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MANAGEMENT OF TUMOUR LYSIS SYNDROME WITHOUT RASBURICASE: A MODEL FOR THE DEVELOPING WORLD

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ABSTRACT

Background: Tumor lysis syndrome (TLS) is a common oncological emergency during the treatment of hematolymphoid malignancies. Rasburicase is recommended in the prevention and treatment of TLS but is an expensive medication.

Aim: Evaluate a protocol for management of TLS without rasburicase in a developing country context.

Methods: Prospective observational study of children with hematolymphoid malignancies to evaluate for laboratory and clinical TLS was conducted. All the patients at risk for developing TLS were included in the study and treatment was initiated as per our protocol. The patients were categorised based on TLS risk stratification and Cairo-Bishop score.

Results: 60 patients were recruited in the study. Forty three had ALL, 9 had AML, 8 had NHL. 37 were classified as high risk, 19 as intermediate and 4 as low risk for TLS. 12 developed hyperuricemia, 7 had hyperphosphatemia, 4 had hypocalcemia and 4 had hyperkalemia. Chemotherapy was delayed due to renal dysfunction in only one patient. Three required PICU care and only one required dialysis. There was no mortality.

Conclusion: Judicious hydration, allopurinol, phosphate binders, diuretics and frequent laboratory monitoring was used in all our patients. We have an excellent outcome even in the high risk group despite not using rasburicase.

KEYWORDS : Tumor lysis syndrome, rasburicase

INTRODUCTION:

Tumour lysis syndrome (TLS) is a life threatening oncologic emergency secondary to the release of intracellular contents of the malignant cells. It can occur either spontaneously or after the initiation of the treatment. The metabolic complications include hyperkalemia, hyperuricemia, hyperphosphatemia and hypocalcemia which may result in acute kidney injury, cardiac arrhythmias, seizures and death. A high index of suspicion and prevention of the TLS is the key in the successful management of various cancers.

TLS occurs commonly in rapidly proliferating tumours, ex. Acute Lymphoblastic leukemia and Non Hodgkin Lymphoma (Burkitt lymphoma, diffuse large B cell lymphoma and lymphoblastic lymphoma). The risk factors for tumour lysis are tumours with high proliferative rate, increased sensitivity to cytoreductive therapies, large tumour burden(high cell count >25,000cells/ microL), pre-existing renal dysfunction, intravascular volume depletion, pretreatment high LDH , urinary tract obstruction from tumor, abdominal organ involvement and concurrent use of nephrotoxic drugs(1,2,3,4). Based on these risk factors, at diagnosis an individual patient can be classified as having high, intermediate or low risk for developing TLS as per previously published guidelines.(2)

Standard treatment protocols (5, 6) include the use of rasburicase for the treatment of patients with high and intermediate risk for TLS. Rasburicase however is an expensive drug. In this study we employed a protocol of fluid management and allopurinol with careful monitoring for tumor lysis in an effort to treat both high and medium risk TLS without rasburicase.

Our objectives of the study were:

1) To describe the outcome of patients at risk for tumour lysis syndrome when treated with a protocol without using rasburicase.
2) To evaluate the incidence of laboratory derangements and symptoms associated with TLS in this series.

MATERIALS AND METHODS:

This prospective observational study was conducted in the Paediatric Haematology-Oncology Unit at St. John's Medical College and Hospital, Bangalore, India, a tertiary care, teaching hospital from April 2012 to August 2014.

Inclusion criteria:

1) All the children <18 years diagnosed with Acute Leukemia or Non-Hodgkin's lymphoma

Exclusion criteria:

1) Patients who have received chemotherapy at another centre prior to admission
2) Patients who opted for treatment elsewhere after diagnosis at our centre

Recruitment of patients:

Children with acute leukemia and non-Hodgkin's lymphoma were assessed at diagnosis and categorised based on the risk of development of TLS. The risk of TLS was assessed as High risk disease (HRD), Intermediate risk disease (IRD) and Low risk disease (LRD) , based on WBC counts and LDH levels, as both factors correlate with TLS risk (1, 2, 6). AML was either LRD(WBC-<$25*10^9$/L,LDH<2 ULN), IRD (WBC >$25*10^9$/L and <$100*10^9$/L and LDH>2 ULN) or HRD(WBC >$100*10^9$/L). ALL was classified into IRD(WBC <$100*10^9$/L and LDH <2 ULN) or HRD(WBC> $100*10^9$/L and LDH >2 ULN). Burkitt lymphoma was classified into HRD.

The definitions used for metabolic derangements were as per the Cairo Bishop definition. Cairo bishop have classified TLS into laboratory TLS and clinical TLS. Any abnormality of the uric acid (>8mg/dl) , increase in phosphorus (>2.1 mmol/L), increase in potassium (>6mg/L) and decrease in calcium (<1.75 m mol/L) , or any change of values by 25 % from baseline. The clinical syndrome categorised into grade 0 to 5, 0 being asymptomatic and 5 indicating mortality. The syndrome is indicated by rise in creatinine levels, seizures, acute kidney injury, cardiac arrhythmia and death. (7)

All patients were treated with potassium free intravenous fluids at 3L/m2/day, oral allopurinol at 100mg/m2/dose q8Hrly. The target urine output was 80-100ml/m2/hr. The prehydration was given for a minimum period of 24 hours before initiation of chemotherapy. Serum uric acid, LDH, potassium, creatinine, calcium and phosphate were monitored at strict 6-8 hourly intervals during the first 3-5 days of initiation of chemotherapy. Decreases in urine output from the target of 80-100ml/m2/hr or rise in uric acid or creatinine were immediately treated with an increase in intravenous fluids and frusemide at 0.5-1mg/kg/day. If the target urine output was not maintained with this, additional doses of frusemide were administered. Derangements in metabolic parameters were treated as per standard guidelines (2). Acute lymphoblastic leukemia and T lymphoblastic leukemia was treated with the BFM 95 protocol with steroid pre-phase. Acute myeloid leukemia was treated with the 7+3 regimen with hydroxyurea started for children with hyperleucocytosis (TLC > 50000/uL) at diagnosis. Burkitt lymphoma and DLBCL were treated with LMB protocol with cytoreductive COP (cyclophosphamide, prednisolone and vincristine) as the first cycle of chemotherapy.

RESULTS:

Sixty patients were recruited in the study. Forty three had ALL (71%)

,9 had AML(15%) ,8 had NHL(13%) . 37 were classified as high risk (61%) ,19 as intermediate (31%) and 4 as low risk for TLS(6%).

Table 1: Diagnosis and TLS Risk Stratification

Disease	Low risk	Intermediate risk	High risk
ALL	0	17	26
AML	4	2	3
NHL	0	0	8
Total	4	19	37

Low risk disease: 4 patients with AML were classified into low risk disease since the counts were less than 25,000 and LDH <2 times the normal. Intermediate risk disease: 19 patients were classified into IRD of which 17 patients had ALL and 2 patients had AML. High risk disease: 37 patients were classified as having high risk disease. 26 patients had ALL, 3 patients had AML, and 8 were diagnosed to have NHL. LDH was high in 16 patients. 5 out of 17 ALL patients and 1 out of 2 AML patients with IRD had LDH more than two times the normal (>450 U/L). Under the category of high risk disease 8 out of 26 ALL patients and 2 out of 3 AML patients had high LDH. The range of total leukocyte count varied from 1000 cells/ cu mm to 2 lakh cells/ cumL.

The metabolic derangements observed were as follows. As per the Cairo Bishop definition (1) of laboratory TLS patients with 25% increase or decrease in the values from baseline were also included. Hyperurecemia (defined as uric acid levels more than 8.0 mg/dl) was seen in 11 patients out of 37 patients who were categorised as HRD. Hyperphosphatemia (defined as phosphorus levels more than 2.1mmol/L) was seen in 6 patients. Rising phosphate levels were treated with oral phosphate binder (sevelamer). Hypocalcemia (defined as calcium less than 1.75 mmol/L) was seen in 4 patients. Two patients had clinical manifestations (muscle cramps) and required i.v calcium gluconate. Hyperkalemia (defined as potassium more than 6mg/dl) was seen in 4 patients. None of them had arrhythmia. The incidence of Tumour lysis (as per Cairo Bishop definition) was 16.6%. Only one patient in our series had acute kidney injury. This child had tumor infiltration of the kidneys with clinically palpable bilateral renomegaly. He required hemodialysis due to progressive deterioration in serum creatinine, oliguria and hyperphosphatemia. None of the patients had arrhythmia or seizures. Three out of 60 patients required PICU care.

DISCUSSION:

TLS is a potentially life threatening complication of cancer treatment. Acute leukemias and lymphomas are not only the commonest malignancies seen in children, they are also the malignancies most prone for the complications of tumor lysis syndrome. The most important principle in management of tumor lysis syndrome is prevention of the metabolic complications which can cause sudden and severe morbidity and mortality. Initiation of chemotherapy in these rapidly progressive tumors is also a medical emergency.

The risk of developing TLS was classified into low risk, intermediate and high risk disease. Low-risk disease (LRD) was defined as an approximate risk of less than 1% of developing TLS, intermediate risk disease (IRD) was defined as a risk of approximately 1–5% of developing TLS and high risk disease (HRD) was defined as a risk of greater than 5% (>5%) of developing TLS based on the incidence defined in the literature. (2,3,4). Identifying the high risk patients and early recognition of the syndrome is crucial in the institution of appropriate treatments. We categorised all the patients according to the above mentioned classification and the treatment was instituted accordingly. For this study we did not include tumors like solid tumors as they usually fall in the low risk category, do not often have severe TLS and do not warrant rasburicase.

In TLS the massive release of the intracellular contents into the blood stream leads to the sequential metabolic complications in TLS. Potassium is primarily intracellular ion, rapid cell destruction causes hyperkalemia. The levels of phosphorus in malignant cells can be up to four times the levels found in normal cells, and rapid release of these stores can result in hyperphosphatemia(8). Intra -nuclear contents predominantly the purines contribute to hyperuricemia, the purines are metabolised by xanthine oxidase to uric acid. Phosphorus binds to calcium and leads to hypocalcemia. Clinically the patient is at a high risk for acute kidney injury, hypotension, tetany, muscle cramps, seizures, cardiac arrhythmia and sudden death.

Drugs that prevent the formation of uric acid or act on the metabolic pathway of uric acid to allantoin are effective for prophylaxix and treatment of TLS. Allopurinol blocks the action of xanthine oxidase and prevents conversion of hypoxanthine and xanthine to uric acid, thereby decreasing the risk of uric acid cyrstallization in the kidneys. Rasburicase is a recombinant urate oxidase. It converts the already formed uric acid to allantoin which is 5- 10 times more soluble in the urine (9,10). International guidelines warrant the use of rasburicase in high and intermediate risk patients of TLS. This medication however is expensive and places an additional burden on the finances when a child is diagnosed with such a malignancy.

Our case series has the following observations. Hematolymphoid malignancies which are the commonest malignancies in children are also the group which is at significant risk for TLS. The majority of cases in our series were categorised as high or intermediate risk for TLS. It is in this group where we studied the incidence of TLS. We evaluated whether the omission of rasburicase affected the outcome of children either in the form of severe symptomatic metabolic derangements needing dialysis or delays in chemotherapy.

The overall incidence of significant metabolic derangements was 16.6% i.e. only ten patients developed significant metabolic derangements needing special intervention. There were no chemotherapy delays. There were also no severe complications of the metabolic derangements like seizures due to severe hypocalcemia or arrhythmias due to hyperkalemia. This protocol of adequate hydration, strict urine output monitoring and frequent laboratory parameter monitoring, helped us manage patients effectively. This is especially relevant in a setting of poor socio-economic conditions where the burden of cost of chemotherapy is itself difficult for a large majority of the population. Using this protocol effectively precludes the need for rasburicase and hence is very important for the developing world.

The role of rasburicase in tumors at high risk for TLS is widely described. In a setting where there are no resource constraints its use has decreased the need for dialysis in the group of patients with high risk for TLS. Modified schedules with lower doses (11) and generic indigenously prepared rasburicase (12) have also been described. A Cochrane database systematic review addressed the use of rasburicase in children. (13) The conclusions were that although urate oxidase might have a role in reducing serum uric acid, it is unclear whether it reduces clinical tumour lysis syndrome, renal failure, or mortality. It also observed that the adverse effects of rasburicase might be more than with allopurinol. It hence suggested the cautious weighing of pros and cons before using rasburicase. Another recent review from the nephrology perspective also pointed out that studies are lacking for the uniform use of rasburicase. (14). Our data has also clearly demonstrated that in the majority of children, rasburicase may not be required and not using it as part of therapy protocol does not lead to the complications of TLS. One of the limitations of our study is that there were relatively few children with Burkitt lymphoma and no child with very high total leucocyte counts. In these clinical scenarios where TLS is particularly challenging, rasburicase may indeed prevent morbidity. Further studies are required to assess if within the subset of high risk patients of TLS there is a subgroup which will definitely benefit from the use of rasburicase.

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