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Overview

Tumour Lysis Syndrome in Solid Tumours

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ABSTRACT:
Tumour lysis syndrome (TLS) is an oncological emergency that results from massive cytolysis of malignant cells with a sudden release of their cellular contents, such as intracellular ions and metabolic by-products, into the systemic circulation. This syndrome is common in tumours with rapid cell turnover and growth rates, and in bulky tumours with high sensitivity to antineoplastic treatments. It is, therefore, a well-recognised clinical problem in haematological malignancies. It is rarely observed in solid tumours. Here, published studies are reviewed, beginning with the first report of TLS in solid tumours. Reported solid TLS cases are evaluated according to their common features and differences, and their similarities with those seen in haematological malignancies. Basic principles for the prevention and management of TLS are mentioned, with particular emphasis on solid tumours. Gemici, C. (2006). *Clinical Oncology* 18, 773–780

Key words: Hyperuricaemia, solid tumour, tumour lysis syndrome

Introduction

Tumour lysis syndrome (TLS) is an oncological emergency characterised by numerous metabolic abnormalities, comprising hyperuricaemia, hyperphosphataemia, hyperkalaemia and hypocalcaemia. Acute oligouric renal failure and cardiac arrhythmias are the ultimate results of these metabolic derangements, which may lead to death if not prevented or intervened appropriately and on time [1–6]. TLS results from the rapid destruction of malignant cells and release of their intracellular contents, such as nucleic acids, potassium and phosphorus, into the systemic circulation. The abrupt release of these tumoural breakdown products into the circulation overwhelms the excretory and re-utilisation capacities of the body, causing the aforementioned metabolic disturbances.

Both host-related and tumour-related factors predispose the patients to TLS. Tumour-related factors associated with an increased risk of TLS include: short doubling time, high growth fraction and cell turnover rate, large tumour burden with disseminated disease, and high sensitivity to antineoplastic treatment [1–6]. Extrinsic compression of the genitourinary tract by the tumour, elevated serum lactate dehydrogenase (LDH) and uric acid levels are among the other tumour-related risk factors. Low urinary flow and dehydration constitute the host-related risk factors. The tumour-related risk factors mentioned above are the common characteristics of haematological malignancies, and TLS is a well-known clinical problem, especially in acute lymphoblastic leukaemias, high-grade non-Hodgkin's lymphomas and particularly in Burkitt's lymphoma [1–6]. Although TLS is a frequently encountered problem during the management of haematological malignancies, its occurrence in solid tumours is relatively rare and it has a grave prognosis. Given the unfavourable clinical course of TLS in solid tumours, particular attention may be necessary for its prevention, early recognition and treatment.

Here, previously reported TLS cases in solid tumours are reviewed, the similarities and differences between haematological malignancies discussed, and an insight into the prevention and treatment of this condition given.

TLS: Definition and Incidence

Although TLS is considered to be a set of metabolic complications arising from the treatment of rapidly proliferating tumours, there is no specific definition of the syndrome that can facilitate a uniform diagnosis and, thus, help to determine the exact incidence of the syndrome in different malignancies [5,7]. Hande and Garrow's [7] definition of TLS, in spite of certain shortcomings, represents the most complete and referenced definition. They classified TLS into two groups, as either laboratory or clinical, which separates patients exhibiting only laboratory findings of the syndrome from patients who also have life-threatening clinical problems as well. According to this classification, laboratory TLS represents a 25% increase in the baseline laboratory values of uric acid, potassium, phosphorous and a decrease in calcium, which occur within 4 days of the initiation of treatment. Clinical TLS is the appearance of significant clinical toxicity in addition to laboratory TLS. These toxicities include acute renal failure, cardiac arrhythmias and seizures that necessitate a specific intervention, such as haemodialysis. Cairo and Bishop [5] modified Hande and Garrow's classification system in an

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attempt to make a more practical and reproducible classification of TLS that also addresses the shortcomings of the Hande and Garrow classification. In the Cairo and Bishop classification, the laboratory TLS definition includes not only a 25% change in baseline values of uric acid, potassium, phosphorous and calcium, but also any abnormal values of the same metabolites. In addition, abnormal values that occur within 3 days before and 7 days after the initiation of treatment are included. The clinical TLS definition of the Cairo and Bishop classification requires the presence of one or more of the three most significant clinical complications of TLS: acute renal failure, cardiac arrhythmias/sudden death and seizures. The Cairo and Bishop definitions of laboratory and clinical TLS are summarised in Table 1. Cairo and Bishop [5], apart from introducing a new classification of TLS, also defined a grading system for it. In this grading system, the maximal clinical manifestation (renal, neurological, cardiac) defines the grade of TLS. The efforts at defining, classifying, and grading TLS, by forming a common language among oncologists, can facilitate the diagnosis of the syndrome and the testing efficacy of different drugs in the setting of hyperuricaemia.

Although the incidence of TLS in haematological malignancies is very high, the overall incidence is unknown. In a retrospective evaluation comprising 788 patients with different haematological malignancies, consisting of non-Hodgkin's lymphomas and acute leukaemias, the incidence of hyperuricaemia and TLS after induction treatment was found to be 18.9% and 5%, respectively. The overall death rate due to TLS-related complications was 1.9% [8]. Hande and Garrow [7], in a retrospective analysis of 102 patients with high-grade non-Hodgkin's lymphomas, found the incidence of laboratory TLS to be 42%, whereas the incidence of clinical TLS was reported to be only 6%. Patte *et al*. [9] compared renal and/or metabolic complication rates observed during the management of acute lymphoblastic leukaemia and non-Hodgkin's lymphoma patients, with or without prophylaxis of hyperuricaemia. For prophylaxis, either non-recombinant or recombinant forms of urate oxidase preparations were used (uricozyme and rasburicase, respectively). In patients without prophylaxis, the complication rates were 21% in one study and 16% in another, whereas with prophylaxis the rates were 9% and 0%, respectively. TLS is also common in haematological malignancies of children [10,11]. In a study [11] evaluating the incidence of TLS in children with haematological malignancies, TLS was observed in 4.4% of the study population, and children with B-cell acute lymphocytic leukemia had the highest incidence (26.4%).

Table 1 — Cairo and Bishop definitions of tumour lysis syndrome (TLS) (modified from Ref. [7])

Laboratory TLS*	
Uric acid	$\geq$ 476 μmol/l or 25% increase from baseline
Potassium	$\geq$ 6.0 mmol/l or 25% increase from baseline
Phosphorous	$\geq$ 2.1 mmol/l (children), $\geq$ 1.45 mmol/l (adults) or 25% increase from baseline
Calcium	$\geq$ 1.75 mmol/l or 25% decrease from baseline
Clinical TLS†	
Creatinine‡	$\geq$ 1.5 ULN§ (age >12 years or age adjusted)
Cardiac arrhythmia/ sudden death‡	
Seizure‡	

*Laboratory TLS is defined as either a 25% change or a level above or below normal, as defined above, for any two or more serum values of uric acid, potassium, phosphate and calcium within 3 days before or 7 days after the initiation of chemotherapy. †Clinical TLS assumes the laboratory evidence of metabolic changes and significant clinical toxicity that requires clinical intervention. Clinical TLS is defined as the presence of laboratory TLS and any one or more of the above-mentioned criteria. ‡Not directly or probably attributable to a therapeutic agent (e.g. rise in creatinine after amphotericin administration). §Patients will be considered to have elevated creatinine if their serum creatinine is 1.5 times greater than the institutional upper limit of normal (ULN) below age/gender defined ULN. If not specified by an institution, age/gender ULN creatinine may be defined as: >1 < 12 years, both male and female, 61.6 μmol/l; $\geq$ 12 < 16 years, both male and female, 88 μmol/l; $\geq$ 16 years, female, 105.6 μmol/l; $\geq$ 16 years, male, 114.4 μmol/l.

TLS in Solid Tumours

TLS is a well-known clinical problem in haematological malignancies [1—6]. Early recognition of the patients susceptible to the development of the syndrome and its prevention are the essential purposes of haematological tumour management. Serum electrolytes, uric acid, phosphorus and renal function tests are monitored closely during the treatment of these malignancies. TLS is rarely observed in solid tumours and is limited to individual case reports. In one review, there were only 45 solid tumour cases identified with TLS between 1977, the first case reported, and 2002 [12,13]. The different incidences of TLS in haematological and solid tumours are mainly considered to be due to the dissimilar treatment sensitivities of these malignancies to the applied antineoplastic agents. However, this is not a valid consideration, as it is in contrast with the observation of the syndrome in solid tumours, which do not respond well to administered antineoplastic agents like malignant melanoma, carcinoma of the vulva, hepatocellular carcinoma and non-small cell lung cancer [14—22]. TLS is also rarely observed in solid tumours having similar treatment sensitivities to haematological malignancies like small cell carcinomas and germ cell tumours.

There are remarkable differences between solid and haematological malignancy-related TLS cases. Sensitivity to antineoplastic treatment, as mentioned above, tumour growth characteristics and kinetics, the onset time of the syndrome after the initiation of treatment and mortality rates can be cited among these major differences. Although haematological tumours presenting with this syndrome comprise a homogeneous group with similar growth kinetics and treatment sensitivities, TLS cases reported in solid tumours represent a heterogeneous group with respect to the above-mentioned characteristics. Although the