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The Pathophysiology of Tumor Lysis Syndrome in Oncology Patients

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Introduction

Patients with oncological conditions are at an increased risk of developing a wide variety of complications from chemotherapy that they would not otherwise be exposed too. One such life threatening complication is tumor lysis syndrome, which is an oncology emergency that frequently lands patients in the intensive care unit. Tumor lysis syndrome (TLS) occurs most frequently after the initiation of chemotherapy or other chemotoxic drugs during the patients' treatment course [8]. It causes faster than normal tumor cell breakdown and release of intracellular contents into the general circulation. [8]. This leads to a very predictable development of electrolyte imbalances to take place within the body, which if not treated can lead to end-organ damage as well as fatal cardiac dysrhythmias [8]. While TLS is fairly uncommon, there are specific factors that place some individuals at a higher risk of developing TLS then others. These include large tumor size, tumors with rapid cell division, and hematological cancers such as leukemia [3]. In addition, TLS can progress extremely quickly and has a high rate of morbidity and mortality [8]. It is important that nurses and physicians are educated and on the look out for TLS in high-risk individuals and initiate prophylactic treatment if indicated. Also, prompt recognition of TLS and initiation of treatment modalities is key to preventing end-organ damage and possibly death.

In oncology specific intensive care units, such as the medical intensive care unit at The James Cancer Hospital in Columbus, Ohio, TLS is one of the most common reasons for patients to receive continuous renal replacement therapy (CRRT) after sepsis. The purpose of this poster is to provide information to nurses on general oncology floors so that they are able to recognize the signs and symptoms of TLS early, in the hopes that early identification and treatment will improve patient outcomes and decrease the number of patients with acute kidney injuries necessitating the need for CRRT.

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Signs/Symptoms

TLS is a rapidly developing oncological emergency characterized by a number of metabolic abnormalities including, hyperuricemia, hyperphosphatemia, hyperkalemia, and hypocalcemia [2]. TLS is asymptomatic initially, but has the ability to affect the renal, gastrointestinal, cardiac, and neuromuscular systems [10].

Hyperuricemia contributes to the development of acute renal failure. Signs and symptoms include [6]:

- Flank pain
- Gross hematuria
- Cloudy urine
- Oliguria
- Lethergy

Hyperkalemia and hypocalcemia may cause gastrointestinal complications such as [6]:

- Nausea
- Vomiting
- Diarrhea
- Intestinal cramping

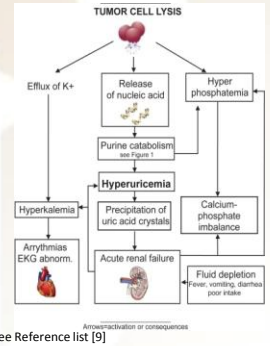
Hyperkalemia will cause electrocardiogram (ECG) and neuromuscular changes these include [6]:

- Atrial tachycardia
- Irregular heart rhythms
- Life-threatening arrhythmias
- Neuromuscular irritability
- Muscle weakness
- Paralysis

Hypocalcemia also affects the neuromuscular system and can manifest as [6]:

- Neuromuscular excitability
- Seizures
- Tetany

Pathophysiologic Process of TLS



See Reference list [9]

Pathophysiology

TLS occurs as the result of tumor cell breakdown, usually after exposure to chemotherapy or chemotoxic drugs. When cancer cells are destroyed they release massive amounts of intracellular contents into the extracellular space, which cause characteristic electrolyte abnormalities such as: hyperuricemia, hyperphosphatemia, hyperkalemia, and hypocalcaemia [2]. These imbalances occur in part due to the fact that cancer cells have an abnormally high amount of potassium, phosphorus, and nucleic acid contained within the cell [6]. Hyperkalemia and hyperphosphatemia normally results 12-24 hours after chemotherapy is initiated [8]. Hyperkalemia results from the high levels of potassium that spills into the extracellular space from the lysed malignant cells, as well as from a disruption in the sodium/potassium adenosine triphosphatase pump which lowers the threshold for potassium exchange into the extracellular space [8]. This potentiates the effects of hyperkalemia by causing additional potassium to leak from uninjured cancerous cells into the extracellular space even before cell lysis has occurred [8]. Hypocalcemia results when extracellular calcium binds to the elevated phosphorus circulating in the bloodstream, which in turn leads to decreased serum calcium [6].

Hyperuricemia generally occurs 48-72 hours after initiation of treatment as the liver converts the excess nucleic acids into uric acid [8]. Under normal circumstances small amounts of uric acid are excreted by the kidneys, while the majority of uric acid is reused by the body through the salvage pathways [8]. Initially, the kidneys will try to compensate for the excess uric acid in the blood stream by increasing urine output, but as intravascular fluid volume is depleted uric acid crystals build up in the renal tubules causing intrarenal crystallization [8]. Uric acid also disrupts the renin-angiotensin aldosterone system by causing renal vasoconstriction, impaired auto-regulation, decreased renal blood flow, oxidation, and inflammation [4]. These electrolyte abnormalities produce clinical toxic effects which may include renal insufficiency, cardiac dysrhythmias, seizures, and multi-organ failure leading to death if not treated [4].

Significance of Pathophysiology

Understanding the pathophysiology of TLS allows practitioners to put measures in place to prevent complications associated with cancer treatments in moderate to high risk individuals. All patients who are high risk should receive intravenous hydration beginning 2 days before treatment and continuing for 2-3 days after chemotherapy [3]. Fluids are administered at a rate of 2 to 3L/day with a goal urine output of 100-200 mL/hour [8]. This helps maintain renal perfusion and minimize uric acid crystal formation in renal tubules [4]. Nurses should pay particular attention to urine output; if output remains low despite aggressive fluids then loop diuretics are recommended to achieve target urine output [4].

However, while allopurinol prevents the formation of new uric acid from forming, existing uric acid in the body must still be excreted [8]. It may take the body up to two days to decrease pre-existing uric acid levels, which may be enough time to cause nephropathy in some individuals [4].

In addition, xanthine, the end by-product of allopurinol, may accumulate in the renal tubules causing xanthine nephropathy [4]. In contrast, Urate oxidase (rasburicase) works by breaking down uric acid into a more soluble compound the body can execrate called allantoin[4]. This prevents the formation of xanthine and secondary accumulation in the renal tubules and decreases the risk of nephropathy [4].

Signs and Symptoms of Tumor Lysis Syndrome

Table 2: Metabolic Abnormalities Associated With Tumor Lysis Syndrome

Abnormality	Associated Signs/Symptoms	Prophylaxis/Acute Therapy
Hyperuricemia	Nausea, vomiting, diarrhea Flank pain, oliguria, or anuria Urate crystals in urine Edema, hypertension	Allopurinol po/IV, rasburicase IV IV hydration (+/- Na^+ HCO_3) Hemodialysis
Hyperkalemia	Nausea, vomiting, diarrhea, anorexia Cardiac arrhythmias Muscle weakness, cramps,parasthesias	Sodium polystyrene sulfonate (kaexylate) dose of 1 g/kg EKG/cardiac monitoring Low potassium diet
Hyperphosphatemia	Nausea, vomiting, diarrhea Oliguria or anuria Lethargy, seizures	Aluminum hydroxide (po or NG) dose of 15 mL every 4 to 6 hours Hemodialysis Low phosphorus diet
Hypocalcemia (due to Ca++ binding to phosphorus)	Muscle cramps or spasm, tetany, and parasthesias Cardiac arrhythmias Confusion, hallucination, seizures	Treat hyperphosphatemia first Do not treat hypocalcemia unless symptomatic, and then treat cautiously with calcium gluconate IV

See Reference list [12]

Patients should also be pre-treated with allopurinol or rasburicase therapy. Both therapies aim to control uric acid levels by interfering with purine catabolism, in an effort to prevent uric acid crystal formation in the renal tubules and preserve kidney function [8]. Allopurinol is a pharmacological medication that works by inhibiting the enzyme xanthine oxidase, which blocks the conversion of enzymes that form uric acid [5].

However, the uricase enzyme that breaks down uric acid in rasburicase is not normally found in humans. Administration of rasburicase in patients has been known to cause allergic reactions, at times leading to anaphylaxis [8]. In addition, high costs to institutions and lack of insurance coverage limits the use of rasburicase in practice [8]. Patients who have a pre-existing uric acid level of >7.5mg/dL would benefit most from rasburicase therapy and should be considered for use in contrast to allopurinol [8].

Significance Cont.

Management of other dangerous electrolyte abnormalities is important as well, specifically hyperkalemia, which can cause lethal cardiac dysrhythmias if left untreated. Administration of 50% dextrose in water and 10 units of regular insulin IV should be given for immediate treatment for potassium levels > 6mEq [8]. This shifts excess potassium into the intracellular space. For milder cases and longer term control sodium polystyrene sulfonate (kayexalate) can be given to help bind with excess potassium in the gut as well as loop diuretics to promote excretion of potassium through the kidneys[8].

It is also important to treat high phosphorus levels in the blood. If phosphorus levels are above 7mg/dL then 20% dextrose in water should be given with insulin [8]. Once phosphorus levels fall below 7mg/dL then oral phosphate binder such as aluminum hydroxide may be given, which works by binding with free phosphate in the intestines to prevent absorption [8]. If phosphorus levels are corrected then hypocalcemia should inversely correct itself. Correcting hypocalcemia is discouraged as it can potentiate the development of calcium deposits in tissues [8]. Replacement should only be given to individuals who are experiencing signs and symptoms of neuromuscular excitability [8].

Despite prophylactic treatment many patients' kidneys may not be able to keep up with the increased workload demanded of them. Dialysis should be considered in patients exhibiting symptoms of oliguria, fluid overload, or signs and symptoms related to abnormal electrolyte levels [8]. Intermittent dialysis or continuous renal replacement therapy (CRRT) may be used to help filter the blood and remove excess byproducts. Generally, CRRT is recommended in patients with TLS because the filters use larger bore sizes, which allows for more rapid clearance of molecules, in particular it is more effective in removing phosphorus from the blood and does not have the rebound effect of hyperkalemia that conventional intermittent dialysis does [4]. The goal of dialysis therapy is to correct the underlying electrolyte imbalances and restore renal function.

Implications for Nursing

The key in TLS is to recognize which patients are at risk and implementing preventative measures before the initiation of therapy [10]. Patients at highest risk of developing TLS include [10]

- Those with rapidly multiplying malignant cells
- The elderly
- Those dehydrated at the start of therapy
- Those with pre-existing renal disease

However, any patient receiving oncological therapies may develop TLS. Nurses administering chemotherapy should be knowledgeable about key abnormal laboratory values and clinical symptoms of:

- Hyperkalemia
- Hyperphosphatemia
- Hypocalcemia

Those at high risk should be placed on continuous cardiac monitoring [4]. Electrolytes, renal function, and uric acid should be measured every 4-6 hours for high-risk individuals, and every 8-12 hours for those at intermediate to low risk [4]. Recognizing signs and symptoms of acute renal failure is of paramount importance as escalation of treatment modalities may be necessary and life saving in these individuals. Practitioners should be on the look out for signs of [8]:

- Oliguria,
- Fluid overload
- Hypertension
- Pulmonary edema

In addition, blood urea nitrogen (BUN) and creatinine should be monitored daily[8].

Patient and family education is also important. Patients should be educated about complications of chemotherapy and TLS if they are at risk. It is important for the nurse to review home medications, especially if the patient is pre-medicating at home with allopurinol or rasburicase before treatment. Information of correct medication administration may be key in preventing complications associated with TLS. Keeping the patient and family informed also allows the patients' and family members to feel more in control and take a more active role in their treatment.

Conclusion

TLS is an oncological emergency and a major cause of morbidity and mortality in cancer patients in the United States and worldwide [1]. TLS causes cell lysis and the release of massive amounts of potassium, phosphate, and nucleic acid into the general circulation [5]. This causes characteristic electrolyte abnormalities within the blood that leads to impaired renal function, cardiac dysrhythmias, end-organ failure, and death if not treated [5]. The key to managing TLS is prevention, along with prompt recognition of symptoms, immediate intervention, and escalation of care when necessary

References

[1] Bose, P., & Qubaiah, O. (2011). A review of tumour lysis syndrome with targeted therapies and the role of rasburicase. *Journal Of Clinical Pharmacy & Therapeutics*, 36(3), 299-326.

[2] Gemici, C. (2006). Tumour lysis syndrome in solid tumours. *Clinical Oncology*, 18(10), 773-780.

[3] Held-Warmkessel, J. (2010). How to prevent and manage tumor lysis syndrome. *Nursing*, 40(2), 26-32.

[4] Howard, S., Jones, D., & Pui, C. (2011). The tumor lysis syndrome. *New England Journal Of Medicine*, *364*(19), 1844-1854.

[5] Maloney, K., & Denno, M. (2011). Tumor lysis syndrome: Prevention an detection to enhance patient safety. *Clinical Journal Of Oncology Nursing*, 15(6), 601-603.

[6] McGraw, B. (2008). At an increased risk: tumor lysis syndrome. *Clinical Journal Of Oncology Nursing*, 12(4), 563-565.

[7] Mughal, T., Ejaz, A., Foringer, J., & Coiffier, B. (2010). An integrated clinical approach for the identification, prevention, and treatment of tumor lysis syndrome. *Cancer Treatment Reviews*, 36(2), 164-176.

[8] Muslimani, A., Zakalik, D., Chisti, M. M., Daw, H., Wills, S., Huang, J., Jaiyesimi, I., (2011). How we treat tumor lysis syndrome. *Oncology*, 25(4), 369-375.

[9] Pessions, A., Melchionda, F., &Castellini, C. (2008). Pitfalls, prevention, and treatment of hyperuricemia during tumor lysis syndrome in the era of rasburicase. *Biologics*, 2(1) 129-141. Retreived from http://www.ncbi.nlm.nih.gov/pubmed/

[10]Rajendran, A., Bansal, D., Marwaha, R., & Singhi, S. (2013). Tumor lysis syndrome. *Indian Journal Of Pediatrics*, 80(1), 50-54.

[11] Wilson, F., & Berns, J. S. (2014). Tumor Lysis Syndrome: New Challenges and Recent Advances. *Advances In Chronic Kidney Disease*, 21(1), 18-26.

[12] Vachani, C. (2007). Tumor Lysis Syndrome. *Oncology Journal*, Retrieved from http://www.cancernetwork.com/articles/tumor-lysis-syndrome/page/