TUMOR LYSIS SYNDROME

Samin Alavi

Professor of pediatric Hematology/Oncology

Shahid Beheshti University of Medical Sciences

Tehran/Iran

Urmia Congress- 27-29 shahrivar 1398/Sep 2019

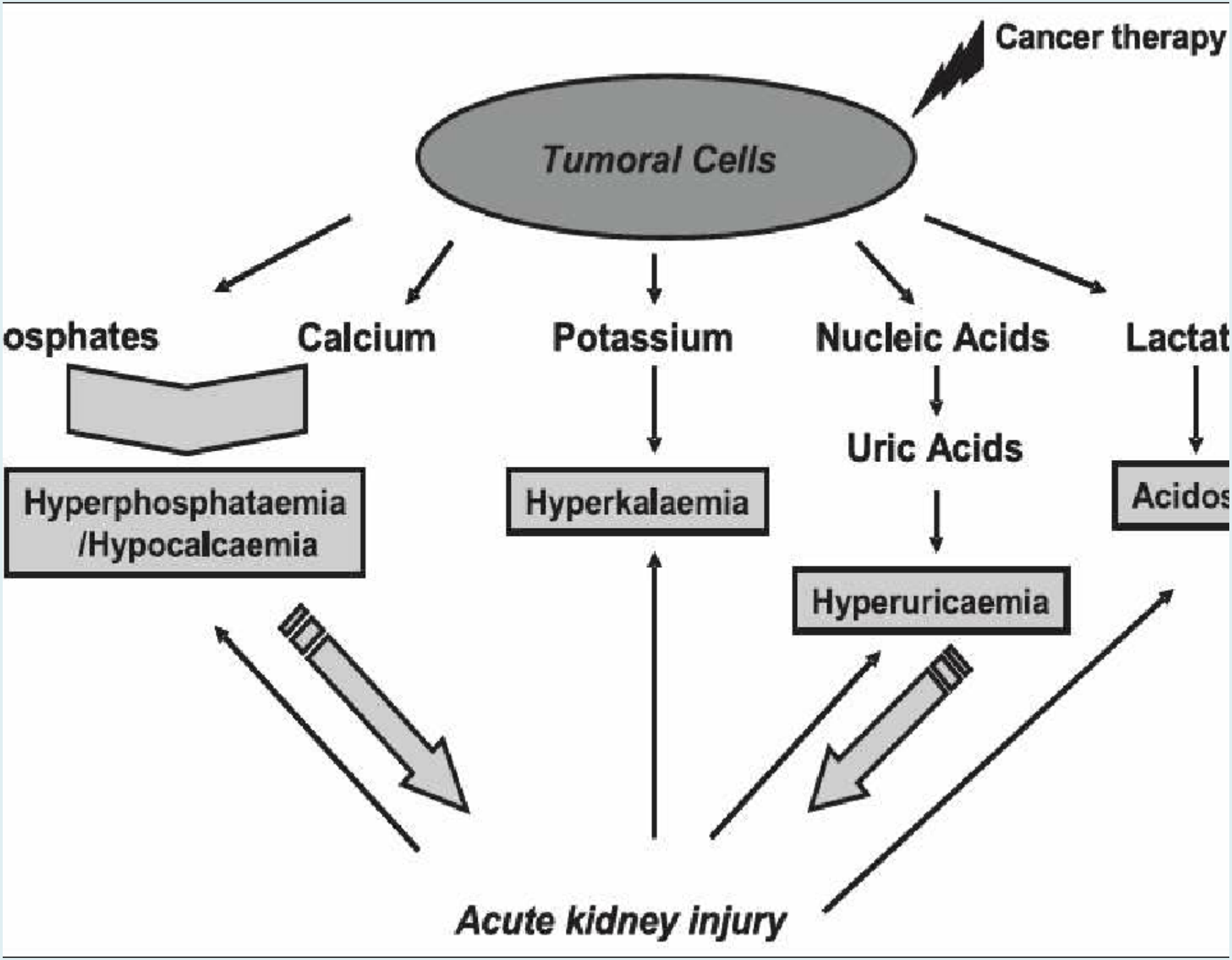

Cancer therapy
Tumoral Cells
osphates
Calcium
Potassium
Nucleic Acids
Lactat
Uric Acids
Hyperphosphataemia
/Hypocalcaemia
Hyperkalaemia
Hyperuricaemia
Acidos
Acute kidney injury

TABLE 1: Reference values of uric acid in children and adolescents.

	Sex**	Uric acid (mg/dL) Age (years)	Mean	SD
Wilcox [1]*	Male	<5	3.6	0.9
		5~10	4.1	1.0
		12	4.4	1.1
		15	5.6	1.1
		18	6.2	0.8
	Female	12	4.5	0.9
		15	4.5	0.9
		18	4.0	0.7
Kubota [6]	Male	≤1	2.9	0.9
		1~3	3.3	0.8
		4~6	3.6	1.0
		7~9	4.2	0.9
		10~12	4.5	0.9
		>13	5.6	1.0
	Female	10~12	4.1	0.8
		>13	4.3	0.9

*The number within brackets indicate the reference number. **The blanks in this column indicate both sexes.

- As a result of the massive production of UA, and its crystallization, UA obstructive uropathy develops which can then progress to AKI

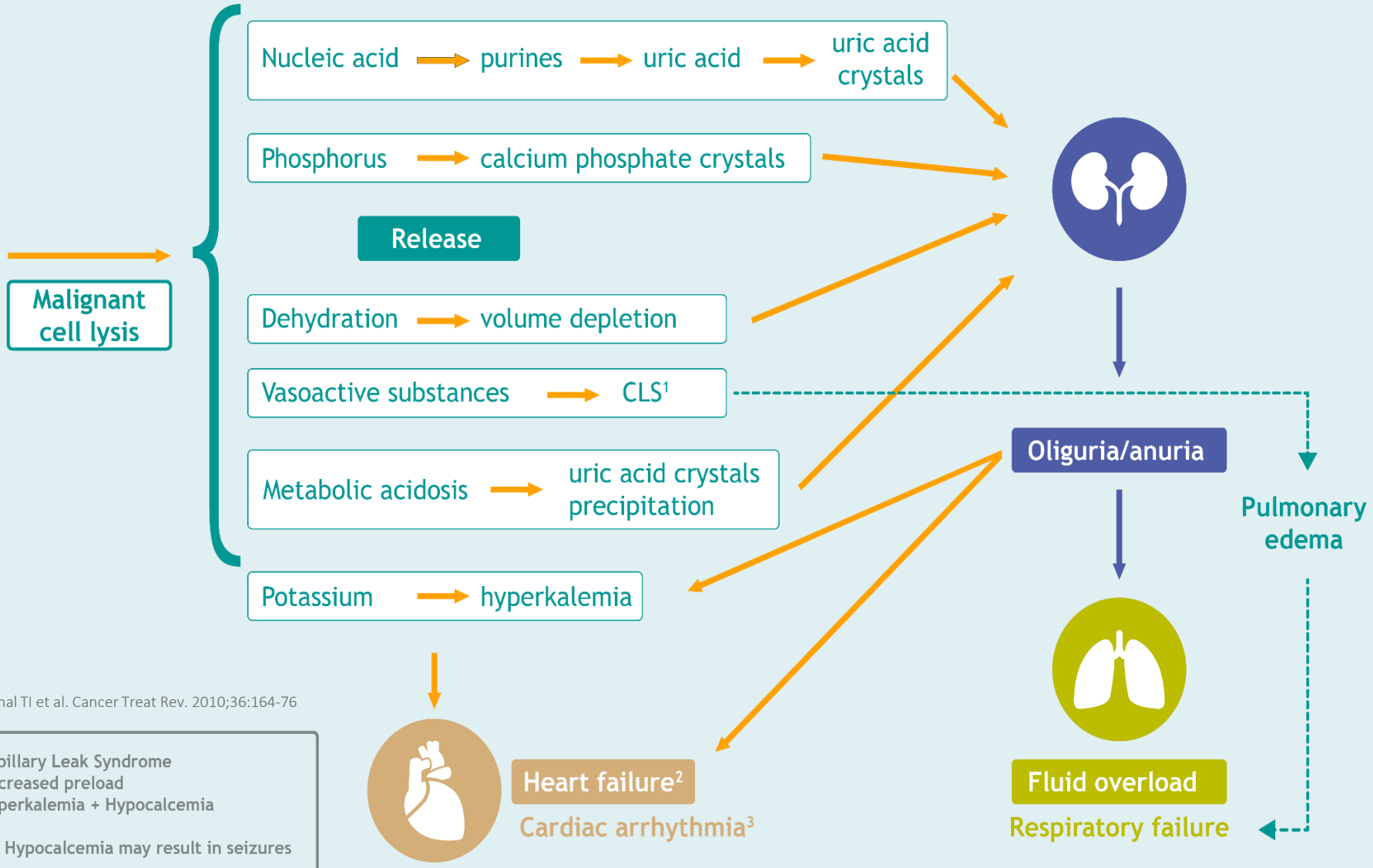
- Nucleic acid Adenine is metabolized to hypoxanthine whereas guanine is metabolized to xanthine. Xanthine is then further metabolized into uric acid in a reaction that is catalyzed by xanthine oxidase.

- UA scavenges NO which is a potent vasodilator. So, Reduction of NO produces vasoconstriction and kidney ischemia.

- UA is also a pro-inflammatory agent and can cause the release of other cytokines that facilitate further injury to the kidney.

- AKI occurs through crystal-dependent and crystal-independent mechanisms.
- Crystal-dependent mechanisms : uric acid and/or calcium phosphate precipitation.
- Decreased urinary output can result in volume overload and cardiac failure, and low flow can, in turn, exacerbate crystal precipitation.
- An alkaline environment keeps uric acid in its more soluble form and prevents crystallization in the renal tubules. However, urine alkalinization may worsen renal function by precipitation of calcium phosphate, which is less soluble in an alkaline environment.
- With the widespread use of hypouricemic agents to prevent hyperuricemia, this controversial practice is no longer recommended.
- Crystal-independent mechanisms include loss of autoregulation, renal vasoconstriction, and local inflammation.
- TLS induced hypercytokinemia can result in hypotension, systemic inflammation, and multiorgan failure.

Metabolic Alterations and Clinical Consequences



Mughal TI et al. Cancer Treat Rev. 2010;36:164-76

1. Capillary Leak Syndrome
2. Decreased preload
3. Hyperkalemia + Hypocalcemia

Note. Hypocalcemia may result in seizures

TLS is an oncologic emergency characterised by metabolic derangements caused by massive and abrupt lysis of malignant cells

- *Characteristic LABORATORY findings of Tumor lysis syndrome include:*
  - *Hyperuricemia*
  - *Hyperkalemia*
  - *Hyperphosphatemia*
  - *Hypocalcemia*

TLS Incidence Today

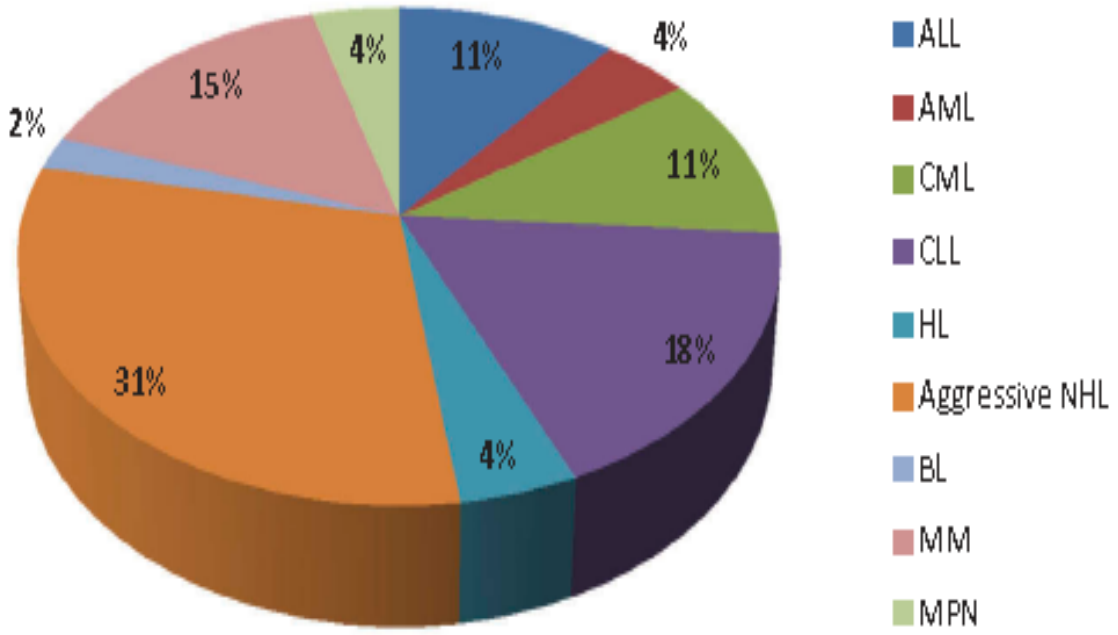


Figure 1. Percentage of TLS in the hematological neoplasms.

ALL: acute lymphoblastic leukemia; AML: acute myeloid leukemia; BL: Burkitt lymphoma; CLL: chronic lymphocytic leukemia; CML: chronic myeloid leukemia; HL: Hodgkin lymphoma; MM: multiple myeloma; MPN: myeloproliferative neoplasms; NHL: non-Hodgkin lymphoma.

Criscuolo M, et al. Expert Review of Hematology 2016; 9(2):197-208

Laboratory TLS (LTLS) _Cairo-Bishop definition

LTLS Is Defined As: Change For Two Or More Electrolytes As Defined Below Within 3 Days Before Or 7 Days After The Initiation Of Chemotherapy:

CRITERIA	STANDARD
URIC ACID	≥ (8mg/dL) or 25% increase from baseline
POTASSIUM	≥ 6 mmol/L or 25% increase from baseline
PHOSPHORUS	• ≥ (6.5mg/dL) in children • ≥ (4.5mg/dL) in adults • or 25% increase from baseline
CALCIUM	≤ (7mg/dL) or 25% decrease from baseline

1.Cairo MS et al. Br J Haematol.2004;127:3-11
2.Coiffier B et al. J Clin Oncol. 2008 Jun 1;26(16):2767-78

Laboratory TLS	Clinical TLS
Uric acid: ≥8.0 mg/dl	AKI (defined as creatinine >1.5× the upper limit of normal for patient age and sex)
Potassium: ≥6.0 mEq/dl	Cardiac arrhythmia
Phosphorus: ≥4.6 mg/dl	Seizure, tetany, or other symptomatic hypocalcemia
Calcium: ≤7.0 mg/dl	

Patients must meet more than two of four laboratory criteria in the same 24-hour period within 3 days before to 7 days after chemotherapy initiation. A >25% increase from "baseline" laboratory values is also acceptable (13). Other causes of AKI (*e.g.*, nephrotoxin exposure, obstruction) should be excluded. TLS, tumor lysis syndrome.

Clinical TLS (CTLS)_Cairo-Bishop definition

Presence of Laboratory TLS and any one or more of the below

CRITERIA	STANDARD
CREATININE	≥ 1.5 x ULN (age > 12 or age adjusted) or increase of 0.3 mg in creatinine in children
CARDIAC ARRHYTHMIA	
SUDDEN DEATH	
SEIZURE	

Cairo MS et al. Br J Haematol.2004;127:3-11

SANOFI GENZYME

Asymptomatic TLS defined by laboratory abnormalities (42%-70%)

symptomatic clinical syndrome (3%–27%)

Risk Factors for the Tumor Lysis Syndrome.

1. Cancer mass:-

Risk Factor	Comment
Bulky tumor or extensive metastasis	The larger the cancer mass have higher risk of clinical TLS
Organ infiltration by cancer cells	Hepatomegaly, splenomegaly, and nephromegaly generally represent tumor infiltration into these organs and a larger tumor burden
Bone marrow involvement	Healthy adults have 1.4 kg of bone marrow A marrow that has been replaced by leukemic cells contains a cancer mass greater than 1 kg and represents bulky disease.
Renal infiltration or outflow-tract obstruction	Decreased urine flow predispose to nephropathy from other causes, such as the tumor lysis syndrome.

Risk Factors for the Tumor Lysis Syndrome.

2. Cell lysis potential

Risk Factor	Comment
High rate of proliferation of cancer cells	LDH is a surrogate for tumor proliferation. The higher level is a risk of TLS
Cancer-cell sensitivity to anticancer therapy	Cancers that are more sensitive to therapy have a higher rate of TLS

Risk Factors for the Tumor Lysis Syndrome.

3. Features on patient presentation:

Risk Factor	Comment
Nephropathy before diagnosis of cancer	Predisposes to TLS
Dehydration or volume depletion	Dehydration decreases the rate of urine flow through renal tubules and increases the level of solutes
Acidic urine	Uric acid has a lower solubility in acidic urine and therefore crystallizes more rapidly
Hypotension	Hypotension decreases urine flow and increases the level of solutes that can crystallize. Hypotension can also independently cause acute kidney injury.
Exposure to nephrotoxins	Vancomycin, aminoglycosides, contrast agents for diagnostic imaging, and other potential nephrotoxins increase the risk of acute kidney injury from lysis of cancer cells.

Risk factors for developing TLS

- TLS occurs mainly after conventional chemotherapy.
- However, corticosteroids, radiation, or monoclonal Abs may also cause a significant TLS.
- Less frequent, spontaneous TLS can develop prior to initiation of anticancer therapy.
- Even invasive procedures like biopsy, embolization and tumor surgery could lead to TLS.

Table 5. Tumor Lysis Syndrome (TLS) Risk Assessment and Recommended Prophylaxis for Lymphomas, Acute and Chronic Leukemias, Myeloma, and Solid Tumors[a]

Cancer Type	High Risk (TLS Risk >5%)	Intermediate Risk (TLS Risk 1%–5%)[b]	Low Risk (TLS Risk <1%)[c]
Lymphomas and acute leukemias			
Lymphomas	Burkitt or lymphoblastic lymphoma Advanced stage or Early stage and LDH ≥2 times the ULN	Burkitt or lymphoblastic lymphoma Early stage and LDH <2 times the ULN	Cutaneous T-cell lymphoma Follicular lymphoma Hodgkin lymphoma MALT lymphoma Mantle cell lymphoma (nonblastoid variant) Marginal zone lymphoma Small lymphocytic lymphoma
ALL	WBC ≥100 × 10^3/μL or LDH ≥2 times the ULN	WBC <100 × 10^3/μL and LDH <2 times the ULN	
AML	WBC ≥100 × 10^3/μL	WBC 25 to <100 × 10^3/μL or LDH ≥2 times the ULN	WBC <25 × 10^3/μL and LDH <2 times the ULN
Other lymphomas (categorized by age and disease stage)			
Anaplastic large cell lymphoma		Children with advanced stage	Children with early stage Adults
ATL, DLBCL, mantle cell lymphoma (blastoid variant), peripheral T-cell lymphoma, and transformed lymphoma	Children with stage III or IV and LDH ≥2 times the ULN Adults with bulky disease and LDH >ULN	Children with stage III or IV and LDH <2 times the ULN Adults with nonbulky disease and LDH >ULN	Children with stage I or II Adults with normal LDH
Chronic leukemias, myeloma, and solid tumors			
CML			Chronic phase
CLL		Treatment using targeted and/or biologic therapies	
Myeloma			Myeloma
Solid tumors		Chemosensitive bulky solid tumors (eg, germ cell tumors, neuroblastoma, SCLC)	Solid tumors not meeting criteria for intermediate risk
Prophylaxis recommendations	Monitoring Hydration Rasburicase[d]	Monitoring Hydration Allopurinol or rasburicase[d,e]	Monitoring Hydration Consider allopurinol[f]

Abbreviations: ALL, acute lymphoblastic leukemia; AML, acute myelogenous leukemia; ATL, adult T-cell lymphoma; CLL, chronic lymphocytic leukemia; CML, chronic myeloid leukemia; DLBCL, diffuse large B-cell lymphoma; LDH, lactate dehydrogenase; MALT, mucosa-associated lymphoid tumor; SCLC, small cell lung cancer; TLS, tumor lysis syndrome; ULN, upper limit of normal; WBC, white blood cell count.

[a] Data derived from Cairo et al.[8]

[b] Patients with leukemia or lymphoma and intermediate-risk disease are high risk when renal dysfunction and/or renal involvement are present, or uric acid, phosphate, or potassium levels are elevated.

[c] Patients with leukemia or lymphoma and low-risk disease are intermediate risk for TLS when renal dysfunction and/or renal involvement are present.

[d] Rasburicase is contraindicated in patients with glucose-6-phosphate dehydrogenase deficiency and should be substituted with allopurinol in these patients.

[e] Rasburicase can be considered in the initial management for intermediate-risk patients and is the preferred agent if hyperuricemia develops.

[f] Allopurinol prophylaxis in low-risk patients is based on clinical judgment.

Cairo-Bishop Grading of clinical TLS

Table 2. Cairo-Bishop Grading of Clinical Tumor Lysis Syndrome (TLS)[a]

	Grade					
Complication	**0**	**1**	**2**	**3**	**4**	**5**
LTLS	Absent	Present	Present	Present	Present	Present
Creatinine[b,c]	<1.5 times the ULN	1.5 times the ULN	>1.5 to 3.0 times the ULN	>3.0 to 6.0 times the ULN	>6.0 times the ULN	Death[d]
Cardiac arrhythmia[b]	None	Intervention not indicated	Nonurgent medical intervention indicated	Symptomatic and incompletely controlled medically; controlled with device (eg, defibrillator)	Life-threatening (eg, associated with CHF, hypotension, syncope, shock)	Death[d]
Seizure[b]	None	Not applicable	One brief, generalized seizure; seizure(s) well controlled by anticonvulsants; infrequent focal motor seizures not interfering with ADL	Seizure in which consciousness is altered; poorly controlled seizure disorder; with breakthrough generalized seizures despite medical intervention	Any prolonged, repetitive, or difficult-to-control seizure (eg, status epilepticus, intractable epilepsy)	Death[d]

Xanthine Nephropathy

- Allopurinol (xanthine oxidase inhibitor) blocks uric acid synthesis

- Blockage of this pathway leads to accumulation of the uric acid precursors xanthine and hypoxanthine, of which hypoxanthine is more soluble and more easily excreted than uric acid.

- Xanthine is a less soluble metabolite than uric acid, and its accumulation can lead to xanthine precipitation.

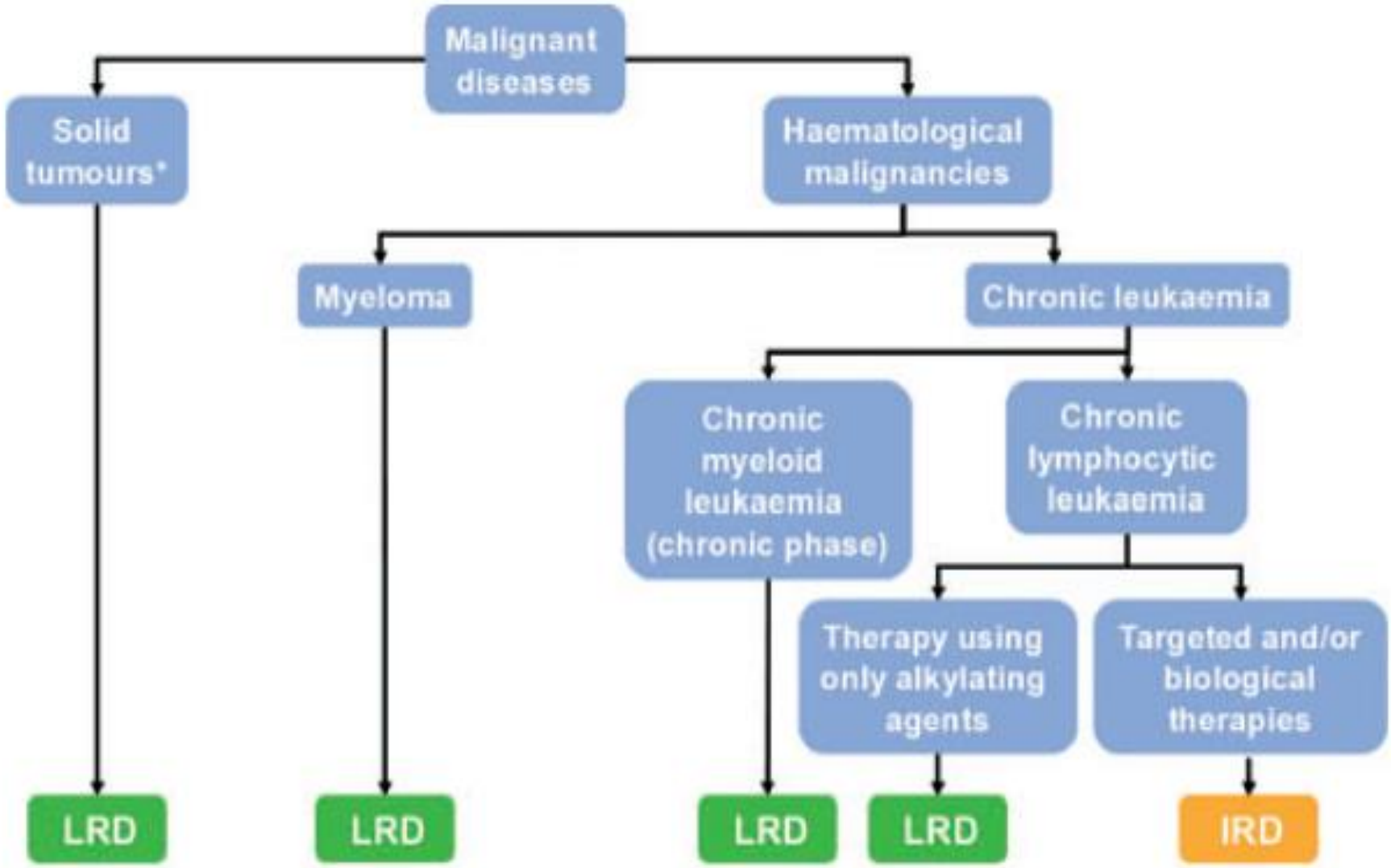
- The exact incidence of xanthine nephropathy is unknown.

- **Low-Risk Tumors for TLS**
- Solid cancers
- Indolent lymphomas
- CML
- AML with a WBC < 25,000 and LDH less than 2 ULN

- **Intermediate-Risk Tumors for TLS**
- AML with WBC between 25,000 and 100,000
- ALL with WBC < 100,000 and a LDH of less than 2 ULN
- DLBCL, non bulky and LDH of > 2 ULN
- Early stage Burkitt lymphoma or leukemia with a LDH < 2 ULN

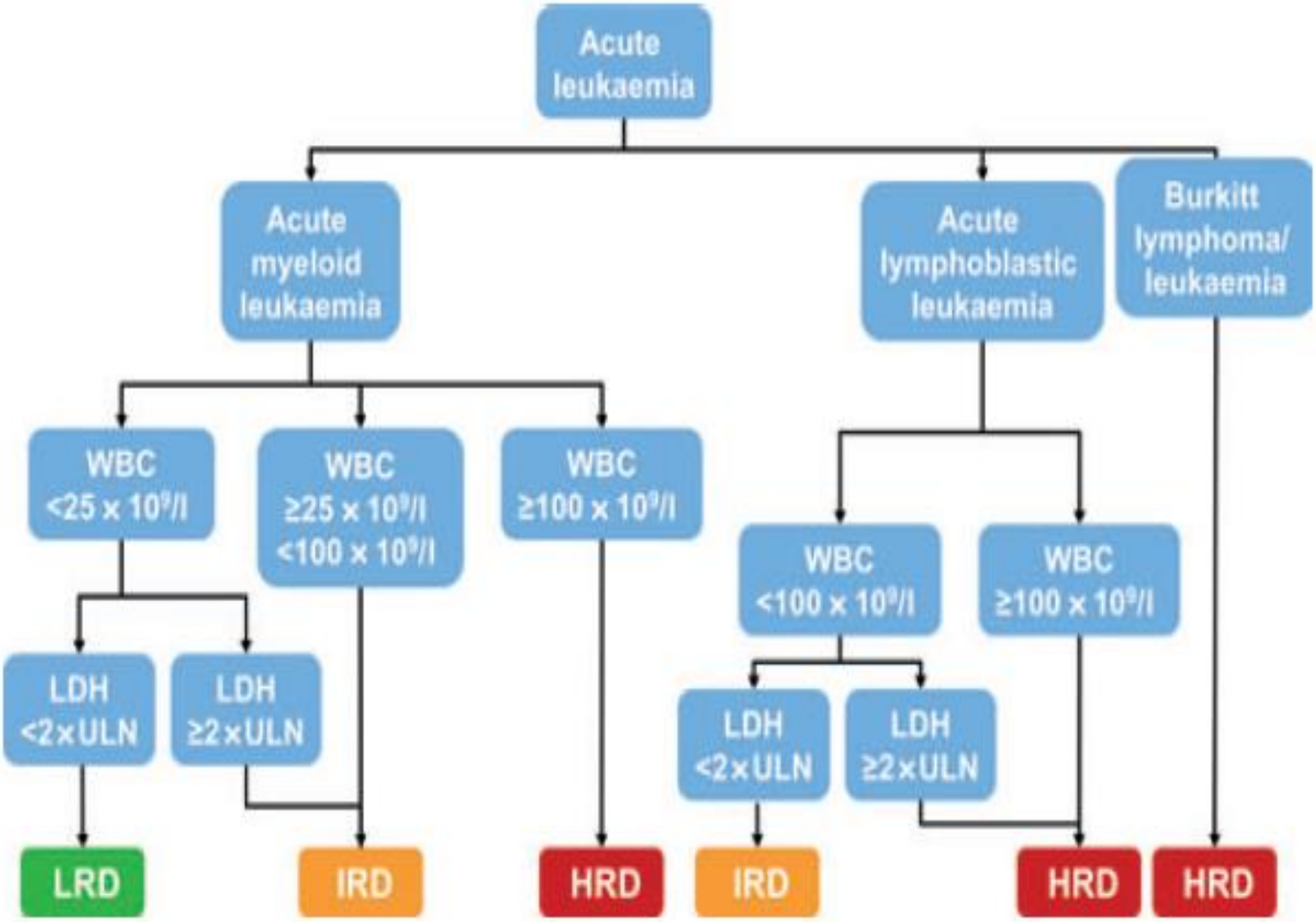
- **High-Risk Tumors for TLS**

- Advanced stage Burkitt OR Early stage Burkitt + LDH of > 2 ULN
- ALL with > 100,000 OR LDH of > 2 ULN
- AML with WBC > 100,000
- DLBCL , bulky disease with an elevated LDH of > 2 ULN

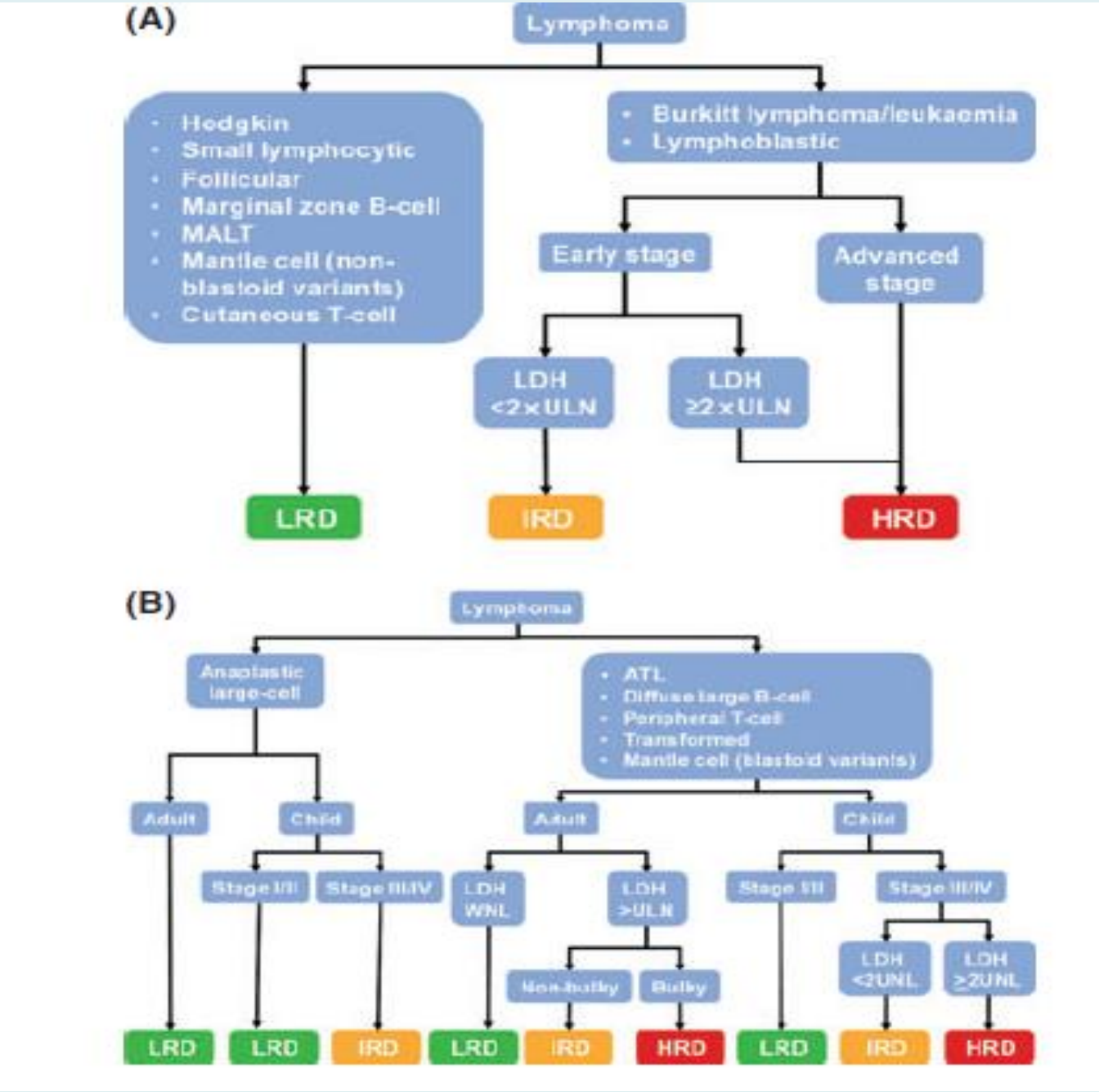


*Bulky, solid tumours, sensitive to chemotherapy, such as neuroblastomas, germ-cell tumours and small-cell lung cancer are **IRD**.

2010, British Journal of Haematology, 149, 578–586

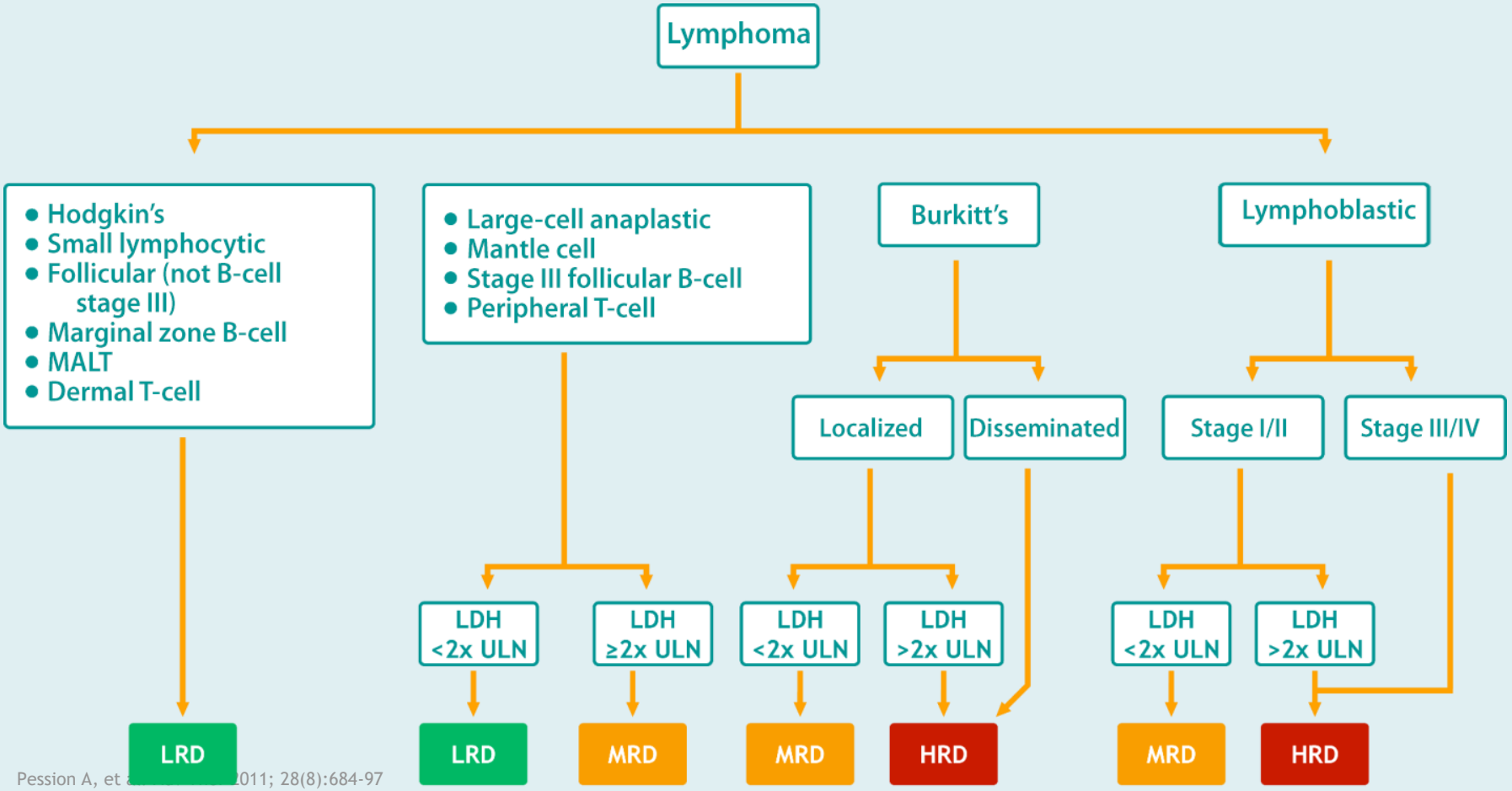


2010, British Journal of Haematology, 149, 578–586



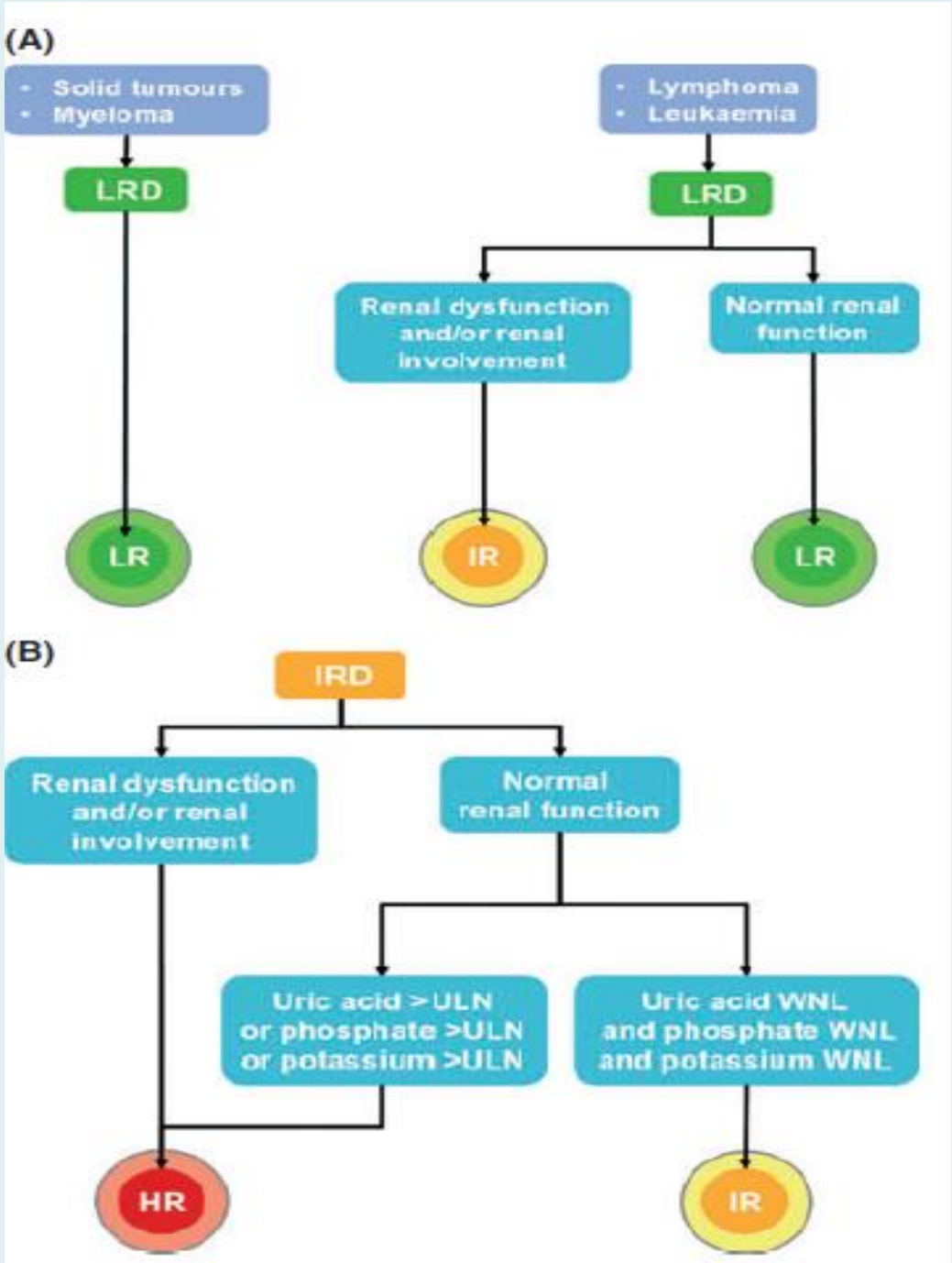
2010, British Journal of Haematology, 149, 578–586

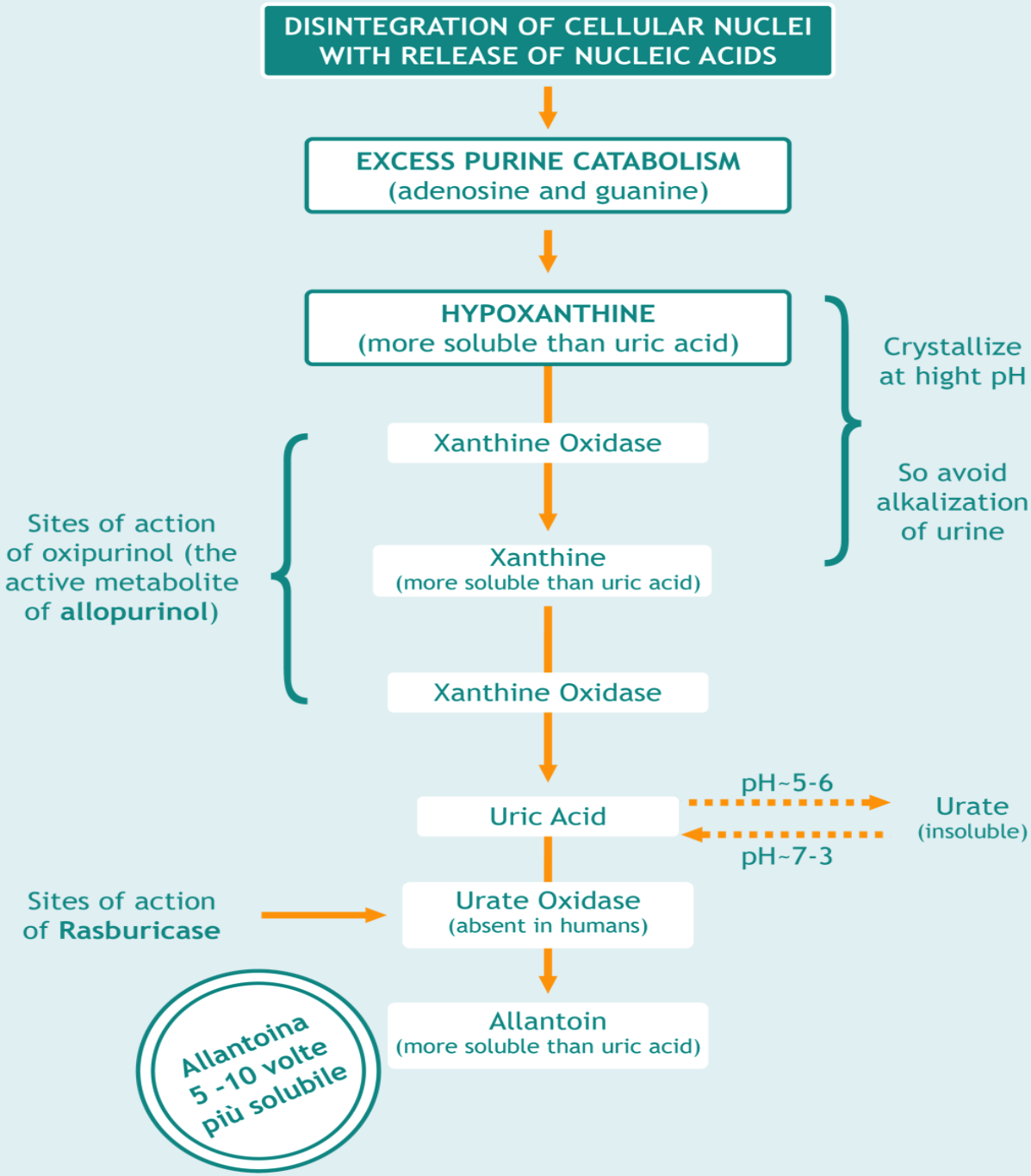
TLS Risk assessment based on disease characteristics



Pession A, et al. 2011; 28(8):684-97

LDH: Lactate Dehydrogenase;
LRD: Low-Risk Diseases; MRD: Medium-Risk Diseases; HRD: High-Risk Diseases


(A)
Solid tumours
Myeloma
LRD
LR
Lymphoma
Leukaemia
LRD
Renal dysfunction and/or renal involvement
IR
Normal renal function
LR
(B)
IRD
Renal dysfunction and/or renal involvement
HR
Normal renal function
Uric acid >ULN or phosphate >ULN or potassium >ULN
Uric acid WNL and phosphate WNL and potassium WNL
IR


DISINTEGRATION OF CELLULAR NUCLEI WITH RELEASE OF NUCLEIC ACIDS
EXCESS PURINE CATABOLISM (adenosine and guanine)
HYPOXANTHINE (more soluble than uric acid)
Crystallize at hight pH
So avoid alkalization of urine
Xanthine Oxidase
Sites of action of oxipurinol (the active metabolite of allopurinol)
Xanthine (more soluble than uric acid)
Xanthine Oxidase
pH~5-6
Uric Acid
Urate (insoluble)
pH~7-3
Sites of action of Rasburicase
Urate Oxidase (absent in humans)
Allantoina 5 -10 volte più solubile
Allantoin (more soluble than uric acid)

- **Medications that block uric acid production:**
  - xanthine oxidase inhibitors (XOIs)
    - Allopurinol (Aloprim, Lopurin, Zyloprim)
    - Febuxostat

- **Medication that improves uric acid removal:**
  - uricosurics
    - Probenecid (Probalan)
    - Lesinurad (Zurampic)

www.mayoclinic.org/diseases-conditions/gout/diagnosis treatment/drc-20372903

Allopurinol (Xanthine oxidase inhibitor)

- Allopurinol inhibits : xanthine → Uric acid
- So the level of xanthine in the serum and urine can be elevated after administration of allopurinol
- Xanthine has limited solubility and can crystallize in the renal tubules making worse the obstructive uropathy.
- Allopurinol is ineffective in the treatment of already existing hyperuricemia.

Allopurinol Limitations

1) It does not break down preexisting uric acid, so urate nephropathy can develop in the 2-3 days until therapeutic effects appears and is not the preferred agent in the presence of hyperuricemia.

2) xanthine nephropathy must be considered in patients who develop TLS while receiving allopurinol.

3) Allopurinol dose must be reduced or discontinued in patients with renal insufficiency.

4) hypersensitivity skin reactions have occurred.

5) Allopurinol reduces purine degradation, so, 6-mercaptopurine must be dose reduced by 50% to 70 when concurrently administered.

Rasburicase, Recombinant urate oxidase

- Rasburicase converts uric acid to the highly soluble form allantoin.
- It is highly effective at preventing and treating hyperuricemia and is the preferred prophylactic agent for patients at high risk for TLS and the treatment of choice for established TLS.
- Unlike allopurinol,rasburicase rapidly reduces uric acid levels without a delay and breaks down existing uric acid.
- Elevated serum phosphate and serum creatinine levels have also been shown to decrease with rasburicase.
- Rasburicase does not require renal dosing.
- Rasburicase is contraindicated in pregnant or lactating women and in patients with G6PD deficiency because of the risk of severe hemolytic anemia and methemoglobinemia
- There may be a risk for severe hypersensitivity reactions, such as anaphylaxis, particularly with repeat dosing.

Recombinant Urate Oxidase (Rasburicase)

- Byproduct of “Hydrogen peroxide” can cause severe methemoglobinemia or hemolytic anemia in patients with G6PD deficiency.

- EMA approved the dosage of 0.15–0.20 mg/kg/day, once daily up to 7 days according to uric acid levels and physician choice.

- Fasturtec is administered as a once daily 30 minute IV infusion in 50 ml of 0.9% solution.

PREVENTION OF TLS

- Expert panels have published guidelines with risk-based prevention strategies for pediatric and adult patients

- There is overlap in the prevention and management of TLS between different risk groups.

PREVENTION OF TLS in Low risk

- A ‘‘watch and wait’’ strategy may be appropriate and includes :

- vigilant monitoring of laboratory parameters and fluid status

- And consideration of allopurinol prophylaxis.

Prevention Of TLS In Intermediate Risk

- Aggressive intravenous hydration

- Administration of prophylactic allopurinol started at least 24 hours before initiation of chemotherapy and should be continued until normalization of uric acid levels or until signs of large tumor burden are absent .
- vigilant monitoring of laboratory parameters and fluid status.

- Rasburicase can be considered as the initial hypouricemic agent or following allopurinol and should be initiated in place of allopurinol if hyperuricemia develops.

PREVENTION OF TLS in High risk

- it is recommended to start aggressive hydration before initiation of treatment (3 liters/m2/day)
- Administration of prophylactic rasburicase, before the initiation of chemotherapy.
- Rasburicase should be used with caution in patients with G6PD deficiency.
- It is advisable to start rasburicase in patients which hyperuricemia might delay the initiation of chemotherapy

Sodium Bicarbonate for Urine Alkalinisation

- **The solubility of uric acid in urine is increased to 10-fold with the alkalinization of urine with adding about 40 to 50 mEq/liter of sodium bicarbonate to the fluid**

- **Alkalinization of urine results in decrease in level of ionized Ca leading to arrhythmia or tetany, favors precipitation of calcium and phosphate salts in the kidney tubules thus making obstructive uropathy and AKI worse.**

- **Alkalinization of urine with sodium bicarbonate is only advised if rasburicase is not readily available.**

- **Calcium gluconate can be administered parenterally to treat hypocalcemia. Administration of calcium can potentiate deposition of calcium phosphate crystals in soft tissues and making "acute kidney injury" worse.**

- Rasburicase reduces uric acid levels within 4 hours after administration and can be initiated before beginning of chemotherapy.

- Where rasburicase is used in the prophylaxis or treatment of TLS, the addition of allopurinol is unnecessary and has the potential to reduce the effectiveness of rasburicase

	Allopurinol	Rasburicase
Formulation	Oral and IV	IV
Mechanism of action	Inhibition of xanthine oxidase	Uricolytic agent that catalyses enzymatic oxidation of uric acid into allantoin
Effects on AU	Decrease UA synthesis; no effect on pre existing UA	Increase of UA catabolism
Speed of Action	Slow (1-2 days)	Fast (4 h)
Plasma half life	• 1-2 h • 15 h oxipurinol (active metabolite)	• 16 h per dose 0,15 mg/kg • 21 h per dose 0,20 mg/kg
Dose adjustment for reduced organ function	• Reduction in case of reduced renal function • No reduction in case of reduced liver function	No reduction in case of reduced kidney or liver function
Drug – drug interaction	Thiazide diuretics, 6-mercaptopurine or azathioprine, dicumarol, clorpropamide, ciclosporin, cyclophosphamide and other cytotoxic agents (increased myelosuppression), ampicillin or amoxicillin (increased rash)	• No data available from clinical studies • No interaction with cytochrome P450 in preclinical in vivo studies

- Serum creatinine and phosphate levels were significantly higher in LTLS group after 24 h of rasburicase administration.

- Although the serum UA level decreased with rasburicase after chemotherapy, it is crucial to monitor serum creatinine and phosphate levels within 24 h.

- Factors that may indicate the onset of TLS and are important to monitor include serum UA, creatinine and phosphate levels.

Molecular And Clinical Oncology 6: 955-959, 2017

- No dose adjustment is necessary in Pediatric, Renal or Hepatic impaired patients
- Administration of Rasburicase does not require any change in the timing or schedule of initiation of chemotherapy.
- Rasburicase solution should be infused through a different line than that used for infusion of chemotherapeutic agents to prevent any possible drug incompatibility.
- No filter should be used for infusion.
- Do not use any glucose solution for dilution due to potential incompatibility.

Reconstitution of the solution:

- Add the content of one ampoule of solvent to one vial containing Rasburicase and mix by swirling very gently under controlled and validated aseptic conditions.
- Do not shake.
- Inspect visually prior to use. Only clear and colorless solutions without particles should be used.
- For single-use only, any unused solution should be discarded.

Special precautions for storage

- Powder in vial: store in a refrigerator (2°C -8°C) and Do not freeze.
- Store in the original package in order to protect from light.

Table 2 Recommendations for prevention and treatment of tumor lysis syndrome

	Low-risk disease	Intermediate-risk disease	High-risk disease
Diagnostic measures	• No specific measures	• Daily monitoring of laboratory abnormalities before and during the first 7 days of anticancer therapy	• At least twice daily monitoring of laboratory abnormalities before and during the first 7 days of anticancer therapy
Preventive measures	• Moderate hydration is recommended	• Vigorous hydration • Keep urinary output >100 mL/h • Treatment with allopurinol or febuxostat should be started at least 24 hours before initiation of anticancer therapy and should be continued till normalization of uric acid levels and signs of large tumor burden are absent	• Vigorous hydration • Keep urinary output >100 mL/h • Single dose 6 mg of rasburicase. Repeat doses as necessary. In case of contraindication treatment with febuxostat
Treatment of established tumor lysis syndrome	• Admission to intensive care unit with continuous cardiac monitoring and monitoring of laboratory abnormalities every 4–6 hours • Early nephrology consultation to estimate the indications for renal replacement therapy • Correction of electrolyte abnormalities • Vigorous hydration, keep urinary output >100 mL/h • Single dose 6 mg of rasburicase. Repeat doses as necessary. In case of contraindication, treatment with febuxostat		

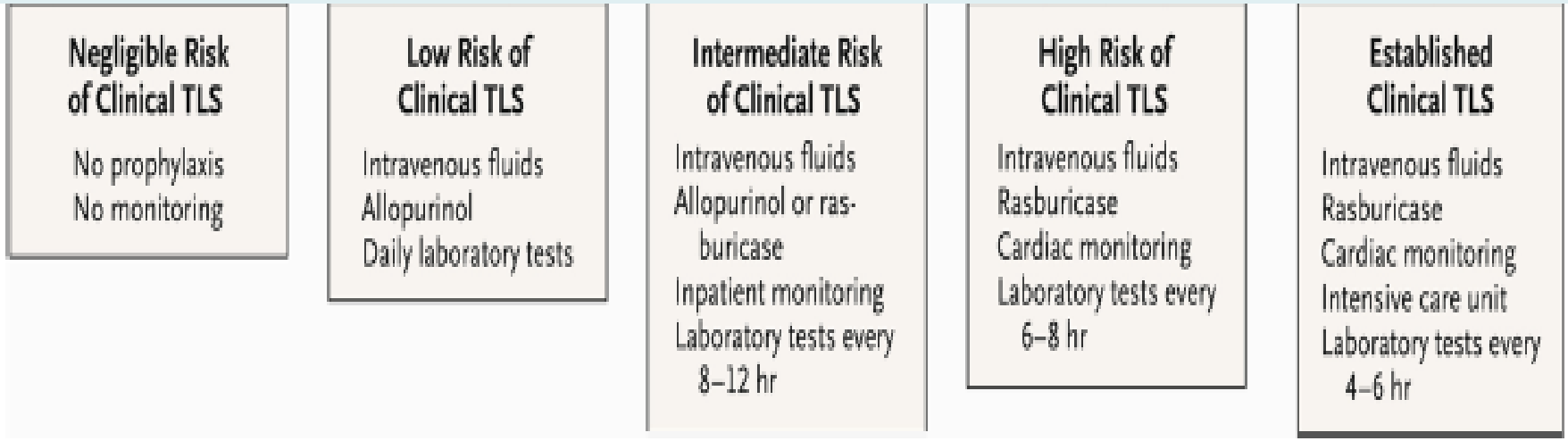


Figure 1 Tumor lysis syndrome treatment (TLS) stratification algorithm [1].

Calcium

Calcium gluconate can be administered parenterally to treat hypocalcemia.

- Treatment of asymptomatic hypocalcemia is generally not recommended.
- In patients with symptomatic hypocalcemia, IV calcium gluconate (50-100 mg/kg /dose) may be administered to correct the clinical symptoms

Hemodialysis

- This is an option that is available to use in situations where the level of potassium and phosphorus is too high in TLS associated AKI.
- If intermittent hemodialysis is utilized for extracorporeal clearance, a rebound hyperkalemia or hyperphosphatemia might develop.
- Because of this, continuous renal replacement therapy is the best modality for solute removal. (high flow rate dialysis)
- For life-threating hyperkalemia and severe hyperphosphatemia, early hemodialysis is recommended.

Hemodialysis

Indications for hemodialysis

- Refractory volume overload
- oliguria or anuria
- persistent hyperkalemia or hyperuricemia despite medical treatment
- persistent hyperphosphatemia, symptomatic hypocalcemia, and a calcium phosphate product of greater than 70 mg/Dl
- preexisting renal disease or ARF at presentation

The need for hemodialysis appears to have been reduced since the addition of rasburicase to induction therapy

Febuxostat

- This medication is also a xanthine oxidase inhibitor that is relatively new to the market (2009 FDA)

- Febuxostat provides better control of hyperuricemia with a good safety profile and preservation of renal functions.

- febuxostat represents an attractive alternative to allopurinol in patients with renal insufficiency or hypersensitivity to allopurinol

Medical Treatment for TLS

Hyperkalemia ($\uparrow K^+$)	Hyperuricemia ($\uparrow$ Urea Acid)	Hyperphosphatemia ($\uparrow PO_4^{3-}$)	Hypocalcemia ($\downarrow Ca^{2+}$)
≥6.0 mmol/L or 6 mg/L or ↑ 25% from baseline	≥476 µmol/L or 8 mg/dL or ↑ 25% from baseline	≥2.1 mmol/L or ↑ 25% from baseline	≤1.75 mmol/L or ↓ 25% from baseline
Administer oral or rectal sodium polystyrene sulfonate (1 g/kg with 50% sorbitol)	Rasburicase therapy:	• Avoid IV phosphate administration	• No therapy for asymptomatic patient
If K^+ >7 mmol/L	Dosage: 0.10-0.2 mg/kg/dose IV over 30 minutes daily until uric acid levels have normalized and patient is clinically stable. Duration of treatment: from 1 to 7 days	• Administration of phosphate binder	• If symptomatic, calcium gluconate 20-100 mg/kg IV administered slowly with ECG monitoring
• calcium gluconate 100-200 mg/kg by slow IV infusion for life-threatening arrhythmias		• Severe ↑ $PO4^-$, hemodialysis, peritoneal dialysis or continuous veno-venous hemofiltration	
• Regular insulin (0.1 U/kg IV) + D25 (2 mL/kg) IV • Sodium bicarbonate (1-2 mEq/kg IV push); sodium bicarbonate and calcium should not be administered through the same line			

Vigorous hydration: 2-3 L/m^2/day (or 200 mL/kg/day if weight ≤10 kg): To maintain renal blood flow and urine flow, promoting urinary excretion of K^+, PO_4^{3-}, and uric acid. Diuretics may be necessary to maintain adequate urine output, but it is

Table 4. Management Recommendations Based on TLS Risk Category

Risk category	Laboratory tests	Monitoring	Hydration	Uric acid control	Phosphorus control	Potassium control
Negligible	None	None	None	None	None	None
Low	Daily	Patient education to call health-care provider if vomiting occurs or unable to take oral fluids	Aggressive oral hydration or maintenance intravenous fluids plus oral intake	None or oral allopurinol	None	Avoid potassium in intravenous fluids
Intermediate	Every 8–12 h	Inpatient observation	Intravenous fluids at ≥ 2,500 mL/m²/d with close monitoring both to ensure adequate urine output and avoid fluid overload	Oral allopurinol or rasburicase, or rasburicase followed by allopurinol	Low-phosphorus diet, oral phosphate binder if phosphorus level elevated	Avoid potassium in intravenous fluids and diet, sodium polystyrene sulfate if potassium is near the upper limits of the normal range
High-risk or established laboratory TLS	Every 6–8 h	Inpatient observation with cardiac monitor	Intravenous fluids at ≥ 2,500 mL/m²/d	Rasburicase	Low-phosphorus diet, oral phosphate binder	Avoid potassium in intravenous fluids and diet, sodium polystyrene sulfate if potassium is near the upper limits of the normal range
Established clinical TLS	Every 4–6 h	Intensive care unit with cardiac monitoring	Intravenous fluids at ≥ 2,500 mL/m²/d	Rasburicase	Low-phosphorus diet, oral phosphate binder	Avoid potassium in intravenous fluids and diet, sodium polystyrene sulfate if potassium is near the upper limits of the normal range
Comments			Once the patient is well hydrated, diuretics may be added if necessary to maintain high urine output	Rasburicase dose of 0.15–0.2 mg/kg/d may be repeated if uric acid levels increase again after responding to an initial dose	Phosphate binders include lanthanum, sevelamer, and others	

J Adv Pract Oncol 2017;8:705–720

Int J Clin Oncol. 2016 Oct;21(5):996-1003. Epub 2016 Mar 26.

Efficacy and safety of febuxostat for prevention of tumor lysis syndrome in patients with malignant tumors receiving chemotherapy: a phase III, randomized, multi-center trial comparing febuxostat and allopurinol.

Tamura K[1], Kawai Y[2], Kiguchi T[3], Okamoto M[4], Kaneko M[5], Maemondo M[6], Gemba K[7], Fujimaki K[8], Kirito K[9], Goto T[10], Fujisaki T[11], Takeda K[12], Nakajima A[13], Ueda T[14].

Author information

Abstract

BACKGROUND: Control of serum uric acid (sUA) levels is very important during chemotherapy in patients with malignant tumors, as the risks of tumor lysis syndrome (TLS) and renal events are increased with increasing levels of sUA. We investigated the efficacy and safety of febuxostat, a potent non-purine xanthine oxidase inhibitor, compared with allopurinol for prevention of hyperuricemia in patients with malignant tumors, including solid tumors, receiving chemotherapy in Japan.

METHODS: An allopurinol-controlled multicenter, open-label, randomized, parallel-group comparative study was carried out. Patients with malignant tumors receiving chemotherapy, who had an intermediate risk of TLS or a high risk of TLS and were not scheduled to be treated with rasburicase, were enrolled and then randomized to febuxostat (60 mg/day) or allopurinol (300 or 200 mg/day). All patients started to take the study drug 24 h before chemotherapy. The primary objective was to confirm the non-inferiority of febuxostat to allopurinol based on the area under the curve (AUC) of sUA for a 6-day treatment period.

RESULTS: Forty-nine and 51 patients took febuxostat and allopurinol, respectively. sUA decreased over time after initiation of study treatment. The least squares mean difference of the AUC of sUA between the treatment groups was -33.61 mg h/dL, and the 95 % confidence interval was -70.67 to 3.45, demonstrating the non-inferiority of febuxostat to allopurinol. No differences were noted in safety outcomes between the treatment groups.

CONCLUSION: Febuxostat demonstrated an efficacy and safety similar to allopurinol in patients with malignant tumors receiving chemotherapy.

TRIAL REGISTRY: http://www.clinicaltrials.jp ; Identifier: JapicCTI-132398

Ann Oncol. 2015 Oct;26(10):2155-61. doi: 10.1093/annonc/mdv317. Epub 2015 Jul 27.

FLORENCE: a randomized, double-blind, phase III pivotal study of febuxostat versus allopurinol for the prevention of tumor lysis syndrome (TLS) in patients with hematologic malignancies at intermediate to high TLS risk.

Spina M[1], Nagy Z[2], Ribera JM[3], Federico M[4], Aurer I[5], Jordan K[6], Borsaru G[7], Pristupa AS[8], Bosi A[9], Grosicki S[10], Glushko NL[11], Ristic D[12], Jakucs J[13], Montesinos P[14], Mayer J[15], Rego EM[16], Baldini S[17], Scartoni S[17], Capriati A[17], Maggi CA[17], Simonelli C[17]; FLORENCE Study Group.

Author information

Abstract

BACKGROUND: Serum uric acid (sUA) control is of key relevance in tumor lysis syndrome (TLS) prevention as it correlates with both TLS and renal event risk. We sought to determine whether febuxostat fixed dose achieves a better sUA control than allopurinol while preserving renal function in TLS prevention.

PATIENTS AND METHODS: Patients with hematologic malignancies at intermediate to high TLS risk grade were randomized to receive febuxostat or allopurinol, starting 2 days before induction chemotherapy, for 7-9 days. Study treatment was blinded, whereas daily dose (low/standard/high containing allopurinol 200/300/600 mg, respectively, or fixed febuxostat 120 mg) depended on the investigator's choice. The co-primary end points, sUA area under curve (AUC sUA1-8) and serum creatinine change, were assessed from baseline to day 8 and analyzed through analysis of covariance with two-sided overall significance level of 5%. Secondary end points included treatment responder rate, laboratory and clinical TLS incidence and safety.

RESULTS: A total of 346 patients (82.1% intermediate TLS risk; 82.7% assigned to standard dose) were randomized. Mean AUC sUA1-8 was 514.0 ± 225.71 versus 708.0 ± 234.42 mgxh/dl ($P < 0.0001$) in favor of febuxostat. Mean serum creatinine change was -0.83 ± 26.98% and -4.92 ± 16.70% for febuxostat and allopurinol, respectively ($P = 0.0903$). No differences among secondary efficacy end points were detected. Drug-related adverse events occurred in 6.4% of patients in both arms.

CONCLUSION: In the largest adult trial carried out in TLS prevention, febuxostat achieved a significant superior sUA control with one fixed dose in comparison to allopurinol with comparable renal function preservation and safety profile.

CLINICAL TRIAL REGISTRATION: NCT01724528.