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CLINICAL STUDY

Our experience with tumor lysis syndrome treatment

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Abstract: Tumor lysis syndrome (TLS) is caused by rapid tumor cell turnover resulting in a release of intracellular contents into the circulation, and subsequent numerous metabolic derangements (hyperkalemia, hypocalcemia, hyperphosphatemia, hyperuricemia). More than 90 % of cases have laboratory manifestations, and only about 10 % have clinical manifestations. The main complications are acute renal failure, cardiac arrhythmia and metabolic acidosis. The management of TLS consists of preventive measures in high-risk patients prior to cancer treatment as well as prompt initiation of supportive care for patients who develop acute tumor lysis syndrome during treatment. The traditional management consists of intravenous hydratation, urinary alkalinization, diuretics and control of hyperuricemia, electrolyte disturbances and dialysis if needed. The use of a new hypouricemic agent (rasburicase) in patients with TLS minimized the need for renal dialysis as well as reduced the incidence of complications seen in hyperproduction of uric acid to minimum *(Tab. 4, Ref. 8).*
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Key words: tumor lysis syndrome, hyperleukocytosis, hyperuricemia, rasburicase, acute renal insufficiency.

Tumor lysis syndrome (TLS) refers to metabolic derangements that may be seen after the initiation of cancer treatment. TLS usually occurs in patients with bulky, rapidly proliferating, and treatment-responsive tumors. It is typically associated with acute leukemias and high-grade non-Hodgkin lymphomas, such as Burkitt lymphoma. TLS has been also reported with other hematologic malignancies and solid tumors (1) (Tab. 1).

Tab. 1. Risk factors of tumor lysis syndrome.

Risk factors of developing	TLS Risk by tumor type
Hematologic malignancy	Burkitt's lymphoma
High proliferation rate	Lymphoblastic lymphoma
Chemosensitivity	Acute leukemia (ALL>AML)
Large tumor burden	Neuroblastoma
Elevated leukocyte count	Germ cell carcinoma (seminoma, ovarian)
Elevated pretreatment LDH level	Low grade lymphoma
Preexisting renal impairment	Medulloblastoma
Dehydratation	Hodgkin's lymphoma

Pathogenesis

Rapid tumor cell turnover results in a release of intracellular contents into the circulation. This release can inundate the renal elimination and cellular buffering mechanisms that lead to numerous metabolic derangements (2). Clinically significant tumor lysis syndrome can occur spontaneously, but it is most often seen 48 – 72 hours after the initiation of cancer treatment. Hyperkalemia is often the earliest laboratory manifestation. Hyperkalemia and hyperphosphatemia result directly from rapid cell lysis. Nucleic acid purines that are also released by cell breakdown, are ultimately metabolized to uric acid by hepatic xanthine oxidase. This conversion leads to hyperuricemia. Hypocalcemia is a consequence of acute hyperphosphatemia with subsequent precipitation of calcium phosphate in soft tissues (3). It is also caused by decreased calcitriol levels in acute renal failure. The kidney is the primary organ involved in the clearance of uric acid, potassium, and phosphate. Preexisting conditions of volume depletion or renal dysfunction predispose the patients to the worsening of metabolic derangements and acute renal failure. Acute renal failure is often oliguric and can be multifactorial in etiology; uric acid nephropathy is the major cause of acute renal failure. Its development is due to mechanical obstruction by uric acid crystals in the renal tubules. With pKA of 5.6, uric acid precipitation is enhanced by high acidity and high concentration in the renal tubular fluid that becomes less soluble when renal tubule pH decreases. Renal medullary hemoconcentration and decreased tubular flow rate also contribute to crystallization. Another cause of acute renal failure is acute nephrocalcinosis from calcium phosphate crystal precipitation, which may occur in other tissues. This occurs in the setting of hyperphosphatemia, and is exacerbated by overzealous iatrogenic alkalinization due to the fact that calcium phosphate, unlike uric acid, becomes less soluble at an alkaline pH. Precipitation of xanthine, which is

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Tab. 2. Forms of tumor lysis syndrome.

Laboratory TLS	Clinical TLS
Uric acid level ≥476 μmol/L	Renal insufficiency (creatinine level ≥1.5 ULN age adjusted)
Potassium level ≥6 mmol/L	Cardiac arrhythmia (sudden death not due to drug)
Phosphorus ≥2.1 mmol/L	CNS (seizure not due to drug)
Calcium level ≤1.75 mmol/L, or decrease in calcium level more than 25 %	–

ULN – upper limit of normal

even less soluble in urine than uric acid, or other purine metabolites whose urinary excretion is increased by use of allopurinol, are other causes of acute renal failure (2, 3).

Manifestations of TLS

Clinically, the syndrome is characterized by rapid development of hyperuricemia, hyperkalemia, hyperphosphatemia, hypocalcemia, and acute renal failure (ARF). There are two forms of TLS to be distinguished (4) (Tab. 2.).

Management of TLS

It is needed to identify high-risk patients before treatment by assessing the tumor burden extent, histopathologic findings, and renal function. Tumor lysis syndrome management requires an initiation of preventive measures in high-risk patients prior to cancer treatment as well as a prompt initiation of supportive care for patients who develop acute tumor lysis syndrome during treatment. Patients with the evidence of pretreatment of acute tumor lysis syndrome should be started immediately on tumor lysis syndrome treatment while cancer therapy should be withheld if possible until all parameters are corrected (5).

Prophylaxis and medical management of TLS in high-risk patients, consists of intravenous hydration, alkalinization of urine, and uric acid reduction by uricemic agents (allopurinol, rasburicase) (6).

Intravenous hydration in amount of 3 L/day should be initiated 24–48 hours before the induction of chemotherapy to maintain urine output at 100 ml/m^2/h, while potassium should not be added into i.v. solution. With the use of allopurinol monitor, urine pH is to be maintained at pH ranging from 6.5 to 7.5 in order to enhance the uric acid solubility and to promote the excretion. Urine alkalinization is achieved by adding sodium bicarbonate 20–40 mEq/L or 0.5–1 mEq/L to i.v. fluid (7).

Rasburicase (recombinant urate oxidase) is a newer therapy that can be used when uric acid levels cannot be lowered sufficiently by standard approaches. Rasburicase is useful in cases of hyperuricemia ≥476 μmol/L. Humans do not express urate oxidase; urate oxidase catalyses the conversion of poorly soluble uric acid to soluble allantoin. By converting uric acid to water-soluble metabolites, it effectively decreases the plasma and urinary uric acid levels. Unlike allopurinol, uricase does not increase the excretion of xanthine and other purine metabolites; therefore, it does not increase the tubule crystallization of these compounds. It is administered by intramuscular injection or intravenous infusion at dosages ranging from 50–100 U/kg/d. It is contraindicated in glucose-6-phosphate dehydrogenase (G-6-PD) deficiency (6, 7).

Material and methods

A total of 22 patients had been diagnosed in years 1998–2004 as hematologic malignancies at high risk of developing TLS according to tumor burden, hyperleukocytosis, hypeuricemia, electrolytes disturbance, high LDH level, and preexisting renal impairment. The hallwark of our diagnostic approaches consisted of laboratory investigations of complete hemogram with diferential white blood count, serum biochemistry (uric acid, creatinine, urea, electrolytes and LDH). These investigations were made at admission before the start of cytoreductive therapy and had been repeated twice per day until we achieved physiological parameters.

Radiological image

CXR was used to assess the mediastinal mass, pleural and pericardial effusion; if present, we indicated CT-scan to assess the burden and extention of the tumor.

Abdominal USG was used to assess the abdominal mass, hepatosplenomegaly, lymphadenomegaly and renal infiltration.

Treatment

In three cases we used the traditional treatment of TLS (hyperhydratation 3 L/m^2/24 hrs of normal saline, alkalinization of urine with HCO_3 0.5–1 mEq/L and allopurinol 5–10 mg/kg) before rasburicase came in use. Other nineteen patients were treated with the use of rasburicase (0.15–0.20 mg/kg). A decrease in hyperuricemia was compared by means of rasburicase versus allopurinol.

Results

Diagnosis: 14 acute lymphoblastic leukemia, 2 acute myeloid leukemia, 5 non-Hodgkin's lymphoma, 1 posttransplantation lymphoproliferative disease.

Laboratory TLS was the main manifestation in nineteen patients (90 %), only three of patients (10 %) had clinical manifestation.

Hyperuricemia in nineteen patients, who had been treated with rasburicase (Fasturtec), was dropped very quickly to normal ratio (Tab. 3).

In 3 cases (case reports) with traditional management, the decrease in uricemia was very slow, and symptoms and signs of ARI developed requiring renal dialysis in two of them (Tab. 4).

Case 1

10-year old male presented with painless epigastric abdominal mass, in last two weeks he had frequent urination. Diagnosed

Tab. 3. Characteristics of patients treated with rasburicase.

No	Diagnosis	Initial UA/μmol/L	Normal UA level	Day	Creatinine	TWB Cx10^9/L	LDH	Tumor mass
1	T-ALL	811	166	2	129	25	12	Med
2	T-ALL	631	120	2	78	209	13	HL
3	T-NHL	516	74	1	44	6.8	14.3	H, S
4	B-ALL	577	217	1	71	15.1	15.3	M, C, H
5	T-ALL	830	236	2	83	154	116	Med
6	T-NHL	604	215	2	45	13.7	11	H, S
7	B-ALL	746	121	3	46	25.7	23	H, S.
8	AML	756	253	2	21	7.3	17	Med+HL
9	T-ALL	855	133	3	55	255	23	Med
10	B-ALL	1055	150	2	58	1.6	18.4	H, S
11	B-ALL	874	123	2	35	135.4	13	H, S+HL
12	B-ALL	560	111	1	59	7	8	H, S
13	B-NHL	682	173	1	105	14	12	H, L.ad
14	T-NHL	482	158	1	49	12.7	20.3	Med
15	PTLD	513	197	1	76	0.7	11.6	L.ad
16	B-ALL	663	127	2	119	8.2	37.9	H, S
17	T-ALL	497	105	1	45	121.8	21.4	Med
18	AML(M5)	494	138	1	29	223.3	22	HL
19	T-ALL	918	148	2	122	148.3	159	Med+S

AML – acute myeloblastic leukemia; B-ALL – B cell acute lymfoblastic leukemia; T-ALL – T cell acute lymphoblastic leukemia; B-NHL – B cell non Hodgkin´s lymphoma; T-NHL – T cell non Hodgkin´s lymphoma; PTLD – posttransplantation lymphoproliferative disease; H – hepatomegaly; S – splenomegaly; C – lymfadenopathy coli; Med – mediastinal mass; UA – uric acid; TWBC – total white blood cell; LDH – lactate dehydrogenase; HL – hyperleukocytosis; L.ad – lymphadenomegaly

Tab. 4. Initial blood uric acid concentration in patients treated with traditional means.

Diagnosis	Initial UA μmol/L	Normal UA μmol/L	Day
T-ALL	1867	117	8
T-ALL	785	531	8
B-ALL	777	898	7

T-ALL – T cell acute lymphoblastic leukemia; B-ALL – B cell acute lymphoblastic leukemia; UA – uric acid

as B-NHL (analysis of fluidothorax), with ascites, fluidothorax, and TLS.

Laboratory findings were hypokalemia (3.23 mmol/L), hypomagnezemia (0.84 mmol/L), hypocalcemia (1.25 mmol/L), hyperphosphatemia (3.84 mmol/L), hyperuricemia (777 μmol/L), high creatinine level (137 μmol/L), and high blood urea level (28.7 μmol/L). Treatment: hyperhydration, allopurinol, alkalinization of urine (bicarbonate).

Inspite of all these measures, the patient developed vomiting and tetany and was more hypocalcemic. Therefore urgent successful renal dialysis was performed on the seventh day after admission. After renal dialysis the patient was clinically stabilized and continued on chemotherapy, afterwards a complete remision was achieved on day 33.

Case 2

12-year-old male was diagnosed as T-ALL (bone marrow aspirate analysis), with mediastinal tumor, renal infiltration, left-sided fluidothorax.

Initial laboratory findings were hyperuricemia (785 μmol/L), high level of blood urea (9.7 μmol/L) and creatinine (87 μmol/L), normal level of blood electrolytes. Treatment: hyperhydration, allopurinol, alkalinization of urine. After the initiation of chemotherapy, the patient developed sings and symptoms of ARI requiring renal dialysis which was successfully performed on eighth day after admission. The patient was continued on chemotherapy; his clinical condition has been stabilized. A complete remision was achieved on day 33.

Case 3

4-year-old female in her third hematologic relapse of T-ALL, syndrome of hyperviscosity, and TLS.

Laboratory findings were hyperuricemia (1867 μmol/L), hyperphosphatemia (3.4 mmol/L), hypocalcemia (1.94 mmol/L) and hypokalemia (3.2 mmol/L). Treatment: hyperhydration, alkalinization, allopurinol. Renal dialysis was about to be performed when the patient died on third day after admission.

Discussion

The patients in our studied group were classified according to tumor type as acute lymphoblastic leukemia, acute myeloid leukemia and non-Hodgkin's lymphoma. More than half of the cases had laboratory manifestation with hyperuricemia, hypocalcemia and hyperphosphatemia. Only 13.6 % of patients had clinical manifestation of TLS as presented in literature, mainly ARI. All patients had large tumor burden, elevated leukocyte count, elevated pretreatment LDH level and in some cases, there was a preexisting renal impairment.

The clinical course and treatment of patients before the use of rasburicase in treatment of TLS, were sometimes inpredictable;, there was always a hazard of too extensive alkalinization of urine and consequencial precipitation of calcium phosphate in renal tubules. No patient of our study group had experienced adverse effects after using allopurinol including mild to severe rash, xanthine stone-induced urolithiasis and acute interstitial nephritis. Allopurinol starts to act after 2–3 days, therefore we used to administer it before the start of chemotherapy. This however was impossible in acute presentation; also it had no effect on already high uric acid level. Unlike allopurinol, rasburicase starts to act within hours, converts uric acid into soulable allantoin, which can be easily excreted in urine.

In 3 cases of our studied group, renal dialysis was needed before the use of Rasburicase. By early initiation of dialysis we avoided irreversible renal failure and other life-threatening complications. Indications for dialysis included persistent hyperkalemia or hyperphosphatemia despite treatment, volume overload, uremia, symptomatic hypocalcemia, and hyperuricemia. Hemodialysis is preferred to peritoneal dialysis because of its better phosphate and uric acid clearance rates. Since hyperkalemia can reoccur after the initiation of dialysis, as well as due to the high phosphate burden in some patients with tumor lysis syndrome, electrolyte levels must be monitored frequently and dialysis repeated when needed. The use of rasburicase rapidly decreased hyperuricemia and there was no need for hyperhydratation or alkalinization of urine. As long as rasburicase was used, hyperuricemia was under control, the need for renal dialysis was minimized, and the incidence of nephrocalcinosis in our patients was reduced to minimum. The use of furosemide or mannitol for osmotic diuresis as a front-line therapy has not been proven as beneficial. In fact, these modalities may contribute to uric acid or calcium phosphate precipitation in renal tubules in a volume-contracted patient. Instead, diuretics should be reserved for well-hydrated patients with insufficient diuresis, and furosemide alone should be considered for normovolemic patients with hyperkalemia or for patients with the evidence of fluid overload (8).

Conclusions

Tumor lysis syndrome management requires the preventive measures in high-risk patients to be initiated prior to cancer treatment. As long as the acute tumor lysis syndrome develops during treatment, the supportive care is to be initiated promptly.

The use of rasburicase maintained hyperuricemia under control, minimized the need for renal dialysis, as well as reduced the incidence of nephrocalcinosis in our patients to minimum. As long as rasburicase was used, there was no need for hyperhydratation or alkalinization of urine. Owing to the latter fact, the hazard of calcium phosphate precipitation was eliminated and the cytoreductive therapy could be started with no delay.

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