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Tumour lysis syndrome; new approaches in diagnosis, follow-up and treatment

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Summary

Tumor lysis syndrome is a clinical picture which occurs with the lysis of malignant cells and causes metabolic abnormalities that threatens life. These metabolic abnormalities are caused by the release of intracellular ions, nucleic acids, proteins and their metabolites from the instantly degraded tumor cells. These rapidly released metabolites can impair the body's normal homeostatic mechanism and cause uremia, hyperuricemia, hyperkalemia and hyperphosphatemia. Hypocalcemia which is commonly seen in tumor lysis syndrome is secondary to hyperphosphatemia. Generally, tumor lysis syndrome occurs after the initiation of chemotherapy, but it is rarely observed in fast growing tumours before the treatment due to spontaneous lysis of malignant cells. The possibility of tumor lysis syndrome is higher in tumours with high proliferative rates and high tumour burden including Burkitt's lymphoma and acute lymphoblastic leukemia. The principle of prophylaxis/treatment of tumour lysis syndrome includes virgous hydration, adequate diuresis, control of hyperuricemia with rasburicase or allopurinol, regulation of serum electrolytes and dialysis, if necessary. If the necessary measures are not taken or the clinal situation is not treated properly, metabolic abnormalities can cause renal insufficiency, cardiac arrhythmia, neurologic complications and propably sudden death in patients with cancer. Alkalization of urine used to be applied to all patients previously, but it is not recommended any longer and this issue is still open to debate. In this paper, new approaches and innovations in the treatment of tumor lysis syndrome are discussed. *(Turk Arch Ped 2013; 48: 188-194)*

Key words: Allopurinole, rasburicase, Tumour lysis syndrome

Introduction

The prevelance of tumor lysis syndrome (TLS) varies substantially depending on the disease (Table 1). It is generally observed in acute leukemias with high tumor burden, high cell destruction, sensitivity to chemotherapeuticals and high leukocyte count and in Burkitt type non-Hodgkin lymphomas. However, TLS may occur unexpectedly in other cases in the low risk group. Therefore, one should be careful in the follow-up of all cancer patients especially during the first one week after treatment is started (1,2,3). 20-50% of the cases may result in mortality, if the diagnosis of TLS is not made accurately and treatment is not started (4).

Pathophysiology

Severe metabolic disorders started to be observed after use of cytotoxic chemotherapeutical drugs in patients w ith malign hematologic and oncologic diseases (5,6,7,8). These metabolic abnormalities found mainly in lymphoma and leukemia patients are known as TLS. Although tumor lysis syndrome may occur spontaneously before treatment, it is generally observed after cytotoxic drug treatment is started. Starting treatment in tumors with a high growth rate and a high tumor burden which are sensitive to cytotoxic drugs cause to rapid release of intracellular anions and kations and metabolic products of proteins and nucleic acids to enter the circulation (9). Hyperphosphatemia

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develops as a result of rapid destruction of malign cells with high phosphorus burden (1) and hyperkalemia develops as a result of inability of the kidneys to clean high levels of potassium released by tumor cells (8). Hypocalcemia develops as a result of agglutination of calcium-phosphorus crystals in the kidney secondary to hyperphosphatemia (10). Another finding of tumor lysis syndrome is uremia (7). Uremia develops as a result of many mechanisms. The most common reason is uric acid crystals agglutinating in the renal tubules as a result of hyperuricemia. The other mechanisms include calcium-phosphate storage, tumor infiltration in the kidney, obstructive uropathy related with tumor, nephrotoxicity related with drugs and/or acute sepsis Figure 1 (5,11).

Clinical picture

Clinically, tumor lysis syndrome may present with nausea, malaise, vomiting, edema, cardiac arrhythmia, convulsion, fluid load, congestive heart failure, tetany, syncope, muscle cramps and sudden death. Although the clinical findings may be observed before starting cytotoxic chemotherapy, they usually appear 12-72 hours after treatment is started. Treatment is based on determining the patients at risk and taking preventive or therapeutic measures immediately.

Laboratory findings in tumor lysis syndrome

Hyperphosphatemia

Hyperphosphatemia is a phosphorus level above 6.5 mg/dL in children and a phosphorus level above 4.7 mg/dL in adults. It develops as a result of destruction of malign cells and rapid release of intracellular phosphorus to the pheriphery. Excessive endogeneous phosphorus burden is present during tumor lysis syndrome, becasue lymphoblasts carry an inorganic phosphorus burden which is four-fold higher compared to mature lymphocytes (9). Mainly the kidney inhibits this state by decreasing tubular reabsorption of phosphorus and increasing urinary release of phosphorus. However, hyperphosphatemia develops after the tubular reabsorption mechanism reaches saturation. High level of phosphate forms complex with calcium, agglutinates in the tubular lumen and renal interstitium and may lead to acute renal failure (10). Acute renal failure which is another complication of tumor treatment and which occurs as a result of uric acid agglutination aggravates this condition (Table1).

Severe hyperphosphatemia may be characterized with nausea, vomiting, diarrhea, malaise and convulsion. More importantly, hyperphosphatemia causes calcium-phosphate complex to agglutinate in the kidney and other tissues, when calcium-phosphorus product exceeds 70 and may lead to hypocalcemia, metastatic calcification, calcification in the kidney, nephrocalcinosis, nephrolithiasis and acute obstructive uropathy (5,6,7,11,12)

A phosphorus level above 6,5 mg/dL necessitates medical treatment. Treatment is started with removal of phosphorus from intravenous fluid and administration of phosphorus-binding drugs by oral route or nasogastric tube including aluminium at a dose of 15 mL every 6 hours (50-150 mg/kg/gün). Intravenous calcium should not be given to patients with hyperphosphatemia unless tetany is found clinically. In cases where severe hyperphosphatemia is present and oral phosporous-binding drugs are inadequate, more intensive therapies may be needed. Continuous peritoneal dialysis, hemodialysis and continuous venovenous hemofiltration (CVVH) provided a decrease in the phosphorus level successfully in hyperphosphatemic patients with acute TLS (13). Hemodialysis is much more successful in removing phosphorus compared to CVHH (13).

Hypocalcemia

Hypocalcemia develops as a result of agglutination of calcium-phosphate complex in the tissue in relation with hyperphosphatemia during TLS. The diagnosis is made with a serum calcium level below 8.4 mg/d L or an ionized calcium level below the normal limits. Severe hypocalcemia is one of the most important complications of TLS and may be associated with symptoms related with muscles and cardiovascular and/or neurological symptoms. Muscle cramps, spasm, paresthesia and tetany are the findings related with muscle, while ventricular arrythmia, heart block, hypotension are cardiac findings and hallucination, delirium, confusion and convulsion are neurological findings. Severe neurological and/or cardiac complications may lead to heart failure, coma and rarely mortality.

Treatment to correct hypocalcemia is not recommended in asymptomatic patients especially in the period of hyperphosphatemia, since the possibility of metastatic calcification is high. Hypocalcemia generally improves spontaneously with improvement of TLS (5,14). In symptomatic patients, intravenous calcium gluconate (50-100 mg/kg/IV/dose) may be used to correct the clinical signs, though this may lead to calcium-phosphorus agglutination and obstructive uropathy.

Hyperkalemia

Hyperkalemia is defined as a serum potassium level above 6.0 mmol/L. Hyperkalemia occurs as a result of excessive potassium release from destructed tumor cells. If renal failure develops, the picture gradually becomes more severe. If the patient is given potassium support by intravenous fluid, iatrogenic hyperpotassemia develops. Therefore, potassium should not be used in fluids, when TLS is suspected. The clinical findings of hyperpotassemia include nausea, malaise, vomiting, diarrhea, muscle weakness, cramps, paresthesia and paralysis. Cardiac side effects include peaked T wave on electrocardiogram (ECG), prolongation of PR interval, enlargement in QRS complex, asystole, ventricular tachycardia or fibrillation, syncope and sudden death (5,12,14,15).

In asymptomatic patients with a serum potassium level below 7.0 mmol/L who do not show any ECG change, the treatment option consists of discontinuation of potasium intake and administration of ion exchange resin (polystyrene sulfonate: 1 g/kg, 4-6 doses a day with 50% sorbitol). A serum potassium level above 7.0 mmol/L and a symptomatic patient is an urgent condition. Acute cardiac toxicity is treated by giving intravenous calcium gluconate slowly (20-30 mg/kg/dose; 2-5 mL 10% calcium gluconate in older children, maximum 2 mL 10% calcium gluconate in infants). The calculated calcium gluconate is given carefully in a period longer than 10 minutes with electrocardiographic monitorization (16). Hyperpotassemia may be corrected by rapid intracellular uptake of serum potassium. For this aim, inhalation with a beta agonist like salbutamol (a single dose of 2.5-5 mg or may be repeated, if necessary), rapid-acting insulin (0.3-0.6 unit/kg/h in newborns, 0.05-0.2 unit/kg/h in all chidren older than one month of age) and glucose infusion in association (0.5-1 gr/kg/h; 5-10 mL/kg 10% glucose or 2.5-5 ml/kg 20% glucose; by a central catheter) or sodium bicarbonate infusion (1-2 mmol/kg) may be used to lower the potassium level (16). Close and continuous monitorization of the cardiac rhythm with ECG and frequent assessment of electrolytes is necessary during the course of hyperkalemia. Oral or intravenous potassium should be avoided during the course of TLS especially if the potassium level is high.

Hyperuricemia

Hyperuricemia occurs as a result of rapid destruction of intracellular nucleic acids (17). Purine nucleic acids are catabolysed primarly to hypoxanthine, then to xanthine and finally to uric acid by way of xantine oxidase enzyme. Uric acid is excreted in the kidneys and normally 500 mg uric acid is excreted by the kidneys daily (18). The pKa value of uric acid ranges between 5,4 and 5,7 and it merely dissolves in water. 99% of uric acid is in the ionized form at the normal intensity and normal pH (18).

Hyperuricemia is defined as an uric acid level above 7,8 mg/dL. As mentioned previously, hyperuricemia is observed as a result of destruction of plenty of nucleic acids found in malign cells (11). The main cause of renal failure is hyperuricemia (19). Since the renal clearance is low (5-8 mL/min), uric acid accumulates in plasma and all body fluids. As the level of uric acid increases, its excretion by the kidnesy also increases until the plasma level reaches 12-15 mg/dL. However, the filtered amount exceeds the limit of tubular reabsorption at levels above this value and results in excessive increase in uric acid excretion. Depending on pH and amount of the urine, the uric acid excreted may lead to crystal formation in the distal and collecting tubules exceeding the solubility limit and cause renal failure (20). When the release capacity of the renal tubules is exceeded, hyperuricemia occurs and in presence of acidic pH, it leads to acute obstructive uropathy by forming obstruction in the lumen in the renal tubules and uric acid crystals which lead to renal dysfunction are formed (12). If hyperuricemia results in acute obstructive uropathy, clinical findings including hematuria, lumbar pain, hypertension, azotemia, acidosis, edema, oliguria, anuria, lethargy and somnolance may be observed (Table 2, 3) (14).

Treatment in tumor lysis syndrome

1. Hydration and diuresis

Treatment is based on strong hydration and diuresis unless acute renal failure and oliguria develop. Increased hydration and accompanying increase in the amount of urine increase the intracellular volume, renal blood flow and glomerular filtration and renal excretion of uric acid and phosphorus (12,21). Patients should be given 2-4-fold of their daily maintenance fluid (approximately 3000 mL/m^2/day or 200 mL/kg/day, if the child weighs below 10 kg) and 100 mL/m^2/h (3 mL/kg/h, if below 10 kg) urine output should be provided. When the desired urine output can not be provided despite adequate hydration, diuretic treatment should be administered in the patient, if findings of obstructive uropathy or hypovolemia are absent. These diuretics may be mannitol (0.5 mg/kg) or furosemide (0.5-1.0 mg/kg). In presence of severe oliguria or anuria, 2-4 mg/kg furosemide may be considered to initiate or increase urine output. The urinary density should be kept below 1010. Potassium, calcium and phosphorus should absolutely not be added to the intravenous fluids at the beginning of treatment, since they would lead to hyparphosphatemia, hyperkalmia or calcium-phosphorus agglutination in the kidney.

2. Alkalinization of urine

Urinary alkalinization used to be recommended in treatment of TLS. (22). Alkaline urine (urinary pH> 6.5) increases release of urate from the kidney (12). However, use of sodium bicarbonate for alkalinization of the urine is controversial currently. Urate is mostly dissolved at a pH level of 7.5. However, the solubility of xanthine and hypoxanthine strongly decreases at a pH level of 6,5 and xanthine crystals are formed during or after allopurinol treatment (21,22). In addition, urinary alkalinization decreases calcium-phosphate solubility and leads to agglutination of calcium phosphate crystals in the renal tubules. Excessive systemic and urinary alkalinization may lead to metabolic alkalosis and/or xanthine may lead to obstructive uropathy. Therefore, administration of fluids balanced in terms of electrolytes such as to maintain the urinary density at about 1010 has come to the forefront instead of urinary alkalinization in recent years (20).

3. Control of hyperuricemia

Allopurinol, when transformed into oxypurinol in vivo, is a xanthine analog which is a competetive inhibitor of xanthine oxidase which inhibits the metabolism of xanthine and hypoxanthine to uric acid (23). It was proved that allopurinol decreased new uric acid formation efficiently and decreased the rate of development of uric acid obstructive uropathy in cancer patients who were at risk in terms of TLS (23). Allopurinol can be used at a dose of 100 mg/m2/dose every 8 hours (10 mg/kg/day; 3 doses a day). The maximum dose is 800 mg/day by the oral route or 200-400 mg/m2/day intravenously; divided in 1-3 doses; the maximum daily dose is 600 mg/day (Table 4). However, allopurinol does not influence the uric acid level formed before allopurinol treatment, since it only prevents new uric acid formation. In addition, it increases the levels of xanthine and hypoxanthine which are precursors of purine (24). Since xanthine is less soluble in urine compared to uric acid, xanthine nephropathy which results in obstructive uropathy may develop with allantoin use (25). Another reason limiting allopurinol use is the fact that it decreases destruction of other purines including 6-mercaptopurine (6-MP) and azathioprine. Therefore, dose limitation of 50-70% is recommended for all purines especially for 6-MP when used in combination with allopurinol. Recently, allopurinol has started to be used intravenously (26). Since allopurinol is excreted by the kidneys, the dose should be adjusted in case of renal failure Figure 2.

Another way of decreasing the uric acid level is providing transformation of uric acid to allantoin by urate oxidase. Compared to uric acid, allantoin dissolves in urine with a 5-10-fold higher rate. Although urate oxidase enzyme is an endogenous enzyme found in many mammalians, it is not found in humans (27). Non-recombinant urate oxidase (Urikozim) obtained from Aspergillus flavus species was proved to decrease the level of uric acid in patients who carried a risk of TLS. It was started to be used since 1975 in France and since 1984 in Italy (28). Recently, recombinant urate oxidase (rasburicase) has also come into use. (29) Rasburicase leads to hypersensitivity reaction with a more lower rate compared to the non-recombinant form. Since Rasburicase also destructs previously present uric acid in contrast to allopurinol, the blood uric acid level decreases rapidly in four hours, xanthine accumulation does not develop and it does not accumulate in the plasma even after multiple-dose administration. It does not have any interaction with any drug. Therefore, it can be used safely even in renal or hepatic failure (30). Rasburicase may lead to hemolytic anemia and methemoglobinemia especially in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency.

Bronchospasm may develop in the beginning of rasburikaz treatment in a small portion of patients. Therefore, the necessary treatment should be present by the patient. Blood and serum samples obtained from patients who are receiving rasburikaz treatment for measurement of uric acid should be kept in a cold environment. Otherwise, uric acid destruction will continue at room temperature and erroneously a lower result may be obtained. In addition, the analysis should be performed in the first four hours after obtaining the blood sample Table 4.

Guideline recommended in treatment/prevention of hyperuricemia

The first step in successful treatment of tumor lysis syndrome is classifying each patient accurately in terms of risk groups before cancer treament and starting the appropriate drug treatment. Cario et al. (31) divided cancer patients into three risk groups for TLS (Table 1). The first step in the follow-up of patients is to evaluate patients in terms of TLS and Clinical Tumor Lysis (CTLS) according to Table 2, to assign patients to the risk groups and finally decide if renal failure is present or not.

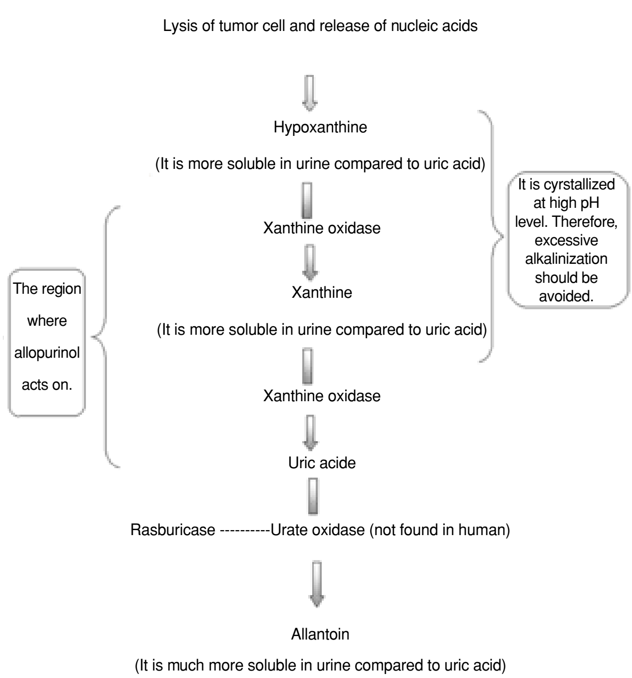

Figure 1. Uric acid metabolism

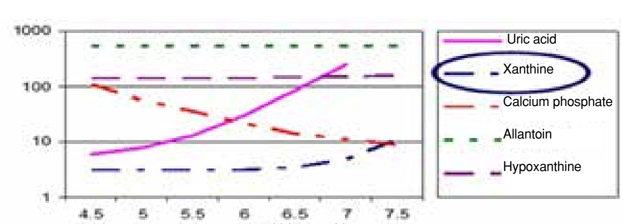

Figure 2. Dissolution in urinary pH

Table 1. Cario et al., 2010, risk classification before treatment in hematologic malignancies in terms of TLS

Malignancy	Risk category		
	Low Risk	**Moderate risk**	**High risk**
NHL	Low risk Slowly progressive NHL Adulthood ALCL Adulthood moderate NHL+ LDH<2xULN LL Grade 1-2 + LDH<2xULN N/A N/A	Childhood ALCL grade 3-4adulthood moderate NHL+LDH>2xULN Childhood moderate NHL Burkitt lymphoma+LDH<2xULN	Burkitt lymphoma grade 3-4 or LDH>2xULN
Hodgkin lymphoma	**Most of the patients***		
ALL	N/A	WBC<100X10^9/L +LDH<2XULN	WBC>100X10^9/L veya LDH>2XULN
AML	u ximab WBC<25x10^{9}L + LDH<2xULN	WBC 25-100^{9}x10 L or WBC<25x10/L+LDH>2xULN	WBC>100X10^9/L
CLL	Hastaların çoğu	Fludarabin/Rituksimab ile tedavi edilen veya WBC>50X10^9/L	
CML	Most of the patients	Akselere blast krizi	
Multiple lyemola	Most of the patients Most of the patients*		

NHL; Non-Hodgkin lymphoma, ALCL; Anaplastic large cell lymphoma, LL; lymphoblastic lymphoma, N/A; not available, ALL; acute lymphoblastic leukemia, AML; acute myeloid leukemia, KLL; chronic lymphocytic leukemia, KML; chronic myeloid leukemia, LDH; lactate dehydrogenase, ULN; upper limit of the normal, WBC; white blood cell count, TLS; tumor lysis syndrome

*Additional risk factors puts the patient in a higher risk category. Additional risk factors; Tumor burden (Bulky disease) (>10 cm), LDH>2 X ULN, renal dysfunction; oliguria or previously present renal failure, baseline uric acid > 450µmol/L; increased tumor cell destruction and/or sensitivity to excessive chemotherapy and TLS at the time of diagnosis before treatment starts.

Table 2. Properties of hypouricemic drugs

Allopurinol (xanthine oxidase inhibitor)	Rasburicase (Recombinant Urate Oxidase)
Present in humans	Present in other mammalians
İnhibits formation of uric acid	Provides excretion of formed uric acid by transforming it to allantoin
Alkalinization of urine facilitates excretion of uric acid	No need for urinary alkalinization
300 mg/m^2/day; maximum dose 800 mg/day	0.05-0.2 mg/kg/day
Dose adjustment is needed in renal failure	No need for dose adjustment in renal failure
Used in glucose-6-phosphate dehydrogenase enzyme deficiency	Not used in glucose-6-phosphate dehydrogenase enzyme deficiency

Table 3. Cario-Bishop laboratory TLS (LTLS) classification	
Uric acid	≥7.8 mg/dL or an increase of more than 25% of the normal value
Potassium	≥6.0 mg/dL or an increase of more than 25% of the normal value
Phosphorus	≥6.5 mg/dL (child) or ≥4.7 mg/dL (adult) or an increase of more than 25% of the normal value
Calcium	≥8.4 mg/dL a decrease of more than 25% of the normal value

Table 4. Cario-bishop clinical tumor lysis syndrome (CTLS) classification
Creatinine* ≥ 1.5X ULN[x] (>12 years)
Cardiac arrhythmia/ sudden death *
Convulsion *

*Independent of the toxicity of any agent used in treatment
x If the patient's creatinine level is 1.5 fold or more higher than the normal value (ULN) for age and gender, it is considered high. If the age/gender limit is not stated specifically, the upper value of creatinine is 61.6 μmol/L for girls and boys aged between 1 and 12 years, 88μmol/L for girls and boys aged between 12 years and 16 years, 105.6 μmol/L for girls above the age of 16 years and 111.4μmol/L for boys above the age of 16.

Since tumors including Burkitt lymphoma and B-ALL carry a high risk in terms of TLS, these patients can be considered to be in the high-risk group, though they do not have additional risk factors. It was shown that the risk of TLS was absolutely higher in some types of acute myeloid leukemia (AML) (AML M4, AML M5) compared to other AML types (32). In the other tumor types, the patient is considered to be in the high-risk group in case of presence of other risk factors including high leukocyte number for acute leukemias, increased size of lymph nodes or a lactate dehydrogenase higher than 2-fold the normal value for lymphomas. Oliguria, presence of hyperuricemia before treatment and disease stage as in chronic myeloid leukemia should be evaluated before assigning the patients to risk groups.

Patient follow-up

Clinically, the follow-up of the patients is based mainly on providing sufficient urine output. By this means, uric acid, phosphorus and potassium released excessively from tumor cells can be cleaned from the blood. All patients should take excessive amounts of fluid and followed up closely with urine monitoring. Follow-up of blood uric acid, phosphorus, creatinine and potassium levels is also important in addition to follow-up of fluid intake and urinary output. In patients in the moderate and high risk groups, intake-output follow-up should be done in 6-hour periods. Biochemical tests should be performed every 12 hours (every 6 hours in patients with higher risk). Hospitals which can not perform hourly monitoring should consider referal of the patient to more experienced centers. However, the patient should absolutely be transferred by giving fluid and by performing intake-output monitoring. The follow-up of the patient should continue for one week or longer (in resistant or irresponsive TLS) depending on the risk group and presence of CTLS.

Dialysis

The definite treatment of uncontrolled Laboratory Tumor Lysis Syndrome (LTLS) or CTLS is dialysis. With introduction of Rasburicase, hyperuricemia causes to dialysis with a much lower rate compared to oliguria and other biochemical abnormalities. Recently, dialysis has been performed most commonly because of hyperphosphatemia in our clinic.

Peritoneal dialysis, hemodialysis and hemofiltration are used in treatment of clinical and laboratory tumor lysis. The least efficient one among these is peritoneal dialysis. The clinical response is slower and clinical control is provided in approximately 48 hours (33). However, its use is limited in presence of hepatosplenomegaly, lymphadenopathy in the abdomen and neutropenia (risk in terms of infection).

A marked superiority of hemodialysis or hemofiltration to each other has not been proved (15). Both treatment methods are considerably efficient and rapidly correct fluid load and biochemical abnormalities. There is evidence which shows that early initiation of hemodialysis in presence of clinical TLS corrects the outcome in patients with multiple-organ failure (15)

Conclusion

Tumor lysis syndrome is a life-threatening problem. Since the human being does not have urate oxidase enzyme which converts uric acid into allantoin, TLS can develop in conditions where purine catobolism is increased including malignancy. The most important part of treatment approach is tailoring the treatment by predicting hig-risk patients who will develop tumor lysis syndrome. The main risk factors include the type of the tumor, the extensiveness of the disease, use of cytotoxic agents, age at the time of diagnosis, previous renal failure and renal involvement of the disease. The most improtant part of treatment clearly consists of adequate hydration, electrolyte monitorization and cardiac-renal monitorization. Alkaline hydration which used to be recommended with the aim to prevent uric acid nephropathy is no longer recommended regularly, because it may lead to xanthine nephropathy and calcium-phosphorus crystals and drugs which can decrease uric acid more efficiently have been introduced. Preference of uric acid lowering drugs may vary according to the morbidity. While allopurinol is recommended for prevention in the moderate-risk group patients, rasburicase is the recommended drug for treatment of hyperuricemia and preventive treatment of high-risk patients. Again, rasburicase should be tried when TLS can not be controlled in patients who use allopurinol.

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