



Towards a risk classification for tumor lysis syndrome in solid neoplasms

Hacia una clasificación de riesgo para el síndrome de lisis tumoral en neoplasias sólidas

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ABSTRACT

Introduction: Tumor lysis syndrome in solid tumors is a rare complication associated with high mortality. Its exclusion from clinical practice guideline risk classifications, as well as its underestimation, exacerbates this gap. Objective: To propose hypotheses for a risk classification model for tumor lysis syndrome in solid tumors. Development: Risk classification for tumor lysis syndrome in solid tumors should include three categories: high, intermediate, and low. In addition, there are factors that can increase the risk, such as metastatic burden, elevated lactate dehydrogenase levels, pre-existing renal and/or hepatic impairment, and disseminated intravascular coagulation. Conclusions: Although traditionally considered low-risk, tumor lysis syndrome in solid tumors should be addressed with classification models that allow for its appropriate stratification in daily clinical practice.

Keywords: Risk classification; Solid tumors; Tumor lysis syndrome.

RESUMEN

Introducción: el síndrome de lisis tumoral en neoplasias sólidas es una complicación poco frecuente, asociado a una alta mortalidad. Su falta de inclusión en las clasificaciones de riesgo de guías clínicas, así como su subestimación, intensifican este vacío. Objetivo: proponer hipótesis para un modelo de clasificación del riesgo para el síndrome de lisis tumoral en neoplasias sólidas. Desarrollo: la clasificación del riesgo para el síndrome de lisis tumoral en neoplasias sólidas debe incluir tres clasificaciones: alto, intermedio y bajo. En conjunto a esto, existen factores capaces de aumentar el riesgo, como: la carga metastásica, valores elevados de lactato deshidrogenasa, lesión renal y/o hepática preexistente y la coagulación intravascular diseminada. Conclusiones: el síndrome de lisis tumoral en neoplasias sólidas, aunque tradicionalmente considerado de bajo riesgo, debe ser abordado con modelos de clasificación que permitan su adecuada estratificación en la práctica clínica diaria.

Palabras clave: Palabras claves: Clasificación del riesgo; Neoplasias sólidas; Síndrome de lisis tumoral.

INTRODUCTION

Tumor lysis syndrome (SLT) is a potentially life-threatening oncologic emergency that results from the massive release of intracellular contents, such as potassium, phosphorus, and uric acid, into the bloodstream following neoplastic cell death, leading to hyperuricemia, hyperphosphatemia, hyperkalemia, and hypocalcemia. If not managed promptly, this metabolic cascade can trigger cardiac arrhythmias, acute kidney injury, and even death (1).

The incidence of SLT in solid tumors is currently known to be less than 0.3% of all positive cases, but with a high mortality rate reaching up to 35%. These data indicate that mortality in SLT from solid tumors exceeds that found in hematological malignancies, with which it has historically been associated, where mortality is only 1.9%. The severity of SLT in solid tumors is clearly demonstrated by these data and underscores the need to reassess the perception of SLT as a rare and low-risk entity (2,3).

Advances in oncological therapies are the main etiology attributed to the appearance of SLT in solid tumors, including its occurrence after radiotherapy, radiofrequency ablation, immune checkpoint inhibitors, and monoclonal antibodies; massive cell lysis is then a consequence of the induction of significant and/or dysregulated tumor responses. Additionally, spontaneous SLT (SLTS), which occurs in cases where antitumor treatment has not yet been initiated, appears in patients with bulky or rapidly growing metastatic disease (2,3).

Despite the consistent inclusion of hematologic neoplasms in the classifications, solid neoplasms are largely excluded, being only included as low-risk diseases (4,5,6,7). Their frequent occurrence and mortality in the literature challenge this paradigm (2,3).

Given the above, the objective is to propose hypotheses for a risk classification model for tumor lysis syndrome in solid neoplasms.

DEVELOPMENT

The initial risk classifications, developed by Cairo and Bishop in 2004, (1) and the consultation with the expert panel in 2010, (5) have represented the standard classifications for tumor lysis syndrome to date. The 2004 guidelines proposed new diagnostic guidelines, which included laboratory and clinical criteria. Laboratory criteria included the presence of two or more abnormalities, including those related to uric acid, potassium, phosphorus, and/or calcium levels, while clinical criteria included one of the laboratory abnormalities plus the occurrence of cardiac arrhythmias, acute kidney injury, seizures, or sudden death.

In the 2010 expert consensus, (5) a new risk classification was developed that grouped neoplasms into low, intermediate, and high risk categories, which included both hematologic and solid neoplasms. For hematologic neoplasms, reference was made to each neoplasm and to modifying factors such as leukocyte count and tumor volume (lactate dehydrogenase and bulky mass). Solid neoplasms were included in the low-risk group, given the low level of evidence, which was based only on case series and case reports.

Since then, solid neoplasms have remained reported as low risk and the level of evidence appears to behave without significant changes. (4,5,6,7) However, case reports and new evidence on the subject are vast, which have allowed clarifying this gap to a certain extent and laying the foundations for a new and hypothetical risk classification. (2,3) Meanwhile, the evidenced pattern is consistent and we could propose it under updated evidence and the criteria of the authors of this article.

Maintaining the classifications of Cairo et al., in 2010 (5), a risk classification for solid neoplasms with three levels could be proposed: high, intermediate, and low, with the actual risk captured by integrating the baseline tumor type and dynamic modifying factors, as well as its basis in the relative frequency of SLT reported in the literature for each tumor type, biological aggressiveness, cell proliferation rate, and the expected cytotoxic response after oncological treatment. (2,3,4,6) Meanwhile, the identification of risk-modifying factors in the presence of any type of solid neoplasm should increase the probability of SLT to higher categories.

In relation to the above, the systematic analysis of the most frequently reported neoplasms could be suggestive of their inclusion in the highest risk. Papapanou et al. (3), in their scoping review on SLTS in solid neoplasms, reported lung cancer as the most frequent neoplasm, followed by stomach, colorectal, and liver cancer, respectively. Similarly, Alqurashi et al. (2), in their systematic review, reported hepatocellular carcinoma among the most frequent cancers, followed by lung cancer and, lastly, melanoma.

In summary, isolated evidence such as case reports show a clear pattern. Cases of adrenocortical carcinoma, (8) lung adenocarcinoma, (9) and small cell lung carcinoma, (10,11) reinforce a high-risk category for those tumors with high proliferation, high metastatic burden, explosive therapeutic response, or ability to trigger spontaneous SLT, (2,3,5,7) as well as a high frequency of appearance in the literature: $\geq 5\%$, according to Cairo et al. (5)

It is recognized that the direct evidence for SLT is not homogeneous across all tumors that may be included. While the aforementioned cancers, according to reports and reviews, support their high risk, others, such as aggressive sarcomas (12,13) and germ cell tumors like metastatic seminoma (14) and metastatic prostate cancer (15), despite having fewer reports in the literature, deserve to be included in the high-risk category because they meet the same previously proposed definition, exhibit biological analogy with already confirmed tumors, and are considered highly chemotherapy-sensitive (2,3,5,7).

For the intermediate risk classification, we suggest that this category includes localized tumors without modifying factors (2,3,5) and, following Cairo et al. (5), a frequency of 1-5%. An example is the case reported by Kikuchi et al. (16) of a localized breast cancer that developed SLT after letrozole doses.

However, examples in the literature are often obscured by publication bias, as only those with unusual or severe characteristics are reported. There is currently insufficient evidence to include other neoplasms. On the other hand, for the low-risk classification, we suggest tumors with no or exceptional reports, an incidence of less than 1%, and those considered for their slower growth, lower cell turnover rate, or lower sensitivity to massive lysis (2,3,5).

Furthermore, the association of modifying factors is important for risk stratification, as the presence of 2 or more such factors, or a single very severe factor, would be sufficient to increase risk, regardless of baseline risk. Among the documented factors are acute kidney injury and/or pre-existing liver insufficiency, extensive hepatic and bone metastatic burdens, elevated lactate dehydrogenase levels (2,3), and inclusion of biopsy or tumor procedure (17,18).

The proposed hypotheses could fill the existing gap and overcome the limitations of previous guidelines (1,4,5,6,7), which grouped all solid neoplasms as a single low-risk block. However, they are based predominantly on scarce evidence given the typology of the article; therefore, their validation through prospective studies, multicenter registries, in addition to more rigorous methodologies, is necessary before evidence-based development and widespread implementation.

CONCLUSIONS

Although tumor lysis syndrome is considered a rare complication in solid neoplasms, the proposed considerations for the development of a new risk classification could fill the gap that clinical guidelines have forgotten for decades. The classification model would be a preliminary proposal that, after clinical validation, could contribute to reducing the underdetection of TLS and facilitate more targeted prophylaxis.

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CONFLICT OF INTEREST

They do not exist.

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