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Tumor Lysis Syndrome Associated with Immune Checkpoint Blockade in Solid Tumors

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Abstract

Background: Immune-checkpoint blocking antibodies including anti-CTLA-4 and anti-programmed death-1 (PD-1) and programmed death ligand-1 (PD-L1) inhibitor therapy have demonstrated marked efficacy in several advanced solid tumors. Optimal use of these agents requires prompt recognition and management of immune-mediated toxicities and other adverse events. The objective of this study was to investigate the clinical characteristics and outcomes of Tumor Lysis Syndrome (TLS), a rare but life-threatening adverse effects in solid tumor associated with the use of immune *checkpoint inhibitor*.

Methods: Retrospective review and pooled analysis.

Result: Six cases of TLS related to checkpoint inhibitors identified. In four case reports with adequate clinical outcome information, the median age of patients was 75 years (73-77). Male to female ratio was 3:1. All patients had extensive liver metastases. The median time from treatment to TLS was 14 days (2-33). All four patients (100%) died from TLS.

Conclusion: TLS associated with CTLA4 and checkpoint blocking immunotherapy in solid tumor can be life-threatening. We discuss potential mechanisms of PD1 blocking immunotherapy associated TLS. Prospective studies should be conducted to investigate the incidence, clinical characteristics, optimal management and outcome of these rare but life-threatening adverse events.

Keywords: Tumor Lysis Syndrome (TLS); Checkpoint Inhibitors; Programmed cell death 1 protein (PD-1); programmed cell death 1 ligand 1(PD-L1); Adverse Effects (AEs); immunotherapies

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Introduction

Immune checkpoint blockade has emerged as an attractive treatment option in a wide spectrum of malignancies. These advances in cancer treatment create new challenges for medical oncologists, who must develop knowledge of the mode of action of these novel agents, and importantly how to diagnose and effectively manage their toxicities [1-3]. Tumor Lysis Syndrome (TLS) is considered to be an oncological emergency that result in severe metabolic abnormalities, including hyperuricemia, hyperkalemia, hyperphosphatemia and hypocalcemia, in patients with rapidly proliferating and chemo sensitive malignancies, such as acute lymphoblastic leukemia or high-grade lymphoma [4]. Although TLS is a well-recognized clinical problem in hematological malignancies, it is understudied in solid tumors and not previously associated with checkpoint inhibitors until recently [5-6]. In 2017, our group reported two cases of TLS after treating check point inhibitors, one patient with metastatic melanoma with liver involvement who was treated with pembrolizumab. Another patient with urothelial carcinoma developed TLS after treatment of nivolumab. We consider these clinical observations deserved further attention, because awareness of the symptoms and management of TLS is critical in the safe and appropriate use of immune checkpoint inhibitors in clinical practice. The objective of this retrospective review was to examine the available published information on clinical characteristics, management and outcomes of TLS in patients with solid tumors associated with Immunotherapy.

Patients and Methods

Literature search strategy

Systematic review of the literature was performed by first searching PubMed for "PD-1 and PD-L1 monoclonal antibody" (including nivolumab, pembrolizumab, atezolizumab, avelumab

Table 1: Review of published reports on tumor lysis syndrome secondary to check point inhibitors in patient with solid tumors.

Author (year)	Age	Gender	Primary cancer	Chemotherapy	Liver metastases	Time to TLS	Rasburicase	Outcome
Brunnhoelzl and Wang et al. [5]	77	F	Renal pelvic urothelial carcinoma	Atezolizumab	Yes	Day 14	No	Death
Brunnhoelzl and Wang et al. [5]	76	M	Metastatic melanoma	Nivolumab	Yes	Day 5	Yes	Death
Herbst et al. [9]	N/A	N/A	Solid tumor	Atezolizumab	N/A	N/A	N/A	N/A
Herbst et al. [9]	N/A	N/A	Solid tumor	Atezolizumab	N/A	N/A	N/A	N/A
Regnault et al. [7]	73	M	Metastatic melanoma	Ipilimumab	Yes	Day 6	N/A	Death
Sater HA et al. [8]	74	M	Metastatic renal cell carcinoma	Nivolumab	No	Day 2	N/A	Death

Time to TLS: Time from treatment to onset of TLS

and durvalumab), "tumor lysis syndrome" and "solid tumor". The identified reports were reviewed and additional articles of interest were identified from reference lists.

Data collection and statistical analysis

Information regarding the patient (patient age at diagnosis, presentation, and comorbidities), the tumor (symptoms, histology, and AJCC stage), examination results (tumor markers, radiologic investigations, and pathology findings), treatment modalities (surgery, chemotherapy and radiation), and the outcome response (response, adverse events, vital status) were recorded, when available. Descriptive statistics, such as frequency counts, medians, and ranges, were used to characterize the pooled sample.

Results

Five publications (4 case reports and one phase I clinical trial report) with total 6 cases of TLS after treatment with the immune checkpoint were identified. There was more detail information on individual patients reported in the four case reports than the one clinical trial report. In all cases, patients presented with metastatic disease and bulky hepatic metastases. Three TLS occurred after administration of Atezolizumab. In two cases, TLS occurred after administration of Nivolumab with fatal outcome. Another patient who had been treated with Ipilimumab for metastatic melanoma. The demographic feature, clinic pathologic features, symptoms and survival outcomes of the two groups were summarized in Table 1. In four case reports with adequate clinical outcome information, the median age of patients was 75 years (73-77). Male to female ratio was 3:1. All patients had extensive liver metastases. The median time from treatment to TLS was 14 days (2-33). All four patients had extensive liver metastases and all (100%) died from TLS. In a phase I clinical trial evaluating the single-agent safety and tolerability of Atezolizumab, a human, monoclonal, engineered anti-PD-L1 antibody administered by intravenous infusion every 3 weeks to patients with locally advanced or metastatic solid tumors or hematological malignancies. A total of 277 patients with advanced incurable cancer were enrolled in this clinical trial. The incidence, nature and severity of Adverse Events (AEs) were graded according to National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0. Two patients were reported with treatment-related grade 3–4 toxicities tumor lysis syndrome. No detail information was provided.

Discussion

Information of TLS secondary to immune checkpoint blockade in patients with solid tumor was limited. In our study, a total of 6 cases of TLS occurred after treatment with the immune checkpoint inhibitors were identified [5-9]. In four case reports with adequate clinical outcome information, patients were generally elderly with median age of 75 years. All four patients had extensive liver metastases and all (100%) died from TLS. The median time from treatment to TLS was 14 days (2-33). Three important findings from this study are noteworthy: first, TLS in solid tumors carries a worse prognosis when compared to hematologic malignancies. The lacks of awareness of risk of TLS in solid tumor in general likely contribute to the higher mortality in this population. Education efforts should be made to increase the awareness for this rare but potentially life-threatening oncologic emergency. Another notable finding from our analysis is that TLS associated with treatment with immune checkpoint blockade agents may occur later than expected: the median time from treatment to TLS was 14 days with a range of 2 to 33 days. This finding is important because it is outside the usual timeframe that is observed with cytotoxic chemotherapy. For high-risk patients with predisposing factors, we suggest that it is critical to monitor patients' electrolytes and renal function at least weekly during the first cycle of therapy. Third, although the findings of elderly patients at risk of this therapy are not new, it should provide a cautionary note for oncology community. Despite the abundant prevalence of cancer in men and women older than 65 years of age, robust data with immunotherapy in various cancers, the subset population of those more than 75 years of age elderly remain under-represented in clinical trials. In addition, elderly participating in clinical trials may not necessarily represent the overall elderly population, given that standard clinical trial exclusion criteria include organ dysfunction and poor performance status. In particular, data on immunotherapy studies in elderly patients are limited due to lack of specific trials utilizing immunotherapy solely in the elderly; the insufficient number patients 75 years of age enrolled in these trials make a reliable analysis in the elderly cohort impossible. We postulated TLS in solid tumor are underdiagnosed and under-reported. It is now well recognized that the Adverse Effects (AEs) of medical treatments are underreported in peer-reviewed journal articles documenting the results of clinical trials [10]. Routine assessment of uric acid, LDH in asymptomatic patients is not required in and outside of clinical trials. In clinical setting, TLS can easily miss-classified as acute kidney injury or electrolytes abnormally. Due to the positive trial results, and considerable marketing, patient demand for this treatment modality is high. In today's health care environment, community oncologists unlikely to put away their attention to "Relative Value Units" (RVUs) aside and write a case report of describing adverse effects. The deficiency of clinical trial design in adequately evaluating and reporting adverse events, in conjunction with lacking of real world reporting mechanisms, may lead to missing information prevents clinicians and patients from

gaining a full understanding of the relation of potential benefit and harm of this attractive cancer intervention. The mechanisms of TLS resulting from checkpoint inhibitor therapy have not been fully elucidated. Checkpoint inhibitors lead to T cell activation causing cytokine depended endothelial toxicity, and massive destructive capacity of tumor cells. Antibody-Dependent Cell-mediated Cytotoxicity (ADCC) has been implicated as an important mechanism in several highly effective antibody-mediated cancer therapies [11,12]. Experiment studies demonstrate that Ipilimumab triggers effector lymphocytes to cytotoxicity and TNF-α release [13,8]. These findings suggest that Ipilimumab, besides blocking CTLA-4, can directly activate the elimination of CTLA-4+ cancer cells. Cytokine storm was also proposed based on clinical observation of rapid deterioration and cardiac dysfunction with hypotension in these patients, and emerging laboratory evidences. Cytokine storms were reported with CAR-T cells, another form of immunotherapy and recently in PD-1 directed therapy [13]. Due to the inherent nature of retrospective studies and lack of accessibility to original medical records in published studies, we were only able to fully assess performance status, comorbid conditions and clinical manifestations of TLS or adverse effects from cancer therapy in the two patients from our own intuition. Despite the limitations, the present study provides the most updated real world insight regarding the diagnosis and outcomes of TLS patients with solid tumors in relation to check point inhibitors. Prospective and retrospective studies are needed to evaluate the true incidence, risk factors, optimal management and molecular markers of TLS in solid tumor. Along with known clinical risk factors [5,6] for TLS, we proposed novel biomarkers [14,15] such as PD-L1 expression, mutation load, MSI status as well as cytokines level should be incorporated into prospective clinical trials which may potentially help identify those at high risk for TLS in future.

Conclusion

In summary, our review highlights the life-threatening nature of TLS, which can occur with CTLA4 and PD1 blocking immunotherapy in solid tumors. The findings of this study would help improve our current understanding and develop optimal multidisciplinary management strategies for this rare, but potential fatal condition.

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