

Tumor Lysis Syndrome Associated with Breast Cancer, a Previously Unrecognized Oncologic Emergency

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Abstract

Background: Tumor lysis syndrome is a common oncologic emergency which has been well documented in patients suffering from hematologic malignancies. However, it is rarely reported in patients with solid tumors, even more rarely in patients with breast cancer. Many emergency room physicians, internists, even oncologists are not aware that TLS can actually occur in breast cancer. The objective of this study was to investigate the clinical characteristics and outcomes of TLS, a rare but life-threatening complication in breast cancer.

Methods: Retrospective literature review and pooled analysis.

Results: Twenty cases of TLS were identified in patients with breast cancer (19 case in published literature and 1 additional case from our tumor registry). The median age of patients was 57 years (31 - 94) with a female to male ratio of 19:1. All patients had extensive metastatic disease at the time of presentation, with visceral metastases documented in 100% of TLS cases. The in hospital mortality rate of entire cohort was 68%. The mortality rate for the patients developing treatment related TLS and spontaneous TLS were 50% and 75% respectively.

Conclusion: TLS in breast cancer can occur both after treatment and spontaneously and is associated with very high mortality. Our findings underscore the importance of heightened awareness, risk assessment and early prevention of this previously unrecognized oncologic emergency.

Keywords: Breast Cancer; Tumor Lysis Syndrome (TLS); Oncologic Emergency; Mortality

Introduction

Tumor lysis syndrome (TLS) is the most common oncological emergency that results in severe metabolic abnormalities, including hyperkalemia, hyperphosphatemia, hyperuricemia and hypocalcemia, in patients with rapidly proliferating and chemosensitive malignancies, such as acute lymphoblastic leukemia or high-grade lymphoma [1,2]. These metabolic abnormalities are responsible for an array of sequelae, the most common which are cardiac arrhythmias, acute renal failure, seizures, and sudden death. Although TLS is a well-recognized clinical problem in hematological malignancies, it continues to remain understudied in solid tumors and until recently [2-17]. Between 2017 and 2019, we treated three cases of TLS associated with breast cancer. We consider these clinical observations deserved further investigation.

Objective of the Study

The objective of this study was to examine the available published information on clinical characteristics, management and outcomes of TLS in patients with breast cancer.

Patients and Methods

Literature search strategy

Systematic review of the literature was performed by first searching PubMed for “tumor lysis syndrome” and “breast cancer”. The identified case reports and abstracts were reviewed and additional articles of interest were identified from reference lists.

Data collection and statistical analysis

Information regarding the patient (age at diagnosis, presentation, and comorbidities), the tumor (histology, grade and AJCC stage), radiologic investigations, treatment modalities (surgery, radiation and systemic therapy), and the outcome (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

Eighteen published case reports associated with metastatic breast cancer with total 19 cases of TLS (16 cases of treatment related and 3 cases of spontaneous TLS) were identified. In addition, we identified one case of spontaneous TLS in our institutional database. The final cohort consistent of a total 20 breast cancer patients with TLS.

The demographic feature, clinicopathologic features, symptoms and survival outcomes of 20 cases of TLS in breast cancer were summarized in table 1. The mean age of patients was 57 years (31 - 94) with majority patients were female (95%). All cases were adenocarcinoma (one with inflammatory breast cancer). In all cases, patients presented with metastatic disease with all patients having visceral metastases and 17 (85%) of the patients having liver metastases. Four patients (20%) in the pool of case reports developed spontaneous TLS, while sixteen of the patients (80%) developed TLS after receiving some type of active cancer treatment. Among them, eight of the patients (50%) developing treatment related TLS received chemotherapy alone which included capecitabine, paclitaxel, 5-FU, doxorubicin, methotrexate, gemcitabine and cyclophosphamide. Two of the patients (12.5%) that developed TLS post treatment received hormone therapy (tamoxifen and letrozole) prior to admission. Monoclonal antibodies, specifically trastuzumab and pertuzumab, was responsible for two out of the sixteen cases of treatment related TLS. One patient developed TLS after receiving a sequence of hormone therapy, immunotherapy, and chemotherapy. Hemi-body irradiation was responsible for one case of treatment related TLS, while there was also one case of chemotherapy and radiation, leading to the development of TLS. All cases were treated with aggressive supportive measures, and three patients received rasburicase.

The mortality rate was 50% among sixteen cases of treatment related TLS, with a median survival from diagnosis of TLS to death was 2 days (range 0.5-16). The mortality rate was 75% in the four patients with spontaneous TLS.

Discussion

Though well-documented in hematological malignancies, TLS was considered relatively rare in other solid tumors [3-5]. Our current study show TLS in breast cancer does indeed occur and is a real, under-recognized oncologic emergency. Although the true incidence of

Author (Year)	Age	Sex	Liver Involvement	Rasburicase given	Outcome	Time from tx to TLS (days)	Cancer Treatment
Cech (1986)	94	F	N	N	Survival	7	Tamoxifen
Melvut (2004)	42	F	Y	N	Death	11 hours	Capecitabine
Vaidya AM (2015)	52	F	Y	Y	Death	7	Weekly paclitaxel
Kurt M (2004)	42	F	Y	NR	Death	11 hours	Capecitabine
Sklar (1995)	62	F	Y	N	Death	N/A	Spontaneous (inflammatory)
Stark (1987)	53	F	Y	N	Death	18 hours	5-FU, doxorubicin, and cyclophosphamide
Rostom (2000)	73	M	Y	N	Death	3	Hemi-body irradiation
Drakos (1994)	31	F	Y	N	Survival	UK	Mitoxantrone
Zigrossi (2001)	50	F	UK	UK	Survival	UK	Letrozole
Barton (1989)	57	F	Y	N	Unknown	2	5-FU, cyclophosphamide, methotrexate
Taira (2015)	69	F	Y	N	Death	6	Trastuzumab
Ustundag (1997)	56	F	Y	N	Death	1.5	Paclitaxel
Elfar(2013)	46	F	Y	UK	Survival	UK	Spontaneous
Goyal (2014)	51	F	Y	uK	Death	UK	Spontaneous
Wang (2018)	37	F	Y	Y	Death	7	Spontaneous
Mott (2005)	47	F	Y	UK	Survival	1	Brain radiation, fluorouracil/epirubicin/cyclophosphamide
Mott (2005)	44	F	Y	UK	Survival	1	tamoxifen and trastuzumab--> docetaxel--> vinorelbine--> gemcitabine and cisplatin
BAudon (2016)	58	F	Y	N	Death	5	Trastuzumab and Pertuzumab
Kawaguchi (2013)	58	F	N	Y	Survival	16	Gemcitabine
Wang (2019)	69	F	Y	Y	Death	-	Spontaneous

Table 1: Review of published reports of tumor lysis syndrome in patients with breast cancer.

UK= Unknown Data Point.

TLS in breast cancer is difficult to assess. It is important to identify reasons for this under recognition to further equip physicians in providing optimal care to patients. One of these reasons, is the fact that many emergency room physicians, internists, even oncologists are not aware TLS can actually occur in breast cancer, therefore, TLS is not included in their initial differential diagnosis, specifically in patients presenting with acute renal failure. Between 2017 and 2019, our group treated three cases of spontaneous TLS associated with metastatic breast cancer. In both cases, the diagnoses were delayed due to failure to consider TLS as potential diagnosis at emergency room. We postulated TLS in breast cancer may be under diagnosed and under-reported. Hopefully the finding from our analysis can convince those skeptical whether TLS is a true phenomenon.

Several findings from this study are noteworthy. First, TLS generally occurs in patients with advanced stage breast cancer with large disease burdens. Distant metastases were documented in all TLS cases in this study, more specifically 90% of cases reported liver metastasis. Secondly, TLS in breast cancer, particularly spontaneous TLS, carries a worse prognosis when compared to hematologic malignancies [18-25,26]. The lack of awareness of risk of TLS in breast cancer in the new era of targeted therapy, delay in diagnosis and suboptimal management likely contribute to the observed high mortality. Urgent education efforts should be made to increase the awareness for this rare but potentially life-threatening oncologic emergency. Another interesting observation is one patient had inflammatory breast cancer with known aggressive biological behaviors and rapid proliferation rate. The current guidelines and consensus on diagnosis and management of TLS were based on previous experience on hematologic malignancies and established at a time when effective therapies for solid tumors were not available, refine the risk stratification and management TLS strategy in the new targeted therapy and immunotherapy era is necessary based on recent findings [2-5]. For patients with high burden of metastatic disease especially elderly cancer patients with extensive liver metastases, it is critical to monitor patients' electrolytes and renal function at least weekly during the first cycle of systemic therapy.

Limitation of the Study

Our study has several limitations. Due to the inherent nature of retrospective studies, we were not able to fully assess factors such as individual patient's performance status, and comorbid conditions that may impact the outcome of TLS. A larger sample size would also provide further insight into the stratification of risk of patients based on therapy type prior to TLS development and presence of rasburicase as an aggressive treatment option. Despite the limitations, the present study provides the most updated real world insight regarding the diagnosis and outcomes of TLS in patients with metastatic breast cancer. Our study will contribute to the evolving understanding of TLS in solid tumors and have implications for future cancer treatment paradigms in target therapy era.

Conclusion

Our study highlights the life-threatening nature of TLS, a previously under-recognized oncologic emergency of breast cancer, especially in patients with extensive liver metastases. Emergency room physicians should consider TLS as a differential diagnosis when evaluating acute renal failure and electrolyte derangement in patients with metastatic breast cancer, especially in those with diffused liver metastases.

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