# IN The Name of GOD

# Tumor Lysis Syndrome
# TLS

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# Outlines

- ✓Introduction
- ✓Definition
- ✓Etiology
- ✓Diagnostic criteria
- ✓IncidenceOutcomes
- ✓AKI in TLS
- ✓**TLS prevention**

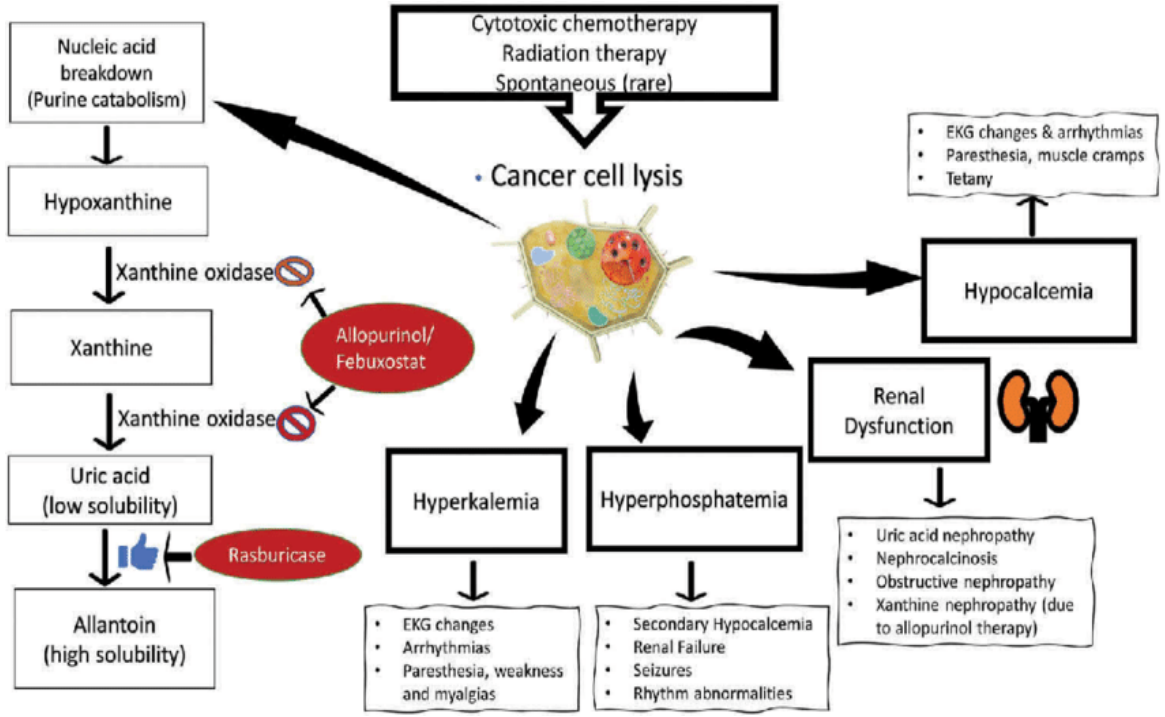
# Introduction

**Tumor lysis syndrome (TLS) is a**

hemato-oncologic emergency,

**characterized by**:

- ❖Hyperuricemia
- ❖ Hyperkalemia
- ❖Hyperphosphatemia
- ❖ Hypocalcemia
- ❖Metabolic Acidosis



# ETIOLOGY OF (TLS)

## A rapid break down of malignant cells

**cytotoxic therapy**

first 48–72 h after its initiation,

✓**laboratory signs** usually observed already 6–24 h after its initiation.

**spontaneous**, :

**rapidly proliferating high-grade hematologic malignancies:**

- Burkitt's lymphoma
- acute myeloid leukemia (AML)
- anaplastic large T-cell or
- diffuse large B-cell lymphoma

# Diagnosis of TLS

| laboratory form | clinical TLS |
| --- | --- |
| **Laboratory diagnosis of TLS**<br>**at least 2 criteria observed within a 24-hour period* | **Clinical diagnosis of TLS**<br>**laboratory diagnosis + at least one clinical criterion needed* |
| 1. Uric acid >8 mg/dl (475 umol/l) | 1. Acute kidney injury defined as creatinine ≥ 1.5 x upper limit of normal - *or* - its increase of ≥0.3 g/dl (26.5 µmol/l) - *or* - diuresis <0.5 ml/kg/hr for 6 hr |
| 2. Phosphate >4.5 mg/dl (1.5 mmol/l) | |
| 3. Potassium >6.0 mmol/l | 2. Cardiac dysrhythmia, sudden death probably or definitely caused by hyperkalemia |
| 4. Corrected calcium <7 mg/dl (1.75 mmol/l) *or* $Ca^{++}$ <4.5 mg/dl (1.12 mmol/l) | 3. Cardiac dysrhythmia, sudden death, seizure, neuromuscular irritability (overt and latent tetany, muscle twiching, paresthesias, broncho- and laryngospasm), hypotension or heart failure probably/definitely caused by hypocalcemia |



TLS, tumor lysis syndrome; AKI, acute kidney injury; ULN, upper limit of normal.

# The Incidence of TLS

**in the first-year decade of the 21st century**,

**novel anticancer therapies**,

- ✓the **Risk of TLS** – at least in certain diseases like
- ✓ **chronic lymphocytic leukemia** (CLL) – seemed **to be even Higher**.

**resulted in the development of:**

- strict preventive measures
- step-wise dosing
- which remarkably decreased the incidence of TLS .

# The Outcome of TLS

**Life threatening,**

**Poor outcomes,**

- ✓ **In-hospital mortality ranging : 21 to 32%,**
- ✓ **79% in AML patients during induction therapy .**

# AKI in TLS

## Oliguric

**crystal-dependent injury** due to precipitation of

- **uric acid**
- **calcium phosphate**

✓ in renal **tubules** with **obstruction of the tubular lumen.**

**Calcium phosphate** also **precipitates in the:**

- **interstitium**
- and **renal microvasculature**,

➢ **leading to nephrocalcinosis**.

- Both types of crystals are **toxic to the tubular epithelium**, inducing **local active inflammatory and pro-oxidative responses.**

- **Soluble uric acid** may induce:
- **hemodynamic changes,**
- **with decreased renal blood flow due to vasoconstriction and impaired autoregulation (crystal-independent pathway) .**

# AKI in TLS

**The aggravating factors include:**

1. **Volume depletion**
2. **Hypotension**
3. **Nephrotoxins**
4. **Radio-contrast exposure**
5. **Sepsis**
6. **Pre-existing kidney dysfunction.**

# Prevention of TLS and AKI

## 3-step algorithm :

1. **Risk factors for TLS :**to **identify**
2. **Prophylactic** measures: TO reduce the risk.
3. **Monitoring :laboratory and clinical.**

# Cancer-Related RISK Factors

- Burkitt lymphoma
- Rapidly growing high-grade non-Hodgkin lymphomas
- B-cell acute lymphoblastic leukemia
- AML with high white blood counts (>50K)
- CLL and when treated with newer anticancer therapies.

# Therapy-Related Factors

Several **novel targeted:**

✓ **molecular and immune cell-based Agents**

in **Combination with conventional cytotoxic agents ‘**

**more neoplasms with a**

- **low proliferation rate,**
- often **refractory to the traditional cytotoxic chemotherapies,**

became responsive to much more effective **new anticancer therapies.**

# Therapy-Related Factors

**the most dramatic changes have been observed** in :

- **CLL**
- **and small lymphocytic lymphoma (SLL).**

In general, the **treatment of CLL/SLL** targets :

## 3 major cell pathways in the pathogenesis of B-cell proliferation:

1. **Bruton tyrosine kinase (BTK)**
2. **phosphoinositide-3-kinase (PI3K)**
3. **B-cell lymphoma-2 receptor (BCL-2)**

# Therapy-Related Factors

**First-line treatment of <u>all</u> patients with CLL**

- ✓**BTK inhibitors (ibrutinib)**
- ✓**BCL-2 inhibitor( venetoclax)**

**Fludarabine,**

**cyclophosphamide,**

**rituximab**

# Therapy-Related Factors

**BTK Inhibitors :**
**ibrutinib**

- shrinking nodal disease
- tumor bulk reduction

**BCL-2 inhibitors**

- clearing CELLS FROM blood and bone marrow,


their **C**ombination and therapeutic sequencing may **p**ermit treatment of

**S**horter **d**uration and **l**ower **i**ntensity than chemotherapy,

# laboratory TLS

**Phase II CAPTIVATE study:**

BTK inhibitor, ibrutinib,

with BCL-2 Inhibitors venetoclax

**3 cases of :laboratory TLS**

**CLARITY study :** relapsed/refractory CLL

- **ibrutinib-venetoclax combination**,
- TLS 2% (**one of 50 patients**) .

# PI3K Inhibitors

**Block B-cell receptor signaling**

**idelalisib** and **duvelisib**,

**to treat** :

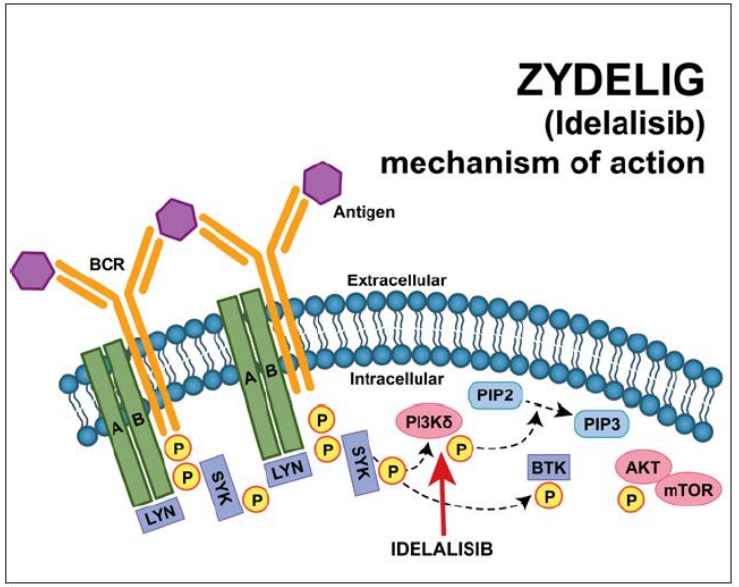
**Relapsed/refractory CLL and SLL**

phase III randomized **DUO study and the DYNAMO study**

**3 case reports of TLS** in patients treated with **idelalisib**,

Duvelisib

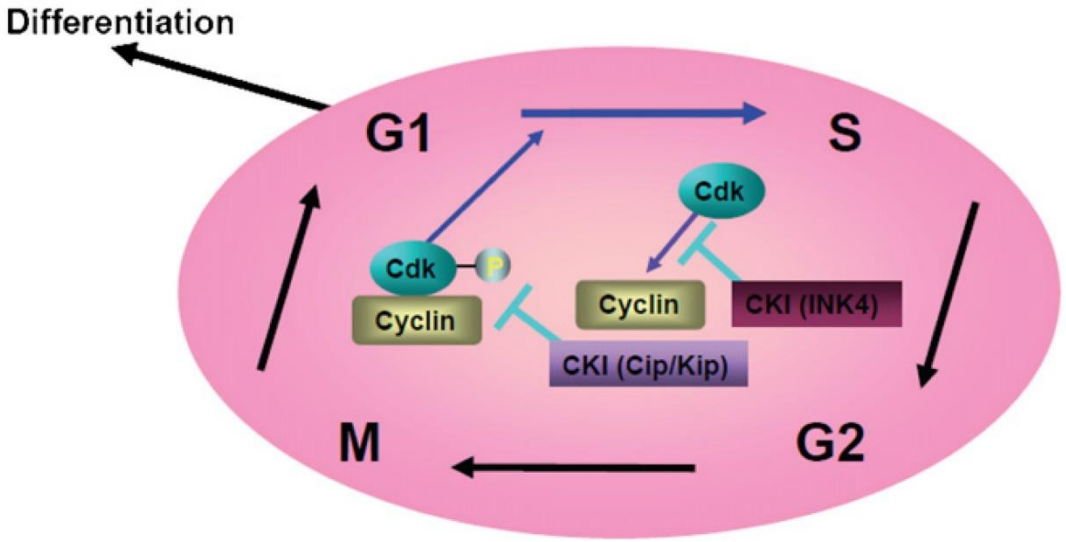




# CDK Inhibitors

CDK : The regulatory role in the **transition of cell steps** that are **necessary for its** **proliferation**

Cyclin: Cyclin A, D1, D2, D3, E
Cyclin-dependent kinase (Cdk): Cdk 2, 4, 6
Cdk inhibitor (CKI): p16, p15, p18, p19 (INK4 family)
p21, p27, p57 (Cip/Kip family)



# CDK inhibitors

**Alvocidib**

**Dinaciclib**,

- high-risk CCL
- acute leukemias
- multiple myeloma
- lymphomas,

nonselective, inhibitory effects

- Toxicity profile to healthy cells,
- severe side effects
- high incidence of TLS,
- 40–50% =laboratory TLS
- 15% = clinical TLS,
- *with many of them requiring immediate* ***hemodialysis***

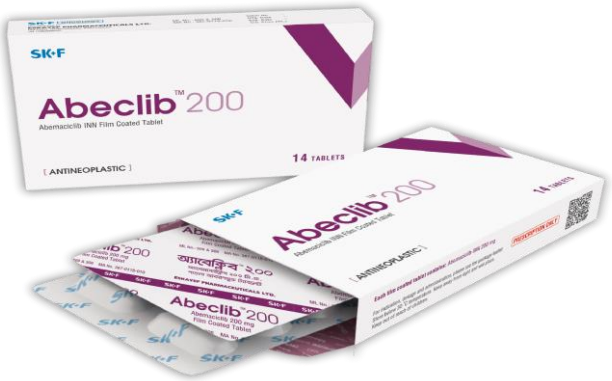

both drugs were **abandoned**

# Selective CDK inhibitors

- **Selective CDK4/6 inhibitors:**
  - **Palbociclib**
  - **Ribociclib**
  - **Abemaciclib**
  - with more favorable safety profile with
  - **no TLS syndrome** reported.
  - These drugs are FDA **approved as a frontline treatment of breast cancer** .



Image courtesy of Novartis.

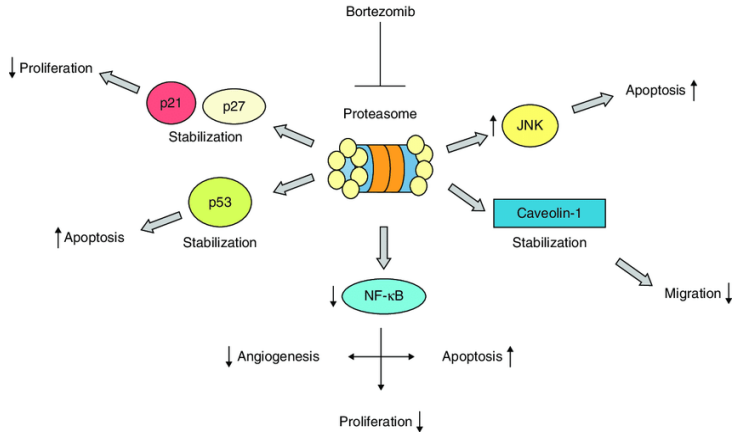


# Proteasome Inhibitors

- **Bortezomib**
- **Oprozomib**
- **Carfilzomib**
- **Ixazomib**

**multiple myeloma**

lymphoma,




after the introduction of ***proteasome inhibitors***,

- an increasing frequency of **TLS** has been reported,
- with an incidence of
- **1.4–5% for bortezomib,**
- **0.4–4.3% for carfilzomib,**
- **2.4% for oprozomib**

, the **risk of TLS** in **multiple myeloma** is **low**, given the disease's low proliferation rate.

# Monoclonal Antibodies

first-generation **anti-CD20 monoclonal antibody :**

**Rituximab**


TLS IS LOW,

Next-generations :**Obinutuzumab**,

in combination with chlorambucil IN : **relapsed/refractory CLL**,

**4.3% incidence of TLS** in **phase 3 ILLUMINATE study.**

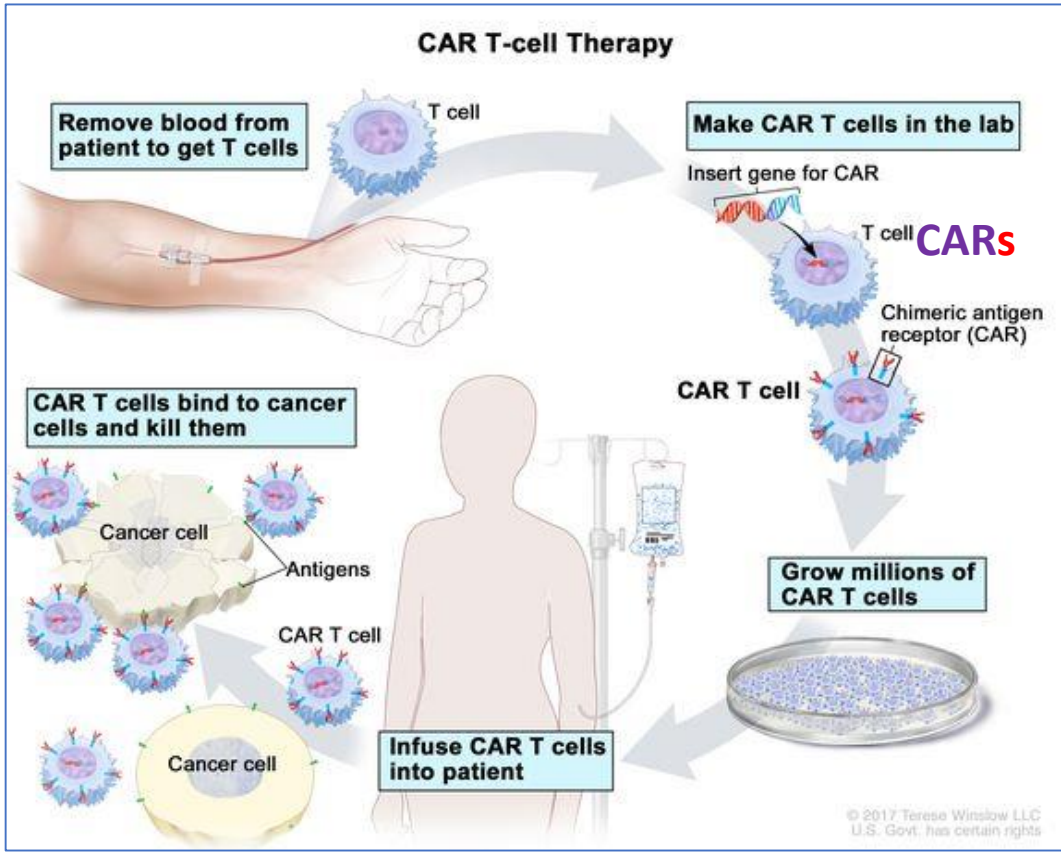
# CAR T-Cell Therapy

The therapy uses the **patient's cells**, **genetically engineered**

- to **produce specific chimeric antigen receptors (CARs) on their surface.**

to direct them **against the leukemic cells.**

these **modified cells are multiplied** and **infused back to the patient as therapy.**



# TLS after CAR T-cell therapy

✓ **In 2 large clinical studies** conducted in **adult patients** with **refractory large B-cell lymphoma,**

1. one with tisagenlecleucel
2. and a second with axicabtagene ciloleucel

✓ **no cases of TLS were reported**


**However, in the recent phase 2, 25-center study, a global study of**

**tisagenlecleucel in children and young adults with relapsed or refractory B-cell ALL,**

**TLS occurred in 3 of 75 patients (4%)**

NOW APPROVED
YESCARTA™
(axicabtagene ciloleucel) Suspension for IV infusion

# Prophylactic Measures

# Prophylactic Measures

- vigorous IV hydration
- urate-lowering therapy
- avoidance of exogenous potassium and phosphate

# Fluid Expansion

✓**Drink:**

*1.5–2.0 L of water daily* starting 2 days before **anticancer drug dosing** .

✓**Intravenous fluids :**

- at **least 24 h before the anticancer drug dosing**,
- provided that the patient is well hydrated,
- and **continued for 24–48 h after completion of the therapy**.

# Intravenous Fluid Expansion

- urinary output **>100 mL/h,**
- with **daily urine volumes of at least 3 L.**

evidence of **fluid overload**,
- or **with insufficient diuresis** despite well hydration,

➢ the **loop diuretics** may be considered.

❖ **Thiazide diuretics are contradicted** :

❖ **increase uric acid levels and interact with allopurinol**.

➢ In the era of

***Rasburicase***,

❑ urinary **alkalinization is no longer recommended.**

# Urate-Lowering Therapy

**xanthine oxidase inhibitor :**

**Allopurinol**

to treat patients at:

**low and intermediate risk of TLS**

**recombinant uricase:**

**rasburicase**

for patients with :

1. high risk,
2. renal failure,
3. and those with already existing TLS .

# Allopurinol

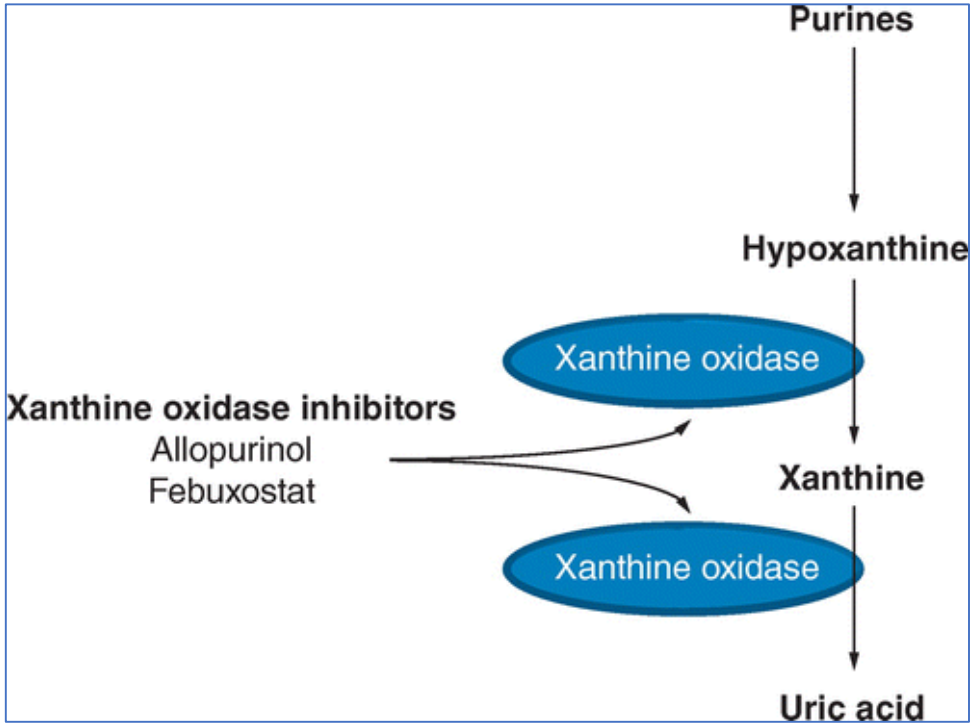
xanthine oxidase inhibitor,

**blocks the** conversion of nucleic acids released from cancer cells to **hypoxanthine to xanthine** and xanthine to uric acid .

Since it **does not remove the existing uric acid, it usually takes a few days to reduce its concentration**.

Therefore, it is ***recommended that***

- ❑the **treatment should be started 2–3 days before chemotherapy**
- ❑**continued at least for 10–14 days**
- ❑ or until the **signs of massive tumor lysis are absent** .



# Allopurinol

- orally
- **600–800 mg daily**.
- excreted by the kidney,

Dose reduction in

- **renal dysfunction**
- in patients **concomitantly treated with;**

**azathioprine**
**cyclophosphamide**
**6-mercaptopurine**
since it can **potentiate their cytotoxic effects**.

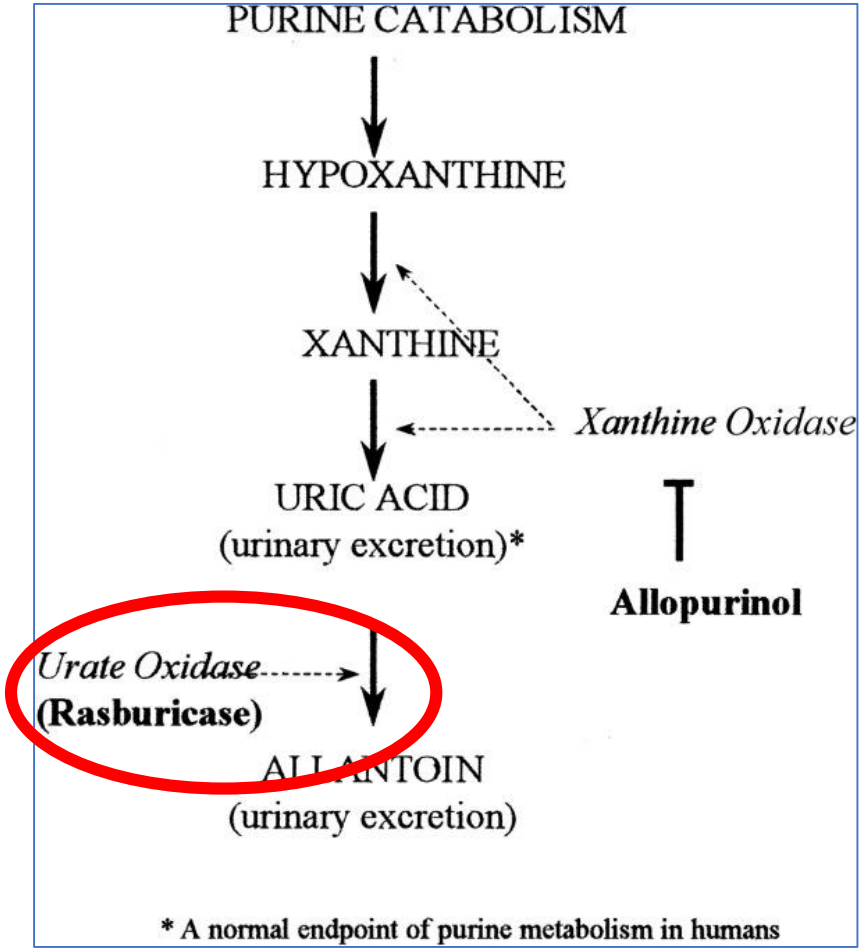
# Rasburicase
# recombinant urate oxidase

It **decreases serum uric acid concentrations** by

converting it into an inactive metabolite,

# allantoin,

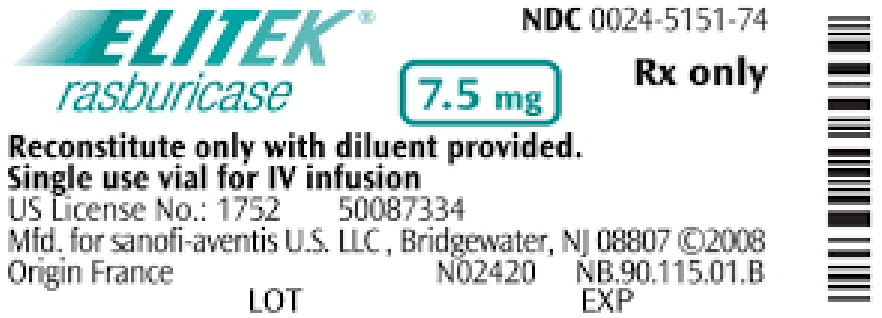
1. **easily soluble in water**
2. **excreted in the urine.**



# Rasburicase

- its action is immediate.,
- **rapid decrease in serum uric acid** concentration.
- **no need for rasburicase dose adjustment** in patients with renal dysfunction.

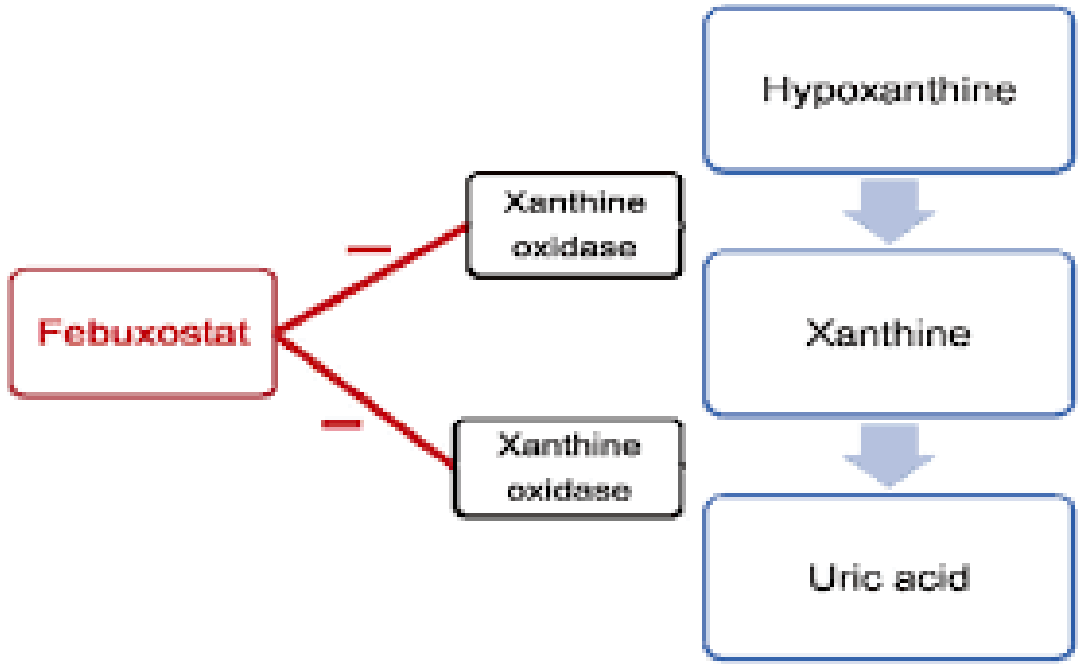
# Rasburicase




- ✓**<u>adults and children</u>.4–24 h before starting chemotherapy.**
- ✓The **labeled dose is 0.2 mg/kg**
- ✓daily :**30-min IV infusion,**
- ✓ for up to **5 days.**

# Febuxostat

- **non purine xanthine oxidase inhibitor**,
- the medication approved **for gout treatment**,
- is being tested in preventing TLS.



# Febuxostat

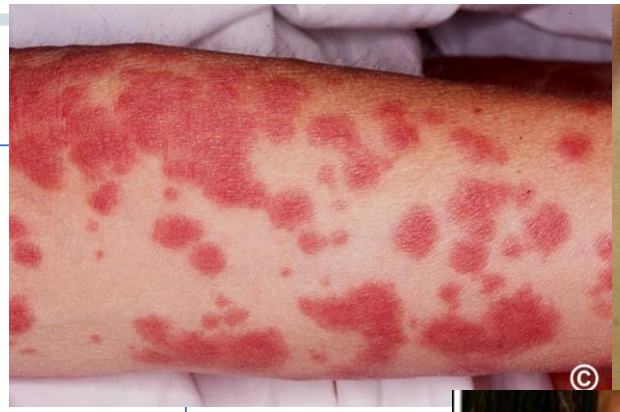
- ✓Since the drug is **metabolized via glucuronidation and oxidation**,
- ✓1–6% of the dose being excreted unchanged via the kidneys,
- ✓ **no dose adjustment is necessary for patients with mild or moderate renal impairment**

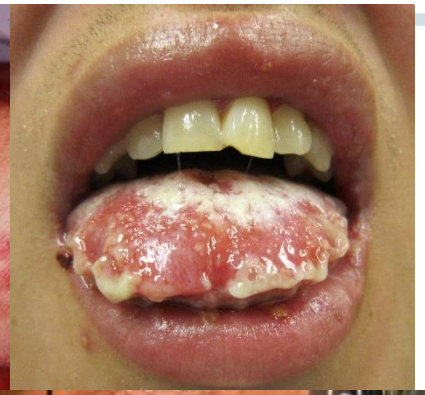
# Febuxostat
## 24 h before chemotherapy

✓**side effects**:

- ❑**Stevens-Johnson syndrome**
- ❑ anaphylaxis
- ❑increased risk of cardiac and all-cause mortality

✓**febuxostat use to the patients with hyperuricemia** who cannot tolerate allopurinol in a setting in which **rasburicase** is **not available** or is contraindicated .





❑Stevens-Johnson syndrome

# Allopurinol vs. Rasburicase

| | Allopurinol | Rasburicase |
|---|---|---|
| Uric Acid Effect | Prevents further uric acid production | Works on existing uric acid levels |
| Onset of Action | Days | Hours |
| Efficacy | Weak | Strong |
| Drug Interactions | Mercaptopurine, Azathioprine, Cyclophosphamide, and others | None known |
| Dosage Adjustments | Adjust for renal impairment | None needed |
| Black Box Warnings | None | Hypersensitivity, Hemolytic reactions, Methemoglobinemia, Effect on blood samples |
| Contraindications | None | G6PD deficient patients |
| Formulations Available | Tablets and extemporaneous suspension | IV |
| Cost | Inexpensive | Expensive |

# Monitoring Approach

- ✓ **In all patients who are beginning anticancer therapy,**
- ✓ several laboratory and clinical parameters should be carefully monitored.
- ✓ **serum potassium**
- ✓ **uric acid**
- ✓ **phosphate**
- ✓ **calcium**
- ✓ **creatinine concentration**
- ✓ **LDH activity**
- ✓ **diuresis and fluid balance**
- ✓ which should be assessed on an ongoing basis.

- The **frequency of laboratory parameter monitoring** depends on the risk of TLS.
- **low-risk patients: once daily**
- **intermediate risk :every 8–12 h**
- **high risk: every 4–6 h**
- to **start the monitoring before initiation of chemotherapy**
- **and continue as long as the patient is at risk for TLS,** which depends on the therapeutic regimen

# Hyperphosphatemia

**Malignant cells** contain up to:

- ✓ 4 times more phosphate than normal cells
- ✓ and this increases further in hyperproliferative states such as **blast crisis** .

# Hyperphosphatemia


**Phosphate-induced nephropathy** may be **aggravated** when:

- urinary **alkalinization** is used,
- **high urine pH favors precipitation of calcium phosphate** in the renal tubules.

# Hyperphosphatemia

✓the treatment :

1. **phosphate intake restriction**
2. avoidance of bicarbonates
3. **oral noncalcium phosphate binders**.

**severe acute serum phosphate increase**,

- ❖ the **prophylactic intensive care unit admission**
- ❖**renal replacement therapy**

**(RRT)**

- ➢ to prevent **disseminated metastatic calcium deposition**.

# Hyperkalemia

## life-threatening abnormality in TLS

**while waiting for hemodialysis,**

- **IV infusion of 10% dextrose with rapid-acting insulin, to drive potassium into the cells,**
- **IV calcium chlorate or gluconate to antagonize the membrane actions of hyperkalemia.**
- **If there is a risk of a longer delay before the dialysis is started, we administer oral gastrointestinal sodium-potassium exchange resins.**

- continuous cardiac rhythm monitoring
- an immediate nephrology consultation
- and urgent hemodialysis should be considered:

In case of emergency

- **(serum potassium >6.5 mmol/L,**
- **cardiac conduction abnormalities,**
- **arrhythmia,**
- **lengthening of the PR interval**
- **and widening of QRS,**
- **muscle weakness, or paralysis),**

# Hypocalcemia

- ✓ **A**symptomatic hypocalcemia often **resolves:**
- ✓ **Symptomatic patients** should be **treated** with:
- ✓ calcium at the **lowest doses** required to relieve symptoms

# Renal Replacement Therapy

- the **threshold for RRT initiation** may be lower than in other clinical situations, **for 3 reasons**.
- **First** is that the process of the cell break down is still ongoing and one cannot predict rapid increases in serum electrolytes in the individual patients, particularly in those with kidney dysfunction and oliguria.
- **Secondly**, early institution of RRT interrupts the pathological cascade with avoidance of life-threatening complications.
- **Last** but not least, it may **prevent irreversible kidney injury**.

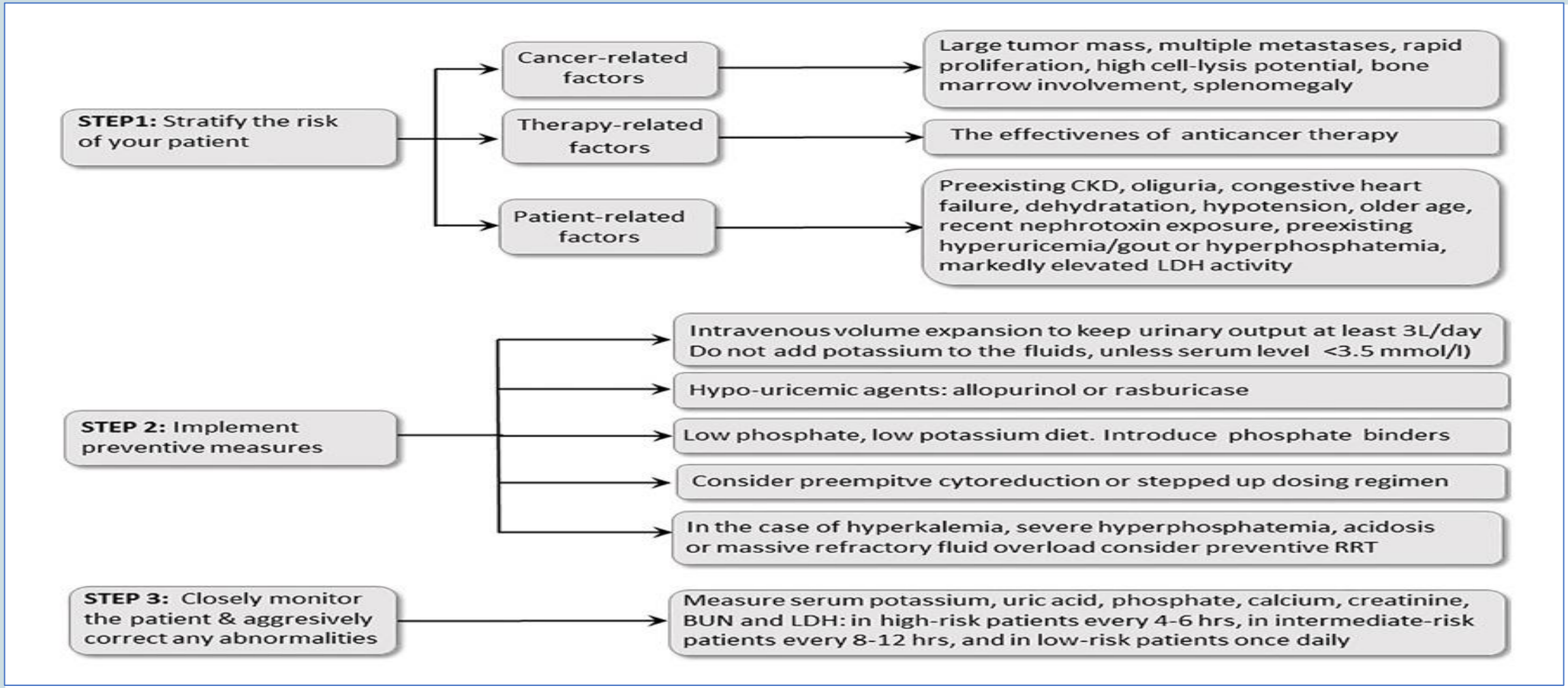
# Renal Replacement Therapy

**Early intervention is particularly favored**

in patients with:

- **congestive heart failure** who cannot tolerate large fluid volumes.

# Take Home Message




Thank you