Review

Clinical review: Specific aspects of acute renal failure in cancer patients

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Abstract

Acute renal failure (ARF) in cancer patients is a dreadful complication that causes substantial morbidity and mortality. Moreover, ARF may preclude optimal cancer treatment by requiring a decrease in chemotherapy dosage or by contraindicating potentially curative treatment. The pathways leading to ARF in cancer patients are common to the development of ARF in other conditions. However, ARF may also develop due to etiologies arising from cancer treatment, such as nephrotoxic chemotherapy agents or the disease itself, including post-renal obstruction, compression or infiltration, and metabolic or immunological mechanisms. This article reviews specific renal disease in cancer patients, providing a comprehensive overview of the causes of ARF in this setting, such as treatment toxicity, acute renal failure in the setting of myeloma or bone marrow transplantation.

Introduction

Acute renal failure (ARF) is a serious complication of malignancies that causes substantial morbidity and mortality. Among critically ill cancer patients (CICPs), 12% to 49% experience ARF and 9% to 32% require renal replacement therapy during their intensive care unit (ICU) stay [1-5]. The risk for ARF seems higher in CICPs than in other critically ill patients [2,6]. In critically ill patients with cancer, acute renal dysfunction usually occurs in the context of multiple organ dysfunctions and is associated with mortality rates ranging from 72% to 85% when renal replacement therapy is needed [1,2]. Moreover, the recent report of Benoit and colleagues [2] suggest that cancer patients admitted with acute kidney injury requiring renal replacement therapy may have a better prognosis if bacterial infection is present at admission. Lastly, prognosis for this population seems to be worse than the prognosis for a control cohort of critically ill patients without malignancy receiving renal replacement therapy [2]. In addition to hospital mortality, development of an ARF may preclude optimal cancer treatment by requiring a decrease in chemotherapy dosage or by contraindicating potentially curative treatment (e.g., high-dose methotrexate in patients with recently diagnosed Burkitt lymphoma) [7].

Unresolved issues in this setting are similar to those in the overall population of patients with ARF, namely, the definition of ARF, the possible benefits from early dialysis, and the optimal dialysis dose.

Multiple causes leading to ARF in critically ill cancer patients are often present in combination (listed in Table 1). Although some of these causes are common to the general ICU population (sepsis, shock, aminoglycosides), some are related to the malignancy itself or to its treatment. Moreover, in several studies, critically ill cancer patients have been admitted with a newly diagnosed malignancy and are therefore at risk to develop such type of malignancy-related acute kidney injury [5,8,9]. A better knowledge of organ failure related to malignant disease may potentially lead to an improvement in these patients' outcomes.

The objective of this review is to describe specific aspects of renal disease in CICPs, to provide a comprehensive overview of the causes of ARF in this population, and to describe recent progress in the management of these complications, including treatment toxicity and bone marrow transplantation (BMT). Because prevention of ARF is mandatory, possible measures for its treatment in CICPs are also discussed.

Methods: search strategy

Combinations of key words related to acute kidney injury (e.g., acute renal failure, dialysis, hemofiltration, ICU) and cancer (e.g., cancer, malignancy, chemotherapy, BMT) were used to search the MEDLINE database and the Cochrane Group database. The last search was performed in February 2006. We checked the bibliographies of retrieved reports and reviews. We carefully checked the reviews and articles,

ARF = acute renal failure; BMT = bone marrow transplantation; CICP = critically ill cancer patient; ICU = intensive care unit; SOS = Sinusoidal obstruction syndrome; TLS = tumour lysis syndrome; TMA = thrombotic microangiopathy.

Table 1

Causes of acute renal failure in cancer patients

Pre-renal failure		Sepsis
		Extracellular dehydration (diarrhoea, mucitis, vomiting)
		Sinusoidal obstruction syndrome (formerly called hepatic veno-occlusive disease)
		Drugs (e.g., calcineurin inhibitors, ACE inhibitors, NSAIDs)
		Capillary-leak syndrome (IL2)
Intrinsic failure		
	Acute tubular necrosis	Ischaemia (shock, severe sepsis)
		Nephrotoxic agents (contrast agents, aminoglycosides, amphotericin, ifosfamide, cisplatin)
		Disseminated intravascular coagulation
		Intravascular haemolysis
	Acute interstitial nephritis	Immuno-allergic nephritis
		Pyelonephritis
		Cancer infiltration (e.g., lymphoma, metastasis)
		Nephrocalcinosis
	Vascular nephritis	Thrombotic microangiopathy
		Vascular obstruction
	Glomerulonephritis	Amyloidosis (AL, myeloma; AA, renal carcinoma or Hodgkin's disease)
		Immunotactoid glomerulopathy
		Membranous glomerulonephritis (pulmonary, breast or gastric carcinoma)
		IgA glomerulonephritis, focal glomerulosclerosis
Post-renal failure		Intra-renal obstruction (e.g., urate crystals, light chain, acyclovir, methotrexate)
		Extrarenal obstruction (retroperitonal fibrosis, ureteral or bladder outlet obstruction)

ACE inhibitors, angiotensin-converting enzyme inhibitors; NSAIDs, non-steroidal anti-inflammatory drugs.

focusing on acute kidney failure in the general ICU population. The most relevant articles were selected by the authors (MC, MD and EA) to give a concise and up-to-date overview of this problem.

Acute renal failure related to intra-renal or extra-renal obstruction

Acute tumor lysis syndrome

Tumour lysis syndrome (TLS) is a potentially life-threatening complication of cancer treatment in patients with extensive, rapidly growing, chemosensitive malignancies. TLS results from the rapid destruction of malignant cells, which abruptly release intracellular ions, proteins and metabolites into the extra-cellular space. ARF may develop, the most common mechanism being uric acid crystal formation in the renal tubules secondary to hyperuricaemia. Another cause may be calcium phosphate deposition related to hyperphosphataemia. TLS may occur spontaneously before treatment, but it usually develops shortly after the initiation of cytotoxic chemotherapy [10]. Although this syndrome typically occurs in patients with high-grade haematological malignancies, there have been anecdotal reports of TLS in a variety of other haematological malignancies, including low-grade non-Hodgkin's lymphoma and Hodgkin's disease, and it has also been reported in patients with fast-growing solid tumours, such as testicular cancer [11,12].

Early recognition of patients at high risk for acute TLS may allow the initiation of prophylactic measures. The clinical presentation, risk factors and prophylactic measures are described in Table 2. Non-recombinant urate oxidase (Uricozyme®) and, more recently, recombinant urate oxidase (Rasburicase®) have been shown to reduce uric acid levels, thereby diminishing the risk of uric acid deposition nephropathy [13]. Urine alkalisation, which was previously recommended to prevent uric acid precipitation within the renal tubules, has become controversial, since urate oxidase therapy considerably reduces the risk of uric acid precipitation, and urine alkalisation may induce calcium phosphate deposition [14].

Calcium phosphate crystal deposition has been reported to occur when the [calcium] × [phosphates] molar product exceed 4.6 [15]. Nevertheless, this study has a number of methodological weaknesses [15]. Therefore, we believe that renal replacement therapy should be started on an emergency basis when hydration fails to produce a prompt metabolic improvement or when ARF develops. Phosphate clearance is higher with sequential dialysis than with haemofiltration, but is frequently associated with a rebound effect after dialysis [16]. Therefore, we often use either repeated sequential haemodialysis or isolated sequential dialysis followed by continuous haemofiltration.

Table 2

Acute tumour lysis syndrome: associated malignancies, risk factors, clinical presentation and prophylactic treatment

Malignancies associated with TLS	
High risk	High-grade non-Hodgkin's lymphoma
	Acute lymphoid leukaemia
	Acute myeloid leukaemia
Intermediate risk	Myeloma
	Low-grade non-Hodgkin's lymphoma
	Small-cell lung carcinoma
Low risk	Medulloblastoma
	Breast or gastrointestinal carcinoma
Risk factors	Tumour spread
	Rapid tumour growth
	Chemosensitive tumour
	LDH >1,500 IU/l
	Hypokalaemia/hypophosphataemia
	Pre-existing renal failure
Clinical presentation	
Hyperkalaemia	Intracellular potassium release
Hyperphosphataemia	Intracellular PO_4^- release
	Calcium phosphate deposition
Hypocalcaemia	Calcium phosphate deposition
	Rarely symptomatic
Hyperuricaemia	Nucleic acid degradation
	Acute renal failure
Prevention	Volume expansion
	Urate oxidase if risk factor for TLS
	Urine alkalisation controversial
	Do not correct hypocalcaemia if asymptomatic
	If [calcium] × [phosphate] remains above 4.6 despite prophylactic measures, initiate renal replacement therapy
	Avoid correction of hypokalaemia or hypophosphoraemia before induction

LDH, lactate dehydrogenase; TLS, tumour lysis syndrome.

Cast nephropathy

Up to 50% of patients with newly diagnosed multiple myeloma have renal failure and up to 10% require dialysis [17]; renal failure is reversible in half of these patients (most of them having cast nephropathy) [18,19]. Several factors may cause renal failure in myeloma patients, with cast nephropathy the most common cause. The clinical presentation of cast nephropathy usually combines ARF and Bence-Jones proteinuria. Numerous casts are present in the renal tubules, which are formed when light chains bind to a specific peptide domain on the Tamm-Horsfall protein [17]; variations in CDR3 in both the κ and λ light chains influence binding [20]. Additionally, hypovolaemia, sepsis, urinary pH <7, or hypercalciuria may promote cast formation. The prevention and treatment of renal failure rests on fluid infusion, elimination of nephrotoxic compounds, urine alkalisation in patients with Bence-Jones proteinuria, and correction of hypercalcemia. Since it may transiently remove light chains, plasma exchange has been supposed to be beneficial in treating some patients with ARF. A recent large randomised study, however, found no conclusive evidence that five to seven plasma exchanges substantially reduce the death rate or dialysis dependence at 6 months [21].

Although renal failure has been considered to indicate a poor prognosis, several studies demonstrate that long-term survival can be achieved. Therefore, prompt evaluation of these patients for autologous stem cell transplantation should be performed, and dependency on dialysis is no longer considered a contraindication to autologous BMT [22,23].

Extra-renal obstruction

ARF can result from obstruction located within the kidneys (crystals and proteins) or downstream of the kidneys. The clinical manifestations vary with the site, degree, and rapidity of obstruction. Urinary findings are classically non-diagnostic, and renal ultrasonography remains the method of choice for investigating extra-renal obstruction. Obstructive uropathy may nevertheless be present without hydronephrosis, during the first few days, when the collecting system is encased in retroperitoneal fibrosis or tumour or when the obstruction is partial [24]. The relief of the obstruction, either by percutaneous nephrostomy or through a ureteral stent, is the cornerstone of treatment. Renal recovery depends on the severity and duration of the obstruction [24].

Thrombotic microangiopathy

The association between thrombotic microangiopathy (TMA) and cancer was first described in 1973 and is now well established. TMA may be associated with the cancer itself, with cancer chemotherapy, or with allogeneic BMT [25]. Thrombocytopenia with microangiopathic haemolytic anaemia (peripheral non-autoimmune anaemia with schizocytes) and no alternative diagnosis is considered sufficient to establish a presumptive diagnosis of TMA. In this setting, disseminated intravascular coagulopathy must be ruled out. The incidence of TMA associated with cancer is difficult to estimate because of possible confusion with disseminated intravascular coagulopathy; it may be as high as 5% [26]. Most of the cases occur in patients with solid tumours, the most common type being adenocarcinoma (stomach, breast and lung) [26]; however, TMA has been reported in patients with other solid tumours or haematological malignancies [25]. The pathophysiology of the TMA-malignancy association remains controversial, although many studies suggest an insult to the vascular endothelium. Nevertheless, recent studies have shown that disseminated cancer was associated with decreased ADAMTS13 activity, without anti-ADMTS13 antibody [27].

The link between TMA and cancer chemotherapy was first described with mitomycin C. Subsequently, TMA has been

reported with many anti-cancer agents, including gemcitabine, bleomycin, cisplatin, CCNU, cytosine arabinoside, daunorubicin, deoxycoformycin, 5-FU, azathioprine and interferon α [25].

Lastly, the association between TMA and BMT has been known since 1980. Although the prognosis has been described as poor, the clinical presentation is heterogeneous, with some patients having renal failure as the only manifestation and others experiencing remissions [28]. Typically, TMA starts 2 to 12 months after BMT and is unresponsive to plasma therapy [29]. Total body irradiation and graft-versus-host disease are the main factors associated with TMA in BMT recipients. Therefore, radiation nephritis may be a contributor, although cases of TMA related to cytomegalovirus infection have been reported [28,30].

The optimal treatment for this highly specific subtype of TMA is unknown. Plasma exchanges have been shown to improve prognosis in the general population of patients with TMA [31]. More recently, a study focusing on patients admitted into the ICU with severe TMA reported similar results [32]. Both these studies excluded patients with cancer related TMA, however, and the study of Penne and colleagues [32] excluded patients with TMA after BMT. Moreover, plasmatherapy is known to be rarely effective in this setting [29,33]. The recent guidelines of the British Society of Haematology did not recommend plasmatherapy in cancer-related TMA or in TMA after BMT [33]. Effective treatment for this group of patients is, however, lacking. Protein-A column immunoabsorption has been proposed as a possible treatment, without strong evidence of its effectiveness (the grade of recommendation by the British Society of Haematology is C) [33]. Causative factors should be looked for and antihypertensive treatment given. Lastly, in the absence of guidelines, we believe that plasma exchange should be proposed in patients with severe cancer treatment-associated TMA.

Renal toxicity related to cancer therapy

Renal toxicity of cancer chemotherapy

We will focus on nephrotoxic anticancer agents and on avenues for kidney protection. Three drugs are commonly associated with ARF, namely, cisplatin, ifosfamide and methotrexate.

Cisplatin-induced renal toxicity

Cisplatin is probably the most extensively studied nephrotoxic anticancer agent. Although direct tubular toxicity may cause ARF, cisplatin has also been associated with chronic dose-dependent reduction of the glomerular filtration rate [34]. The most widely used protective measure is saline infusion to induce solute diuresis. Cisplatin is usually administered in divided doses for 5 days. The maximum dose should not exceed 120 mg/m^2 body surface area, and renal dysfunction may require a dosage reduction. Repeated administration up to a cumulative dose of 850 mg was associated with a 9% reduction in glomerular filtration rate over a 5 year period, compared to a 40% reduction in patients given more than 850 mg [34]. Amifostine (inorganic thiophosphates) has been found to be effective in preventing renal failure, even after repeated exposure. Therefore, the American Society of Clinical Oncology stated that amifostine (910 mg/m^2) may be considered for the prevention of nephrotoxicity in patients receiving cisplatin-based chemotherapy (grade of recommendation A) [35]. Stevens-Johnson syndrome and toxic epidermic necrolysis have been reported in patients given amifostine.

Methotrexate

Methotrexate is widely used to treat cancer. High-dose methotrexate (>1 g/m^2) is part of the treatment of acute lymphoid leukaemia, high-grade lymphoma and sarcoma. These high doses are associated with a high risk of ARF due to precipitation of methotrexate or its metabolite, 7-OH-methotrexate, within the renal tubules. When ARF occurs, the resulting decrease in methotrexate clearance leads to extra-renal toxicity (neutropenia, hepatitis, orointestinal mucositis and/or neurological impairment). Thus, methotrexate toxicity may manifest as multiple organ failure [24].

Prevention of nephrotoxicity, together with methotrexate level monitoring, is crucial to prevent extrarenal methotrexate toxicity. During methotrexate infusion and elimination, fluids should be given to maintain a high urinary output and urinary alkalisation should be performed to keep the urinary pH above 7.5. Rescue with folinic acid (50 mg four times a day) should be started 24 hours after each high-dose methotrexate infusion and serum methotrexate concentrations should be measured every day. Patients are considered at high risk for methotrexate toxicity when serum levels are greater than 15 μM/l at 24 h, 1.5 μM/l at 48 h, or 0.5 μM/l at 72 h. Unless absolutely necessary, patients should not be given medications that inhibit folate metabolism (e.g., trimethoprim-sulfamethoxazole), exhibit intrinsic renal toxicity (e.g., non-steroidal anti-inflammatory agents and contrast agents), or decrease the fraction of methotrexate bound to albumin (e.g., aspirin). When all these measures were taken, the incidence of ARF was 1.8% in patients with sarcoma [36].

In patients with ARF, methotrexate removal by renal replacement therapy (peritoneal dialysis, haemodialysis, haemofiltration or haemoperfusion) has been used, with disappointing results. Although haemodialysis may achieve a 52% reduction in plasma methotrexate concentrations, post-dialysis rebound has been described [36]. Carboxypeptidase-G_2 is a bacterial enzyme that converts methotrexate into an inactive metabolite (2,4-diamino-N10-methylpteroic acid), thus providing an alternative route of elimination. Its use lowered plasma methotrexate concentrations to non-toxic levels (by 98% in 15 minutes), although rebounds (with an increase no greater than 10% in plasma methotrexate concentrations) occurred in 60% of patients [37]. Carboxypeptidase-G_2 and high-dose leucovorin have been tested in patients with methotrexate

intoxication and ARF, with similar results [38]. Therefore, no recommendations can be made concerning renal replacement therapy or carboxypeptidase-G_2 in this population.

Alkylating agents

The main anticancer agents responsible for haemorrhagic cystitis are alkylating agents, such as cyclophosphamide and ifosfamide. Maintaining a high urinary output and concomitantly administering the bladder epithelium protectant mesna virtually eliminated haemorrhagic cystitis related to the toxicity of anticancer agents [35,39]. However, several other toxic effects of these drugs have been described, including emesis, alopecia, myelosuppression and neurotoxicity. Moreover, ifosfamide has been associated with ARF or acute tubular dysfunction [40]. In a paediatric study, up to 22% of patients experienced either ARF or Fanconi syndrome [40].

Acute renal failure in allogenic hematopoietic progenitor cell recipients

ARF is among the most common potentially life-threatening complications in BMT recipients. Occurrence rates of 30% to 84% have been reported [30,41]. Sinusoidal obstruction syndrome (SOS; previously known as veno-occlusive disease of the liver) is the main cause of ARF in this setting [41]. This may explain why the incidence of ARF remains higher in allogeneic than in autologous BMT recipients [42,43]. A retrospective review showed that SOS was present in 90% of patients who experienced ARF in the early post-BMT period [41]. Nevertheless, BMT recipients are exposed to multiple risk factors for acute renal dysfunction, including toxicity from medications (e.g., amphotericin and aminoglycoside) and contrast agents, sepsis, and extracellular dehydration. These risk factors may increase the incidence or precipitate the development of ARF associated with a specific disease [44]. The prognosis of ARF remains ominous, with a reported mortality rate as high as 85% in patients requiring renal replacement therapy [41]. This grim prognosis seems related in large part to the association between ARF and severe SOS [30,44].

Marrow infusion toxicity (haemoglobinuria)

Overt haemoglobinuria due to marrow infusion develops in 75% to 100% of patients who receive cryopreserved marrow infusions [45,46]. Cryopreservation of harvested bone marrow is associated with erythrocyte disruption and requires the addition of dimethyl sulfoxide (DMSO), of which high concentrations may cause *in vivo* haemolysis during infusion [44]; however, haemoglobinuria due to marrow infusion rarely leads to ARF [44]. Although a classic complication, haemoglobinuria has become rare since the introduction of routine prophylactic volume expansion and improvements in cryopreservation and marrow infusion modalities [44].

Sinusoidal obstruction syndrome

Liver damage is a common complication of cytoreductive therapy and develops in 20% to 40% of BMT recipients [47].

Table 3

Factors associated with sinusoidal obstruction syndrome

Patient characteristics	Age
	Pre-existing liver disease
	Hormonal treatment
Conditioning regimen	Cyclophosphamide
	Total body irradiation
	Busulfan
	Carmustine
	Carboplatin
	Thiotepa
	Melphalan
	Gemtuzumab ozogamicin
Transplant source	HLA-identical non-related donor
	HLA mismatch donor
Infection or antibiotics	Cytomegalovirus reactivation
	Amphotericin during conditioning
	Acyclovir during conditioning
	Vancomycin during conditioning

The main site of liver damage in this setting is the hepatic sinusoid, and the resulting clinical syndrome is called SOS. Numerous risk factors for SOS have been identified (Table 3). Diagnostic and prognostic criteria are listed in Table 4. SOS early after BMT is the main complication leading to ARF [30,44]. Up to 55% of patients with SOS go on to experience ARF [44]. Most cases of SOS are clinically obvious, with jaundice, liver pain, oedema and ascites. These clinical manifestations may be associated with ARF mimicking hepato-renal syndrome, with normal kidney histology [41].

SOS can be classified as mild (clinically obvious, requires no treatment, and resolves completely), moderate (signs and symptoms require treatment but resolve completely), or severe (requires treatment but does not resolve before death or day 100). Severe SOS carries a bleak prognosis, with 98% mortality in a cohort study [47]. ARF, similar to any other organ failure, influences the prognosis of SOS. In patients with moderate SOS, diuretic therapy and/or analgesics are usually sufficient. In patients with severe SOS, the treatment rests on supportive care. No satisfactory specific treatments are available. Defibrotide (a polydeoxyribonucleotide with anti-ischemic, anti-thrombotic and thrombolytic properties) produced promising results in an open-label study but has not yet been investigated in randomised studies [48]. Thrombolytic therapy is of uncertain efficacy and carries a risk of fatal bleeding.

Viral infections

Viral infections are an emergent cause of ARF in BMT patients. Several studies confirm that ARF is associated with adenovirus, polyomavirus (BK virus or JC virus) and simian

Table 4

Diagnostic and severity criteria for sinusoidal obstruction syndrome

Diagnostic criteria	Hepatomegaly
	Sudden weight gain (+ 2% of body weight)
	Jaundice (total bilirubin >34 μmol/l)
	Right upper quadrant pain
	No other cause:
	Budd-Chiari syndrome
	Sepsis
	Heart failure
	Graft versus host disease
Other symptoms	Cytolysis
	Gall bladder wall thickening
	Portal hypertension
	Multiple organ failure
	Thrombocytopenia
Severe sinusoidal obstruction syndrome	Multiple organ failure
	Thrombocytopenia
	Cytolysis with ASAT or ALAT >750 IU/l
	Confusion or disorientation
	Maximum total bilirubin or severity of weight gain

polyomavirus. The well-documented association between the BK virus and haemorrhagic cystitis may explain not only the high incidence of haemorrhagic cystitis after BMT (20% to 25%), but also the occurrence of nephropathy [39,49]. The simian 40 virus was recently found in association with ARF and haemorrhagic cystitis [50]. Finally, adenovirus is associated with disseminated infections, encephalitis, pneumonitis and ARF [51]. To allow either a prompt reduction in immunosuppression or the initiation of antiviral therapy, the diagnosis of adenoviral disease must be made early. Polymerase chain reaction testing or enzyme-linked immunosorbent assay may help to achieve this goal [51].

Conclusion

ARF is a common and severe complication in CICPs. It results from various causes, including metabolic disturbances, renal infiltration by malignant cells, sepsis and drug-induced toxicity. Prevention of ARF is mandatory in CICPs. Fluid expansion and uricolytic treatment in patients with a high risk of acute TLS, prevention of contrast nephropathy, elimination of nephrotoxic drugs in high-risk patients, and monitoring of serum methotrexate concentrations are among the measures that may reduce the risk of ARF. Few studies have focused on ARF in CICPs and, therefore, supportive care in these patients did not differ from that in the overall population of ICU patients with ARF. Further studies are needed to improve the prognosis of these patients, to determine optimal treatments and to identify additional causative factors.

Competing interests

The authors declare that they have no competing interests.

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