Sevelamer is an Effective Drug in Treating Hyperphosphatemia Due to Tumor Lysis Syndrome in Children: A Developing World Experience

Dilraj Kaur Kahlon · Veronique Dinand ·
Satya Prakash Yadav · Anupam Sachdeva

Received: 8 June 2014 / Accepted: 20 November 2014 / Published online: 3 December 2014
© Indian Society of Haematology & Transfusion Medicine 2014

Abstract We report here a study on efficacy of sevelamer hydrochloride in treating hyperphosphatemia due to tumor lysis syndrome (TLS) in a developing world setting. Twenty one children with hyperphosphatemia due to TLS were included. All received hyper-hydration, allopurinol and sevelamer. Efficacy was assessed by decrease in serum phosphate level, calcium-phosphate product and TLS score as per Cairo Bishop definition. Four children who underwent dialysis were excluded from analysis. Among the remaining 17 patients with hyperphosphatemia, laboratory TLS was recorded in 15 patients and clinical TLS in five. Sevelamer was given according to weight, most often 400 mg twice to thrice daily. Mean phosphatemia decreased from 8.3 ± 3.0 to 6.7 ± 2.1 mg/dl within 24 h of starting sevelamer ($p = 0.02$), 6.0 ± 2.1 mg/dl at 48 h, 4.9 ± 1.5 mg/dl at 72 h and 4.39 ± 1.7 mg/dl at 96 h. TLS was corrected in 72 h in 14 patients, 96 h in 1 and 120 h in another patient. Mean calcium-phosphate product decreased from 63.0 ± 14.0 to 49.2 ± 9.7 mg/dl ($p = 0.002$) at 24 h, 46.1 ± 17.0 mg/dl at 48 h and 39.7 ± 13.5 mg/dl at 72 h. There was no mortality due to hyperphosphatemia. Sevelamer is efficacious in children with malignancy-associated hyperphosphatemia in the developing world.

Keywords Sevelamer · Hyperphosphatemia · Tumor lysis syndrome · Efficacy

Introduction

Tumour lysis syndrome (TLS) is a constellation of metabolic disturbances seen either spontaneously or after initiation of chemotherapy in patients with bulky, rapidly proliferating malignancies like leukaemia, lymphoma and some solid tumours [1]. Clinically, the syndrome is characterized by rapid development of hyperuricemia, hyperkalemia, hyperphosphatemia, hypocalcemia, and acute kidney injury (AKI) usually within 48–72 h after initiation of chemotherapy. These metabolic disturbances occur when large numbers of neoplastic cells are killed rapidly, leading to release of intracellular ions and metabolic by products into the systemic circulation.

Hyperphosphatemia as a part of TLS can occur spontaneously or after starting chemotherapy [1]. It along with other metabolic derangements can worsen with pre-existing volume depletion. Renal tubular deposition of phosphate along with calcium can lead to AKI. Prolonged hyperphosphatemia promotes metastatic calcification, an abnormal deposition of calcium phosphate in previously healthy connective tissues such as cardiac valves and in solid organs such as muscles [2]. The risk of calcium phosphate precipitation increases if calcium phosphorus product is above 72 mg/dl [3].

Dietary phosphorus restriction and dialysis play important role in the management of hyperphosphatemia but additional support from phosphate-binding therapies is necessary. Other available treatment options include phosphorus sequestering metallic agents like aluminium hydroxide and calcium acetate. Both of these act by

D. K. Kahlon · V. Dinand · S. P. Yadav · A. Sachdeva
Pediatric Hemato-Oncology and Bone Marrow Transplant Unit,
Sir Ganga Ram Hospital, New Delhi, India

S. P. Yadav (✉)
Pediatric Hemato-Oncology and Bone Marrow Transplant Unit,
Fortis Memorial Research Institute, Gurgaon 122002, Haryana,
India
e-mail: satya_1026@hotmail.com

combining with dietary phosphate to form insoluble phosphate product, which is excreted in the stool. But there is a significant risk of neurological and renal toxicity in case of aluminum containing agents [4] and increased calcium load with calcium-containing phosphate binders [5]. The aim should be to correct hyperphosphatemia effectively and safely without increasing serum calcium levels and thus decreasing the risk of hypercalcemia. Metal-free, calcium-free phosphate binders have an important role in this regard.

Sevelamer hydrochloride is a metal free phosphate binder indicated for the control of serum phosphorus in patients with chronic kidney disease on dialysis. This polymeric amine is administered orally. By binding phosphate in the dietary tract and decreasing the absorption, it lowers the phosphate concentration in the serum [6]. In addition to effects on serum phosphate levels, sevelamer hydrochloride has been shown to bind bile acids in vitro and in vivo in experimental animal models.

Various studies have been done on use of sevelamer in chronic renal disease [5, 7] but there is limited data available on its use in children. The cut off values of hyperphosphatemia in children vary according to age [8]. TLS and hyperphosphatemia can lead to morbidity and mortality especially in the developing world setting [9]. There is a need for an agent which can perhaps lead to avoidance of dialysis for hyperphosphatemia and reduce cost and save lives. Sevelamer can possibly be that drug but data is lacking for its usage in this setting. A single study reports its use in treating hyperphosphatemia due to TLS in children [10]. We conducted a retrospective study to assess the efficacy and the role of sevelamer in safely treating hyperphosphatemia in children with haematological malignancies or solid tumours.

Patients and Methods

This retrospective study was conducted at Sir Ganga Ram Hospital, New Delhi, in pediatric oncology patients with hyperphosphatemia. Records of all children younger than 18 years who were started on chemotherapy for various malignancies from January 2007 to June 2010 were reviewed. All children with hyperphosphatemia at the time of presentation or after starting chemotherapy and treated with sevelamer were included. All were started on sevelamer after obtaining informed consent. Hyperphosphatemia was defined as serum phosphorus level higher than the upper limit as per age (Normal values are 3.8–6.5 mg/dl in 1–3 years of age, 3.7–5.6 in 4–11 years, 2.9–5.4 in 12–15 years, 2.7–4.7 in 16–19 years) [8]. Patients requiring dialysis were excluded.

TLS was defined as per Cairo Bishop scoring system [1]. Laboratory TLS (LTLS) is present if two or more serum

values of uric acid, potassium, phosphorus are more than normal or calcium is less than normal at presentation or if they change by 25 % within 3 days before or 7 days after initiation of treatment. Clinical TLS (CTLs) requires the presence of LTLS in addition to one or more of the following significant clinical complications: renal insufficiency, cardiac arrhythmias, sudden death and seizures. Record was made of the dose, duration of treatment and simultaneous administration of other drugs such as allopurinol, calcium acetate and recombinant urate oxidase (Rasburicase). TLS was treated in all patients as per protocol (double maintenance fluids, diuretics, allopurinol or rasburicase and dialysis if needed). Side effects were also recorded in these patients. Serum phosphate, calcium phosphate product and TLS score were recorded at 0, 24, 48, 72 h from time of starting sevelamer (50 mg/kg/day rounded off to 200 mg which is ½ tablet) and daily thereafter as required till the time the drug was stopped. Calcium phosphate product was calculated by multiplying calcium and phosphate values in mg/dl.

Statistical Analysis

Tests of normality were applied to confirm non-normality of continuous variables. Chi square test, Spearman correlation analysis and Mann–Whitney *U* test were used as applicable. Pre and post-sevelamer values of phosphorus and calcium-phosphorus product were compared by Mc Nemar test.

Results

A total of 260 patients diagnosed with various childhood malignancies were started on chemotherapy during the study period. Of these, 21 patients who developed hyperphosphatemia with or without TLS received sevelamer. Four out of 21 patients underwent dialysis during induction chemotherapy and were excluded from the efficacy study as efficacy of Sevelamer cannot be assessed if patient undergoes dialysis during sevelamer therapy. The remaining 17 patients are included in this report.

Underlying diagnoses were T cell acute lymphoblastic leukemia (ALL)/non-Hodgkin lymphoma (NHL) in four cases, pre-cursor B-cell ALL in four cases, Burkitt's lymphoma in three cases, acute myeloid leukemia (AML) in three cases, biphenotypic leukemia, diffuse large B-cell lymphoma (DLBCL) and stage IV neuroblastoma in 1 case each (Table 1). Eleven patients were males and six were females with a median age of 6 years (range 3–16 years).

Hepatomegaly was present in 13 patients and splenomegaly in 9 patients. Median lactate dehydrogenase (LDH) at presentation was 677 IU/l (range 141–3,246). Median

Table 1 Patients' characteristics at presentation and TLS after starting chemotherapy

S.no	Diagnosis	Sex	Age	Liver (cm) ^a	Spleen (cm) ^a	LDH (IU/l)	TLC (1,000/ μ l)	CTLS	LTLS
1	DLBCL	F	3	8	4	318	6,800	No	Yes
2	Biphenotypic ALL	M	6	9	10	561	248,000	No	No
3	Pre-B ALL	F	13	7	0	141	1,800	No	Yes
4	T-cell ALL	M	4	4	3	474	6,600	Yes	Yes
5	AML	M	5	0	0	651	106,200	No	No
6	Burkitt leukemia	F	6	8	0	945	10,100	Yes	Yes
7	AML	F	13	1	0	434	63,200	No	Yes
8	Pre-B ALL	M	12	0	0	677	17,300	Yes	Yes
9	T-cell ALL	M	14	2	0	2,396	30,320	No	Yes
10	Pre-B ALL	F	16	19	16	632	8,500	No	Yes
11	Neuroblastoma	M	4	4	2	3,246	5,500	No	Yes
12	AML	M	3	7	5	1,632	59,400	No	Yes
13	T-cell NHL	M	14	1	2	677	21,400	No	Yes
14	T-cell ALL	M	7	5	4	1,153	7,600	Yes	Yes
15	Burkitt lymphoma	F	4	4	3	1,169	10,100	No	Yes
16	Pre-B ALL	M	9	1	0	1,050	17,300	Yes	Yes
17	Burkitt lymphoma	M	3	7	0	1,985	14,000	No	Yes

TLC total leucocyte count, CTLS clinical TLS, LTLS laboratory TLS, DLBCL diffuse large B cell lymphoma, ALL acute lymphoblastic leukemia, AML acute myeloid leukemia, M male, F female, LDH lactate dehydrogenase
^a Maximum size below costal margin

total leucocyte count (TLC) at presentation was 14,000/ml (range 1,800–248,000). There was no statistically significant association between organomegaly, LDH levels, elevated TLC and degree of TLS.

Laboratory TLS was recorded in 15 patients, including five with clinical TLS (Table 2). Hyperphosphatemia was present in all 17 patients. Two patients received Rasburicase. Calcium acetate was given to 9 patients, but with no benefit. Sevelamer dose was given according to weight (50 mg/kg/day). Most children received 400 mg twice a day (Table 3). Median duration of treatment was 4 days (range 2–10 days). Sevelamer was well tolerated by all children, without significant side effects. Two patients had minimal nausea and vomiting responding to routine antiemetics.

Mean phosphatemia decreased from 8.3 ± 3.0 to 6.7 ± 2.1 mg/dl within 24 h of starting sevelamer ($p = 0.02$), 6.0 ± 2.1 mg/dl at 48 h, 4.9 ± 1.5 mg/dl at 72 h and 4.39 ± 1.7 mg/dl at 96 h. Hyperphosphatemia was corrected within 24 h in 4 patients, at 48 h in 4 patients, at 72 h in 5 patients and at 96 h in 3 patients. In only one patient with Burkitt's lymphoma, TLS and hyperphosphatemia subsided on the 5th day, when further chemotherapy led to TLS recurrence and further correction of hyperphosphatemia within 5 days. TLS was corrected in 72 h in 14 patients, 96 h in 1 and 120 h in 1 patient. Mean calcium-phosphate product decreased from 63.0 ± 14.0 to 49.2 ± 9.7 mg/dl ($p = 0.002$) at 24 h, 46.1 ± 17.0 mg/dl at 48 h and 39.7 ± 13.5 mg/dl at 72 h (Table 2). There was no mortality due to hyperphosphatemia. One patient

died of pulmonary hemorrhage within 48 h due to very low platelets, while phosphatemia and TLS were corrected after 24 h of sevelamer.

Discussion

In the developing world induction mortality is high for children with leukemia [9, 11]. Sepsis is major barrier to improving outcome but other factors like TLS and hyperphosphatemia add to both morbidity and mortality. Management of TLS is difficult in developing countries because of limited availability of Rasburicase, hemodialysis and lack of pediatric intensive care units to handle sick children with AKI and sepsis [12]. Because of the rapidity with which TLS progresses and the seriousness of common clinical consequences such as AKI, TLS is associated with significant morbidity and potential mortality. Kulkarni et al. from India reported 6.8 % induction deaths due to TLS in children [9]. Hyperphosphatemia being an important component of TLS can further compromise the renal functions.

The management of hyperphosphatemia includes maintaining good hydration, avoiding urine alkalisation, dietary phosphate restriction and use of oral phosphate binders. Sevelamer is efficacious and safe in children with chronic renal failure. Mahdavi et al. mentioned that sevelamer can be effectively used to reduce serum phosphate concentration in children treated with dialysis [7]. Runowski et al. in their small study showed that sevelamer is

Table 2 Laboratory findings at the time of starting of sevelamer and phosphatemia at 24, 48 and 72 h

S.no	Diagnosis	S.K meq/L	S.Ca mg/dl	S.Ph mg/dl	S.U.A mg/dl	S.Cr mg/dl	Ca Ph product	CTLS score	LTLS score	S.Ph at 24 h	S.Ph at 48 h	S.Ph at 72 h	S.Ph end point	Hours to Ph correction
1	DLBCL	4.1	7.2	7	1.8	0.8	50.4	0	1	4.6 ^a	3.7			24
2	Biphenotypic ALL	4.2	9	6.1	2.5	0.6	54.9	0	0	6.2	2.8 ^a	4.8		48
3	Pre-B ALL	3.6	8.9	6.4	6.1	0.77	56.96	0	1	4 ^a				24
4	T-cell ALL	3.3	7.9	9	21.5	1.79	71.1	2	1	4.1 ^a	3	3.6		24
5	AML	4.1	9.5	7.4	4	0.6	70.3	0	0	5.9	6.1	5.9	5.0 ^a	96
6	Burkitt leukemia	3.9	3.8	15.8	9.4	1.25	60.04	2	1	9.7	5 ^a	3.7		48
7	AML	3.5	8.6	7	2.8	0.72	60.2	0	1	6.5	7.1	6.1	5.2 ^a	96
8	Pre-B ALL	5	8.5	11.5	16.2	2.6	97.75	3	1	6.5	4.4 ^a	4.3		48
9	T-cell ALL	4.3	8.8	6.3	4.2	0.66	55.44	0	1	6.6	4 ^a	2.7		48
10	Pre-B ALL	5.1	7.6	8	6	0.9	60.8	0	1	6.3	6.5	4.0 ^a		72
11	Neuroblastoma	4.2	9.9	6.5	8.7	0.35	64.35	0	1		6.3	5.5 ^a		72
12	AML	3.4	8.8	6.2	6.5	0.53	54.56	0	1	4.7	7.2	6 ^a		72
13	T-cell NHL	3.7	8.4	6.3	6.6	0.59	52.92	0	1	8.9	7.2	3.9 ^a		72
14	T-cell ALL	4.3	8.7	7.2	10.9	1.78	62.64	2	1	5.4 ^a				24
15	Burkitt lymphoma	2.5	6.4	6.4	5.6	1	40.96	0	1	8.3	9.5	3.5 ^a		72
16	Pre-B ALL	4.6	6.1	14.9	8.1	1.6	90.89	2	1	11.4	7.8	6.9	4.8 ^a	96
17	Burkitt lymphoma	4.3	7.2	9.2	20.6	0.93	66.24	0	1	8.5	9.5	7.5	4.6 ^a	120

CTLS clinical TLS score, LTLS laboratory TLS score, DLBCL diffuse large B cell lymphoma, ALL acute lymphoblastic leukemia, AML acute myeloid leukemia, K potassium, Ca calcium, Ph phosphate, UA uric acid, S serum

^a Normal for age

Table 3 Management of patients with hyperphosphatemia

S.no	Diagnosis	CTLS score	LTLS	Management	Sevelamer dose	Duration (days)	Hyperphos. corrected (h)
1	DLBCL	0	Yes	a, b, Rasburicase	400 mg tds	3	24
2	Biph. ALL	0	No	a, b	400 mg bd	2	48
3	pre B ALL	0	Yes	a	400 mg tds	4	24
4	T-cell ALL	2	Yes	a, b	200 mg bd	4	24
5	AML	0	No	a	200 mg bd	4	96
6	Burkitt's L	2	Yes	a, b	400 mg bd	6	48
7	AML	0	Yes	a	400 mg tds	5	96
8	pre B ALL	3	Yes	a, b	800 mg bd	5	48
9	T-cell ALL	0	Yes	a, b	800 mg bd	4	48
10	pre B ALL	0	Yes	a, b	800 mg bd	4	72
11	Neuroblastoma	0	Yes	a	400 mg tds	8	72
12	AML	0	Yes	a	400 mg bd	8	72
13	T-cell NHL	0	Yes	a	400 mg tds	5	72
14	T-cell ALL	2	Yes	a, b	800 mg bd	3	24
15	Burkitt's L	0	Yes	a, b, Rasburicase	400 mg tds	4	72
16	pre B ALL	2	Yes	a	800 mg bd	4	96
17	Burkitt's L	0	Yes	a	400 mg bd	10	120

DLBCL diffuse large B cell lymphoma, Biphen biphenotypic, ALL acute lymphoblastic leukemia, L lymphoma, AML acute myeloid leukemia, NHL non hodgkin lymphoma, CTLS clinical tumor lysis syndrome, LTLS laboratory tumor lysis syndrome, Hyperphos hyperphosphatemia, Hrs hours

^a Double maintenance fluids, allopurinol and sevelamer

^b Calcium acetate

also effective in treating resistant hyperphosphatemia in children with CKD along with correction of calcium phosphate product without affecting calcium concentration [13]. A randomised study comparing sevelamer with calcium acetate in children with CKD has shown that both the agents cause decrease in phosphate concentration [5]. But there is increased incidence of hypercalcemia with calcium acetate and increased metabolic acidosis with sevelamer. In our retrospective study we could not analyse metabolic acidosis although clinically none of the children developed such symptoms.

The only study in children with hyperphosphatemia due to TLS by Abdullah et al. retrospectively includes 13 children [10]. Out of these two dialysed patients were excluded from efficacy analysis. The author has shown sevelamer to be efficacious and safe in children in their study. Our study on the efficacy of sevelamer in treating hyperphosphatemia due to TLS included 17 children with various malignancies. Eleven of our patients had significant hepatosplenomegaly, which was massive in one. Patients with massive organomegaly and high TLC have a high risk of developing TLS. TLS occurred in 11 patients after starting sevelamer which was managed symptomatically. Burkitt's lymphoma is an aggressive tumour and is very commonly associated with spontaneous TLS. Two out of five children in our study with Burkitt's lymphoma and TLS, required dialysis and were excluded from efficacy analysis, rest three were managed without dialysis. Rasburicase has an important role in management of aggressive tumours prone to TLS. The timely use of Rasburicase can prevent renal failure [14]. But in resource-poor countries like India, limited availability and high cost of Rasburicase hinders its free use. Non-availability and high cost of dialysis is also a big hurdle in managing patients with TLS [9]. Although without a control group, our study cannot conclude that dialysis can be avoided in such patients, it has shown that sevelamer is equally useful in aggressive tumours like Burkitt's lymphoma. Overall cost of treatment might decrease significantly with use of sevelamer as compared to dialysis.

Sevelamer has some limitations: big tablet size, higher cost of treatment than other phosphate binders and interference in action by agents like proton pump inhibitors [15]. Being a retrospective study, and without a control group it is difficult to comment on the role of sevelamer in decreasing phosphatemia beyond the contribution of other measures like hyper-hydration. However this is one of the few paediatric oncology studies suggesting the effectiveness of sevelamer in hyperphosphatemia. Hyperphosphatemia was safely and effectively controlled in all 17 patients of our study. There was a significant decrease in

calcium-phosphorus product and TLS score and no TLS-related mortality was seen.

Sevelamer hydrochloride is an effective and cheap modality to treat children with hyperphosphatemia associated with TLS in the developing world. Randomised controlled trials may confirm its role in terms of cost benefit, reducing need for dialysis and mortality, especially in resource-constraint settings.

References

1. Cairo MS, Bishop M (2004) Tumour lysis syndrome: new therapeutic strategies and classification. *Br J Haematol* 127:3–11
2. Schucker JJ, Ward KE (2005) Hyperphosphatemia and phosphate binders. *Am J Health Syst Pharm* 62:2355–2361
3. Block GA, Hulbert-Shearon TE, Levin NW, Port FK (1998) Association of serum phosphorus and calcium $\times$ phosphate product with mortality risk in chronic hemodialysis patients: a national study. *Am J Kidney Dis* 31:607–617
4. Sedman A (1992) Aluminum toxicity in childhood. *Pediatr Nephrol* 6:383–393
5. Pieper AK, Haffner D, Hoppe B et al (2006) A randomized crossover trial comparing sevelamer with calcium acetate in children with CKD. *Am J Kidney Dis* 47:625–635
6. Chertow GM, Burke SK, Lazarus JM et al (1997) Poly [allylamine hydrochloride] (Renagel): a non-calcemic phosphate binder for the treatment of hyperphosphatemia in chronic renal failure. *Am J Kidney Dis* 29:66–71
7. Mahdavi H, Kuizon BD, Gales B et al (2003) Sevelamer hydrochloride: an effective phosphate binder in dialyzed children. *Paediatr Nephrol* 18:1260–1264
8. Lo SF (2011) Reference intervals for laboratory tests and procedures. In: Kliegman RM, Stanton BMD, Geme JS, Schor N, Behrman RE (eds) *Nelson textbook of pediatrics*, vol 708, 19th edn. Saunders, Philadelphia
9. Kulkarni KP, Marwaha RK, Trehan A, Bansal D (2009) Survival outcome in childhood ALL: experience from a tertiary care centre in North India. *Pediatr Blood Cancer* 53:168–173
10. Abdullah S, Diezi M, Sung L et al (2008) Sevelamer hydrochloride: a novel treatment of hyperphosphatemia associated with tumor lysis syndrome in children. *Pediatric Blood Cancer* 51:59–61
11. Yadav SP, Dua V, Sachdeva A (2011) Sepsis is a major barrier to improving survival in childhood acute lymphoblastic leukemia in the developing world. *J Pediatr Hematol Oncol* 33(8):636
12. Ramzan M, Yadav SP, Gupta D, Arora S, Sachdeva A (2012) Pediatric intensive care unit: an essential service to improve survival of childhood cancer in developing world. *Indian J Pediatr* 79(12):1669–1670
13. Runowski D, Jachimik B, Cieślak-Puchalska A et al (2009) The use of sevelamer in the treatment of resistant hyperphosphatemia in children with chronic renal disease. *Pol Merkur Lekarski* 26(154):318–321
14. Pui C-H, Jeha S, Irwin D, Camitta B (2001) Recombinant urate oxidase (rasburicase) in the prevention and treatment of malignancy-associated hyperuricemia in pediatric and adult patients: results of a compassionate-use trial. *Leukemia* 15:1505–1509
15. Capitanini A, Lupi A, Osteri F et al (2005) Gastric pH, sevelamer hydrochloride and omeprazole. *Clin Nephrol* 64:320–322