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Review Article

Management of Pediatric Tumor Lysis Syndrome

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Abstract

Introduction: Tumor lysis syndrome (TLS) is a serious complication of malignancies and can result in renal failure or death.

Review: In tumors with a high proliferative rate with a relatively large mass and a high sensitivity to cytotoxic agents, the initiation of therapy often results in the rapid release of intracellular anions, cations and the metabolic products of proteins and nucleic acids into the bloodstream. The increased concentrations of uric acid, phosphates, potassium and urea can overwhelm the body's homeostatic mechanisms to process and excrete these materials and result in the clinical spectrum associated with TLS. Typical clinical sequelae include gastrointestinal disturbances, neuromuscular effects, cardiovascular complications, acute renal failure and death. Tumor lysis syndrome can also compromise the efficacy or administration of curative therapies. Available evidence suggests that the incidence of clinical TLS is approximately 3–7% for acute leukemias and 4–11% for lymphomas. Pediatric cancers are the leading cause of death by disease in children. The most common pediatric cancers include the leukemias, lymphomas, central nervous system tumors and neuroblastoma. Thus, TLS is a major concern to practitioners caring for pediatric oncology patients. Given the complexity of TLS prevention and treatment, a multidisciplinary approach involving the collaboration of medical oncologists/ hematologists and nephrologists has the greatest potential of ensuring optimal patient outcomes. Rehydration is fundamental in the management of TLS in addition to the current standard therapy for hyperuricemia which include rasburicase and allopurinol.

Conclusion: The early recognition and treatment of metabolic abnormalities often prevents the severe and life-threatening complications associated with tumor lysis syndrome.

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Introduction

Infection remains the leading cause of organ failure in critically ill cancer patients, but several reports point out the increasing proportion of patients admitted into intensive care units with organ failure related to the malignancy itself [1]. Some of these complications may be directly related to the extent of the malignancy. This may include acute renal failure, acute respiratory failure and coma. Most of these specific organ failures will require initiation of cancer therapy along with the initiation of organ support.

Tumor lysis syndrome (TLS) is characterized by a number of metabolic abnormalities that may arise from rapid and massive lysis of malignant cells and the concomitant release of intracellular contents into the blood stream. Metabolic abnormalities characteristic of TLS include abnormally high serum uric acid levels (hyperuricemia) resulting from the breakdown of purine-containing nucleic acids and major electrolyte imbalances such as hyperkalemia, hyperphosphatemia and hypocalcemia [2, 3].

TLS typically occurs after the initiation of anti-cancer therapies, including cytotoxic drugs, biological agents, corticosteroids, hormones and radiation therapy, in patients with hematologic malignancies or solid tumors that are highly sensitive to treatment. Rarely, TLS arises spontaneously as a consequence of increased tumor cell lysis before any definitive anti-tumor therapy has been initiated [2]. Diagnosis of TLS may distinguish between laboratory TLS, defined by specific abnormalities in the serum concentrations of uric acid and/or electrolytes, and clinical TLS, defined as laboratory TLS accompanied by symptomatic complications of the underlying metabolic imbalances [4]. Clinical manifestations of TLS typically

occur 12–72 hours after treatment initiation and may include renal failure, seizures, and cardiac arrhythmias [3, 5]. Because of the rapidity with which TLS progresses and the seriousness of common clinical consequences such as acute renal failure, TLS is associated with significant morbidity and potential mortality. Prevention of TLS relies on the identification of at-risk patients who would benefit from close monitoring and early implementation of prophylactic measures [4]. Given the complexity of TLS prevention and treatment, a multi-disciplinary approach involving the collaboration of medical oncologists/hematologists and nephrologists has the greatest potential of ensuring optimal patient outcomes. The key to the management of TLS includes awareness of its causes, identification of high-risk patients, implementation of appropriate prophylactic measures, vigilant monitoring of electrolyte levels in patients undergoing chemotherapy, and initiation of more active treatment measures when necessary.

Pediatric Considerations

TLS which occurs in both pediatric and adult cancer patients is considered as a potential oncologic emergency. TLS is a constellation of clinical signs and symptoms resulting from severe electrolyte and metabolic abnormalities that usually occur in response to cytotoxic chemotherapy. Pediatric cancers are the leading cause of death by disease in children. The most commonly occurring pediatric cancers include leukemias (25%), lymphomas (23%), central nervous system tumors (16.6%) and neuroblastoma (8% to 10%) [6]. Lymphomas seen in the pediatric population include both Hodgkin's disease and non-Hodgkin's lymphoma, such as Burkitt's lymphoma. Because TLS is most prevalent in patients with malignancies that are highly proliferative and that have a high tumor burden (most notably the lymphomas and leukemias), it is no surprise that pediatric patients with cancer are at significant risk for TLS during treatment.

The precise incidence of TLS is not known, however, like in the adult population, it appears to occur with the greatest frequency in patients with Burkitt's lymphoma and lymphoblastic lymphoma [7]. Although TLS does occur in pediatric patients with solid tumors, it is relatively uncommon. However, it has been documented in patients with stage IV neuroblastoma [8]. Thus, while it does not exclusively affect pediatric patients, TLS is a major concern to practitioners caring for pediatric oncology patients.

Pathophysiologic Characteristics

In tumors with a high proliferative rate, a relatively large mass and a high sensitivity to cytotoxic agents, the initiation of therapy often results in the rapid release of intracellular anions, cations, and the metabolic products of proteins and nucleic acids into the blood stream [9]. The increased concentrations of uric acid, phosphates, potassium and urea can overwhelm the body's homeostatic mechanisms to process and excrete these materials and result in the clinical spectrum associated with TLS [10].

Hyperuricemia and its associated complications are the most frequently recognized manifestations of tumor lysis syndrome, and predispose to many of the other clinical derangements. Hyperuricemia results from rapid release and catabolism of intracellular nucleic acids. Purine nucleic acids are catabolized to hypoxanthine, then xanthine, and finally to uric acid by xanthine oxidase [11].

Hyperphosphatemia results from the rapid release of intracellular phosphates from malignant cells, which may contain as much as four times the amount of organic and inorganic phosphates as normal cells [5, 12]. Hyperphosphatemia can lead to the development of acute renal failure after precipitation with calcium in the renal tubules during tumor lysis syndrome. The serum concentration of calcium rapidly decreases as precipitation with phosphate occurs. Hypocalcemia is one of the most serious clinical manifestations of TLS and has been associated with the developmentof severe muscle cramping, tetany, and cardiac arrhythmias. Hyperkalemia may also be a life-threatening consequence of tumor lysis syndrome. Hyperkalemia results from the kidneys' inability to clear the massive load of intracellular potassium released by lysed tumor cells. Neuromuscular signs and symptoms may include muscle weakness, cramps, paresthesias and possible paralysis. Cardiac manifestations may include asystole, ventricular tachycardia or fibrillation, syncope and possible sudden death [5, 8]. Increase in blood urea nitrogen and creatinine levels occur as a result of renal impairment associated with acute uric acid crystal nephropathy, calcium-phosphate crystals and nephrocalcinosis or a combination of both, leading to an acute obstructive uropathy syndrome. Acute clinical manifestations may include uremia, edema, hypertension, congestive heart failure and exacerbations of metabolic disturbances.

Incidence and Risk Factors

Most reports describing TLS portray patients with malignancies of hematopoietic origin, including leukemias and lymphomas. Determination of the incidence of TLS for specific leukemia and lymphoma subtypes is difficult because of differences among studies regarding patient populations analyzed and inconsistently applied definitions of TLS. Available evidence suggests that the incidence of clinical TLS is approximately 3–7%

for acute leukemias and 4–11% for lymphomas [13, 14]. However, certain subgroups of leukemia patients, such as those with mature B acute lymphoblastic leukemia (ALL) and Burkitt's lymphoma/leukemia, have been reported to have incidences of TLS as high as approximately 25% [15, 16].

Rare cases of TLS have been reported for patients with solid tumors characterized by high cell proliferation rate, large tumor burden or high chemo-sensitivity, with hepatic metastases being an additional risk factor [17, 18]. However, TLS derived from solid tumors generally is far more unpredictable than that caused by hematologic malignancies in terms of tumor characteristics and timing of occurrence. For instance, solid tumor-related TLS may arise despite low chemosensitivity of the neoplastic disease and may occur a few weeks after initiation of anticancer treatment [17, 18]. Because available data for TLS in patients with solid tumors are limited to individual case reports and small case series, the overall incidence of solid tumor-related TLS is difficult to quantify but appears to be low. However, mortality is high in cases of fully manifested clinical TLS related to solid tumors [17, 18].

The risk of TLS is influenced by a number of characteristics including the type of malignancy, the type and intensity of anti-cancer treatment, and the presence of pre-existing conditions including renal insufficiency. In particular, high-risk patients are those who have malignancies with high rates of cell turnover and are highly sensitive to chemotherapy. The neoplastic cells associated with such malignancies are characterized by high nucleic acid and phosphorus content and have active purine metabolism[19]. These characteristics are typical of certain hematologic malignancies, especially acute lymphoid leukemia and high-grade Non Hodgkin lymphoma (NHL) [20]. Burkitt's lymphoma has one of the highest rates of cell division of any human tumor, putting patients with this particular type of NHL among those with the highest risk of TLS [21]. In patients with high tumor burden or with highly proliferative solid tumors, there is also a risk of spontaneous or therapy-induced TLS [9].

A number of pre-existing conditions, in particular those linked with renal insufficiency and reduced clearance of uric acid, also increase the risk of TLS. These include dehydration, oliguria/anuria, preexisting hyperuricemia and acidic urine which reduces the solubility and clearance of uric acid [22].

Clinical Consequences of Tumor Lysis Syndrome

The clinical consequences of TLS-related hyperuricemia, hyperkalemia, and hyperphosphatemia are serious. Typical clinical sequelae include gastrointestinal disturbances, neuromuscular effects, cardiovascular complications, acute renal failure and death. Tumor lysis syndrome can also compromise the efficacy or administration of curative therapies [20].

Consequences of hyperkalemia

Hyperkalemia may appear from 6 to 72 hours after the initiation of chemotherapy [7] and is the most serious manifestation of tumor lysis syndrome. Potassium is generally concentrated intracellularly. Cell lysis results in the liberation of large amounts of intracellular potassium into the extracellular fluid. Chronic kidney disease, acute renal failure or concurrent acidosis may exacerbate hyperkalemia as the excretory capacity of the kidney can be overwhelmed by transcellular shifts due to potassium release from lysing cells as well as acidosis. Symptoms of hyperkalemia include weakness, paresthesias, muscle cramps, nausea, vomiting, diarrhea, and anorexia. Severe hyperkalemia (>7mEq/liter) can adversely affect skeletal and cardiac muscle function. Electrocardiographic changes include widening of the QRS complex and peaked T waves. Hyperkalemia must be corrected rapidly before potentially fatal ventricular arrhythmias occur.

Consequences of Hyperphosphatemia and Hypocalcemia

Hyperphosphatemia develops from 24 to 48 hours following initiation of chemotherapy [23]. Release of intracellular phosphate can exceed the renal threshold for phosphate excretion, leading to hyperphosphatemia. Malignant hematologic cells may contain up to four times more intracellular phosphate compared with normal mature lymphoid cells [13]. Additionally, acute destruction of tumor cells during chemotherapy prevents the rapid reuse of phosphate for newly synthesized tumor cells. Precipitation of calcium phosphate occurs when the solubility product of calcium and phosphate is exceeded, possibly leading to hypocalcemia. Muscle cramps, tetany, cardiac arrhythmia and seizures can result. Acute nephrocalcinosis or precipitation of calcium phosphate in the renal tubules with an inflammatory response, may lead to acute renal failure. Calcium and phosphate abnormalities should be identified and treated early [24].

Consequences of Hyperuricemia

Hyperuricemia develops from 48 to 72 hours following initiation of treatment [7]. Tumor cell lysis releases purine nucleic acids, which are metabolized into uric acid. Malignant cells carry a large burden of nucleic acid products due to their high cellular activity and turnover. The high turnover rate of neoplastic cells leads to ongoing DNA catabolism. The breakdown of purine nucleotides yields high amounts of hypoxanthine. Xanthine oxidase

catalyzes the conversion of hypoxanthine into uric acid. After spontaneous or cytotoxic therapy induced lysis, large amounts of uric acid are produced, leading to rapid increases in plasma and renal tubular concentrations of uric acid [13]. Hyperuricemia may lead to nausea and vomiting, oliguria or anuria, diarrhea, hematuria, and anorexia. Cardiovascular disease has also been linked with hyperuricemia [25]. However, acute renal failure represents one of the most frequent, serious clinical consequences of TLS and hyperuricemia [13].

Prevention and Treatment of Tumor Lysis Syndrome

Epidemiologic considerations

The potential severity of complications resulting from the development of TLS necessitates measures for prevention in high risk patients and prompts treatment if symptoms arise. Recognition of risk factors, close monitoring of at-risk patients and appropriate interventions are the key to preventing or managing TLS. General principles for the management of patients at risk of or presenting with TLS, after eliminating other potential causes for the metabolic abnormalities classically encountered in TLS, are aggressive volume repletion and/or expansion; therapy for hyperkalemia, hyperphosphatemia and secondary hypocalcemia; and prevention and therapy of hyperuricemia. These measures will have an impact on patient outcomes in general and kidney function in particular.

Comorbidities predisposing to higher risk of developing TLS are elevated pre-treatment serum uric acid level, pre-existing renal damage, tumor infiltration of the kidney, obstructive uropathy and advanced age [2, 26, 27].

Cytotoxic therapies more frequently associated withTLS are those employing highly active, cycle specific drugs (cytosine arabinoside, etoposide and cisplatin). Corticosteroids have often been implicated in the pathogenesis of TLS probably because they are used as primary therapy for highly proliferating lymphoid disorders. Less frequently, TLS has been reported after administration of intrathecal methotrexate, monoclonal antibodies (rituximab), radiotherapy, interferon, hydroxyurea and imatinib. It has rarely been described also as a spontaneous event [28].

TLS occurs most commonly in Burkitt's lymphoma, lymphoblastic lymphoma, B-cell acute lymphoblastic leukemia (ALL) and T-cell ALL with hyperleukocytosis and extensive extramedullary disease because of a high proliferative fraction, large tumor burden or wide dissemination and high chemo-sensitivity [15, 29].

Incidence and complications of TLS has been analyzed by Wossmann*et al* in 1,791 children with NHL [14]. Patients with Burkitt's lymphoma or B-ALL had a higher incidence of TLS (8.4%) and anuria (4.4%). In particular, patients with B-ALL had the highest risk of developing a TLS (26.4%) and anuria (14.1%). The incidence of TLS was 19.1% for patients with LDH levels >1,000 u/l. TLS has also been documented in childhood solid tumor such as neuroblastoma, medulloblastoma and germ cell tumors [30].

Fluids and Hydration

Supportive care should be implemented immediately to prevent delay in the initiation of cytotoxic therapy, which should be started as soon as it is safely possible. Volume depletion can further increase the risk of uric acid and calcium-phosphate precipitation. Volume repletion/ expansion is one of the most important interventions in patients at risk of or with TLS because it maintains renal blood flow and urine flow, promoting urinary excretion of potassium, uric acid and phosphate [31].

Aggressive hydration and diuresis are fundamental to the prevention and management of TLS. The combination of hydration and enhanced urine flow promotes the excretion of uric acid and phosphate by improving intravascular volume, renal blood flow, and glomerular filtration [29, 32]. The use of diuretics may also be necessary to maintain adequate urine output, but use of diuretics is contraindicated in patients with hypovolemia or obstructive uropathy.

Pediatric patients should receive 2 to 3 liters/m2/day (or 200 ml/kg/day if weight ≤10 kg; volume adapted to patient age, cardiac function, and urine output) intravenous (IV) solution consisting of half of normal saline / 5% dextrose. Urine output should be monitored closely and be maintained within a range of 80 to 100 ml/m2/hour (4 to 6 ml/kg/hour if weight ≤ 10 kg) [2]. If there is no evidence of acute obstructive uropathy and/or hypovolemia, diuretics may be used to maintain output within this range if necessary. Because of the concurrent risks of hyperkalemia, hyperphosphatemia, and/or calcium phosphate precipitation, potassium, calcium and phosphate should be withheld initially from hydration fluids.

Patients with oliguria that is not believed to be caused by volume depletion or is unresponsive to volume expansion should have an immediate evaluation by a nephrologist. This will permit a full evaluation for the potential presence of acute kidney injury (AKI) and identify the best therapeutic options based on volume status and other clinical and laboratory parameters. It will help also in deciding the role of diuretics and potential benefit of converting an established oliguric AKI to non-oliguric

AKI as this may permit temporary management while renal replacement therapy is being considered.

Urinary Alkalinization

Solubility of the purine catabolism metabolites xanthine, hypoxanthine, and uric acid in urine differs and is dependent on urinary pH [33]. Uric acid solubility is low and increases as urinary pH becomes more alkaline. Although hypoxanthine is soluble, xanthine solubility increases to a much lesser degree in alkaline urine given its higher pKa (log of dissociation constant for anacid) compared with uric acid [34].

The goal of urinary alkalinization is to maintain urinary pH at 7.0 to enhance uric acid solubility, therefore promoting its excretion. This can typically be achieved by adding 20-75 mEq/liter of IV sodium bicarbonate or a bolus with 0.5-1.0 mEq/kg for urine pH <7.0. Historically, urinary alkalinization has been recommended during treatment with allopurinol. Urinary alkalinization is not required with the use of rasburicase because the action of urate oxidase converts uric acid to allantoin, which is highly soluble and not dependent on urinary pH. Routine urinary alkalinization has recently become more controversial and possibly contraindicated [4, 33]. Levels of hypoxanthine and xanthine may be increased in patients treated with allopurinol and, as mentioned, urinary alkalinization does not significantly improve xanthine solubility. In addition, calcium phosphate is more soluble at an acidic pH; therefore, urinary alkalinization may lead to increased calcium-phosphate crystallization and precipitation. There is also the risk of developing metabolic alkalosis, especially if the glomerular filtration rate (GFR) is compromised. These limitations and associated risks have led experts in the field not to recommend urinary alkalinization [4, 33]. Alkalinization may be considered in patients treated with allopurinol who have moderately increased uric acid levels, but no associated hyperphosphatemia.

Allopurinol

One approach to preventing or managing TLS associated hyperuricemia is to block the conversion of xanthine and hypoxanthine to uric acid. Allopurinol is a xanthine analog which, when converted in vivo to oxypurinol acts as a competitive inhibitor of xanthine oxidase, thereby blocking the conversion of the purine metabolites to uric acid [35]. Use of allopurinol has been shown to decrease the formation of uric acid and to reduce the incidence of obstructive uropathy caused by uric acid precipitation in patients at risk for developing TLS [35]. In pediatric patients, allopurinol is administered at a dose of 50 to100 mg/m^2 every 8 hours orally (maximum dose, 300 mg/m^2/day) or 10 mg/kg/day divided every 8 hours (maximum dose, 800 mg/day). For patients unable to take allopurinol orally, IV administration may be considered, at a dose of 200 to 400 mg/m^2/day in one to three divided doses (maximum dose, 600 mg/d) [36].

Non-recombinant Urate Oxidase (uricozyme)

A second approach to the management of hyperuricemia is to promote the catabolism of uric acid. In most mammals, there exists an enzyme, urate oxidase, that converts uric acid into allantoin, which is five to 10 times more soluble in urine than uric acid [37]. However, this enzyme is not present in humans because of a nonsense mutation in the coding region. A non-recombinant form of urate oxidase with a high specific activity was initially isolated from Aspergillus flavus [38].

Kissel *et al* [39] reported results of a phase I/II study in 61 adults demonstrating that non- recombinant urate oxidase at a dose of 800 U/day reduced uric acid levels in the blood and increased allantoin excretion. A second study by Masera *et al* [40] demonstrated the efficacy of non-recombinant urate oxidase in 30 pediatric patients with leukemia. Toxicities included allergic reactions and methemoglobinemia or hemolytic anemia in patients with a deficiency of the glucose-6-phosphate dehydrogenase (G6PD) enzyme [41].

In a study of 134 pediatric patients treated with non-recombinant urate oxidase from 1994 to 1996, Pui *et al* [42] reported that when compared with historical control patients treated with hyperhydration and allopurinol, non-recombinant urate oxidase led to more rapid decreases in uric acid levels. Nearly 50% of patients in the non-recombinant urate oxidase treatment cohort had urate concentrations less than 1 mg/dl after 2 days of therapy versus 2% of those treated with allopurinol (P<0.001).

Recombinant Urate Oxidase (rasburicase).

A second strategy for the treatment of hyperuricemiais to use rasburicase. Rasburicase is a recombinant urate oxidase that converts uric acid to the more water-soluble product allantoin. It is approved by the FDA for the prevention and management of hyperuricemia in pediatric and adult oncology patients at a dose of 0.20 mg/kg IV in a 30-minute infusion as a single dose for up to 5 days [43]. Because the enzyme can maintain its activity in blood samples ex vivo, it is imperative that blood samples obtained from patients who received rasburicase therapy be placed immediately on ice before transferring them to a diagnostic laboratory for measurement of serum uric acid. Failure to do so may result in false readings of low uric acid values. The safety, efficacy and pharmacokinetics of rasburicase for the prevention and treatment of hyperuricemia were evaluated in a phase 2 study of 131 patients aged ≤ 20 years with newly diagnosed

leukemia or lymphoma. Patients received rasburicase at a dose of 0.15 or 0.20 mg/kg for 5-7 consecutive days. Rasburicase was well tolerated and effective, leading to a rapid decrease in plasma uric acid levels in patients with hyperuricemia (median decrease from 9.7-1 mg/dl after 4 hours) witha mean plasma half-life of 16.0 ± 6.3 and 21.1 ± 12.0 hours at doses of 0.15 and 0.20 mg/kg, respectively. Plasma uric acid levels remained low throughout the treatment [44]. The safety and efficacy of rasburicase were shown further in a compassionate-use study conducted in adults (n = 387) and pediatric patients (n = 682) in the United States and Canada [45]. Although the current FDA-approved rasburicase dose and schedule in pediatric and adult patients are 0.20 mg/kg/day for up to 5 days, several studies suggested that a shorter schedule may be sufficient to treat most patients.

In an open-label multicenter randomized trial, Goldman *et al* [11] compared treatment with rasburicase to oral allopurinol in 52 pediatric patients with lymphoma (39 patients) or leukemia (13 patients) that were at high risk of developing TLS. All patients received approximately 3 liter/m^2 of hydration daily. Average uric acid levels at study initiation were 7.1 mg/dl in the rasburicase group and 7.8 mg/dl in the allopurinol group. Potential serious adverse reactions were rare and included anaphylaxis, rash, hemolysis, methemoglobulinemia, fever, neutropenia (with or without fever), respiratory distress, sepsis and mucositis. Other adverse reactions included vomiting, fever, nausea, headache and diarrhea [46].

Management of Acute Kidney Injury

The role of the nephrologist becomes crucial in the care of patients at risk of or presenting with TLS to help prevent AKI and optimize the patient's condition as quickly as possible to avoid delay in initiation of cyto-reductive therapy and dosage reduction. Supportive care must focus on managing volume status and addressing any metabolic abnormalities unless there is an acute indication for dialysis. Nephrotoxic medications should be avoided, and it is best to not use angiotensin converting enzyme inhibitors and angiotensin receptor blockers given their hyperkalemic and potentially GFR reducing effects, especially if in situations of hypovolemia or hypoperfusion. Iodinated contrast and gadolinium-based contrast agents also are best avoided in patients with established AKI or unstable kidney function [47].

Medication dosage should be based on GFR oradjusted for AKI. Dialysis therapy should be initiated when indicated using standard criteria for AKI. There are no specific benefits for initiating dialysis therapy for hyperuricemia per se. High-flux hemodialysis can be performed daily if needed, but excess ultrafiltration and hypotension should be avoided to prevent additional kidney injury. Peritoneal dialysis may not be effective in the setting of TLS given the need for high clearance rates and is not recommended as a modality of first choice [48]. Continuous venovenous hemodialysis is a renal replacement therapy option in patients with hypotension, large metabolic burden or fluid requirements has also been used in a prophylactic manner [49]. However, prophylactic dialysis or continuous renal replacement therapy in patients at risk of TLS has not been well studied and cannot be routinely recommended. It may need to be considered in patients with advanced Chronic kidney disease (CKD), end-stage renal disease or AKI at presentation. Patients should bemonitored carefully and assessed for renal recovery, which may be delayed in some cases.

Conclusion

Successful management and treatment of tumor lysis syndrome is highly dependent on the prompt identification of clinical and laboratory characteristics, signs and symptoms of patients at risk. Establishment of vascular access and the initiation of prophylactic measures, especially hydration and administration of allopurinol or rasburicase, are vital. The early recognition and treatment of metabolic abnormalities usually prevents the severe and life-threatening complications associated with tumor lysis syndrome.

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