Tumor Lysis Syndrome in Multiple Myeloma: An Increasingly Recognized Risk—A Report of Seven Cases

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Abstract Tumor lysis syndrome is a constellation of metabolic disturbances commonly seen during therapy of bulky, rapidly proliferative tumors. Multiple myeloma is a low proliferation tumor with rare incidence of tumor lysis syndrome in the pre-Bortezomib era. Post Bortezomib use, a rise in the incidence of tumor lysis has been noted. We present seven cases of tumor lysis syndrome with three patients in spontaneous tumor lysis and four developing the same after chemotherapy. In the previous studies, elevated LDH and deletion of chromosome 13 has been associated with risk of TLS. In our study, we noted several abnormal karyotypes including del 9p13, del 17 and monosomy 13 were more frequently found but larger studies are needed to explore the causative nature of these associations. Prognosis in these patients is relatively poor reflecting the higher tumor burden. However, further studies are needed to learn about other poor prognostic markers.

Keywords Tumor lysis · Bortezomib · Multiple myeloma

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Introduction

Tumor lysis syndrome (TLS) is a combination of clinical and biochemical manifestations which occurs more commonly as a result of cytotoxic chemotherapy in the presence of rapidly proliferating tumors although can occur spontaneously in the presence of tumors with rapid proliferation index [1].

The proliferative rate of plasma cells in myeloma is low and the proportion of cells at a particular time in the S phase is small. Hence tumor lysis in myeloma is infrequent.

Bortezomib is a proteasome inhibitor used in the treatment of multiple myeloma and has been reported to induce tumor lysis in patients with multiple myeloma. Data on spontaneous TLS in MM is even more tenuous.

Patients and Methods

Charts of all patients with multiple myeloma undergoing treatment at Department of Hematology at the John H Stroger Jr Hospital of Cook County, Chicago were screened prior to and after administration of chemotherapy. Patients satisfying the clinical and biochemical criteria for tumor lysis were included in the study. A retrospective chart review of the cases was done for diagnosis, treatment initiation time, medications used, timing of tumor lysis, management and eventual outcome.

Tumor lysis syndrome, for the purpose of this review was diagnosed based on Cairo Bishop Classification and was defined as abnormalities in two of the following

1. Uric acid >8 mg/dl
2. Calcium <7 mg/dl
3. Potassium >6 meq/l

Table 1 Patient characteristics—demographic profile, immunofixation and $\beta 2$ microglobulin levels

	Age (years)	Gender	Ig type	BM plasma cells (%)	Cytogenetic analysis	$\beta 2$ M	Chemo and timing of onset	Outcome	SP
1	52	M	IgA	92	Del17q, mono13, t [4, 14] (p16;q32)	NA	1 cycle of D + Bort	Died	N
2	75	M	LC ^a	83	Normal	7.2	13 cycles of M + P + Bort	Alive	N
3	50	M	IgG	95	Del 9p13	NA	Prechemo	Died	Y
4	70	F	LC ^a	31	Normal	50	10 cycles of Th +D	Died	N
5	49	F	LC ^b	98	Del 5q11, 9p13, 1p13, 10p11, 11q23	12.5	Prechemo	Died	Y
6	59	F	IgG	98	Del17p13, mono13	25.4	1 cycle of Len + D + Bort	Alive	N
7	58	M	IgA	80	Normal	NA	Prechemo	Alive	Y

LC Light chains, $\beta 2$ M beta 2 microglobulin, Bort bortezomib usage, Chemo Chemotherapy, M melphalan, Cyc cyclophosphamide, Bort bortezomib, D dexamethasone, Th thalidomide, P prednisone, Len lenalidomide, Sp spontaneous

^a Lambda light chain

^b Kappa light chain

4. Phosphate >4.5 mg/dl

in addition to one of the following

1. Increase in Serum creatinine by 1.5 times of upper limit of normal
2. Arrhythmia
3. Seizures

Results

Seven inpatients with tumor lysis syndrome in multiple myeloma were identified. There were four males and three females and the median age was 58 years. Table 1 highlights the patient demographic profile, immunofixation and cytogenetic characteristics.

Laboratory Investigations

Three of our patients had light chain disease, two had IgA and two had IgG subtype. Two patients had hypercalcemia prior to starting chemotherapy which improved while on therapy. The patients had 24-h urine proteinuria varying

from 1.26 to 16.6 g/24 h. Table 2 presents the laboratory manifestations pre, post chemotherapy and post rasburicase. Since patient 3, 5 and 7 presented with spontaneous TLS, only peak and post rasburicase values are reported in the table. Four patients (No. 2, 4, 6 and 7) presented with hyperkalemia and all except patient 7 had hyperphosphatemia of some degree at their peak levels. Only one of the three patients with spontaneous TLS showed significant hyperphosphatemia while all patients with therapy related TLS showed significant elevation in phosphate levels. Renal dysfunction was noted in all patients at baseline except patient 6 but all of them had worsening of renal function with >50 % increase in the serum creatinine with administration of chemotherapy. All the three patients with spontaneous TLS had renal failure at the time of diagnosis.

Patient 4 did not have any variations in his LDH levels, unlike the rest. Six patients had extensive disease with >5 lytic lesions and there was a single patient (No. 4) with no bone involvement.

BM

Bone marrow evaluation identified 31–98 % plasma cells with three patients with circulating peripheral plasma cells

Table 2 Laboratory parameters of the patients

	Uric Acid			Potassium			P			Cr			Dia	LDH		
	Pr	Pk	Po	Pr	Pk	Po	Pr	Pk	Po	Pr	Pk	Po		Pr	Pk	Post
1	8.8	18.6	2.8	4	6	4.2	4.2	11.2	6.7	2.5	7.9	5.9	Y	170	2089	1365
2	12.4	14.4	1.4	4.6	5.4	4.8	6.3	8.4	6.2	3.3	5.4	5.6	N	155	1107	204
3		18.9	2.2		4.7	4		7.6	5.3		5.7	4.4	Y		412	379
4	10.1	14.5	5.8	4.1	4.6	4.2	4.4	6.8	6.6	3.3	7.8	7.2	Y	157	178	174
5		21.2	1.7		4.4	3.7		5.6	4.5		2.4	2.9	N		1625	678
6	4.3	10.1	2.2	4.3	6.8	3.5	4.5	8.5	8.2	0.9	18.2	13.8	N	115	287	153
7		12.7	8.1		5.7	4		4.2	3.6		6.2	1.2	N		420	166

Pr Prechemotherapy, Pk peak, Po post rasburicase, Dia dialysis

(patients 1, 2 and 4) though no one meeting the criteria for plasma cell leukemia. Cytogenetic analysis done by Fluorescent in situ hybridization (FISH) revealed del 9p, del 17 and monosomy 13 as the most common cytogenetic abnormality, each identified in two patients.

Therapy

All but one patient were given bortezomib based therapy. Three patients had evidence of spontaneous TLS prior to the start of therapy and needed therapy for myeloma and TLS simultaneously. Two patients were given thalidomide and one received melphalan in addition to other forms of treatment.

All patients received Rasburicase as part of therapy for TLS along with aggressive hydration. Serum alkalization was done in three patients for persistent metabolic acidosis. Renal replacement therapy with dialysis was performed in three patients with patient No. 1 needing up to 11 sessions of it. All three of these patients died reflecting the severity of TLS in these settings.

Outcome

Four of the seven patients succumbed to the severity of the illness. All three patients requiring renal replacement therapy died. Only one patient with spontaneous tumor lysis syndrome survived probably reflecting the tumor burden.

Discussion

The purpose of this report is to increase awareness into various forms of tumor lysis syndrome in patients with multiple myeloma.

Incidence of tumor lysis syndrome in multiple myeloma is extremely low given the low proliferation rate of multiple myeloma. About 1 % of MM patients receiving high dose of chemotherapy with stem cell support have been shown to develop TLS [2]. The post bortezomib era has seen a modest rise in the reported tumor lysis syndrome patients [3–11]. However, what makes our report unique is the number of patients with spontaneous tumor lysis syndrome which so far has been reported once in literature in patients with multiple myeloma [12]. Wang et al. [13] in their paper on utility of Rasburicase in hematological malignancies did report nine patients with MM and TLS but data on therapy in relation to timing of TLS was not provided.

Efficacy of Bortezomib is already established in MM based on several trials including the CREST, SUMMIT and the VISTA trials. It acts in myeloma by inhibiting the

breakdown of inhibitory kappa B and stabilizing the NFkB complex [14]. The other mechanisms of action of Bortezomib include decreased adhesion of plasma cells to stromal cells, inhibition of angiogenesis, interruption of IL-6 mediated prosurvival cytokine loops and inhibition of DNA repair. Sezer et al. in their astute report of seven patients of bortezomib induced TLS in MM patients provided a heightened awareness into this complication. All patients in their study had a high tumor burden and most had deletion of chromosome 13 [6]. In another abstract by Tanimura, extramedullary plasmacytoma, unfavorable cytogenetics and elevated LDH were identified key risk factors for TLS. However, their primary patient population included relapsed/refractory disease which in itself might indicate adverse outcome and dismal tumor characteristics [8].

Majority of our patients had abnormal karyotype but none had del 13. Del 9p13 and monosomy 13 were the most frequently noted chromosomal abnormalities. Further none of our patients with therapy related TLS had LDH elevation at initial evaluation but rapid worsening with therapy. This provides insight into the fact tumor biology in addition to tumor burden might be responsible for this process and further research into the same might help identify and prevent this rare but ominous complication. No uniform abnormal karyotypes have been identified as predictors of TLS but higher frequency of abnormal cytogenetics has been noted in this subgroup of MM patients [3, 6, 7]. Another feature to note is the high mortality especially if TLS is severe enough to require renal replacement therapy. Early identification and intervention has been reiterated by Wang et al. to improve prognosis [11].

Compliance with Ethical Standards

Conflict of interest There was no external funding received for the study. The authors have no conflicts of interest to declare.

Research Involving Human Participants All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed Consent This study was a retrospective chart review and no intervention was planned. Hence keeping in accordance of confidentiality protocol of the institute, no additional informed consent was obtained from the patient after approval from the IRB.

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