phosphate, bicarbonate, potassium, and active vitamin D is often necessary to prevent metabolic bone disease, rickets, and growth retardation (75,76). Nutritional support and endocrinological evaluation are frequently required to address the complex metabolic derangements that accompany chronic renal tubular acidosis (77). For the unfortunate subset of pediatric cancer survivors who progress to end-stage renal disease, renal replacement therapy becomes necessary (78). The transition to dialysis or kidney transplantation in this population is fraught with unique medical and psychosocial complexities (79). These patients often have a history of multiple abdominal surgeries, radiation-induced vascular damage, and a high burden of cardiovascular comorbidities, making the creation of arteriovenous fistulas for hemodialysis technically challenging and increasing the risk of peritoneal dialysis complications (79). Kidney transplantation is the preferred modality for end-stage renal disease in children, offering the best survival and quality of life outcomes (80). However, the immunosuppressive regimens required to

prevent allograft rejection, particularly those containing calcineurin inhibitors, carry a high risk of recurrent nephrotoxicity (81). Furthermore, survivors must be carefully evaluated for the risk of cancer recurrence or the development of secondary malignancies, which can be exacerbated by chronic immunosuppression (82). In the next steps an appropriate care involving pediatric nephrologists, oncologists, transplant surgeons, and psychologists is essential to navigate these challenges and ensure the long-term success of the allograft and the overall well-being of the patient (83).

Horizons of pediatric onconeurology

Looking toward the future, the field of pediatric onconeurology is poised for significant advancements driven by the discovery of novel biomarkers and the integration of pharmacogenomics (84). Traditional markers of renal function, such as serum creatinine and blood urea nitrogen, are late indicators of kidney injury, often rising only after substantial nephron mass has been lost (85). The identification and validation of novel urinary biomarkers, such as kidney injury molecule-1, neutrophil gelatinase-associated lipocalin, and liver-type fatty acid-binding protein, offer the potential for the real-time, non-invasive detection of subclinical tubular injury (86). The incorporation of these biomarkers into clinical trials and routine care could allow for the preemptive dose adjustment or discontinuation of nephrotoxic agents before irreversible damage occurs (87). Concurrently, pharmacogenomic research is unraveling the genetic basis of inter-individual variability in chemotherapy toxicity (7). Meanwhile, polymorphisms in the genes encoding organic cation transporter 2 and multidrug and toxin extrusion proteins have been linked to an increased risk of cisplatin-induced nephrotoxicity and ototoxicity (88). Accordingly, the eventual integration of pharmacogenomic profiling into pre-treatment risk assessment could pave the way for truly personalized onconeurology, where chemotherapy regimens are tailored not only to the molecular profile of the tumor but also to the unique genetic susceptibility of the patient's kidneys (89,90).

Conclusion

In summary, pediatric onconeurology represents an indispensable and complex discipline dedicated to preserving the renal health of children battling cancer. The mechanisms of renal involvement are diverse, ranging from the direct infiltrative and obstructive effects of the malignancy to the profound and multifactorial toxicities of chemotherapy, radiation, and surgery. The developing pediatric kidney is uniquely susceptible to these insults, making the preservation of renal function as a critical component of comprehensive cancer care. Through a deep

understanding of the pathophysiological mechanisms of injury, the implementation of rigorous preventative and mitigative modalities during treatment, and a lifelong commitment to survivorship monitoring, the medical community can significantly reduce the burden of chronic kidney disease in this vulnerable population. As research continues to uncover novel biomarkers and genetic predictors of toxicity, the field will move closer to the eventual goal of maximizing curative outcomes while ensuring that the children who survive cancer are able to thrive with optimal renal health throughout their adult lives.

Conflicts of interest

The author declares that she has no competing interests.

Ethical issues

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the author.

Declaration of generative AI and AI-assisted technologies in the writing process

During the preparation of this work, the author utilized Perplexity to refine grammar points and language style in writing. Subsequently, the author thoroughly reviewed and edited the content as necessary, assuming full responsibility for the publication's content.

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