

Tumour Lysis Syndrome in Solid Tumours Associated with Tyrosine Kinase Inhibitors – A Case Illustrated Review

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Abstract

There are a variety of tyrosine kinase inhibitors (TKIs) that are used in oncology for the treatment of malignancies now and consequently there have been increased observations of tumour lysis syndrome (TLS) associated with these drugs. As per the Cairo-Bishop criteria, laboratory and clinical TLS is typically diagnosed within 3 days before and 7 days after cytotoxic chemotherapy is started. In this report, we describe a case of TLS in a patient with gastrointestinal stromal tumour (GIST) that occurred 15 days after commencement of imatinib. In addition, in a review of the literature, we have found that TLS in solid tumours is observed on average 10 days (95% confidence interval [CI] 7.8–13.7) and up to 3 weeks after initiating TKIs. By comparison, TLS in patients with solid organ tumours treated with cytotoxic chemotherapy occurs within 3 days (95% CI 2.9–4.4). Given the high rate of mortality and the morbidity inherent to TLS, clinicians should be aware that in solid tumour, TKIs may be associated with a delayed onset of TLS.

Keywords

Gastrointestinal stromal tumour, imatinib, sorafenib, sunitinib, acute kidney injury, Cairo-Bishop criteria, renal cell carcinoma, hepatocellular carcinoma

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Compliance with Ethics: All procedures were followed in accordance with the responsible committee on human experimentation and with the Helsinki Declaration of 1975 and subsequent revisions, and informed consent was received from the patient involved in this case study

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Tyrosine kinase inhibitors (TKIs) are small anticancer molecules targeting protooncogenic tyrosine kinase signalling pathways.¹ TKIs are now therapies used routinely in the treatment of many solid tumours such as gastrointestinal stromal tumour (GIST), renal cell carcinoma (RCC), hepatocellular carcinoma (HCC), medullary thyroid cancer, breast cancer and non-small-cell lung carcinoma (*Table 1*). As opposed to cytotoxic chemotherapy, TKIs target specific mutated kinases that promote tumour angiogenesis and neoplastic cells growth, proliferation, and resistance to apoptosis. In some cases, such as the c-Kit mutation observed in GIST, tumour cells can be highly “addicted” to one or more oncogenic kinases^{2–4} and the inhibition of these kinases with a TKI can lead to a striking tumour response and trigger tumour lysis syndrome (TLS).⁵ It is noteworthy that in high-risk patients with haematological malignancies, targeted therapy including TKIs, monoclonal antibodies, chimeric antigen receptors and proteasome inhibitors are often associated with TLS.⁶

The pathophysiology of TLS is characterised by an extensive breakdown of tumour cells releasing intracellular contents into the bloodstream, leading to acidosis, hyperuricemia, hyperphosphatemia, and hyperkalemia.⁷ These metabolic disturbances may in turn cause hypocalcaemia, acute kidney injury (AKI), cardiac arrhythmia, seizures, and death. Albeit considerably more common in haematological malignancies such as

acute leukaemia and Burkitt’s lymphoma, it is now recognised that TLS may also occur in solid tumours.⁸ Most authors and oncologic societies define TLS according to the laboratory and clinical criteria proposed by Cairo & Bishop in 2004 (*Table 2*).⁹ As per this definition, TLS is typically diagnosed within a specific timeframe – i.e. 3 days before or 7 days after cytotoxic therapy initiation. However, TLS in solid tumours treated with TKIs has been repeatedly described during the second and third weeks following the initiation of therapy rather than within the first week.⁵ Against this background, we report a case of delayed TLS in a patient with advanced GIST treated with imatinib.

Case report

A 63-year-old female of Mediterranean origin presented with a three-month history of tiredness, anorexia, 20-kg weight loss and one-month history of vague abdominal discomfort. She was referred to our centre after a computed tomography (CT) scan had revealed extensive intra-abdominal neoplasm along with tumour deposit in the liver and along the hepatic and renal capsules (*Figure 1*). A core needle biopsy of the omentum demonstrated a neoplasm composed of mixed spindle and epithelioid cytology. The spindle component showed interlacing fascicles of bland tumour cells with spindle nuclei (*Figure 2*). The tumour had a low mitotic index of <5/50 high-powered fields (HPF). Immunostaining revealed a strong expression of CD117 (c-Kit), DOG1

Table 1: Multitargeted tyrosine kinase inhibitors currently approved for targeted therapy in solid organ tumours in Canada

TKIs	Targeted Kinases **	Solid tumours
Afatinib	EGFR, ErbB2, ErbB4	NSCLC
Axitinib	VEGFR-1,-2,-3, c-Kit, PDGFR α , β	RCC
Crizotinib	ALK, HGFR, c-MET, ROS1, RON	NSCLC
Dabrafenib	CRAF, BRAF, BRAF ^{V600E-K-D}	Melanoma
Erlotinib	EGFR	NSCLC
Gefitinib	EGFR	NSCLC
Imatinib	SCF, c-Kit, ABL, PDGFR α	GIST
Lapatinib	EGFR, ErbB2	Breast
Pazopanib	VEGFR-1,-2,-3, PDGFR α , β , c-Kit, FGFR-1,-3, Ltk, Lck, c-Fms	RCC, Sarcoma
Regorafenib	VEGFR-1,-2,-3, Tie2, c-Kit, Ret, Abl, Raf-1, BRAF, BRAF ^{V600E} , PDGFR α , β , FGFR-1,-2, DDR2, Trk2A, EPH2A	CRC, GIST
Sorafenib	CRAF, BRAF, VEGFR-1,-2,-3, PDGFR β , FLT3, c-Kit, RET	RCC, HCC
Sunitinib	PDGFR α , β , VEGFR-1,-2,-3, c-Kit, FLT3, CSF-1R, RET	RCC, GIST, pancreas NE
Trametinib	MEK-1,-2, BRAF ^{V600E}	Melanoma
Vandetanib	VEGFR, EGFR, Ret, Brk, Tie2, Src, Ephr	Thyroid
Vemurafenib*	CRAF, ARAF, BRAF, BRAF ^{V600E}	Melanoma

*Vemurafenib is a BRAF serine-threonine kinase inhibitor. **Targeted kinases are listed as published on www.fda.gov. ABL = abelson murine leukemia; ALK = anaplastic lymphoma kinase; Brk = breast tumour kinase; c-FMS = colony-stimulating factor-1 receptor; c-kit = tyrosine-protein kinase Kit; c-MET = tyrosine kinase receptor MET; CRC = colorectal cancer; CSF-1R = colony stimulating factor-1 receptor; DDR2 = discoidin domain-containing receptor 2; EGFR = epidermal growth factor receptor; EPH2A = ephrin type-A receptor 2; ErbB2/4 = avian erythroblastosis oncogene B receptor tyrosine kinase 2 and 4; FGFR = fibroblast growth factor receptor; FLT3 = Fms-like tyrosine kinase 3; GIST = gastrointestinal stromal tumour; HCC = hepatocellular carcinoma; HGFR = hepatocyte growth factor receptor; Lck = lymphocyte-specific protein tyrosine kinase; Ltk = leukocyte tyrosine kinase; NE = neuroendocrine; NSCLC = non-small-cell lung carcinoma; PDGFR = platelet-derived growth factor receptor; RCC = renal cell carcinoma; RON = recepteur d'Origine Nantais kinase; ROS1= ROS proto-oncogen 1; SCF = stem cell factor; TKI = tyrosine kinase inhibitor; VEGFR = vascular endothelial growth factor receptor.

("Diagnosed on GIST-1") and CD34, consistent with a diagnosis of GIST, mixed cellularity subtype.

The patient was a life-long non-smoker and never consumed alcohol. She denied personal or familial history of cancer. Her past medical history was significant for type 2 diabetes mellitus treated with metformin and sitagliptin; hypertension treated with losartan, hydrochlorothiazide, and bisoprolol; and gastroesophageal reflux disease managed with omeprazole. On physical examination, the patient had an Eastern Cooperative Oncology Group (ECOG) performance status of 2 and was somewhat cachectic. The abdomen was diffusely tender with right flank fullness.

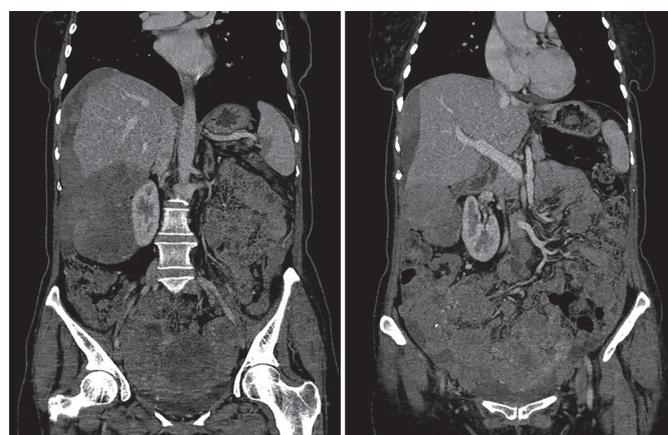
As per current recommendations, the patient was initiated on imatinib mesylate, at a dose of 400 mg daily. During the second week of treatment, she developed progressive anorexia, nausea, vomiting, and loose stools. Fifteen days after initiation of imatinib, she presented to the emergency department with dyspnoea, hypotension, tachycardia and confusion. Laboratory tests (with pre-therapy baseline) revealed: Creatinine 527 (53) [22–75 $\mu\text{mol/L}$], pH <6.8 [7.33–7.46] with undetectable bicarbonate, lactate was 12.9 [0.4–2 mmol/L], potassium 5.8 [3.5–5.1mmol/L], phosphorus 3.04 (1.25) [0.81–1.58 mmol/L],

Table 2: Criteria for laboratory and clinical tumour lysis syndrome as defined by Cairo-Bishop⁹

Cairo-Bishop criteria		
Laboratory TLS	≥ 2 among	Clinical TLS
Uric acid	$\geq 476 \mu\text{mol/L}$	Laboratory TLS and ≥ 1 among: • Acute kidney injury • Seizure • Arrhythmia • Sudden death
Potassium	$\geq 6 \text{ mmol/L}$	
Phosphorus	$\geq 2.1 \text{ mmol/L}$ (children) $\geq 1.5 \text{ mmol/L}$ (adults)	
Calcium	$\leq 1.75 \text{ mmol/L}$	

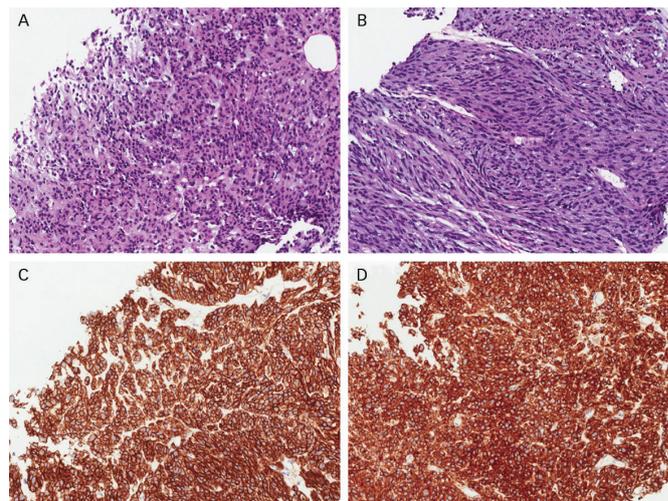
Laboratory alterations should be measured within the same 24 hours and must occur within 3 days before and 7 days after therapy. TLS = tumour lysis syndrome.

Figure 1: Coronal enhanced CT scan



Coronal enhanced CT scan May 29, 2014 at presentation with bulky solid tumour dissemination through the abdomen and pelvis. Extensive solid tumour deposits over the liver capsule and into the right hepatic lobe, the renal capsule, and encasing the right colon, small bowel and pelvic organs. CT = computed tomography.

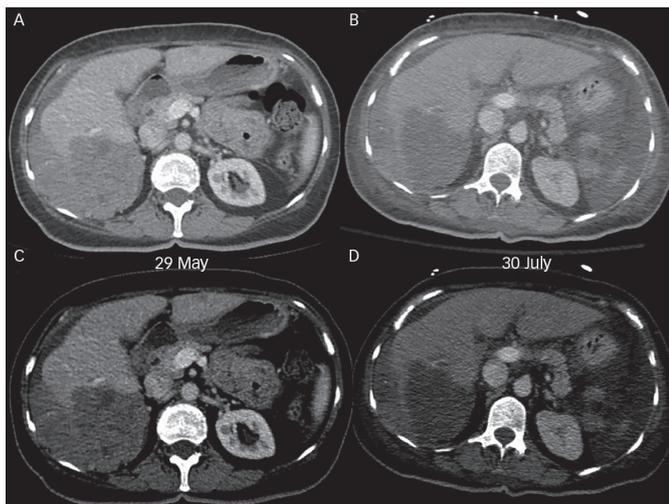
Figure 2: Morphology of GIST



A) Epithelioid component, with larger cells, with round nuclei and abundant cytoplasm, in a fibromyxoid stroma (Hematoxylin and Eosin stain, 50X). B) Spindle cell component, forming interlacing fascicles of elongated cells with spindle nuclei (Hematoxylin and Eosin stain, 50X). C) Immunohistochemical stain for DOG1 showing strong cytoplasmic and membranous positivity of both spindle and epithelioid components (50X) and D) Immunohistochemical stain for CD117 (c-Kit) showing strong cytoplasmic staining of both spindle and epithelioid components (50X). GIST = gastrointestinal stromal tumour.

corrected calcium 2.39 (2.57) [2.12–2.52 mmol/L], urate 1094 (547) [155–357 $\mu\text{mol/L}$], white blood count 17 [3.5–105 $\times 10^9/\text{L}$], haemoglobin

Figure 3: Axial images of the upper abdomen showing the tumour invading the liver surface



The images are all obtained at the same level of the liver (A, C) 35 days before starting therapy with imatinib; and (B, D) 16 days after starting. There is new ascites and no significant change in the size of the tumour deposits after treatment, however the tumour has reduced in density from 52 HU (Hounsfield units) to 27 HU, a drop of almost 50% (> 15% drop in density qualifies as partial response by Choi criteria). The upper image slices are viewed with "routine abdomen windows" (W 400, L 50), and the lower slices are anatomically identical but viewed with narrow "hepatic windows" (W 270, L 125).

Table 3: Risk factors for developing a tumour lysis syndrome³⁷

Cancer-Related Risk factors

- Large burden of tumour
- Neoplastic infiltration of the bone marrow, liver, spleen, kidneys
- Tumour with high mitotic rate
- Tumour highly chemosensitive
- Haematologic malignancy

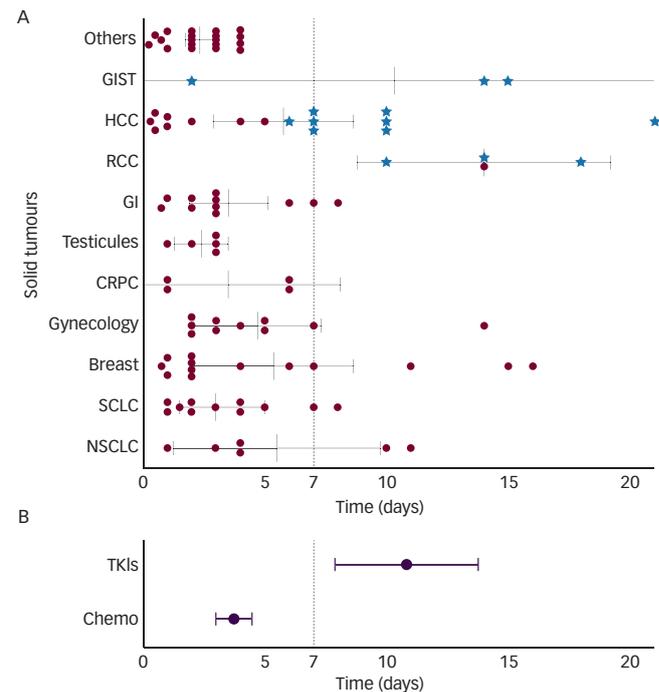
Patient-Related Risk Factors

- Pre-existing nephropathy
- Hyperuricemia
- Hypotension
- Dehydration
- Nephrotoxins (drugs, contrast)
- Exogenous potassium or phosphorus intakes

111 [115–155 g/L], and platelets 598 [130–380 x 10⁹/L]. The patient underwent aggressive fluid resuscitation and was transferred to the critical care unit on vasopressor support, with the intent to initiate sustained low-efficiency dialysis (S.L.E.D.). Four hours after initial bloodwork and prior initiation of S.L.E.D., corrected calcium had decreased to 2.21 mmol/L, phosphorus had decreased to 2.83 mmol/L, and potassium had increased to 6.3 mmol/L. Calcium phosphate product went from 90.2 to 77.4 mg²/dL². A septic workup, including chest X-ray, blood and urine cultures was negative. CT scan of the abdomen and pelvis performed the following day ruled out visceral perforation but did demonstrate clear evidence of tumour response with a decrease in tumour density by nearly 50%, meeting Choi criteria for partial response (Figure 3).¹⁰ Imatinib was held pending her improvement.

The patient was discharged from the intensive care unit after 4 days. Natural diuresis recovered progressively after one week of anuria and intermittent haemodialysis was weaned after 2 weeks. Imatinib 100 mg daily was reintroduced and progressively titrated to 400 mg over the subsequent month.

Figure 4: Tumour lysis syndromes in solid organ tumours



Tumour lysis syndromes in solid organ tumours after A) cytotoxic chemotherapy (empty circle) or tyrosine kinase targeted therapy (dark stars) according to the timing of onset. Mean delay of onset \pm standard deviation is illustrated for each tumour type/site. B) Mean time of onset \pm standard deviation for tumour lysis syndrome induced by chemotherapy or targeted therapy. Mann-Whitney test, one-tailed p value < 0.0001. Statistical significance assumed if $p \leq 0.05$. CRPC = castrate-resistant prostate cancer; GI = gastrointestinal and pancreatic tumours; GIST = gastrointestinal tumour; HCC = hepatocellular carcinoma; NSCLC = non-small-cell lung carcinoma; RCC = renal cell carcinoma; SCLC = small-cell lung carcinoma; TKIs = tyrosine kinase inhibitors.

Discussion

The present case illustrates well the typical laboratory and clinical manifestations of TLS. To our knowledge, there are only two other cases of TLS in GIST reported in the literature, one with sunitinib¹¹ and another with imatinib.¹² Although extremely rare in GIST, TLS can occur in presence of known risk factors (Table 3). In our case, the high tumour burden, the dehydration, the high baseline level of urate, and the patient exposure to various nephrotoxic compounds such as metformin, losartan and hydrochlorothiazide may all have predisposed our patient to develop a TLS. Once happening, the hyperuricemia and the high calcium-phosphate products lead to both urate crystals and calcium-phosphate precipitate in the renal tubules, causing potentially life-threatening AKI.¹³

Contrary to the diagnostic criteria of TLS proposed by Cairo & Bishop in 2004,⁹ the onset of the TLS occurred more than one week later than expected and 15 days after the initiation of imatinib. Of note, the diagnostic criteria were updated from the initial report of Hande and Garrow in 1993,¹⁴ who based their observation on a cohort of 102 patients with high-grade non-Hodgkin's lymphoma. Hence, the conventional Cairo-Bishop definition antedates the introduction of most TKIs in oncology and did not include solid organ tumours.

Review of TLS reported in solid organ tumours

MirraKhimov et al. published a review (PubMed/Medline, Scopus, Embase and Web of Science) of all reported cases of TLS in solid tumours between 1950 and February 2014.⁵ Using the same methodology, we conducted a comprehensive review the literature

extending the timeframe to August 2014. We identified TLS in six cases of hepatobiliary tumours,^{15–20} two of gastrointestinal tumour,^{21,22} five cases of melanoma,^{23,24} and one case of non-small-cell lung carcinoma,²⁵ RCC²⁶ and metastatic carcinoma of unknown primary site.²⁷ We pooled these cases with those identified by Mirrakhimov et al., and we excluded patients with spontaneous TLS (n=14) or TLS triggered by either radiation/radiofrequency (n=8), surgery/biopsy (n=1), coil embolisation (n=3), and those where the time of onset after treatment initiation was not provided (n=6).

Among the 101 cases reported, 14 were associated with the use of TKIs, namely sunitinib (three RCC and one GIST¹²), sorafenib (eight HCC^{15,19,20,28–32}), and imatinib (two GIST¹² in addition to the present case). From Figure 4A, it seems that TKIs may trigger TLS later than traditional cytotoxic chemotherapy does. Indeed, 12 out of 14 cases occurred between 7 and 21 days following the initiation of therapy, which is beyond the upper time limit defined by Cairo-Bishop. The average timing of occurrence of TLS was 10 days [7.8–13.7] following initiation of TKIs compared to 3 days [2.9–4.4] for cytotoxic chemotherapy (p<0.0001) (Figure 4B). To our knowledge, it is also the first time that timing of TLS is reported for non-haematological malignancies treated with conventional chemotherapy. We found that the risk for TLS is the highest during the first week of treatment, similar to what was described by Hande and Garrow¹⁴ in lymphomas.

The reasons why TKIs induce TLS at a later time point compared with cytotoxic chemotherapy is unknown. However, most cytotoxic chemotherapies damage rapidly dividing cells by disrupting cell

cycle and inhibiting DNA and may provoke extensive simultaneous breakdown of cells in tumours harbouring several mitotic figures. On the other hand, TKIs increase tumour cell death by targeting mutated kinase receptors and their downstream signalling that allow tumours to grow or escape host immunity. Initiation of TKI might therefore not result in immediate cytolysis comparable to cytotoxic chemotherapy. One hypothesis may be that cellular death could be delayed depending on the level of tumour addiction to the mutated kinase and how critical the mutation is for the cell survival.⁴ The sensitivity of GIST to targeted therapy depends on the genetic alterations harboured in the *KIT* gene with an activating mutation of the exon 11 leading to a higher response rate to imatinib³³ while GIST lacking driver genomic alterations in the protooncogenes c-Kit or platelet-derived growth factor receptor^{34,35} are essentially not responsive to imatinib.³⁶

In summary, our review and case presentation highlight the life-threatening nature of TLS, which can occur with targeted therapy with TKIs. It is crucial for clinicians to recognise that TLS associated with treatment with a multitargeted TKI may occur later than expected (i.e., outside the usual timeframe that is observed with cytotoxic chemotherapy) and caution should be exercised when initiating therapy particularly in patients who are at higher risk. For high-risk patients with predisposing factors, we suggest that it is reasonable to monitor patients' electrolytes and renal function at least weekly during the first month of therapy. The currently accepted Cairo-Bishop definition should be revised to specify that in the cases where a TKI is commenced, laboratory and clinical TLS could be diagnosed up to 3 weeks following its introduction. ■

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