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Tumor lysis Syndrome: Pathogenesis and Risk Factors with Special Reference to Hepatocellular Carcinoma – A review

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Abstract: *Tumor lysis syndrome is a major oncometabolic emergency associated with clinicolaboratory derangement of cellular metabolism, leading to severe renal impairment, cardiac dyssrhythmia, seizures and even death. Hepatocellular carcinoma (HCC) is one of the most common tumors worldwide. Tumor lysis in HCC may be spontaneous or secondary to cancer targeted specific treatment. The present review analyses the pathophysiology, risk factors, presentation and management of tumor lysis syndrome, especially in patients with Hepatocellular carcinoma*

1. INTRODUCTION

Tumor lysis syndrome (TLS) is a major oncometabolic emergency and is associated with clinicolaboratory derangement of cellular metabolism, which can lead to severe renal impairment, cardiac dyssrhythmia, seizures due to central nervous system toxicity and even death [1]. The cellular death mediated by tumor cell targeted treatment leads to an efflux of cellular material rich in potassium, phosphorus, and uric acid into the bloodstream. The diagnostic criteria proposed by Cairo et al [1] are

a. **Laboratory Tumor Lysis Syndrome (L-TLS):** This occurs within three days before or seven days after chemotherapy. Diagnosis is based on two or more of the following i.e. serum uric acid > 8 mg/dL or 25% increase, serum potassium > 6 meq/L or 25% increase, serum phosphate > 4.5 mg/dL or 25% increase or serum calcium < 7 mg/dL or 25% decrease.
b. **Clinical Tumor Lysis Syndrome (C-TLS)**: L-TLS in combination with one or more of the following i.e. increase in serum creatinine (1.5 times upper limit of normal) or cardiac dyssrhythmia or sudden death or seizure

A person is therefore likely to have L-TLS when TLS is clinically silent and is detected by only work up, or C-TLS, when laboratory TLS is complicated by clinical symptoms.

2. TUMOR LYSIS IN HEPATOCELLULAR CARCINOMA

HCC is one of the most common tumors worldwide. Men are affected more than women and it is most common between the 30 and 50 years of age. [2,3] The major causes of TLS in HCC are either spontaneous [4] i.e. when cancer cells die without preceding chemotherapy, embolization, or radiation therapy, or secondary to cancer targeted specific treatment e.g. following transarterial chemoembolisation / radiofrequency ablation[5-6], sorafenib therapy[7-10], or on low dose of steroids or thalidomide [11-12] or glypican derived peptide vaccination in experimental studies[13].

3. PATHOPHYSIOLOGY

The pathobiology of TLS and its complications are largely mediated by release of intracellular potassium, phosphorus and uric acid rich cancer cells. Hyperkalemia results in severe skeletal muscle dysfunction, weakness and electrocardiogram (ECG) changes including peaked narrow T waves, prolongation of PR and QRS interval. Ultimately, the cardiac effects of excess potassium lead to ventricular tachyarrhythmias and death. [14-16]

High uric acid can crystallize and obstruct the flow of urine in the renal tubules, leading to acute kidney injury. It can also cause endothelial dysfunction and local ischemia, proinflammatory and proxidative states, and impairment of local renal repair mechanisms [17, 18].

When in excess, phosphorus tends to bind to calcium, forming calcium phosphorus product or calcium phosphate [19, 20]. This product can be deposited in kidneys, mediating acute kidney injury, and in the cardiac tissue, leading to arrhythmia. Central nervous toxicity such as seizures, tetany and psychiatric complaints, [21] ensues due to secondary reduction in free calcium concentration. An interesting observation in spontaneous TLS has been a lower rate of hyperphosphatemia. This has been attributed to enhanced phosphate uptake by rapidly dividing tumor cells [19,20].

4. RISK FACTORS

Host Factors: These include

a. Old age and reduction in glomerular filtration rate [22]

b. Dehydration due to poor intake, nausea and vomiting

c. Concomitant use of drugs affecting the renal function like non-steroidal anti-inflammatory drugs, angiotensin converting enzyme inhibitors, and angiotensin receptor blockers

d. Co-morbidity like diabetes, cardiac and renal disease

Tumor Related Factors

Cairo et al[23] have stratified cancers into three risk groups: a high risk group, an intermediate risk group, and a low risk group. Hepatocellular carcinoma, being a solid tumor, falls into low risk group. (Table 1)

Table 1 .*risk stratification of tumors for TLS*

Stratification based on risk of TLS	Examples	Prophylaxis recommendations
Low risk	Solid tumours, multiple myeloma, chronic myeloid leukaemia, non-Hodgkin lymphoma, Hodgkin lymphoma	Monitoring, hydration, +/- allopurinol
Intermediate risk	Rare solid tumours, such as neuroblastoma, germ cell tumours and small cell lung cancer or others with bulky or advanced stage disease, may be classified as IRD	Monitoring,Hydration, allopurinol
High risk	Acute Myeloid Leukaemia and WBC $\geq 100 \times 10^9$/l Acute Lymphoblastic Leukaemia and WBC $\geq 100 \times 10^9$/l and/or LDH $\geq 2 \times$ ULN, Burkitt's Lymphoma stage III/IV and/or LDH $\geq 2 \times$ ULN	Monitoring, hydration, rasburicase

The clinical presentation and symptoms in any cancer are directly linked to the biochemical derangements observed in that disorder. Common symptoms include nausea, vomiting, muscular hyperactivation such as spasms and tetany, seizures, prolongation of QT interval on the ECG, cardiac dysrhythmias, and alterations of mental status. Blood investigations reveal the classical findings associated with tumor lysis. Imaging studies like computed tomography or magnetic resonance imaging may show evidence of tumor lysis.

5. PREVENTION BY RISK STRATEGY MANAGEMENT

One should always be aware of patient risk factors predisposing to TLS. Coiffier et al recommend adequate hydration to maintain urine output of at least 2 mL/kg per hour to minimize the risk of acute kidney injury. The choice of the fluid varies. Recommendations include the use of dextrose in one quarter normal saline as the initial fluid of choice [24]. Those with *intermediate risk* should be started on allopurinol at least 24 to 48 h prior to chemotherapy or radiation therapy to reduce the risk of uric acid nephropathy [24]. Patients who do not tolerate oral medication such as those with severe nausea, vomiting, or altered function of the gastrointestinal tract can be given intravenous allopurinol. The recommended dose of allopurinol is up to 800 mg a day orally or 100 mg per square meter, and up to 600 mg a day for intravenous formulation [24]. Allopurinol works by blocking the xanthine oxidase

enzyme. Febuxostat (xanthine oxidase inhibitor) can be used in patients with renal disease and does not seem to have allergy cross-reactivity with allopurinol [25]. A medication mimicking urate oxidase named rasburicase has also been approved by Food and Drug Association in 2012 for use in subjects at risk of TLS [26].

Urine alkalization has been used in the past to prevent TLS. It promotes uric acid solubility and its removal. Typically, a carbonic anhydrase inhibitor acetazolamide or sodium bicarbonate is used to acquire a urine pH of at least 6.5. However, this approach is not shown to be superior to the use of normal saline alone [27] and is not currently recommended.

6. MANAGEMENT

Patients with TLS, unless anuric, are managed with aggressive parenteral intravenous fluids (IV) with a goal to maintain a urine output of at least 2 mL/kg per hour. Individuals deemed to be at increased risk of fluid overload, such as those with cardiac and baseline renal disease, the administration of intravenous loop diuretics such as furosemide can decrease the risk of pulmonary edema and augment urine output.

Hemodialysis or renal replacement therapy is indicated in patients with refractory hyperphosphatemia, symptomatic hypocalcemia, and in presence of an elevated calcium phosphorus product of at least 70 $mg^2/dL^{2.}$

In the cardiac arrest setting, it is important to follow the advanced cardiac life support (ACLS) guidelines for its management and to rule out other possible causes of cardiac arrest such as hyperkalemia, hypokalemia, hypovolemia, acidosis, hypothermia, tension pneumothorax, cardiac tamponade, thrombosis of the coronary and/or pulmonary circulation, as well as toxin exposure[28].

The approach to seizure in the TLS setting should include exclusion of hypoglycemia (and corrected if present), other metabolic abnormalities (hypo- or hypernatremia, hypomagnesemia), cerebrovascular abnormalities (hemorrhagic and ischemic strokes, subarachnoid hemorrhage, etc.), brain tumors or metastatic disease, toxin exposure (such as amphetamines, cocaine, tricyclic antidepressants, etc.), alcohol withdrawal, benzodiazepine withdrawal, brain infection etc. [29].

7. CONCLUSION

TLS is today being increasingly recognized during management of hepatocellular carcinoma. This is partly related to the multimodality approach for treatment in patients with advanced age and renal dysfunction. Treating oncologists should be aware of this rare but potentially lethal entity to prevent morbidity and mortality. Management is supportive for the precipitating factors.

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