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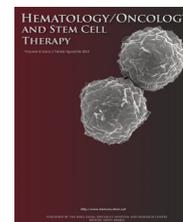
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## CASE REPORT

# Sorafenib-induced tumor lysis syndrome in a patient with metastatic hepatocellular carcinoma <sup>☆</sup>

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**Abstract**

Tumor lysis syndrome is a potentially lethal complication of chemotherapy, usually associated with aggressive hematologic malignancies. We describe the case of a young patient with metastatic hepatocellular cancer who developed rapid and fatal tumor lysis syndrome following initiation of sorafenib therapy. Although rare with sorafenib therapy for hepatocellular carcinoma, tumor lysis syndrome is serious complication. Patients with a high burden of disease at therapy initiation should have their metabolic parameters measured prior to starting therapy and closely followed for the first 1–2 weeks while being treated.

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**Introduction**

Tumor lysis syndrome (TLS) is a serious and potentially lethal complication of chemotherapy that ensues following rapid necrosis of malignant cells [1], often with underlying heavy disease burden. It is most commonly associated with chemotherapy administered for rapidly proliferating hematologic malignancies like acute leukemia or high grade

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lymphomas. It is unusual for TLS to occur with hepatocellular cancer (HCC) following treatment with sorafenib, an oral tyrosine kinase inhibitor, which is the only drug approved for use in metastatic HCC [2]. Only seven cases of sorafenib-associated TLS have been reported in literature to date [3–9]. We review the relevant literature and describe the case of a patient with metastatic HCC who developed fatal TLS within seven days of initiation of sorafenib.

### Case summary

49 year old man was admitted to the hospital via the emergency department after he presented with abdominal swelling, decreased appetite, nausea, weight loss and lower extremity edema. He was noted to have microcytic anemia (hemoglobin 7.5 g/dL; MCV 65 fL), platelets of  $308 \times 10^9/L$ , INR of 1.1, alkaline phosphatase of 288 U/L, total bilirubin of 1.72 mg/dL and albumin 3.8 g/dL. Additional laboratory values are listed in Table 1.

A computed tomography (CT) scan of the chest, abdomen and pelvis showed an enlarged liver with innumerable masses (largest  $11.3 \times 10.1$  cm), 2.3 cm portacaval lymphadenopathy, 2.4 cm left adrenal nodule and multiple sub-centimeter mediastinal lymph nodes. Alpha fetoprotein was 70,753 ng/mL. He was categorized into the Child Class A (Child-Pugh score = 6) and an ultrasound guided biopsy of the largest hepatic mass was confirmatory for well differentiated HCC.

On day 0, he was started on palliative therapy with sorafenib, 200 mg twice daily. He was seen in clinic for follow up on day 7 and was noted to several metabolic abnormalities suggestive of tumor lysis syndrome as summarized in Table 1.

The patient was admitted to the hospital and given rasburicase, 10 mg intravenously. The nephrology service was involved and he also received furosemide, sodium polystyrene sulfonate and midodrine. Unfortunately, he continued to get progressively oliguric and acidotic, developing severe anasarca with associated hypoxia. He elected not to proceed with intubation, declined dialysis and left the hospital against medical advice on day 6. He was brought back to the emergency room on day 14, when he suffered a cardiopulmonary arrest and unfortunately passed away.

### Discussion

TLS is characterized by development of acute kidney injury and other metabolic abnormalities including hyperuricemia, hyperkalemia, hypocalcemia and hyperphosphatemia after exposure to chemotherapy [1]. These derangements arise from rapid breakdown of neoplastic cells with release of intracellular contents into the circulation which can then exert deleterious effects on the kidneys and other organ systems which complicates treatment course. It is most frequently encountered in the initial treatment of aggressive and, notably, chemo- and radio-sensitive, hematologic malignancies. It is less common in solid tumors, which have a relatively lower proliferative index and treatment sensitivity.

Advanced (metastatic or multinodular) HCC is currently treated with sorafenib, which works by inhibiting serine-threonine kinases, as well as tyrosine kinases associated with vascular endothelial growth factor receptors (VEGFRs) 1,2,3 and platelet-derived growth factor receptor  $\beta$  (PDGFR- $\beta$ ) [2]. In the seminal SHARP trial [2], sorafenib monotherapy for advanced HCC demonstrated an improved overall survival compared to best supportive care alone. No complete responses were seen, while partial response was noted in only 2% of the patients. 71% of patients had stable disease which was in part due to tumor necrosis without a change in size meeting criteria for response.

Based on the usually slow-growing nature of HCC (in comparison to hematologic malignancies), and the low response rates and mechanism of action of sorafenib, most clinicians do not expect to encounter TLS when sorafenib therapy is initiated. To the best of our knowledge, there are only seven previous reports of sorafenib-induced TLS in HCC patients reported in literature [3–9]. Most of these reports are from far-east Asia with one from the US and none from Europe or Africa. It is difficult to say whether this geographic difference is due to different underlying disease biology in the far-east-Asian population (including the greater prevalence of viral hepatitis), or simply due to different levels of interest in reporting and publishing. A detailed comparison of the seven published cases is presented in Table 2.

As can be noted, all cases had a relatively high disease burden, with either frank metastatic disease, or multiple nodules in the liver. In some cases, prior local therapy to

**Table 1** Laboratory values at the time of sorafenib initiation, discontinuation of therapy on day 7 and demise of patient at day 14.

Laboratory parameter	Day 0 (initiation)	Day 7 (admission)	Day 14 (demise)
Serum potassium (mEq/L)	3.8	5.37	7.8
Serum creatinine (mg/dL)	0.7	2	5.3
Serum uric acid (mg/dL)	10.3	>20	3.2 (s/p rasburicase)
Alanine transaminase (U/L)	84	49	515
Aspartate transaminase (U/L)	166	291	3424
Total bilirubin (mg/dL)	1.72	2.98	2.4
Lactate dehydrogenase (U/L)	815	2096	20,779
Serum calcium (mg/dL)	8.6	8.8	7.5
Serum phosphorus (mg/dL)	Not checked	5.2	18.9

**Table 2** Reported cases of tumor lysis syndrome in patients with hepatocellular carcinoma treated with sorafenib [2–9].

Author (year) [reference]	HCC stage at the start of sorafenib therapy (AFP)	Other relevant characteristics	Days from sorafenib therapy to development of TLS	Final outcome of TLS
Kim et al. [3]	Metastatic (1795 µg/L)	Hepatitis B Tumor thrombus in LHV, IVC & RA	8	Declined HD; Transferred to nursing home
Kudo et al. [4]	Multifocal (11 ng/mL)	Fever and anorexia at day 5	7	Mild CKD
Habib et al. [5]	Metastatic (>1500 IU/mL)	Hepatitis B Had liver transplant History of PE	21	Fatal
Abbass et al. [6]	Unresectable	Hepatitis B Alcoholism	7	Declined HD Fatal
Joshita et al. [7]	Metastatic (2580 ng/mL)	Previous TACE	7	Recovered
Shiozawa et al. [8]	Multifocal	Hepatitis C	10	Recovery
Huang et al. [9]	Multifocal (9828 µg/L)	Child score 8 Hepatitis B PV thrombus	30	Fatal

AFP; alpha-fetoprotein, CKD; chronic kidney disease, HCC; hepatocellular carcinoma, HD; hemodialysis, IVC; inferior vena cava, LHV; left hepatic vein, PE; pulmonary embolism, PV; portal vein, RA; right atrium, TACE; transarterial chemoembolization, TLS; tumor lysis syndrome.

the liver nodules had already been attempted. Furthermore, four out of the seven cases had underlying hepatitis B [3,5,6,9], while one had hepatitis C [8]. The time of onset of TLS ranged from 7 days to 30 days while 3 out of the 7 cases were fatal, as was the case with our patient. Good outcomes were noted when TLS was detected early, sorafenib was discontinued at the earliest suspicion of TLS and aggressive supportive care was initiated early in the course [4,7,8]. This corroborates that early detection and intervention are paramount in preventing more serious sequelae. TLS in the present case was also detected early, and the outcome could have potentially been non-fatal. Unfortunately, the patient left the hospital against medical advice before supportive and interventions, including hemodialysis, could be started.

It is also interesting to note that our patient developed TLS despite the fact that we had begun treatment with a 50% dose reduction from the standard 400 mg daily dose. Notably, our patient had a slightly elevated serum uric acid level prior to initiation of therapy. It is conceivable that he was already in a state of spontaneous tumor lysis even before therapy, but that may be less likely given the rarity of spontaneous TLS in solid tumors [10].

To conclude, although rare, TLS is a potential complication during sorafenib treatment for advanced HCC with heavy disease burden. The time of onset is usually within the first 1–3 weeks. Early recognition, drug discontinuation and aggressive supportive measures are crucial for a favorable outcome. Patients with a high burden of disease at therapy initiation should have their metabolic parameters prior to therapy and closely followed for the first 1–2 weeks. Prospective studies may lead to further insights into TLS after sorafenib therapy and development of risk stratification methods to institute preemptive therapy to improve patient outcomes.

## Conflict of interest

The authors of this manuscript have no conflicts of interest to declare.

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