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Anticancer Drug–Induced Kidney Disorders

Incidence, Prevention and Management

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Abstract

Nephrotoxicity is an inherent adverse effect of certain anticancer drugs. Renal dysfunction can be categorised as prerenal uraemia, intrinsic damage or postrenal uraemia according to the underlying pathophysiological process. Renal hypoperfusion promulgates prerenal uraemia. Intrinsic renal damage results from prolonged hypoperfusion, exposure to exogenous or endogenous nephrotoxins, renotubular precipitation of xenobiotics or endogenous compounds, renovascular obstruction, glomerular disease, renal microvascular damage or disease, and tubulointerstitial damage or disease. Postrenal uraemia is a consequence of clinically significant urinary tract obstruction. Clinical signs of nephrotoxicity and methods used to assess renal function are discussed.

Mechanisms of chemotherapy-induced renal dysfunction generally include damage to vasculature or structures of the kidneys, haemolytic uraemic syndrome

and prerenal perfusion deficits. Patients with cancer are frequently at risk of renal impairment secondary to disease-related and iatrogenic causes.

This article reviews the incidence, presentation, prevention and management of anticancer drug-induced renal dysfunction. Dose-related nephrotoxicity subsequent to administration of certain chloroethylnitrosourea compounds (carmustine, semustine and streptozocin) is commonly heralded by increased serum creatinine levels, uraemia and proteinuria. Additional signs of streptozocin-induced nephrotoxicity include hypophosphataemia, hypokalaemia, hypouricaemia, renal tubular acidosis, glucosuria, aceturia and aminoaciduria. Cisplatin and carboplatin cause dose-related renal dysfunction. In addition to increased serum creatinine levels and uraemia, electrolyte abnormalities, such as hypomagnesaemia and hypokalaemia, are commonly reported adverse effects. Rarely, cisplatin has been implicated as the underlying cause of haemolytic uraemic syndrome. Pharmaceutical antidotes to cisplatin-induced nephrotoxicity include amifostine, sodium thiosulfate and diethyldithiocarbamate. Dose- and age-related proximal tubular damage is an adverse effect of ifosfamide. In addition to renal wasting of electrolytes, glucose and amino acids, Fanconi syndrome, rickets and osteomalacia have occurred with ifosfamide treatment.

High dose azacitidine causes renal dysfunction manifested by tubular acidosis, polyuria and increased urinary excretion of electrolytes, glucose and amino acids. Haemolytic uraemia is a rare adverse effect of gemcitabine. Methotrexate can cause increased serum creatinine levels, uraemia and haematuria. Acute renal failure is reported following administration of high dose methotrexate. Urinary alkalisation and hydration confer protection against methotrexate-induced renal dysfunction. Dose-related nephrotoxicity, including acute renal failure, are reported subsequent to treatment with pentostatin and diaziquone. Acute renal failure is a rare adverse effect of treatment with interferon-α. Haemolytic uraemic syndrome occurs with mitomycin administration. A mortality rate of 50 to 100% is reported in patients developing mitomycin–induced haemolytic uraemic syndrome. Capillary leak syndrome occurring with aldesleukin therapy can cause renal dysfunction. Infusion-related hypotension during infusion of high dose carmustine can precipitate renal dysfunction.

1. Renal Dysfunction in the Patient with Cancer

Nephrotoxicity is an inherent toxicity of certain anticancer drugs (table I). Impaired renal function also occurs subsequent to the infusion-related adverse effects of some anticancer agents. Renal dysfunction is a problematic adverse effect that can hinder continued administration of anticancer treatment, in addition to impeding the optimal use of ancillary and supportive medications and measures.

Renal dysfunction is generally classified as prerenal, intrinsic, or postrenal, according to the underlying pathophysiological cause of impairment relative to the kidneys. Prerenal uraemia is a consequence of renal hypoperfusion, which can occur secondary to hypovolaemia, low cardiac output, renal vasoconstriction, impaired autoregulation of renal blood flow and hyperviscosity syndrome. Characteristic laboratory findings include increased serum creatinine and blood urea nitrogen levels, and reduced urinary sodium excretion. The renal tubules remain intact and functional with rapid recovery of normal renal blood flow and glomerular ultrafiltration.[1] However, severe and prolonged renal hy-

Table I. Anticancer drugs with inherent nephrotoxicity

Alkylating and platinating agents
Chloroethylnitrosoureas
carmustine
semustine
streptozocin
Cisplatin
Carboplatin
Ifosfamise
Antimetabolites
Azacitidine
Gemcitabine
Methotrexate
Pentostatin
Miscellaneous
Diaziquone
Interferon-α
Mitomycin

poperfusion can promote intrinsic renal damage.[1,2] In addition to ischaemia, intrinsic renal damage can result from exposure to nephrotoxic xenobiotics, release of endogenous nephrotoxins, precipitation of xenobiotics or endogenous compounds within the renal tubules, renovascular obstruction, glomerular disease, renal microvasculature damage or disease, and tubulointerstitial damage or disease.[1]

Intrinsic renal dysfunction, which can develop in an insidious or fulminate manner, is evidenced by laboratory findings that correlate with the anatomic location and degree of damage.[1,2] Clinical signs of injury to the renal tubules includes electrolyte wasting, renal tubular acidosis, loss of urine concentrating ability and reduction in the rate of glomerular filtration. Glucosuria, amino aciduria, increased excretion of uric acid and increased excretion of small proteins can accompany tubular damage.[1] Fanconi syndrome is distinguished by generalised proximal tubular dysfunction with excess urinary excretion of serum sodium, bicarbonate, potassium, phosphorous, uric acid, amino acids and glucose. In fact, rickets or osteomalacia can evolve from severe and prolonged periods of hypophosphataemia and metabolic acidosis in patients with Fanconi syndrome.[3] Increased urinary excretion of alanine aminopeptidase, N-acetyl-β-D-glucosaminidase (NAG), α_1-acid glycoprotein, or β_2-microglobulin is used as a marker of proximal tubular lesions.[4-9] Disruption of glomerular integrity is distinguished by proteinuria. Increased urinary excretion of albumin, or immunoglobulin is used as a marker of glomerular damage.[7,10,11]

Postrenal uraemia results from mechanical obstruction of urine outflow. Clinically significant urinary tract obstruction occurs with obstruction of the urethra, bilateral ureteral obstruction or unilateral ureteral obstruction in a person with a single functioning kidney or chronic renal failure.[1]

Thorough assessment of renal function in adult and paediatric patients optimally includes concurrent evaluation of glomerular filtration, proximal tubular function and distal tubular function. This can be achieved through a battery of tests including measurement of serum chromium-51 ethylenediamine tetra-acetic acid (^{51}Cr-EDTA) clearance to assess glomerular filtration rate. Proximal tubular function is evaluated by means of fractional excretion of glucose, uric acid, calcium, phosphorous and magnesium. Determination of the renal threshold for phosphate, bicarbonate excretion and low molecular weight protein excretion are also used to gauge proximal tubular function. Urine osmolality and pH are used to evaluate distal tubular function. Combined with urinalysis for excretion of proteins, enzymes, cells, casts and sediment, the aforementioned tests provide a comprehensive picture of the extent and anatomic location of kidney damage.[12] Measurement of lithium clearance provides a useful tool to assess glomerular filtration and proximal tubular reabsorption of isoosmotic fluid.[13] In clinical practice, estimation of glomerular filtration rate using creatinine clearance is used extensively to assess renal function.

Creatinine clearance is optimally determined by a 24 hour collection of urinary creatinine, although collection times of 8 to 24 hours have been successfully utilised.[14-16] Although, the most expedient method routinely employed is calculation of creatinine clearance using 1 of several validated formulas that utilise patient-specific parameters, such as age, gender, body size and serum creatinine

level, for mathematical calculations based on the relationship between creatinine production and excretion.[14,16,17] Unfortunately, serum creatinine level, which represents the most readily accessible tool for calculation of creatinine clearance and assessment of renal function, does not always provide an accurate indicator of creatinine clearance in the patient with cancer.[18,19]

Reduction of serum creatinine level secondary to loss of muscle mass or limited protein intake can cause artifactual overestimation of creatinine clearance and glomerular filtration rate. Decreased muscle mass secondary to disease- or treatment-related effects reduces creatinine production with a subsequent reduction in serum creatinine level. Reasons for loss of muscle mass in the patient with cancer include decreased nutritional intake, cachexia, decreased physical activity, corticosteroid-induced myopathy and limb amputation.[20] The rate of glomerular filtration can be determined by several more stringent methods, including clearance of inulin, clearance of radioactive markers [^{51}Cr-EDTA, technecium-99metastable diethylenetriamine pentaacetic acid (^{99m}Tc-DTPA), technecium-99metastable mercaptoacetyltriglycine (^{99m}Tc-MAG3), ^{125}I-iothalamate, ^{131}I-diatrizoate] and clearance of radiocontrast agents (iothalamate, diatrizoate), although these tests are generally reserved for use in clinical research.[14-16,21]

Mechanisms of chemotherapy-induced renal dysfunction commonly include damage to vasculature or structures of the kidneys, haemolytic uraemic syndrome (HUS) and prerenal perfusion deficits. Since human kidneys are perfused with approximately 20% of the resting cardiac output,[22] these organs are extensively exposed to systemic xenobiotics. Subsequently, the kidneys are susceptible to injury by anticancer drugs that covalently bind crucial cellular proteins or seriously perturb metabolic function. HUS is characterised by the triad of anaemia, thrombocytopenia and acute renal failure. Anaemia is secondary to increased erythrocyte destruction and accompanied by reticulocytosis, schistocytosis and red blood cell fragmentation. In addition, serum lactate dehydrogenase level and direct bilirubin can be elevated secondary to red blood cell haemolysis. Coagulation tests including prothrombin time and activated partial thromboplastin time remain normal in patients with HUS. Additional findings include normal levels of fibrin degradation products and negative direct Coomb's test. Microangiopathic damage, which is characterised by fibrin deposition within the afferent arterioles and glomeruli, is generally a component of drug-induced HUS.[1,23] Chemotherapy-related prerenal perfusion deficits are generally secondary to administration of anticancer drugs that cause moderate to severe hypotension.

Patients with cancer are frequently at risk for renal dysfunction secondary to disease-related and iatrogenic factors. Renal dysfunction is part of the pathophysiological process of certain malignant diseases, such as multiple myeloma and renal cell cancer.[20] Patients with advanced prostate cancer or cervical cancer are at risk for disease-related postrenal obstructive uropathy.[1] In addition, hypercalcaemia, which is a consequence of multiple myeloma, and some advanced solid tumours, can precipitate renal dysfunction. Patients with multiple myeloma are also at risk for prerenal uraemia from hyperviscosity syndrome. Tumour lysis syndrome resulting from chemotherapy-induced cytolysis of certain malignancies with a high tumour burden and cellular turnover, such as high grade lymphomas, acute myelogenous leukaemias and acute lymphoblastic leukaemias, is another cause of renal impairment in the patient with cancer.[20] Moreover, the incidence of malignant disease increases as age increases [24]. Since a steady decline in glomerular filtration normally accompanies the aging process,[17] geriatric patients have a lower threshold for debilitating nephrotoxicity. As patients age they are also more likely to develop comorbid conditions such as hypertension, diabetes mellitus and heart failure that make the kidneys more vulnerable to injury.[25] In the paediatric patient, developmental changes occurring from term to 3 to 5 years of age effecting proximal tubular function and, to a lesser degree, glomerular function may increase the vulnerability of young kidneys to toxic insults.[26-28] The occur-

rence of sepsis-related hypotension, or the need for nephrotoxic antimicrobial therapy promote renal impairment in the patient with persistent febrile neutropenia following chemotherapy. Furthermore, renal failure is a component of disease- or regimen-related hepatorenal failure or multiorgan failure.[29]

Administration of nephrotoxic anticancer, ancillary and supportive care drugs is limited in the patient with renal impairment to reduce the likelihood of exacerbating deterioration of organ function. Moreover, administration of renally eliminated anticancer, ancillary and supportive care drugs is limited in the patient with renal impairment to reduce the likelihood of adverse effects from systemic drug accumulation. The decision to reduce drug doses, or interrupt therapy in the management of patients with cancer and renal dysfunction must always be made with respect to the ultimate goal of therapy and the patient's baseline health. Greater drug-induced toxicity is deemed acceptable during curative treatment of cancer versus palliative therapy or best supportive care. In addition, comorbid conditions can greatly impact the patient's ability to withstand adverse effects subsequent to anticancer drug therapy.

Clinical trials, clinical series and case reports describing the occurrence, pathophysiology, clinical presentation, prevention and management of anticancer drug-induced renal dysfunction were identified through a search of the English language literature from 1966 to 2000 using Medline. Search terms used included specific anticancer drug names, nephrotoxicity, haemolytic uraemic syndrome and renal failure. The purpose of this article is to review anticancer drug-induced renal dysfunction and approaches used to manage this adverse effect.

2. Nephrotoxicity of Anticancer Drugs

2.1 Alkylating and Platinating Agents

2.1.1 Chloroethylnitrosoureas

The chloroethylnitrosoureas carmustine, semustine and streptozocin are alkylating agents with activity against an array of tumour types. Delayed and protracted bone marrow suppression is generally the dose-limiting adverse effect of treatment with carmustine or semustine. Less commonly, pulmonary fibrosis occurs subsequent to treatment with these agents. In contrast, severe gastrointestinal toxicity can limit administration of streptozocin. Long term administration of chloroethylnitrosourea anticancer drugs can produce renal dysfunction. Renal dysfunction is common in patients receiving a cumulative carmustine or semustine dose of 1200 mg/m^2 or greater.[30-32] Renal impairment has been reported in 26% (7 of 27) patients receiving semustine ≥1400 mg/m^2 (200 mg/m^2 every 6 weeks) for treatment of malignant melanoma, and 99% (17 of 18) patients receiving carmustine or semustine ≥1400 mg/m^2 (200 mg/m^2 every 8 weeks) for the treatment of brain tumours.[31]

Common signs of chloroethylnitrosourea-induced nephrotoxocity include increased serum creatinine levels, uraemia and proteinuria.[30,31,33] An elevation of serum creatinine level is noted in most patients 1 to 24 months following completion of therapy with carmustine or semustine.[31,32] Increasing serum creatinine level during the course of therapy with semustine has preceded acute renal failure in 2 of 2 patients with malignant melanoma.[30] In addition to increased serum creatinine level, uraemia and proteinuria, signs of streptozocin-induced nephrotoxicity include hypophosphataemia, hypokalaemia, hypouricaemia, renal tubular acidosis, glucosuria, acetouria and aminoaciduria.[34,35] Hypophosphataemia, which has been observed after the first dose, is often the earliest sign of renal dysfunction from streptozocin.[34] Renal dysfunction from administration of carmustine, semustine, or streptozocin can continue to progress despite discontinuation of the chloroethylnitrosourea drug.[34] Haemodialysis has been required for the management of some patients with chloroethylnitrosourea-induced anuria and life-threatening electrolyte abnormalities.[30-32,36]

Pathological findings obtained from percutaneous biopsy or at autopsy included glomerular sclerosis, glomerular basement membrane thickening, focal areas of tubular atrophy, focal areas of interstitial necrosis, plus arterial and arteriolar sclero-

sis.[30-32,26] Pathological findings from patients with clinically severe renal dysfunction included widespread glomerular sclerosis and obliteration of capillary lumens.[31] Irregular and hyperchromic DNA has been observed in the nuclei of glomerular and tubular cells.[30,31] Animal studies reveal a correlation between semustine-induced nephrotoxicity with alkylation of renal tubular macromolecules.[37]

Ancillary treatments or antidotes useful for the reduction of chloroethylnitrosourea-induced nephrotoxicity have not been identified. Carmustine, semustine and streptozocin should be used with great caution in patients at risk for renal dysfunction. If possible, these agents should be discontinued in the patient with signs of acute renal dysfunction.

2.1.2 Cisplatin and Carboplatin

The platinating agents cisplatin and carboplatin have dose-related anticancer activity against a wide variety of tumour types. Substitution of chlorine constituents subsequent to aquation of cisplatin rapidly yields a reactive moiety that is responsible for the anticancer and toxic drug effects. The anticancer effect of this agent is secondary to DNA intrastrand crosslinking and adduct formation.[38,39] Cisplatin also forms chemical bonds with RNA and protein. Hydrolysis of carboxylato groups within carboplatin must precede aquation and evolution of the reactive cytotoxic species.[40,41] Dose-related nephrotoxicity is the prominent dose-limiting toxicity of cisplatin.[42] Although myelosuppression is the primary dose-limiting adverse effect of carboplatin, nephrotoxicity is the dose-limiting toxicity when this agent is used in high dosages with stem cell rescue and colony-stimulating factor support.[43,44]

A 20 to 40% reduction of glomerular filtration rate (GFR) following treatment with cisplatin is common. Reduction of mean GFR from 109 ml/min to 68 ml/min following three 21 day cycles of cisplatin 200 mg/m^2 (40 mg/m^2/day for 5 days) is reported.[10] GFR was assessed by measurement of serum ^{51}Cr-EDTA clearance. Interestingly, this study found a good correlation between ^{51}Cr-EDTA clearance and measured creatinine clearance before initiation of chemotherapy and 3 months or later following initiation of chemotherapy, with a poor correlation between ^{51}Cr-EDTA clearance and measured creatinine clearance during the periods immediately preceding or following actual chemotherapy administration. Moreover, during the actual treatment period serum creatinine level was a poor predictor of ^{51}Cr-EDTA clearance and tended to normalise despite reduced ^{51}Cr-EDTA clearance.[10]

Measurement of renal function in 22 paediatric patients (ages 1.3 to 10 years) receiving cisplatin 100 mg/m^2 every 21 to 28 days for neuroblastoma (n = 20) or malignant germ cell tumours (n = 2) revealed a mean reduction in GFR of 8% per cycle cisplatin.[19] Measured 24 hour creatinine clearance did not correspond closely with concurrent measurement of ^{51}Cr-EDTA clearance. Measured creatinine clearances varied from ^{51}Cr-EDTA clearance by a mean of 41% overall, and 67% in patients with GFR <60 ml/min. Moreover, a serum creatinine level within the normal range was a frequent finding in patients with regimen-related renal dysfunction. Additional cytotoxic drugs administered to patients with neuroblastoma included vincristine, cyclophosphamide and teniposide. Patients with malignant germ cell tumours also received bleomycin and vinblastine.[19]

Retrospective analysis of 22 patients with testicular cancer treated with 1 to 5 cycles of cisplatin-based chemotherapy reported a reduction in mean GFR from 137 ml/min to 106 ml/min. GFR was evaluated by serial measurement of ^{51}Cr-EDTA clearance.[45] Medical records of 17 patients indicated normalisation of GFR and improvement of renal function in respectively 12 and 18% of patients. Impaired renal function remained stable in 41% and continued to decline in 29% of patients. Patients received a cumulative cisplatin dose of 180 to 900mg.[45]

Measurement of creatinine clearance at 6 month intervals in 15 patients with testicular cancer receiving 3 or more cycles of cisplatin 100 mg/m^2 (20 mg/m^2/day for 5 days) repeated every 21 days re-

vealed a reduction in mean creatinine clearance from 112 ml/min to 68 ml/min during the initial 6 month period following initiation of treatment.[18] A corresponding increase in serum creatinine and blood urea nitrogen levels was reported. Additional chemotherapy administered included vinblastine and bleomycin.[18]

Kidney function throughout 3 cycles of high dose cisplatin was monitored in 30 patients (age 18 to 52 years) undergoing treatment for poor prognosis germ cell tumours.[46] The chemotherapy regimen included cisplatin 40 mg/m^2/day for 5 days, and etoposide 200 mg/m^2/day for 5 days. Patients received a cumulative cisplatin dosage of 800 to 1200mg. All patients had a normal rate of glomerular filtration (78 to 139 ml/min/1.73 m^2), as assessed by ^{51}Cr-EDTA clearance, at study entry. Mean plasma clearance of ^{51}Cr-EDTA decreased significantly, from 123 ml/min to 92 ml/min, after the first cycle of chemotherapy. GFR continued to decline throughout subsequent cycles of chemotherapy. The mean GFR 6 months following the initiation of chemotherapy, was 89 ml/min. Additional chemotherapy drugs administered included etoposide and bleomycin.[46]

Results of 1 study indicated that concurrent administration of aminoglycoside antibiotics increased the degree of cisplatin-induced renal impairment.[18] Furthermore, older patients demonstrate reduced clearance of total and unbound platinum, with increased severity of cisplatin-induced nephrotoxicity.[7,47]

Electrolyte abnormalities subsequent to cisplatin administration occur acutely and can persist for years following cessation of therapy. Hypomagnesaemia is a frequent adverse effect of treatment with cisplatin. In fact, hypomagnesaemia occurs more commonly following cisplatin than hypokalaemia, other electrolyte abnormalities, or acid-base disorders.[48-50]

The incidence of hypomagnesaemia is related to the cumulative cisplatin dose, and may be inversely related to the duration of each administration interval.[50] The incidence of hypomagnesaemia following cisplatin 50 mg/m^2 in combination with vincristine, cyclophosphamide, lomustine and doxorubicin for the treatment of lung cancer was 41% (11 of 27 patients) after the first cycle, 86% (12 of 14 patients) after the fifth cycle, and 100% (2 of 2 patients) following the sixth cycle of chemotherapy.[50] Hypomagnesaemia, coincident with increased renal excretion of magnesium, occurred in 30 of 30 patients (age 18 to 52 years) receiving a cumulative cisplatin dosage of 800 to 1200mg for the treatment of germ cell tumours. Decreased serum magnesium level was noted after the first cycle of cisplatin 40 mg/m^2/day for 5 days. Patients received concurrent etoposide and bleomycin.[46]

The mean cumulative dose of cisplatin precipitating persistent hypomagnesaemia in 10 of 22 paediatric patients (age 1 to 15 years) treated with various platinum-containing chemotherapy regimens was 500 mg/m^2.[48] Albeit, increased magnesuria and decreased serum magnesium level were detected soon after initiation of cisplatin therapy in each of the 22 evaluated patients. Chronic hypomagnesaemia, accompanied by a moderately elevated serum creatinine levels, was reported in 6 of 18 patients followed for a mean of 2.3 years after discontinuation of cisplatin. Chronic hypocalciuria and hypokalaemia were reported in respectively 5 and 1 of the 18 paediatric patients followed for a mean of 2.3 years after completion of treatment with cisplatin. Interestingly, this series failed to find a correlation between the total dose of cisplatin, or the duration of time from last cisplatin dose, and chronic hypomagnesaemia. Although comparison of patients receiving different doses and administration schedules of cisplatin may confound this issue.[48]

Proximal tubular damage, which is the initial toxic effect, is followed by disruption of glomerular filtration and impaired distal tubular function.[7,10] The character of acute kidney damage following administration of cisplatin 100 mg/m^2 to chemotherapy naive patients with squamous cell cancer of the head/neck or oesophagus has been evaluated by measurement of urinary α_1-acid glycoprotein, albumin and immunoglobulin G (IgG) ex-

cretion.[7] Increased excretion of α_1-acid glycoprotein provides a measure of proximal tubular injury,[6] whereas increased excretion of albumin and IgG represents disruption of glomerular filtration.[11] During the first 24 hours following drug administration, marked elevation of urinary α_1-acid glycoprotein was observed in 80% of patients (n = 10). Three weeks following cisplatin administration, the urinary excretion of α_1-acid glycoprotein decreased; however, it remained elevated above baseline in 67% of patients evaluated (n = 9). In contrast, urinary excretion of albumin and IgG increased modestly 24 hours following cisplatin administration in respectively 30 and 20% of patients (n = 10), with measurement of markedly increased urinary albumin and IgG excretion 3 weeks after drug administration.[7]

The anatomic location of kidney damage following administration of combination chemotherapy including cisplatin 200 mg/m^2 (40 mg/m^2/day for 5 days) repeated every 21 days to 30 patients with poor prognosis germ cell tumours has been evaluated by measurement of urinary excretion of β_2-microglobulin as a marker of proximal tubular damage[8] and IgG as a marker of glomerular damage.[10,11] The chemotherapy regimen also included etoposide and bleomycin. Analysis of urinary protein excretion before cisplatin administration, plus days 6, 9 and 16 of the chemotherapy cycle revealed a significant elevation of urinary β_2-microglobulin during the first week of each cycle with a subsequent decline during the second and third week of each cycle. Urinary excretion of albumin and IgG were increased significantly when measured day 9 of the first chemotherapy cycle. Urinary excretion of albumin increased in the same manner with the second cycle of chemotherapy, and remained elevated when measured prior to the third cycle of chemotherapy. The pattern of urinary IgG excretion was comparable to that of albumin, although the fluctuation did not reach statistical significance.[10] The findings of the aforementioned studies support acute proximal tubular damage followed by a progressive loss of filtration capability consequent to administration of cisplatin.

Saline-based hydration and diuresis are routinely utilised to minimise nephrotoxicity by reduction of renal drug exposure with dilution of cisplatin passing through the renal tubules and decreasing transit time.[51-53] As indicated by body size, cardiac function and renal function, infusion of 0.9% sodium chloride 1 to 4 litres within the 24 hour period of cisplatin administration is generally adequate to reduce nephrotoxicity. The goal of hydration is to maintain at least 125 ml/h (1.7 L/m^2/24h) of urine output.[53,54] Hypertonic saline (sodium chloride 3%) has been used to reduce cisplatin-induced nephrotoxicity. The protective effect of hypertonic saline may be secondary to an augmented chloride level which stabilises cisplatin and reduces evolution of the reactive aquated platinum species within the renal tubules.[55,56] Widespread use of hypertonic saline is limited by inconsistent findings of renoprotection,[54] and an increased risk of adverse effects relative to isotonic saline.

Mannitol is commonly administered as an ancillary medication to reduce cisplatin-induced nephrotoxicity. The protective mechanism is presumably conferred by drug dilution within the renal tubules secondary to expansion of urine volume by mannitol.[51,52,57] The utility of furosemide for reduction of cisplatin-induced nephrotoxicity is controversial;[53] however, this loop diuretic is commonly used to maintain adequate urine output during administration of ancillary vigorous hydration. Prompt repletion of serum magnesium level deficits and administration of supplemental magnesium reduce the risk of adverse effects from hypomagnesaemia. Administration of cisplatin as divided daily doses or a continuous infusion may reduce nephrotoxicity by decreasing the intensity by renal drug exposure.[58,59]

Pharmaceutical antidotes to cisplatin include amifostine, sodium thiosulfate and diethydithiocarbamate. Amifostine (WR 2721) is an organic thiophosphate prodrug that is metabolised to the sulfhydryl donor WR 1065. Preferential direction of WR 1065 to nonmalignant cells is influenced by the distribution of activating enzymes. Conversion is achieved by alkaline phosphatase enzymes which

are more prevalent on normal versus malignant cells. In addition to exposing the sulfhydryl constituent, cleavage of the phosphate group from amifostine markedly increases the drug's lipophilicity which facilitates intracellular distribution.[60,61] The nephrotoxicity of cisplatin is reduced with amifostine pretreatment. Administration of amifostine 740 to 910 mg/m^2 ≤15 minutes before cisplatin 100 to 120 mg/m^2 every 21 to 28 days for 5 to 6 cycles reduces the incidence of regimen-related nephrotoxicity.[62-64] Moreover, amifostine has not been shown to interfere with the anticancer effect of cisplatin, carboplatin, or other chemotherapeutic agents.[62-64]

The cyanide antidote, sodium thiosulfate, has been studied as an antidote for cisplatin-induced nephrotoxicity.[65,66] Sodium thiosulfate acts as a competitive ligand for aquated cisplatin molecules, subsequently it is capable of reducing drug-induced toxicity and anticancer activity.[66-68] Subsequently, the principal use of sodium thiosulfate has been as an intravenous infusion (4 g/m^2 bolus, followed by 2 g/m^2/hr for 5 to 12 hours) administered concurrently with intraperitoneal cisplatin (90 to 270 mg/m^2) to reduce regimen-related nephrotoxicity.[66,68] The incidence of renal dysfunction subsequent to intraperitoneal administration of cisplatin (100 to 200 mg/m^2) and concurrent intravenous infusion of thiosulfate is 2 to 4% of treatment courses.[68,69]

The disulfiram metabolite diethyldithiocarbamate, which is a chelating agent used as an antidote for heavy metal poisoning, has shown some promise as an antidote to cisplatin-induced nephrotoxicity in preclinical and clinical studies.[70,71] However, the clinical utility of this agent may be limited by adverse effects that occur frequently at doses necessary to confer renal protection. Common adverse effects observed with administration of diethyldiothiocarbamate include diaphoresis, chest discomfort, flushing, hypertension and anxiety.[71] Additional antidotes undergoing preclinical testing include an organic selenium containing compound known as ebselen, and the renal cortex uptake inhibitor betamipron.[72,73]

The maximum tolerated dose of carboplatin without stem cell transplantation is 1200 mg/m^2. Stem cell transplantation allows dose-escalation of carboplatin to 2.1 g/m^2, at which point nephrotoxicity, ototoxicity and hepatitis become dose-limiting.[74] Common signs of carboplatin-induced nephrotoxicity include increased serum creatinine levels, uraemia and electrolyte abnormalities. Extreme cases of renal failure may require haemodialysis for correction of serum electrolytes and fluid balance. Transient renal dysfunction occurs frequently, and irreversible renal dysfunction occurs infrequently following administration of high dose carboplatin.[43,75-81]

Evaluation of renal function in 23 children (age 0.4 to 15 years) treated with various regimens of carboplatin revealed decreased GFR, and decreased serum magnesium level subsequent to treatment.[82] The mean dose of carboplatin administered per cycle was 648 mg/m^2 (range 454 to 1194 mg/m^2). The median cumulative dose and dose intensity of carboplatin administered were respectively 2590 mg/m^2 (range 1364 to 7133 mg/m^2) and 169 mg/m^2/week (range 106 to 282 mg/m^2/week). The mean reduction of GFR, as assessed by measurement of ^{51}Cr-EDTA clearance, was 22 ml/min/1.73 m^2. The mean reduction of serum magnesium level following treatment was 0.17 mmol. In the majority of patients, GFR and serum magnesium level decreased most dramatically during the first month following carboplatin administration. Moreover, post-treatment changes in renal function and serum magnesium levels did not markedly improve or worsen at 6-, 12- and 24-month follow-up. Measures of renal toxicity that did not change markedly in this patient group included ionised serum calcium level, fractional excretion of magnesium, fractional excretion of glucose and urinary excretion of certain proteins [retinol binding protein, lactate dehydrogenase, alanine aminopeptidase, alkaline phosphatase, NAG]. Cumulative carboplatin dose was related to mean post-treatment reduction of serum magnesium level. Interestingly, carboplatin cumulative dose, calculated area under the concentration versus time curve, and dose intensity

were not shown to be statistically significant predictors of regimen-related renal dysfunction in this study.[82]

The area under the concentration time curve for carboplatin was calculated using the paediatric formula validated by Newell et al.[83] Additional nephrotoxins administered during or following carboplatin administration included high dose methotrexate (n = 3), aminoglycosides (n = 4), and amphotericin B (n = 4). All of the children had received carboplatin prior to study enrollment, although none had previous treatment with cisplatin or ifosfamide.[82]

High dose carboplatin (1 to 2.1 g/m^2) is generally administered in combination with other chemotherapy drugs such as ifosfamide, etoposide, melphalan, vincristine and cyclophosphamide.[43,75-81] Nephrotoxicity is reported with concurrent administration of high dose carboplatin and melphalan preceding autologous bone marrow transplantation for treatment of neuroblastoma. Vincristine and etoposide were also administered; however, these agents are not suspected of contributing to the regimen-related nephrotoxicity.

Acute renal failure occurred in 4 of 16 patients (age 16 months to 14 years) receiving carboplatin 1 g/m^2, melphalan 180 mg/m^2, vincristine 1.5 mg/m^2 and etoposide 250 mg/m^2 prior to autologous bone marrow transplantation.[84] Patients received all 4 chemotherapy drugs within a 6 hour period of time 2 days preceding the infusion of bone marrow. Glomerular filtration was assessed using ^{51}Cr-EDTA clearance before treatment, then 3 days, and 7 months following bone marrow transplantation. An increase in serum creatinine level was noted within 24 hours of chemotherapy administration in 4 of 16 patients. Serum creatinine level began to increase on the day of chemotherapy, or within 48 hours of chemotherapy administration for all patients progressing to acute renal failure. Three of 4 patients with acute renal failure required dialysis, individually for a period of 3 days, 14 days and 136 days. GFR was reduced by a mean of 24% in 10 patients evaluated 7 months following transplantation.[84]

WHO grade III to IV renal dysfunction occurred in 3 of 20 patients (age 2.5 to 12 years) treated with high dose carboplatin 1 to 1.75 g/m^2, melphalan 140 to 180 mg/m^2, vincristine 2 mg/m^2 and etoposide 1 g/m^2, divided over a 6 day period prior to autologous bone marrow transplantation.[85] Previous treatment for most of these patients included combination chemotherapy with cisplatin, vincristine, cyclophosphamide and etoposide or teniposide. In addition, combination chemotherapy including both carboplatin and ifosfamide increases the risk of renal dysfunction since each of these agents is inherently nephrotoxic. Vigorous saline-based hydration, 3 L/m^2/24h, with appropriate diuretic use to maintain fluid balance is utilised with high dose carboplatin to reduce the risk of regimen-related renal dysfunction.

Cisplatin has been implicated as the precipitating factor for HUS when administered as a single agent or in combination with bleomycin and vinblastine.[86-89] Onset of haemolytic uraemia after 4 courses of treatment with cisplatin (80 to 150 mg/m^2) has been reported.[86,87] Signs of HUS including increased serum creatinine level, uraemia, increased lactate dehydrogenase, anaemia, schistocytosis and platelet consumption have occurred 1 to 4 months following the last cisplatin dose.[86-89] Antemortem and postmortem pathological findings include cortical atrophy with focal necrosis, increased mesangial and capillary wall thickness, glomerular sclerosis and occlusion of afferent arterioles and glomeruli by fibrin thrombi.[87,88] Interventions used for the management of cisplatin-associated HUS have included red blood cell transfusions, plasma exchange, fresh frozen plasma, haemodialysis or peritoneal dialysis, aspirin (acetylsalicylic acid) and dipyridamole.[87,88]

Cisplatin and carboplatin should be used cautiously in patients at risk for renal dysfunction. Adequate saline-based diuresis and appropriate diuretic administration are crucial for reduction of cisplatin-induced nephrotoxicity with maintenance of proper fluid balance. Amifostine should be considered in patients at risk for renal dysfunction who require cisplatin therapy. Adequate saline-based di-

uresis and appropriate diuretic administration are important for reduction of platinum-induced nephrotoxicity and maintenance of proper fluid balance in patients receiving treatment with high dose carboplatin. If possible, alternatives to cisplatin or high dose carboplatin should be utilised in the patient at risk for drug-induced renal dysfunction.

2.1.3 Ifosfamide

Ifosfamide is metabolically activated to become an alkylating moiety with activity against a wide array of tumour types. Ifosfamide is used primarily for the treatment of certain solid tumours.

The dose-limiting adverse effects of ifosfamide include myelosuppression and haemorrhagic cystitis. Haemorrhagic cystitis is subsequent to urinary excretion of reactive metabolites capable of binding sulfhydryl constituents within proteins of bladder epithelium. Mesna and vigorous saline-based hydration are administered concurrently to reduce the incidence and severity of haemorrhagic cystitis.[90] Renal dysfunction can occur with ifosfamide treatment, particularly with long term and repeated administration. Although the exact underlying mechanism has not been elucidated, ifosfamide-induced nephrotoxicity is probably caused by reactive metabolites. Mesna does not confer protection against ifosfamide-induced nephrotoxicity.[91,92]

Cumulative ifosfamide dose exceeding 45 g/m^2 and patient age are the 2 greatest predictors of risk for development of nephrotoxicity.[91,93-96] The likelihood of renal dysfunction increases as the cumulative dose of ifosfamide increases.[91,93-96] In addition, the incidence and severity of nephrotoxicity is greater in patients younger than 5 years.[94,96] Evaluation of 174 paediatric patients (median age 8.7 years, range 0.4 to 21 years) receiving treatment with monthly ifosfamide (median cumulative dose 45.5 g/m^2, range 12.4 to 76.6 g/m^2) revealed that the median age of patients developing severe drug-induced nephrotoxicity was 2.2 years compared with 7.0, 8.2 and 10.5 years for patients experiencing moderate, mild and no nephrotoxicity, respectively.[96] Previous or concurrent administration of cisplatin increases the risk of nephrotoxicity.[91,93-97] In fact, increased cumulative cisplatin dose has been associated with increased severity of ifosfamide-induced renal dysfunction.[96] Administration of ifosfamide as a continuous infusion versus intravenous bolus does not have an apparent effect on the likelihood of nephrotoxicity.[98]

Signs of ifosfamide-induced nephrotoxicity include increased serum creatinine and blood urea nitrogen levels, oliguria and proximal tubular wasting of electrolytes, glucose and amino acids. Proximal tubular damage following administration of ifosfamide occurs more frequently than glomerular dysfunction.[96,97,99] Proximal tubular damage is also evidenced by increased fractional excretion of β_2-microglobulin, or increased urinary levels of alanine aminopeptidase, NAG and total protein.[4,5,73] In fact, ifosfamide-induced renal dysfunction can present as Fanconi syndrome, even including rickets or osteomalacia.[92,93,98,100-104] Uncommonly, ifosfamide-induced renal dysfunction may progress to the point of end stage renal disease requiring long term dialysis.[93] Fanconi syndrome occurs in 1 to 7% of children receiving repeated doses of ifosfamide.[99,105,106] Moreover, the renal effects of ifosfamide persist following discontinuation of therapy.

One year following treatment with ifosfamide 36 to 90 g/m^2 (cumulative dose) 22% (16 of 74) cisplatin-naive paediatric patients had renal abnormalities including Fanconi syndrome (n = 4), increased β_2-microglobinuria only (n = 7) and increased β_2-microglobinuria with impaired phosphate reabsorption (n = 5).[105] Fanconi syndrome and subclinical generalised tubulopathy developed in respectively 7 and 9% of 75 patients (median age 12 years, range 1 to 24 years) during a median of 31 months following treatment with various ifosfamide-containing chemotherapy regimens. Urinary excretion of amino acids and phosphorous became markedly increased in respectively 28 and 17% of patients. Aminoaciduria invariably preceded impaired phosphorous reabsorption. Severe renal dysfunction was heralded by impaired phosphorous reabsorption occurring early during the course of follow-up.[106] Eventual improvement of GFR and resolution of electrolyte wasting has been observed

over a period of 3 to 4 years following ifosfamide-induced Fanconi syndrome in a one-year-old patient treated with 2 cycles of ifosfamide 3 g/m^2/day for 2 days. The sole remaining renal abnormality was slightly increased glucose excretion. Radiographic evidence of rickets also resolved.[107] Chronic tubular dysfunction persisting throughout a period of 5 years is reported in 44% (7 of 16) and 25% (4 of 16) of patients with respectively severe and moderate ifosfamide-induced nephrotoxicity.[96]

Serum and urinary markers of ifosfamide-induced nephrotoxicity must be monitored in patients receiving repeated doses of this agent. Ifosfamide should be used cautiously in patients at risk for renal dysfunction, particularly those previously treated with cisplatin. If possible, ifosfamide should be discontinued in patients developing signs of moderate to severe acute renal dysfunction during therapy.

2.1.4 Mitomycin

Mitomycin, which is isolated from the broth of *Streptomyces caespitosus*, is an alkylating agent administered intravenously for the treatment of adenocarcinoma of the stomach, pancreas and colon. Historically, intravenous mitomycin has also been used for the treatment of advanced breast cancer.[108,109]

Renal dysfunction secondary to HUS occurs in up to 10% of patients receiving mitomycin for treatment of adenocarcinoma. Drug-induced microangiopathic haemolytic anaemia generally manifests within 5 to 12 months of initial treatment with mitomycin.[110-118] Patients receiving a cumulative dose of mitomycin exceeding 60mg are more prone to development of drug-induced HUS.[116] The syndrome generally persists and frequently worsens following discontinuation of mitomycin. Common pathophysiological effects include elevated serum creatinine level, uraemia, proteinuria, pulmonary oedema, anaemia, elevated lactate dehydrogenase and elevated total bilirubin levels, thrombocytopenia and hypertension. Most patients present with acute renal failure, and many ultimately require haemodialysis.[110-118] Circulating immune complexes, that can be separated into antibody and antigen components, are a prominent feature of mitomycin-associated HUS.[110,116] Reticulocytes and shistocytes are a common finding on the blood cell differential. Measures of coagulation, including prothrombin time, partial thromboplastin time and fibrinogen split products (fibrinogen degradation products) remain normal. Moreover serum haptoglobulin level is not decreased, and the direct Coomb's test is negative in patients with this syndrome.[108,111,113-117] The incidence of associated neurological effects, including seizures and cortical blindness, is 17 to 25%.[110,116,117] Mortality occurs in 50 to 100% of patients developing mitomycin-associated HUS. Mortality in this population is generally attributed to complications of renal failure, although death secondary to noncardiogenic pulmonary oedema following blood transfusions has been reported.[109,113,116,117]

Pathological findings at autopsy germane to renal dysfunction universally include fibrin deposition within the glomerular capillaries and afferent arterioles.[110,112,114,115,117] Areas of fibrinoid necrosis within the afferent arterioles and glomerular capillaries have also been described.[110] Arteriolar intimal hyperplasia, which can contribute to occlusion of blood flow, is a common finding. Additional pathological findings include thickening of the glomerular basement membrane, diffuse interstitial fibrin deposition, scattered areas of tubular atrophy and large atypical endothelial cell nuclei.[110,117,118]

Approaches to management of mitomycin-associated HUS have included staphylococcal protein A immunopheresis, plasma exchange, corticosteroids, heparin, aspirin, dipyridamole and suitable supportive care for related complications.[111-113,115,116,118] The goal of treatment with staphylococcal protein A immunopheresis, or plasma exchange is to remove or dissociate circulating immune complexes. Stabilisation of renal function, and improvement of thrombocytopenia and anaemia have been reported in 10 of 21 patients following staphylococcal protein A immunopheresis. Survival following onset of HUS was 6 months for patients treated with staphylococcal protein A

immunopheresis, in comparison to the median survival of 2.5 months (1 day to 17 months) for the cohort of 75 patients who did not receive comparable treatment.[115] Two case reports describe treatment of mitomycin-associated HUS with plasma exchange. Stabilisation of renal function, resolution of anaemia and thrombocytopenia, and improvement of neurological effects are described subsequent to plasma exchange. Unfortunately, improvement of renal dysfunction did not occur with either of these interventions.[110,111,116] Therapeutic benefit from administration of corticosteroids, heparin, aspirin, or dipyridamole has not been clearly demonstrated.[111,112,115,116,118]

Intravesicular mitomycin, which is indicated for the treatment of noninvasive bladder cancer, is not appreciably absorbed into the systemic circulation. Subsequently, adverse effects of intravenous mitomycin therapy, including nephrotoxicity, are not observed with intravesicular administration of this drug. Ancillary treatments or antidotes to mitomycin–induced nephrotoxicity have not been developed. Subsequently, mitomycin should be used with great caution in patients at risk for renal dysfunction. Mitomycin should be discontinued in patients with signs and symptoms of acute renal dysfunction, or microangiopathic haemolytic anaemia.

2.2 Antimetabolites

2.2.1 Azacitidine

The pyrimidine analogue azacitidine interferes with DNA, RNA and protein synthesis and function.[119] Myelosuppression is the primary dose-limiting adverse effect of this agent, although, the adverse effect profile of azacitidine also includes renal tubular toxicity.

Administration of azacitidine 200 mg/m^2/day for 5 to 7 days in combination with various other chemotherapeutic drugs produced polyuria, glucosuria, acidosis and hypophosphataemia in respectively 21, 27, 73 and 66% of 33 treatment courses administered to 22 patients.[120] Maximum urine output noted in patients developing polyuria was 4.2 to 16.5 litres per 24 hours. The median onset of polyuria was day 4 of chemotherapy, with resolution generally noted within 3 to 4 days of onset. Urinary excretion of glucose 0.3 to 8.g per day was measured in 3 of 8 patients exhibiting glucosuria in the presence of serum glucose levels <135 mg/dl. Inappropriate glucosuria was the sole sign of renal dysfunction in 2 patients. Nonanion gap acidosis appeared on day 2 to 3 of chemotherapy, and persisted for a median of 9 days. The contribution of renal tubular function to development of acidosis was evidenced by a coincident increase in urinary pH. Hypophosphataemia was noted concurrently with low serum bicarbonate levels in two thirds of hypophosphataemic patients. Moreover, hypophosphataemia occurred concurrently with low serum bicarbonate levels, polyuria and glucosuria in approximately one third of hypophosphataemic patients. Urinary excretion of amino acids increased 2- to 10-fold above normal in the 7 of 22 patients evaluated for aminoaciduria. Hypomagnesaemia, hypokalaemia and hypocalcaemia were observed during treatment with azacitidine, however, the magnitude and frequency of these electrolyte abnormalities were consistent with that anticipated for the aggressive hydration and ancillary antibiotics included in therapy. Electrolyte abnormalities secondary to drug-induced renal dysfunction contributed to the mortality of 2 (9%) patients treated with azacitidine.[120]

Antidotes or ancillary care to reduce azacitidine–induced nephrotoxicity have not been identified, subsequently, this agent should administered with great caution to patients at risk for renal dysfunction.

2.2.2 Gemcitabine

Gemcitabine is a pyrimidine analogue used for the treatment of certain solid tumours, including pancreatic cancer, bladder cancer and nonsmall cell lung cancer. Bone marrow suppression is the dose-limiting adverse effect of this drug. HUS is a rare adverse effect associated with its use. Based on adverse event reports from clinical trials and the manufacturer's safety data base, the estimated incidence of HUS is 0.015% in patients treated with gemcitabine.[121]

Acute uraemia, microangiopathic haemolytic anaemia and thrombocytopenia occurred in twelve patients treated with gemcitabine for pancreatic cancer (n = 6), nonsmall cell lung cancer (n = 4), gastric cancer (n = 1) and biliary cancer (n = 1). Eight of 12 affected patients (67%) required treatment with dialysis. Acute onset or worsening hypertension occurred in 7 (58%) of twelve affected patients. HUS-associated pulmonary symptoms and central nervous system symptoms were reported in respectively 6 (50%) and 4 (33%) of twelve affected patients. The median duration of treatment with gemcitabine was 5.8 months (range = 3.8 to 13.1 months). Signs and symptoms of HUS developed within 1 to 2 months of the last gemcitabine treatment in all patients. Two of 12 patients (17%) had previously received treatment with a mitomycin-containing regimen.[121]

Ancillary treatments or antidotes that effectively prevent or reduce the severity of gemcitabine-associated HUS have not be identified. Use of gemcitabine is not precluded by the potential for development of HUS because of the rarity of this adverse effect. However, since this adverse effect is frequently associated with a poor outcome, patients should be monitored for signs and symptoms of HUS during and for 3 months following completion of treatment with gemcitabine. Gemcitabine should be discontinued if signs of HUS develop.

2.2.3 Methotrexate

The dihydrofolate reductase inhibitor methotrexate is a widely used anticancer drug. Methotrexate dosages are classified as conventional dose (15 to 50 mg/m^2), intermediate dose (50 to 1000 mg/m^2), or high dose (1 to 12 g/m^2) therapy. Leucopenia is the dose-limiting adverse effect of methotrexate. Mucositis is also problematic, particularly following administration of intermediate or high dose methotrexate, or administration of any dose to the patient with moderate or severe renal dysfunction. Calcium folinate (leucovorin calcium) is generally administered following high dose methotrexate to reduce the severity of drug-induced leucopenia.[119]

Increased serum creatinine level, uraemia, dysuria and haematuria are reported with methotrexate administration. Acute renal failure has been reported following administration of high dose methotrexate. Nephrotoxicity occurs primarily with high dose methotrexate therapy; however, it can also occur with long term administration of conventional dose methotrexate.[122-124] Acute tubular necrosis subsequent to crystallisation of parent drug and the metabolite 7-hydroxymethotrexate within renal tubules is the purported underlying mechanism of methotrexate-induced renal dysfunction.[125-127]

The solubility of methotrexate in renal tubules is pH-dependant. Methotrexate is several-fold more soluble at pH 6.9 versus pH 5.7.[128] Urinary alkalisation is generally achieved with intravenous or oral administration of sodium bicarbonate. One approach to initiation of urinary alkalisation begins with continuous infusion of sodium bicarbonate in 5% dextrose solution, 0.5 to 1.5 mmol/kg/24h, with frequent urine dipstick analysis (every 4 to 6 hours) to maintain urinary pH > 7.[122] Oral administration of sodium bicarbonate (3g every 3 hours) has been used to alkalinise the urine of patients receiving high dose methotrexate.[129] Polycitrate solution, 1 to 1.5 mmol/kg/24h in divided doses, can also be considered as a tool for urinary alkalisation. Hydration and urinary alkalisation should begin 12 hours before infusion of high dose methotrexate, and continue for 48 to 72 hours.[128,129,130]

Adequate hydration and urinary alkalisation should be administered to patients receiving high dose methotrexate. Methotrexate should be used with great caution in patients with impaired renal function, and those at risk for renal dysfunction. In fact, dosage reduction or an alternative anticancer drug should be considered for patients with pre-existing renal dysfunction receiving treatment with methotrexate at any dosage range.

2.2.4 Pentostatin

Pentostatin modulates intracellular adenosine concentrations through irreversible inhibition of adenosine deaminase. Lymphoid tissue, circulating T cells and circulating B cells have an extensive compliment of adenosine deaminase enzymes.[119]

Subsequently, pentostatin has been used for the treatment of certain lymphocytic leukaemias and lymphomas including hairy cell leukaemia, chronic lymphocytic leukaemia and mycosis fungoides. Dose-limiting adverse effects of pentostatin include neurotoxicity and nephrotoxicity. Haematuria and dysuria have been associated with pentostatin treatment.[131,132]

Pentostatin-related nephrotoxicity is a dose-related adverse effect. Increased serum creatinine level and uraemia are common after treatment with pentostatin; however, the risk of drug-induced acute renal failure increases with administration of pentostatin >4 mg/m^2/week.[131]

Hydration with 5% dextrose injection or 0.45% sodium chloride injection 250 to 600 ml/m^2 before and 300 ml/m^2 following infusion of each pentostatin dose is recommended to reduce the risk of nephrotoxicity.[133] Pentostatin should be used with great caution in patients with impaired renal function, and those at risk for renal dysfunction. Dosage reduction should be considered when pentostatin must be administered to patients with impaired renal function. If possible, an alternative chemotherapeutic agent should be used for patients with or at risk for renal dysfunction.

2.3 Miscellaneous

2.3.1 Diaziquone

The synthetic aziridinylbenzoquinone diaziquone is a small lipophilic drug that is believed to exert an anticancer effect by crosslinking DNA strands. Myelosuppression is the dose-limiting adverse effect of diaziquone 28 mg/m^2/120h administered for the treatment of brain tumours, or acute leukaemias.[134,135] However, nephrotoxicity has been identified as the dose-limiting adverse effect following dose escalation of diaziquone.[136]

The maximum tolerated dose of diaziquone followed by autologous bone marrow transplantation is 245 mg/m^2/24h. Renal toxicity is the nonhaematological dose-limiting adverse effect. Diaziquone-induced nephrotoxicity commonly includes increased serum creatinine and uraemia occurring 9 to 16 days following administration of diaziquone ≥245 mg/m^2/24h. Nephrotoxicity is reported in 4 of 13 (31%) patients receiving diaziquone 245 to 355 mg/m^2/24h.[136] Anuric renal failure occurred in 3 of the 4 (75%) patients developing drug-induced nephrotoxicity. Anuric renal failure was heralded by an increase in serum creatinine level within 1 week of drug administration. All 3 patients developing renal failure were dialysed, and each died secondary to complications of renal failure. Proteinuria, occurring approximately 3 days following drug administration, is a frequent effect of diaziquone ≥125 mg/m^2/24h. Moreover, excess renal loss of phosphate, potassium, uric acid and glucose can accompany drug-induced proteinuria. Aminoaciduria and hyperchloraemic acidosis subsequent to diaziquone-induced renal tubular acidosis have been observed. In fact, Fanconi syndrome has been reported in 1 patient. Typically, signs and symptoms of diaziquone-induced renal toxicity resolve gradually.[136]

Ancillary treatments or antidotes that effectively reduce high dose diaziquone-induced nephrotoxicity have not be identified. Subsequently, high dose diaziquone should be used with great caution in patients at risk for renal dysfunction.

2.3.2 Interferon-α

The recombinant protein interferon-α exerts an anticancer effect against certain haematological and solid cancers following receptor-mediated cellular internalisation and degradation. The most frequent adverse effects of interferon-α include flu-like symptoms such as hyperpyrexia, chilling, slight tachycardia, malaise, myalgias and headaches. Fatigue and anorexia are also common complaints of patients treated with interferon-α.[137,138] Proteinuria is a common adverse effect, occurring in 15 to 20% of patients treated with interferon-α.[137-141] Uncommon adverse effects also include myelosuppression, nausea and emesis, diarrhoea, nephrotoxicity, hepatotoxicity and neurotoxicity.[137,138] Acute renal failure is a rare adverse effect of this drug.[137-142]

Acute renal failure has been reported in patients receiving various doses of interferon-α for treatment of solid tumours, lymphoid malignancies, hepatitis and hypereosinophilia. Interferon-α dosages

administered to patients developing acute renal failure include the following: 3 to 5 MU daily, 5 MU 5 times/week, and 18 MU 3 times/week. Signs of acute renal failure include uraemia and increased serum creatinine level, which are generally accompanied by proteinuria.[137-142] Haemodialysis may be required to manage interferon-α-induced renal failure.[142] Although normalisation of serum creatinine level generally occurs within weeks to months of drug discontinuation.[139-142]

Pathological evidence of renal dysfunction secondary to interferon-α consists of degenerative changes limited to the renal tubules,[142] or more extensive damage including interstitial nephritis, membranoproliferative glomerular sclerosis, focal segmental glomerular sclerosis and thrombotic microangiopathy, in addition to acute tubular necrosis.[139,142,143]

Patients receiving interferon-α should be monitored for signs of acute renal dysfunction. If possible, treatment with interferon-α should be discontinued with the onset of acute renal dysfunction.

2.4 Indirect Nephrotoxicity of Anticancer Drugs

2.4.1 Aldesleukin

Aldesleukin is a biological response modifier primarily used for the treatment of renal cell cancer. Renal dysfunction, which is related to the dose and duration of aldesleukin administration, is characterised by oliguria, increased serum creatinine and uraemia. Hypotension and bodyweight gain of 5 to 20% above baseline precede the changes in kidney function. Changes in kidney function generally occur within 24 to 48 hours of initiating therapy with high dose intravenous aldesleukin (600 000 IU/kg every 8 hours for 14 doses).[144-147] Signs of renal dysfunction tend to resolve within 1 week of drug discontinuation, and lasting tubular damage is unusual.[144,148]

Prerenal syndrome secondary to drug-induced changes in capillary permeability (capillary leak syndrome) with subsequent extravascular fluid distribution and accumulation promotes aldesleukin renal dysfunction. Subsequently, management includes supplemental crystalloid fluid administration and diuresis to expand intravascular volume and maintain urine output.[144-146,149]

Patients with an elevated serum creatinine level at baseline, history of nephrectomy, or hypertension at baseline are at increased risk of aldesleukin-induced renal dysfunction.[147,149] Moreover, persistent renal dysfunction following treatment with aldesleukin is reported more frequently in male patients than female patients.[147] Sepsis during therapy with aldesleukin increases the risk of chronic renal dysfunction following treatment.[147] Moreover, since there is a prerenal basis for this adverse effect, patients with impaired cardiac function or ascites prior to treatment are at increased risk for drug-induced renal dysfunction. If possible, antihypertensive medication should be stopped 24 hours preceding initiation and withheld for the duration aldesleukin administration. Aldesleukin should be used with caution in patients at increased risk for treatment-related renal dysfunction.

2.4.2 Carmustine

Indirect nephrotoxicity can occur following administration of high dose carmustine secondary to infusion-related hypotension.[150] Because each 100mg of reconstituted carmustine includes 3ml of absolute ethanol,[119] high doses (300 to 600 mg/m^2) deliver a sufficient amount of intravenous ethanol (12 to 23 g/m^2) to cause infusion-related hypotension. Although infusion-related hypotension generally resolves within a few hours after completion of carmustine administration, transient renal hypoperfusion can promote a transient increase in serum creatinine and blood urea nitrogen levels.[150]

Infusion-related hypotension is managed by administration of supplemental crystalloid fluid, reduction of the carmustine infusion rate by 50% and vasopressor administration. If possible, antihypertensive medication should be stopped 24 hours preceding and withheld on the day of carmustine administration. High dose carmustine should be used with caution in patients at risk for renal dysfunction.

3. Discussion

Successful treatment of malignant disease can be limited by the toxicity of anticancer drugs. The ability to effectively reduce and support certain acute adverse effects, such as bone marrow suppression and emesis, has progressed substantially during the preceding decades. Nonhaematological major organ toxicity still limits the utility of many anticancer drugs.

Progress has been made with the development of antidotes, such as amifostine and sodium thiosulfate, plus the effective use of saline-based hydration to reduce cisplatin-induced nephrotoxicity. Moreover, urinary alkalisation is a useful tool to minimise intratubular crystallisation of methotrexate. Otherwise, approaches used to circumvent drug-induced nephrotoxicity generally include appropriate and adequate hydration, *pro re nata* electrolyte repletion, plus avoidance of concurrent nephrotoxins and other renal insults. Hopefully, development of antidotes and ancillary measures for the prevention and management of drug-induced major organ toxicity will provide improved approaches to patient care in the future.

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