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A Review of Antineoplastic Agents Associated Nephrotoxicity, an Understood Complication

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Abstract

In the recent decades, the survival of children with cancer has improved dramatically. This improvement is due to use of different chemotherapeutic agents, but the majority of these drugs have kidney toxicities. Deterioration of renal function due to antineoplastic agents is the main limiting factor for administration of these drugs. Chemotherapeutic agents could result in an acute or chronic injury in glomeruli or tubules. Overall childhood cancer survivors have a nine-fold higher risk of developing kidney function impairment when compared with their sibling. In this review, the nephrotoxicity due to some chemotherapeutic drugs such as platinum agents, ifosfamide, methotrexate(MTX), doxorubicin, gemcitabine and imatinib have been discussed.

Keywords: Antineoplastic; Cancer; Chemotherapy; Nephrotoxicity.

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Introduction

In recent decades, the survival of children with cancer has improved dramatically. Nephrotoxicity is an important side effect of antineoplastic agents (1). The kidney toxicity of chemotherapeutic drugs may vary from subclinical impairment of renal function to overt kidney failure (2). The spectrum of renal function disorders in patients with cancer is wide and include acute kidney injury (AKI), kidney parenchymal infiltration, paraneoplastic glumerulopathies, reno-vascular disorders, fluid and electrolyte imbalance, tumor lysis syndrome and anti-cancer drug related nephrotoxicity (3). Kidney disorders in oncology patients can affect their immediate survival and also limit the adequate treatment of the underlying malignancy. The kidneys are the major elimination pathway for majority of chemotherapeutic agents and their metabolites. Kidney impairment can lead to delayed drug excretion and therefore increased systemic toxicity.

In the presence of renal function disorders, it is necessary to adjust the dose of many antineoplastic agents (4). However, the nephrotoxicity of chemotherapeutic agents can be avoided by volume repletion, hydration and not to use other drugs with nephrotoxic potential such as aminoglycosides. Prompt recognition of kidney toxicity of chemotherapeutic agents could allow clinicians for early intervention and thus prevention of adverse side effects (5). In this review, the nephrotoxicity of commonly used antineoplastic drugs in childhood cancers, have been discussed.

Clinical manifestations and pathophysiologic mechanism

It is important for oncologists to detect early signs and symptoms of kidney toxicity due to antineoplastic drugs. Also in majority of cases, small changes in serum creatinine are asymptomatic.

Four main clinical presentations have been reported: acute kidney injury (AKI), tubulopathies, nephritic/nephrotic syndrome and chronic kidney disease (6). Ifosfamide, cisplatin and carboplatin can effect on both glumeruli and tubules, but the pattern of tubulopathy differ between ifosfamide and platinum agents. The range of tubulopathy due to ifosfamide varies from hypophosphatemia to a fanconi syndrome; otherwise platinum compounds usually cause hypomagnesemia (7). Chemotherapeutic drugs such as bevacizumab and gemcitabine may cause renal vascular injury and consequently thrombotic microangiopathy (TMA). The manifestations of TMA include: microangiopathic hemolytic anemia, thrombocytopenia, hypertension, hematuria, proteinuria and finally AKI. Also nephrotoxicity due to MTX commonly occurs with high dose therapy (1-12 gr/m^2) and rarely with conventional dose. The mechanism of this toxicity is crystal nephropathy (8). The nitrosoureas such as carmustine or lomustine may lead to chronic tubulointerstitial nephritis. Also one of the common complications of cyclophosphamide is hemorrhagic cystitis (9).

Evaluation of kidney function in cancer patients

It is critical to remember that nephrotoxic potential of chemotherapeutic agents could be exaggerated in the presence of other disorders such as sepsis, heart disease or an underlying chronic insult (10). At first the most common method for assessment of renal function in cancer patients is estimation of glomerular filtration rate (GFR) based on serum creatinine, although the level of this marker may be falsely low in oncology patients. Low muscular mass, cachexia or fluid overload could result in a wrong estimation of GFR in these cases (4). Janus et al. in a study on 1218 patients with cancer have shown that 10.9% of patients had elevation of serum creatinine (≥1.2 mg/ 100 mL), but 64% had a GFR <90 mL/min/1.73m^2) (11). It is important to notify even mild elevation in serum creatinine, because at least 50% of kidney parenchymal loss must occur before detectable changes in creatinine level. Baseline screening tests even for asymptomatic cancer patients include serum electrolyte such as calcium, phosphorus, magnesium, BUN, creatinine and urinalysis. Also regular monitoring of blood pressure has a critical importance. In cases of progressive kidney dysfunction, proteinuria or hypertension, prompt referral to pediatric nephrologists has been considered (1). Al Tonbary et al. in a study on 34 children with various types of neoplasms, have demonstrated that cystatin c is a more sensitive marker than creatinine for evaluation of glomerular filtration rate during induction phase of chemotherapy (12). Bardi and their colleagues in another study on 200 children with leukemia or solid tumors have found that cystatin c increases significantly after cisplatin, methotrexate, cyclophosphamide, ifosfamide and multimodality treatment. These authors have recommended that cystatin c is a useful marker for evaluation of GFR in children with cancer (13). Pedrosa in a recent study in Brazil on 64 children have shown that urinary kidney injury molecule-1 (KIM-1) measured 24 hours after the beginning of drug infusion, can predict acute kidney injury in early phases in pediatric patients treated with platinum agents or methotrexate (14).

Cisplatin

Cisplatin is a chemotherapeutic agent which has been used extensively in many childhood solid tumors. Glomerular or renal tubular toxicity or both can occur during treatment with cisplatin or carboplatin. In many published articles nephrotoxicity of platinum agents has been shown (15-27). Nephrotoxicity occurs in 25% to 42% of patients treated with cisplatin. Kidera et al. in a study on 401 patients with cancer have reported that 32% of cases who have received cisplatin at a dose of at least 60 mg/m^2 developed kidney toxicity despite intensive hydration and mannitol (28). Higher dose of cisplatin results in high peak plasma free concentration and hence more severe nephrotoxicity. Previous chemotherapy with cisplatin, underlying kidney disease and concurrent treatment with other nephrotoxic agents such as aminoglycosides or non-steroidal anti-inflammatory drugs (NSAIDs) are other risk factors for cisplatin nephrotoxicity (29). Also dehydration and hypoalbuminemia can exaggerate cisplatin nephrotoxicity. Increased magnesuria and hypomagnesemia are early toxicities of cisplatin administration. 20% to 40% reductions of GFR following cisplatin treatment have been reported. Fujieda have shown elevation of urinary β_2–microglobulin during the first week of each cycle and then a prominent decline in the next course of treatment. Also these authors have shown increased

urinary excretion of albumin and IgG following the treatment with cisplatin (2). The onset of kidney failure after treatment with cisplatin is gradual and often occurring 3 to 5 days after exposure. Mild proteinuria (<500 mg/dL), glycosuria, enzymuria and marked urinary electrolyte wasting are other manifestations of cisplatin nephrotoxicity. Repeated exposure with this drug may lead to reduce GFR in a dose related pattern. Also radiotherapy results in intensification of cisplatin nephrotoxicity, (30). A number of drugs such as theophylline, spironolactone, allopurinol and gemcitabine have been reported to augment the nephrotoxicity of cisplatin (31). Various methods have been recommended to prevent or diminish cisplatin induced nephrotoxicity. The most important strategy is full intravenous hydration before and after administration of cisplatin (29). Also chemotherapy protocols with lower dose of cisplatin could decrease the nephrotoxicity of this agent without lowering the therapeutic efficacy in patients (32). One of the strategies which can reduce cisplatin induced nephrotoxicity is hydration with simultaneous serum mannitol before, during and after cisplatin administration (15). Santoso et al. have reported that saline alone or with furosemide has better renal protection in cisplatin nephrotoxicity compared with saline plus mannitol (33). Also antioxidants may have a role in protection against kidney toxicity of cisplatin. Hemati et al. in a study have shown that selenium and vitamin E have efficacy in diminishing oxidative toxicity of cisplatin (34). Moreover, delivery of anti–oxidants to mitochondria is another strategy for prevention of cispatin nephrotoxicity. Dimethylthiourea is one of these agents which could diminish toxic oxidative stress injury (35). Also amifostine (an organic thiophosphate) could reduce cisplatin induced nephrotoxicity (36). Administration of cisplatin results in magnesium depletion which increase nephrotoxicity of cisplatin. Therefore, magnesium supplementation is strongly recommended to diminish the kidney toxicity of cisplatin (29).

Carboplatin

Carboplatin is a chemotherapeutic agent which belongs to second generation platinum group with less nephrotoxicity compared with cisplatin. Almost 70% of administered dose have been excreted from kidneys and in patients with kidney dysfunction, dose adjustment is required. (2). Carboplatin could be used at doses 5 fold higher than cisplatin without evidence of nephrotoxicity or neurotoxicity. This agent binds DNA resulting in killing of dividing neoplastic cells (26). Carboplatin nephrotoxicity occurs less frequently and also milder than ciplatin (25). Rarely high dose carboplatin especially in conditioning may lead to chronic renal failure (37). High dose carboplatin similar to cisplatin could induce tubular injury (38). Like cisplatin, after carboplatin administration, hypomagnesemia may occur; hence magnesium supplementation during usage of this agent is recommended (39).

Ifosfamide

Ifosfamide is an alkylating agent of nitrogen mustard group. This drug has been used to treat many malignancies such as sarcoma and lymphoma in children. This agent and its metabolite, chloroacetaldehyde can cause proximal tubular injury and chronic renal failure. Ifosfamide administration may lead to hypokalemia, hypophosphatemia, metabolic acidosis, renal glycosuria and aminoaciduria (40). This drug may cause fanconi syndrome, which is proximal tubular defect. The principal manifestations of fanconi syndrome is due to generalized loss of reabsorption capacity, resulting in loss of glucose, sodium, potassium, bicarbonate, phosphate, aminoacids and proteins (41). Approximately in 1% to 4% of cases, administration of this drug leads to glomerular toxicity that can be presented either as acute or chronic renal dysfunction. Other manifestations of kidney toxicity due to this drug include: subclinical impairment of urinary concentration, nephrogenic diabetes insipidus, proteinuria and hypertension (41). Even with simultaneous use of uro-protectant mesna, administration of ifosfamide can lead to kidney damage (1). Berrak et al. have reported in 25% of patients under treatment with high dose ifosfamide, a reduction in GFR have been occurred (42). If cumulative dose of this drug was more than 60 to 100 gr/m^2, the risk of chronic ifosfamide toxicity increases. Also some factors such as age (<3–5 years), concurrent or previous platinum agents therapy, kidney radiation and unilateral nephrectomy or hydronephrosis could augment the ifosfamide renal toxicity. Moreover, this agent can cause sub clinical magnesium wasting (1).

Cyclophosphamide is another alkylating agent that has similar chemical structure with ifosfamide but

lesser nephrotoxicity. The metabolite of both of these drugs is acrolein and urinary excretion of this agent results in hemorrhagic cystitis. In order to prevent this complication, vigorous hydration with saline based fluids and mesna are strongly recommended (38). Furthermore, the kidney effects of ifosfamide persist after discontinuation of this drug (43). Lee in a case control study has shown that β_2-microglubuline can be used as on early indicator of ifosfamide – induced nephrotoxicity (44).

Methotrexate

Methotrexate (MTX) is a chemotherapeutic agent that has been used widely in different pediatric neoplasms such as ALL (acute lymphoblastic leukemia) and many solid tumors. However high dose MTX can cause kidney injury. MTX can be administered over a wide dose range ranging from 20 mg/m^2 per week in the maintenance phase of ALL to dose of 1000-33000 mg/m^2. High dose MTX must be administered with hydration and leucovorin rescue (45). Administration of high dose MTX may be associated with AKI and therefore leading to delayed clearance of MTX. Elevation of MTX level is a main risk factor for occurrence of severe mucositis, bone marrow suppression and even death. Treatment of high dose MTX induced kidney dysfunction and delayed MTX clearance is a medical emergency. Several strategies have been used for treatment of this life threatening complication. One of these methods is administration of high dose (HDL), but this modality of treatment alone could not prevent tissue toxicity (46).

Another approach is administration of glucarpidase which is an enzyme that converts MTX into inactive agent. Many authors recommend this drug as a standard treatment for high dose MTX associated kidney impairment and delayed MTX clearance. (47-50). Glucarpidase is indicated for the treatment of high MTX level in toxic range (>1 µmol/L) in patients with kidney function impairment. This drug was approved in USA in January 2012. However, this agent is expensive and is not available in most oncology centers (51). Also thymidine has been used for treatment of high dose MTX induced renal dysfunction (46).

In patients with MTX induced acute renal failure, charcoal hemoperfusion and then hemodialysis could reduce MTX level in serum and acts as a lifesaving procedure (40).

Vincristine

Vincristine is another Antineoplastic agent from Vinca alkaloid family. Vincristine has been used in many protocols for different childhood malignancies such as ALL, non–Hodgkin lymphoma and sarcomas (52). Vincristine and other vinca alkaloids may cause SIADH (Syndrome of inappropriate anti diuretic hormone secretion). Also an association between vincristine and DITMA (drug induced thrombotic microangiopathy), have been shown (53).

Nitrosoureas

Carmustine (BCNU) and lomustine (CCNU) have been used for treatment of childhood brain tumors. Streptozocin is the most nephrotoxic drug from nitrosoureas family, followed by semustin. These two drugs result in nephrotoxicity in 75% to 99% of patients, especially when high doses (>1400 mg/m^2) are administered. CCNN and BCNN cause nephrotoxicity in 10% of patients (9). Clinical finding due to nephrotoxicity of these drugs include hypophosphatemia, hypokalemia, hypouricemia, renal tubular acidosis (RTA), glycosuria, acetonuria, aminoaciduria and other manifestations of tubular dysfunction. Rarely streptozocin may induce acute renal failure and nephrogenic diabetes insipidus (54). Streptozocin may cause injury both the glomeruli and tubules and sometimes lead to a rise in serum creatinine level, which may be an irreversible finding (38). Also infusion of high dose of carmustine may lead to hypotension. Each 100 mg of reconstituted carmustine include 3 mL of ethanol. Therefore, use of high dose carmustine results in infusion of enough amount of ethanol to cause hypotension. The therapeutic strategies for infusion related hypotension includes administration of crystalloid fluid, vasopressor drugs and reduction the carmustine infusion rate (43).

Gemcitabine

Gemcitabine is a pyrimidine analog which is indicated in pancreatic carcinoma, bladder and lung cancer (38). Also in pediatric oncology this drug has been used for treatment of relapsed and refractory pediatric sarcoma (55). One of the manifestations of kidney toxicity of gemcitatine is hemolytic uremic syndrome (HUS). This complication is very rare but could be fatal. Therefore, patients on treatment with this drug should be monitored for signs of anemia, hemolysis, thrombocytopenia and renal failure. In

patients who are on treatment with platinum drugs, the risk of nephrotoxicity due to gemcitabine increase (9). The incidence of HUS due to gemcitabine is approximately 0.015% (38). Clinically, the first sign of this syndrome is hypertension that precedes the diagnosis by several weeks. The majority of patients who develop this complication have received gemcitabine for 3-5 months before (40). The mechanism of gemcitabine induced thrombotic microangiopathy (TMA) is due to endothelial injury and reduction of ADAMTS–13 (von Willebrand factor protease) activity (56). The kidney toxicity of gemcitabine is usually reversible after discontinuation of treatment (4). The role of therapeutic plasma exchange in treatment of gemcitabine – induced TMA is controversial (57). Also in some case reports, rituximab has a role in treatment of this complication (58, 59).

Doxorubicin

Doxorubicin (Adriamycin) is an anthracyclin agent which has been used extensively in treatment of many pediatric neoplasms. The main toxicity of anthracyctins is cardiotoxicity but nephrotoxicity should not be neglected (52). Although the main mechanism of doxorubicin nephrotoxicity is not clear, but proposed theories include free radical formation, membrane lipid peroxidation, protein oxidation and iron–dependent oxidative injury to macromolecules (60). In animal studies on rats have been reported that adriamycin causes an increase in plasma creatinine phosphokinase (CPK), LDH, urea and creatinine level (52).

Imatinib

Imatinib is a tyrosine kinase inhibitor which has been used in treatment of chronic mylogenous leukemia (CML). Also this drug has been used in ALL with positive chromosome Philadelphia. Gastrointestinal stromal tumors (GIST) and idiopathic hypereosinophilic syndrome (HES) (40). In many case reports have been shown that imatinib administration causes acute renal failure (61-63).

The principal mechanism of imatinib–induced nephrotoxicity is renal proximal tubules injury (40). Marcolin et al. in a study on 105 patients with CML have demonstrated that after imatinib therapy, 7% of patients developed acute kidney injury and 12% of them developed chronic renal failure (64). Other manifestations of imatinib associated kidney injury include thrombotic microangiopathy and fanconi syndrome (40). Also this agent may lead to hypophosphatemia (65). Therefore, monitoring of phosphate level during imatinib therapy is recommended. In majority of patients who have developed kidney function impairment with imatinib, discontinuation of this agent results in recovery of renal function (9). Dasatinib, a drug similar to imatinib may cause acute renal failure, requiring dialysis (66). Newer tyrosin kinase inhibitors with effect on vascular endothelial growth factor pathway such as sorafenib, valatinib and axitinib can lead to hypertension and proteinuria (9).

Conclusion

Many chemotherapeutic agents are cleared by kidney and therefore nephrotoxicity is an important limiting factor for administration of these drugs in cancer patients. Physician must be familiar with the nephrotoxicity of these agents, especially clinical and laboratory signs. Preventive and supportive strategies should be used, when possible, to prevent or diminish these side effects. Therefore, a close working relationship between pediatric oncologist and nephrologist strongly recommended in order to increase the survival of children with cancer.

Conflict of Interest

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