Review Article

Preventing acute renal failure is crucial during acute tumor lysis syndrome

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Abstract

Tumour Lysis syndrome (TLS) is characterized by the massive destruction of tumoral cells and the release in the extracellular space of their content. While TLS may occur spontaneously before treatment, it usually develops shortly after the initiation of cytotoxic chemotherapy. These metabolites can overwhelm the homeostatic mechanisms and cause hyperuricemia, hyperkalemia, hyperphosphatemia and hypocalcemia. Moreover, TLS may lead to an acute renal failure (ARF). In addition to the hospital mortality induced by the acute renal failure itself, development of an ARF may preclude optimal cancer treatment. Therefore, prevention of the acute renal failure during acute tumor lysis syndrome is mandatory. The objective of this review is to describe pathophysiological mechanisms leading to acute tumor lysis syndrome, clinical and biological consequences of this syndrome and to provide up-to-date guidelines to ensure prevention and prompt management of this syndrome.

Key words: Acute renal failure, hyperkalemia, hyperphosphatemia, hyperuricemia, intensive care unit, leukemia, non-Hodgkin's lymphoma, urate nephropathy

Introduction

If clinical infection remains the leading cause of organ failure in critically ill cancer patients (CICPs), several reports point out the increasing proportion of patients with cancer admitted into intensive care unit (ICU) with organ failure related to the malignancy.[1-3] Some of these complications may be directly related to the extent of the malignancy. This may include, acute renal failure related to specific infiltration by non-Hodgkin's lymphoma or cancer, acute respiratory failure related to pulmonary leukemic infiltration or a bulky mediastinal tumor and coma that may be due to specific central nervous system involvement.[4-7] Most of these specific organ failures will require initiation of cancer chemotherapy along with the initiation of organ support. Our team and Benoit *et al* already demonstrate that it can be performed allowing a hospital survival superior to 50%.[2,3] Tumor Lysis syndrome (TLS) may occur spontaneously, as consequences of cancer chemotherapy initiation or even after a single dose of steroids.[8,9] This syndrome is characterized by the massive destruction of tumoral cells and the release in the extracellular space of their content.[8,9] Therefore, TLS may lead to the development of an acute renal failure which may, in itself, cause substantial morbidity and mortality.[10] Indeed, in the critically ill cancer patients acute renal dysfunction is associated with mortality rates ranging from 72% to 85% when a renal replacement therapy is needed.[11,12] Moreover, the association between TLS and acute renal failure will promote a dramatic increase of kaliemia and phosphatemia leading potentially to cardiac arrhythmia or sudden death.[8,9] Last and in addition to the hospital mortality associated with ARF, development of an ARF may preclude optimal cancer treatment by requiring a

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decrease in chemotherapy dosage or by contraindicating potentially curative treatment.[13]

Therefore, prevention of acute renal failure during acute tumor lysis syndrome is mandatory. The objective of this review is to describe pathophysiological mechanisms leading to acute tumor lysis syndrome, to describe clinical and biological consequences of this syndrome and to provide up-to-date guidelines to ensure prevention and prompt management of TLS.

Materials and Methods

Search Strategy: Combinations of key words related to acute renal failure (e.g., acute renal failure, dialysis, hemofiltration, ICU…), cancer (cancer, malignancy, chemotherapy, bone marrow transplantation…) and TLS (acute tumor lysis syndrome, TLS, "Tumor Lysis syndrome" [MeSH], hyperuricemia, hyperphosphatemia, urate nephropathy, nephrocalcinosis [MeSH]) were used to search the MEDLINE database, OVID database and the Cochrane Group database. The last search was performed in April 06. We checked the bibliographies of retrieved reports and reviews. We carefully checked the reviews and articles focusing on acute kidney failure in the general ICU population and the articles focusing on the critically ill cancer patients.

Most relevant articles were selected by the authors (GT, MD and EA) in a way so as to give a concise and an up-to-date overview of the problem.

Pathophysiology and Clinical Presentation

TLS occurs as results of a massive destruction of malignant cells both spontaneously and after initiation of cancer chemotherapy. While TLS may occur spontaneously before treatment, it however usually develops shortly after the initiation of cytotoxic chemotherapy.[14] Critically ill cancer patients with specific organ failure could be an exception to that rule. We recently described a 31% incidence of spontaneous TLS manifestations at ICU admission in a selected population of critically ill cancer patients.[3]

Massive cells destruction will lead to a rapid release of intracellular anions, cations and metabolic products of proteins and nucleic acids into the bloodstream.[15] As consequences of their high intracellular concentration, potassium, calcium, phosphates and uric acid will be released in the extracellular space. ARF may develop, the most common mechanism being uric acid crystal formation in the renal tubules secondary to hyperuricemia. Another cause may be calcium phosphate deposition related to hyperphosphatemia. While ARF leads to further increase in above describe metabolites, a vicious circle will therefore be initiated. Mechanisms and consequences of TLS are summarised in the Figure 1.

Uric acid

Malignant cells carry a large burden of nucleic acid products due to their high cellular activity and turnover. The release in the extracellular space of purine nucleic acid and their subsequent transformation into uric acid will lead to hyperuricemia.[16-18] Renal handling of this urate load involves free filtration at the glomerulus, partial proximal tubular reabsorption and distal renal tubular secretion.[19,20] Hyperuricemia is considered to be necessary for the development of urate nephropathy.[20] Indeed, uric acid is only poorly soluble in water and may therefore lead to crystals deposit. However, there is only a relatively poor correlation between the plasma urate levels and degree of renal dysfunction suggesting that additional factors may modify the rate of urate precipitation and the severity of the subsequent renal damages.[21] At least two additional mechanisms can be involved in this process. First, the uric acid pKa (5.4-5.7) is responsible of a further decrease in its solubility in presence of an acidic pH.[22] Urinary pH may have therefore accounted for the lack of correlation between urate level and ARF development. Second, variations in urinary flow are associated with high variations of tubular concentration of uric acid.[21] In presence of a low urinary flow and of an acidic pH, the threshold at which uric acid precipitates into crystals may

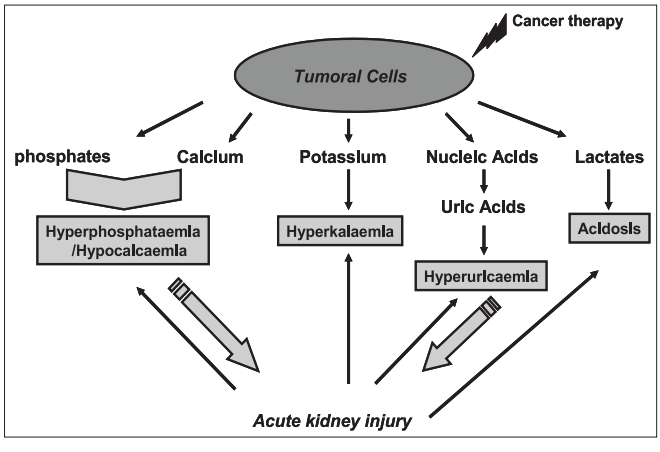

Figure 1: Pathophysiology of the tumor lysis syndrome

be reached leading to tubular obstruction.[21]

Hyperphosphatemia and hypocalcemia

Cell death will lead to the release of degenerated nuclear material, including nucleotides and phosphate. Malignant cells may contain as much as four times the intracellular phosphorous contained in a mature lymphocyte.[23] This large burden may saturate the renal capacity to excrete it. This phenomenon will be amplified in presence of a decrease urinary flow. The phosphates concentration will therefore raise leading to precipitation of calcium-phosphate crystals. These crystals will lead to nephrocalcinosis, urinary obstruction and tissue deposits. As consequences of the hyperphosphatemia and calcium-phosphates precipitation, hypocalcemia may appear. This hypocalcemia is only rarely symptomatic and do not require any treatment if asymptomatic.

Calcium phosphate crystal deposition has been reported to occur when the [Calcium] X [Phosphates] molar product exceed 4.6.[24] Nevertheless, the study suggesting this threshold had however number of methodological weaknesses and this cut-off must be interpreted with caution. In addition, hypocalcemia that appears as consequence of the calcium phosphate deposition will lead to an underestimation of the [Calcium] X [Phosphates] molar product.

Hyperkalemia

Potassium is known to be a predominantly intracellular ion. The large burden of potassium released as consequences of the cells destruction may overwhelm the renal excretion ability and lead to a hyperkalemia. Moreover, the potential acute renal failure or acidosis associated with the TLS may exacerbate this hyperkalemia. Last, it has been supposed that stress due to radiotherapy or chemotherapy may reduce ATP levels, resulting in leakage of potassium out of the tumor cells before complete lysis and therefore to an early peak in serum potassium concentration.[15]

Acidosis

Lactic acidosis as been retrieved in association with this syndrome and its extent is correlated with the severity of TLS.[25] Pathophysiological mechanisms leading to this lactic acidosis are probably multiple, including hepatic failure and tumor ischemia resulting from the poor neovascularization of the tumors.[26] However, it has been recently demonstrated that lactic acidosis can be caused by the loss of mitochondrial membrane potential during apoptosis.[25] Therefore, massive apoptosis of a tumor mass during cancer chemotherapy may lead to a lactic acidosis and may be a pathological event of the tumor lysis syndrome.

In addition, the high phosphates concentration in serum, in itself, provokes an additional metabolic acidosis.

Clinical presentation

Although TLS may be responsible of several symptoms, the biological abnormalities usually remain the preeminent consequences of this syndrome. Acute renal failure can lead to fluid overload and pulmonary edema; Hyperkalemia or hyperphosphatemia may lead to cardiac arrhythmia or sudden death; and last, calcium and phosphate abnormalities may lead to infrequent muscle cramps or seizures. However, in the great majority of the patients, these symptoms are the markers of very advanced tumor lysis syndrome and must be considered as a failure to prevent it or treat it aggressively. In addition to these clinical and life-threatening consequences, this delay will have an impact on the ability to offer complete remission to these patients, via the development of an acute renal failure.[13] Our aim should therefore be to identify patients at risk of acute TLS, in way to prevent or to treat TLS aggressively.

Risk Stratification

Early recognition of patients at high risk for TLS is mandatory and allows the initiation of prophylactic measures. TLS is classically described in patients with extensive, rapidly growing, chemosensitive tumours. This syndrome typically occurs in patients with high-grade hematological malignancies, especially high grade non-Hodgkin's lymphoma or both acute myeloid and acute lymphoid leukemia.[14,23,27-30] Classical risk factors include large tumor burdens, lactate dehydrogenase levels above 1500 IU, extensive bone marrow involvement and high tumor sensitivity to chemotherapeutic agents.[28] TLS has also been reported in patients with fast-growing solid tumours such as testicular cancer.[15,31] Additionally, several low grade hematological malignancies including chronic lymphoid lymphoma, solid tumors or myeloma have been described to be associated with TLS.[32-36] This may be at least partially due to the increasing efficiency of novel anticancer therapies. Several of the new

treatments (namely rituximab, bortezumib, thalidomide, tamoxifen or interferon α) have been associated with the development of TLS in low grade malignancies.[34-39] The wide spectrum of situations associated with TLS is listed in the Table 1.

Prevention and Treatment

The goal of the TLS treatment is to prevent acute renal failure, which may enhance dramatically TLS biological and clinical consequences. Since the development of a hyperkalemia remains uncommon in the absence of acute renal failure, two primary end-points can be delineated: the control of hyperuricemia and the prevention of nephrocalcinosis. If acute renal failure develops despite prevention, extra-renal therapy should be initiated quickly, aimed at clearance of uric acid and phosphate in way to limit further kidney impairment.[40] In addition, hypophosphatemia and hypokalemia might be present before cancer chemotherapy initiation. These abnormalities give evidence of a high tumour burden and of a high risk of TLS and should therefore not be corrected. Preventive measures are summarized in the Table 2.

Fluid expansion

Treatment's cornerstone remains the aggressive hydration through isotonic saline and the maintenance of a high urinary output allowing the urinary elimination of both uric acid and phosphates.[8,21,40] Moreover the volume expansion will decrease uric acid, phosphates and potassium serum concentrations.[9] If urinary output decreases despite adequate fluid intakes, diuretics have been proposed, sometime in addition with mannitol.[8] However, in our experience, diuretics are only poorly effective. Moreover, development of an oliguria indicates an acute renal failure and diuretics may delay the initiation of renal replacement therapy. Lastly, use diuretics may be far from innocuous in ARF.[41] We therefore believe that development of an oliguria despite fluid therapy might be a signal for the physician and leads to initiation of renal replacement therapy each time possible.

Urine alkalinization has initially been recommended, in way to promote urinary elimination of urate.[42] This treatment is nowadays controversial for three reasons. First, the availability of recombinant urate oxidase therapy considerably reduces the risk of urate nephropathy.[30,43] Second, urine alkalinization may induce calcium phosphate deposition.[44,45] And last, it has been long-recognized that a high tubular fluid flow is the primary mechanism of protection in acute urate nephropathy, when urine alkalinization seems to play only a minor preventive role.[21] Therefore, we believe that this poorly effective and potentially harmful treatment should not be recommended routinely anymore.

Hypouricemic agents

In addition to the hydration, several hypouricemic agents may reduce uric acid levels. Nonrecombinant urate oxidase (Uricozyme®), available in Europe from 1975 to 2002, was very effective but has been associated with high rate of allergic reactions. More recently, recombinant urate oxidase (Rasburicase) has been shown to reduce uric acid levels, thereby diminishing the risk of uric acid deposition nephropathy.[30,43] This agent transforms the uric acid into a compound five to 10 times more soluble in the urine: the allantoin.[8] Recombinant urate oxydase has been shown to decrease median uric

Table 1: Risk factors of acute Tumors Lysis syndrome

High risk malignancies	Intermediate and low risk	Anecdotal reports	Other risk factors
- High-grade non-Hodgkin lymphoma	Intermediate risk:	- Rhabdomyosarcoma[31]	- Tumor spread
- Acute lymphoid leukaemia	- Myeloma[33,34,36]	- Vulvar carcinoma[31]	- Rapid tumor growth
- Acute myeloid leukaemia	- Low-grade non-Hodgkin Lymphoma[48]	- Ovarian carcinoma[31]	- Chemosensitive tumor
	- Small-cell lung carcinoma[31]	- Thymoma[15]	- Lactates dehydrogenase >1500 IU/L
	Low risk:	- Soft tissue sarcomas[31]	- Hypokalaemia/ hypophosphataemia before treatment
	- Medulloblastoma[44]	- Metastatic seminoma[15]	- Preexisting renal failure
	- Breast or gastrointestinal carcinoma[31]	- Melanoma[39]	
		- Prostatic neoplasm[49]	
		- Hepatoblastoma[31]	
		- Hepatocarcinoma[37,50]	
		- Colonic carcinoma[50]	
		- Pheochromocytoma[50]	

Table 2: Prevention and treatments of the Tumour Lysis syndrome

Prevention and treatment of the Tumour Lysis syndrome
- Volume expansion
- Urate oxidase if high risk factor for Tumour Lysis syndrome, Al lopurinol otherwise
- Delete phosphate, potassium and calcium from perfusion
- If [Ca] x [Ph] remains above 4.6 despite prophylactic measures, initiate renal replacement therapy
Avoid:
• correction of hypokalemia or hypophosphoremia before induction
• Urine alkalization
• Correction of hypocalcemia, unless symptomatic
• Use of diuretics

acid concentration from 577 to 60 µmol/l within four hours of therapy.[29] Moreover, Recombinant urate oxydase has been shown to reduce significantly uric acid exposure time when compared to allopurinol.[30] Last, used in a population of adult patients with aggressive nonHodgkin's lymphoma, Recombinant urate oxydase allowed the control of plasma uric acid within 4h of injection and none of the patients developed hyperuricemia throughout the observation period.[43] In addition, in the same study, no patient experienced acute renal failure.[43] Although very effective, the recombinant urate oxydase is however also very expensive and its use should be limited to the prevention of TLS in high risk patients or treatment of established tumor lysis syndrome.[46] Moreover, Rasburicase is contraindicated in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency.[47] Indeed, recombinant urate oxydase causes excessive hydrogen peroxide production when breaking down uric acid and may lead to hemolysis in such patients.[47]

In patients with low or intermediate TLS risk, allopurinol can be used as hypouricemic agent. Allopurinol is a xanthine analogue that will decrease transformation of xanthine into uric acid.[30] However, if it may limit the risk of urate nephropathy in some patients, Allopurinol will also induce an increased xanthine and hypoxanthine serum concentrations. The solubility of these compounds is lower than that of uric acid and xanthine nephropathy may therefore develop.[45] This complication is however uncommon and allopurinol is still indicated in this population.

Prevention of nephrocalcinosis

The prevention of nephrocalcinosis relies on the treatment of hyperphosphatemia and the eviction of any calcium therapy, except for the uncommon manifestations of hypocalcaemia. Concerning the treatment of hyperphosphatemia, only few treatments can be proposed in addition to hydration. Oral phosphates binders have been proposed but are only poorly effective. The persistence of a hyperphosphatemia despite saline infusion should lead to initiate renal replacement therapy. Moreover, it is crucial for the physician to keep in mind that the coexistence of a hyperphosphatemia and of a hypocalcemia is the signature of calcium phosphate crystals deposition.

Indication and timing of the renal replacement therapies

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. In addition to metabolic control, renal replacement therapy allows to protect kidney from further injuries. Phosphate clearance is higher with sequential dialysis that with hemofiltration but is frequently associated with a rebound effect after dialysis.[9] Moreover, hemofiltration might be unable to produce an efficient metabolic control during the most severe TLS. Therefore, extended daily dialysis or isolated sequential dialysis followed by continuous hemofiltration should be the standard of care for TLS requiring renal replacement therapy. A study is currently ongoing to precise pharmacokinetic of cancer chemotherapies during renal replacement therapy.

Conclusion

TLS is a frequent and a life-threatening complication of the newly diagnosed malignancies. Both development of an acute renal failure or metabolic derangements may lead to ICU admission. It is critical for the physician in charge of the cancer patients to be able to recognize patients at high risk of developing TLS and to prevent it. Although the availability of uricolytic treatments has dramatically reduced the risk of urate nephropathy, calcium-phosphates crystals deposition may lead to acute renal failure and limit further cancer treatments. Therefore, when prevention measures do not allow a fast metabolic control, it is crucial to start renal replacement therapy on an emergency basis in way to allow an adequate renal protection. Further studies are needed to determine the optimal timing and modalities of the renal replacement therapy and to re-evaluate the risk factors of TLS.

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