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Emergencies in hematology: tumor lysis syndrome

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SUMMARY:
TLS (tumor lysis syndrome) is a serious consequence of haematologic malignancies and their treatment. The condition is defined by laboratory abnormalities alone (laboratory TLS) or in conjunction with clinical consequences such as renal failure, seizures, and arrhythmias (clinical TLS). Clinical TLS is a risk factor for increased morbidity and death in cancer patients, although it may be avoided. As a result, accurate prediction is crucial to the effective management of patients at risk for TLS, and it takes into account both disease characteristics (tumor kind and load) and patient factors (baseline renal insufficiency or hyperuricaemia). In low- and intermediate-risk individuals, water and allopurinol are used to prevent TLS, whereas rasburicase is used in high-risk patients.

Keywords: tumor lysis syndrome, renal failure, leukemia,lymphoma.

I. DEFINITION:

Tumour lysis syndrome (TLS) continues to be a significant comorbidity in the treatment of haematologic malignancies, resulting in greater costs and worse results. The Cairo-Bishop criteria for laboratory and clinical TLS (Table I) form the basis of the contemporary concept of TLS. TLS in the laboratory is defined as a 25% increase from baseline or an abnormal change in two of the following electrolyte/metabolite levels: uric acid, potassium, or phosphorus (elevations), and calcium (decrease). Clinical TLS is merely laboratory TLS plus an increased creatinine (at least 15 times the upper limit of normal) that is not due to another cause, such as cardiac arrhythmia/sudden death or seizures. Both types of TLS may have clinical consequences, given updated treatment/preventive techniques.

Pathogenesis:

Chemotherapy-induced TLS emerged shortly after effective medicines for leukemia and lymphoma were identified in the early part of the twentieth century. Several publications (Kravitzet al., 1951; Richmond& Beardsley, 1953; Freiet al., 1963) described uric acidnephropathy and abrupt renal failure within days of treatment with these new drugs.Lysis of tumor cells, as later established, leads in the discharge of cell contents such as electrolytes, proteins, and nucleic acids into the circulation. These nucleic acid and protein contents are promptly broken down in the liver, resulting in uric acid generation. Tumor cell lysis causes the release of additional electrolytes, such as potassium and phosphorus. Rapid potassium elevations, which can be exacerbated by renal failure, can cause cardiac arrhythmias.

Hypocalcaemia can cause muscular cramps, tetany, arrhythmias, and even seizures as a result of calcium phosphorus precipitation and tissue deposition (Davidson et al., 2004). Though the exact prevalence is unclear, spontaneous TLS has been described in lymphoma, multiple myeloma, leukemia, and uncommon solid tumors (Riccioet al., 2006; Opyrchalet al., 2010; Okamotoet al., 2015; Huzmeliet al., 2016).The cause of acute renal damage in TLS is multifactorial. By causing direct crystallization inside the renal tubules, hyperuricemia can cause acute renal failure. Furthermore, increased phosphorus levels can produce calcium phosphate crystal deposition in the kidney, which directly contributes to renal damage. Indirect damage, on the other hand, may play a role in TLS-related renal failure. Uric acid-induced renal vasoconstriction leads to tissue hypoxia, reperfusion damage, and local inflammation, according to one suggested mechanism of indirect injury (Shimadaet al., 2009).

Risk classification:

and Bishop (2004) developed a grading sy stem based on serum creatinine, the presence of arr hythmia and/or seizures, and the most severe clinic al sequela in addition to detailing the criteria for TL S diagnosis.

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However, these assessments are based on expert op inion and have not yet been validated in a prospecti ve cohort.

A previous study of hospitalized patients with tumo r lysis syndrome between 2010 and 2013 discovere d that a significant proportion (58%) had acute rena l failure but a very low rate of reported seizures (1 %), implying that clinicalTLS is being recognized e arlier and metabolic derangements are being treated more aggressively.Identifying persons who are mo re at risk of clinical TLS may be a more therapeutic ally helpful strategy for predicting outcomes.

Only 45 occurrences of TLS in solid tumors were d escribed in a 2003
literature analysis, including 37 in tumors that were moderately or
very susceptible to treatment and 39 in metastatic d isease (Baeksgaard & Sorensen, 2003).

Solid tumors and indolent haematologic malignanci es are thought to be at lesser risk for TLS due to lo wer proliferative rates, smaller tumor burden, and p oorer susceptibility to treatment (Coiffiere et al., 20 08).

The majority of patients in this series had elevated l actate
dehydrogenase (LDH) and uric acid levels at baseli ne.

In this case series, almost onethird of the patients di ed from arrhythmias or uraemia caused by tumor ly sis (Baeksgaard & Sorensen, 2003).

However, as a result of publication bias, this death rate for solid
tumor therapy is likely abnormally high.

Chronic myeloid leukemia (CML) and chronic lymphocytic leukemia (CLL) were also deemed low-risk diseases under these recommendations. CLL, on the other hand, is classified as intermediate-risk if the white blood cell count is more than or equivalent to 509109/l or if the patient is receiving targeted therapy such as venetoclax. The risk of acute leukaemia is determined by baseline white blood cell counts and LDH levels as a proxy for "tumor bulk." Acute leukaemia and Burkitt's lymphoma, on the other hand, are regarded the highest-risk disease categories for TLS because to their fast proliferation rate. Low-grade lymphomas, on the other hand, include tiny lymphocytic, follicular, marginal zone, non-blastoid mantle cell, and cutaneous T-cell lymphomas.

Diffuse large B-cell lymphoma, peripheral T-cell lymphoma, transformed lymphoma, and blastoid mantle cell lymphoma are all intermediate- to high-risk cancers. In these circumstances, tumor size and baseline LDH may influence risk assessment (Cairoet al., 2010). Aside from underlying disease, patient factors such as pre-existing renal dysfunction and elevated levels of uric acid, phosphorus, and potassium influence the severity of TLS, and thus baseline abnormalities in these areas would place a patient in a higher risk category than that based solely on tumor type.A multivariate study of one of the biggest retrospective investigations of TLS in acute myeloid leukemia (AML) found that baseline white blood cell counts, uric acid, LDH, and creatinine were independently predictive for both clinical and laboratory TLS (Montesinoset al., 2008).

A clinical riskscore has been created and validated for use in the AML community (Montesinoset al., 2008). At the University of Pennsylvania, a prior scoring system for all TLS (clinical and laboratory) in AML was devised, and baseline uric acid and LDH were found to be prognostic, in addition to male sex (Matoet al., 2006). Other patient characteristics, such as dehydration, acid urine, and hypotension, are regarded to be risk factors by some, however their impact in the absence of renal failure is uncertain (Howardet al., 2011).The type of treatment used also influences TLS risk. TLS can occur after radiation or targeted medicines, despite being traditionally linked with chemotherapy. Notably, TLS has been recorded in response to all anti-CD20 monoclonal antibody therapy.

Other medicines have been linked to TLS instances, including ibrutinib, lenalidomide, pazopanib, and trastuzumab (Baudonet al., 2016; Chesonet al., 2017; van Kalleveenet al., 2018). Furthermore, radioligand treatments have been linked to TLS instances. Four individuals experienced clinical TLS after three days of therapy in one retrospective analysis of 205 patients receiving 177Lu-DOTATATE, -DOTATOC, and -PSMA-617 in Germany (Huanget al., 2019). Only a few cases of radiation-induced lysis have been recorded. Because these treatment-related accidents have only been reported in a small number of instances, determining the real incidence and danger associated with these medicines is challenging.

Because these treatment-related accidents have only been reported in a small number of instances, determining the real incidence and danger associated with these medicines is challenging. Venetoclax, a B-cell lymphoma-2 (BCL-2)-specific inhibitor, is one targeted drug that has prompted major worry about TLS occurrences. In the first in-human trial of venetoclax, 3/56 participants had clinical TLS and seven had laboratory TLS (Robert et al., 2016).

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One patient died from a suspected TLS-related cardiac arrest (Robert et al., 2016). Risk stratification is based on three criteria: high [absolute lymphocyte count (ALC)259109/l and largest diameter of all measurable lymph nodes5 cm or largest diameter of all measurable lymph nodes10 cm alone], intermediate (either ALC259109/l or largest diameter of all measurable lymph nodes5 cm alone), and low (neither of the above) (Robertset al., 2016). However, with dosage changes and ramp-up schedules, life-threatening clinical TLS can typically be avoided.

In a recent study of 54 patients taking ibrutinib with venetoclax, just one TLS incident occurred, which cleared with dosage stoppage and did not recur after venetoclax re-introduction and ramp-up (Hillmenet al.,2019). Pre-induction treatment with two cycles of obinutuzumab resulted in the lowering of TLS risk in 25 of 30 patients in another study of obinutuzumab and venetoclax in patients unsuited for fludarabine-based chemotherapy, indicating promise for pretreatment as a TLS risk mitigator (Kateret al., 2018). Our usual venetoclaxin CLL ramp-up regimen follows the product insert (20 mg97 days, 50 mg97 days, 100 mg97 days, then 200 mg97 days, followed by 400 mg daily).2018 (AbbVie Inc.) In AML, on the other hand, the ramp-up is much faster (100 mg91 day, 200 mg91 day, 400 mg daily) (AbbVie Inc., 2018).

In AML, on the other hand, the ramp-up is much faster (100 mg91 day, 200 mg91 day, 400 mg daily) (AbbVie Inc., 2018). ClinicalTLS did not develop in trials with venetoclax in combination with decitabine, azacitidine, and low-dose cytarabine, despite AML being a "higher risk" condition (DiNardoet al., 2018; DiNardoet al., 2019).

Management

Prevention.TLS treatment strategies mostly include supportive care (electrolyte management, dialysis, etc.), thus prevention is crucial. Table III depicts a simplified diagram of risk-based management solutions. Intravenous hydration is the cornerstone of both TLS prevention and therapy. The objective is to optimize volume status and establish an ideal environment for uric acid and phosphate excretion (Tosiet al., 2008). Giving around 3 l/m2/day (Hochberg & Cairo, 2008) or aiming for urine production of at least 100-150 ml/h are common guidelines. Previous research has looked at the effect of alkalinizing urine with sodium bicarbonate in lowering the risk of uricacid nephropathy in patients (Holland & Holland, 1968;Andreoliet al., 1986).

While increasing the pH of the urine may limit the development of uric acid crystals, it might lower the solubility of xanthine and so encourage the creation of xanthine crystals (Jonesetal., 1995). Furthermore, allopurinol, a uric acid-lowering drug, can cause increased xanthinuria, potentially amplifying the effect of alkalization on xanthine crystal formation (Stapleton et al.,1988). Urine alkalinization can also raise the risk of calcium phosphate precipitation, which is less soluble at alkaline pH (Veenstraet al., 1994; ten Harkelet al., 1998). Alkalization is a contentious method and is not currently suggested with the administration of allopurinol, a medicine known to create large quantities of xanthine in the urine.

When the link between hyperuricaemia and renal failure in TLS patients was discovered, uric acid-lowering medications were believed to be potential preventative treatments. Unless the patient looks to have a very proliferative illness, metabolic abnormalities, or a very bulky disease, these medications are normally only utilized in intermediate or high-risk instances (Cairoet al., 2010). Allopurinol, a xanthine oxidase inhibitor, was used to treat/prevent TLS in patients with haematologic malignancies from the beginning (DeConti & Calabresi, 1966; Holland & Holland, 1968; Andréoliet al., 1986). It can reduce blood uric acid levels by blocking the oxidation of xanthine and hypoxanthine to uric acid, lowering the risk of uric acid crystallization and acute renal failure.

Adults should take 600-800 mg per day (split into 2-3 doses), while lesser dosages such as 300 mg are frequently used, depending on baseline uric acid level, underlying malignancy, and renal impairment (Mylan Pharmaceuticals, 2018; DeConti & Calabresi,1966). This should be begun 1-2 days before chemotherapy, along with rigorous hydration (oral or IV), and should be continued for roughly a week following chemotherapy (DeConti & Calabresi, 1966; Goldman et al., 2001).

In the FLORENCE study, fuxostat, another oral xanthine oxidase inhibitor, was compared to allopurinol (Spinaet al., 2015). Although the mechanism of action is similar to that of allopurinol, febuxostat has several pharmacologic benefits over allopurinol. It inhibits both the oxidized and reduced forms of xanthine oxidase, resulting in higher inhibitor efficacy (Takano et al., 2005). Furthermore, unlike allopurinol, febux-ostat does not require dosage modification in renal failure. However, despite much lower mean serum uricacids in the febuxostat

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arm, the FLORENCE study failed to establish advantage over allopurinol in avoiding renal failure or clinical TLS.As a result, while it may be a viable option for those who cannot take allopurinol, it is not the recommended agent.

Because allopurinol and febuxostat act by blocking further uric acid generation, uricacid levels may take several days to fall. Rasburicase, on the other hand, is a recombinant urate oxidase that converts uric acid to allantoin, a uric acid metabolite that is 5-10 times more soluble and hence readily eliminated through the kidneys (Pui, 2002; Jehaet al., 2004). Rasburicase reduces blood uric acid levels quickly (within 4 hours) compared to allopurinol, which can take up to a day to restore uric acid levels (Goldman et al., 2001; Pui, 2002). An early comparator-use trial found that lowering blood uric acid levels in hyperuricaemic people taking chemotherapy was 100% effective (Puiet al., 2001a; Boslyet al., 2003; Jehaet al., 2004).

Other studies have shown similar results in terms of rapidly and dramatically decreasing uric acid; however, one of the studies was only a single-arm trial, and the other did not show a difference in clinically significant outcomes such as renal failure and the need for dialysis (Goldmanet al., 2001; Puiet al., 2001b). Another randomized trial of chemotherapy for children with lymphoma and acute lymphoblastic leukemia found that the French cohort had a significantly lower risk of renal insufficiency, TLS, and dialysis than the US cohort, and attributed this difference to the availability of non-recombinant urate oxidase in France but not in the US (Cairoet al., 2007).

However, because the two cohorts were not randomized, the results were not conclusive (Cairoet al., 2007). While rasburicase studies compare favorably to historical cohorts in terms of reducing dialysis requirements, no randomized trials have found a significant difference between rasburicase and allopurinol in terms of clinically relevant outcomes, and the majority of studies have been performed in paediatric cohorts (W€ossmannet al., 2003). Despite these limitations, rasburicase is now advised in high-risk patients because to the possible consequences of severe TLS (Howard et al., 2011).However, even in high-risk condition, our normal approach is to only administer rasburicase if the baseline uric acid is considerably increased (>8 mg/dl).

Furthermore, while rasburicase is generally tolerated, individuals with glucose-6-phosphate dehydrogenase (G6PD) impairment are at risk for acute hemolytic anaemia after rasburicase administration (Sanofi-Aventis, 2009).The Food and Drug Administration advises testing for G6PD enzyme activity in individuals of African or Mediterranean heritage (Sanofi-Aventis, 2009; Rellinget al., 2014).

Prognosis

Renal failure, seizures, and/or cardiac arrhythmias have traditionally been used to characterize clinical TLS. However, because to more regular lab testing and preventative treatment, the latter two sequelae are less common in recent decades. In a hospital-based study of individuals with cancer and TLS, only 1% had seizures, but 58% had some kind of renal failure (Duraniet al., 2017). The overall mortality rate was 21%. Tumor lysis was, however, seldom the primary diagnosis in this population, which frequently had concomitant infections and sepsis (Duraniet al., 2017). In a study of 772 individuals with AML, a condition that is typically thought to be at high risk for TLS, 17% had TLS, 5% of which were clinical (Duraniet al., 2017).

While laboratory TLS formation had no effect on mortality during induction treatment, clinical TLS was linked with a considerably greater death rate (79% vs. 23%). In individuals with clinical TLS, the most prevalent reasons of mortality were hemorrhage and renal failure. TLS in solid tumors, however rare, appears to have a poor prognosis—in one case series of 19 patients with TLS (nine of which were spontaneous), 63% died during follow-up (Caravaca-Fontanet al., 2017).Although these individuals may have died as a result of a large disease load rather than directly from TLS, our analysis of TLS in-patients indicated that those with solid tumors were more likely to die in the hospital than those with lymphoma, CLL, myeloma, or even ALL (Duraniet 2017).

II. CONCLUSIONS

Disease type, tumor mass (as defined by size, LDH, or white blood cell count), renal function, and baseline metabolic abnormalities are all associated with the chance of developing clinical TLS and must thus be included in the risk categorization of newly diagnosed cancer patients. Preventive measures such as intravenous hydration, allopurinol, and rasburicase should be used based on risk assessment. Rasburicase should be taken with caution in high-risk patients because to its high cost and lack of evidence for therapeutic advantage over allopurinol. While the prognosis for individuals with laboratory TLS is similar to that of those without laboratory TLS, clinical TLS can indicate a poorer result in terms of dialysis demand and death.

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