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Review Articles

Management of Tumour Lysis Syndrome in Non-Hodgkin Lymphoma

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Abstract Tumour lysis syndrome is an oncological emergency and non-Hodgkin lymphoma is one of the high risk groups to develop this complication before or during chemotherapy. This article provides an overview and evaluates the role of urate oxidase in management of this condition. Retrospective review of forty-four cases in our hospital showed that four patients (9%) developed grade 3 to grade 4 tumour lysis syndrome and two of them required renal replacement therapy. All of them recovered from this acute complication after vigorous supportive therapy. Burkitt's lymphoma with intra-abdominal presentation and huge tumour load with multiple sites involvement are the main risk factors for development of tumour lysis syndrome.

Key words Non-Hodgkin lymphoma; Tumour lysis syndrome

Introduction

Lymphoma is the third commonest childhood malignancy which accounts for approximately 7% of paediatric oncology patients. Non-Hodgkin Lymphoma (NHL) is commonly classified into three categories: (i) B-cell NHL included Burkitt's and Burkitt-like lymphoma and diffuse large B-cell lymphoma; (ii) lymphoblastic lymphoma (primarily precursor T-cell lymphoma and less frequently, precursor B-cell lymphoma); and (iii) anaplastic large cell lymphoma (T-cell or null cell lymphoma).[1,2] This is a fast-growing tumour and may also disseminate widely, especially to bone marrow and central nervous system. The abdomen is the most common primary site (30%-45%), and mostly are Burkitt's lymphoma. Mediastinal tumours (25%-35%) are typically T-cell lymphoblastic lymphoma. The third most common site is at head and neck region (10%-20%).

A diagnosis can be rapidly obtained by tissue biopsy or bone marrow for histology, immunohistochemistry, cytogenetic and molecular studies. The most widely use staging scheme for childhood NHL is the St Jude Children's Research Hospital Staging (Table 1).[3] Until 1970s, childhood NHL had a poor prognosis and the majority of children died within weeks of diagnosis because of progression of primary disease, or dissemination to bone marrow or central nervous system (CNS). Significant improvements in survival have been achieved in the past 20 years mainly due to advances in chemotherapy. In Hong Kong, from the year 1995 to 2007, 133 new cases of NHL were reported. The overall 5-year event-free survival of Burkitt's lymphoma was 87.7%, lymphoblastic lymphoma was 79.7% and large cell lymphoma was 60.7%.[4] In our hospital, 44 cases were diagnosed from 1995 to 2007 (33 males; 11 females). The median age of presentation was 9.2 years old. Twenty-six cases were B-cell NHL included Burkitt's and Burkitt-like lymphoma and diffuse large B-cell lymphoma, 14 cases were lymphoblastic lymphoma; and 4 cases were anaplastic large cell lymphoma. Abdomen was the most common presenting site (14 cases in abdomen; 11 cases in mediastinum; 4 cases in head and neck; 7 cases

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at cervical lymph nodes; 4 cases had multiple sites involvement; 3 had involvement at other anatomical sites which included 1 skin, 1 bone, 1 pericardium). The cases are predominately stage III and stage IV diseases (18 cases and 13 cases respectively). Chemotherapy regimen differs according to the histological subtype. Burkitt and large B-cell NHL are treated with intensive, pulsed chemotherapy whereas T-lymphoblastic NHL is treated with prolonged chemotherapy, and currently most centers adopt treatment protocol for acute lymphoblastic leukaemia. CNS-directed therapy is essential and is based on intrathecal chemotherapy rather than radiotherapy. There is little role for surgery in management of NHL.

There are two potentially life-threatening conditions that are often seen in children with NHL: (i) pressure effect on vital organ such as mediastinal tumour with major airway obstruction, most often seen in lymphoblastic lymphoma; and (ii) tumour lysis syndrome, most often seen in lymphoblastic and Burkitt or Burkitt-like NHL. In this article, we will focus on the management of tumour lysis syndrome (TLS) in patients with non-Hodgkin lymphoma.

Overview of Tumour Lysis Syndrome (TLS)

TLS is an oncologic emergency caused by rapid and massive destruction of cancer cells and leads to release of large amount of breakdown products, of which purine metabolites (xanthine or hypoxanthine), uric acid, potassium, phosphate are most relevant to the pathophysiology and clinical features of TLS. Cairo and Bishop developed a system to define clinical tumour lysis syndrome (CTLS) and laboratory tumour lysis syndrome (LTLS). Under this classification, LTLS is present if levels of two or more serum values of uric acid, potassium and calcium are more than or phosphate less than normal at presentation; or if there is a 25% change within 3 days before or 7 days after initiation of treatment. CLTS requires the presence of LTLS and with clinical complications including renal insufficiency, cardiac arrhythmias, seizures and sudden death (Table 2).[5]

In children, the high risk groups include those rapid growing lymphoproliferative malignancies namely Burkitt's lymphoma, acute lymphoblastic leukaemia and other high

Table 1 St. Jude's staging for childhood non-Hodgkin's lymphoma

Stage	Criteria for extent of disease
I	A single tumour or nodal area is involved, excluding the abdomen and mediastinum.
II	A single tumour with regional node involvement, two or more tumours or nodal areas involved on one side of diaphragm, or a primary gastrointestinal tract tumour (completely resected) with or without regional node involvement.
III	Two single tumours (extranodal) on opposite sides of diaphragm. Lymph node areas occur on both sides of diaphragm. It also includes any primary intrathoracic (mediastinal, pleural, or thymic) disease, extensive primary intra-abdominal disease or any paraspinal or epidural tumours.
IV	Any of the above with bone marrow and/or central nervous system disease.

Table 2 Cairo-Bishop classification of clinical tumour lysis syndrome and grading

Clinical parameters	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Creatinine	≦1.5 x ULN*	1.5 x ULN	>1.5-3.0 x ULN	>3.0-6.0 x ULN	> 6.0 x ULN	Death
Arrhythmia	None	Not required intervention	Non-urgent medical intervention	Symptomatic and incompletely controlled medically or controlled by device	Life-threatening	Death
Seizure	None	None	Well controlled	Frequent breakthrough seizure	Status epilepticus / intractable epilepsy	

*ULN: upper limit of normal. For ≧1 to <12 years, male and female: 61.6 µmol/L; ≧12 to <16 years, male and female: 88 µmol/L; For ≧16 years, female: 105.6 µmol/L; male 114.4 µmol/L

grade lymphomas. Concerning the incidence of tumour lysis syndrome in children with NHL, a study of 1791 children with NHL, 78 (4.4%) developed TLS. In a subgroup of children with Burkitt's lymphoma, the rate was 8.4%.[6] Another review of 59 children with NHL, 7 patients (12%) developed laboratory TLS and another 7 patients (12%) developed clinical TLS which 5 out of the 14 patients required haemodialysis to correct metabolic abnormalities and 3 TLS-related deaths were reported. Sex, age, serum lactate dehydrogenase (LDH) and initial white blood cell (WBC) count were not associated with higher incidence of TLS but pre-treatment renal involvement by disease was significantly associated with TLS (p=0.027) and renal involvement was based on ultrasonography (USG) and computerised tomography (CT) findngs.[7] In another study, 27% in 30 patients with Burkitt's lymphoma (median 11 years; range 2-30 years) developed metabolic abnormalities consistent with TLS (6 hyperkalaemia; 2 hypocalcaemia; 2 hyperphosphataemia; 1 lactic acidosis) and 4 resultant deaths, two of which were attributed to hyperkalaemia.[8] The studies show that patients with Burkitt's lymphoma are at higher risk of developing laboratory or clinical TLS especially those patients with renal involvement or pre-treatment renal impairment. In our series, 4 out of 44 patients (9%) had tumour lysis syndrome. Two patients belonged to grade 4 and required renal replacement therapy and two belonged to grade 3 according to Cairo-Bishop classification. All cases were Burkitt's lymphoma with primary disease in abdomen or multiple sites involvement. They were all recovered after vigorous supportive therapy. Our findings were consistent with reported literatures.

Patients with Burkitt's lymphoma, lymphoblastic lymphoma and B-ALL are high risk patients. Intermediate risk group are those with diffuse large-cell lymphoma or other rapidly proliferating malignancies. Low risk patients are defined as those with indolent NHL or other slowly proliferating malignancies. Moreover, patients with pre-existing uraemia, hyperuricaemia, oliguria, dehydration or renal insufficiency are additional risk factors.[9,10]

TLS can occur before or during treatment. For effective prevention of TLS, patients with non-Hodgkin lymphoma will be put on hyperhydration (3000 ml/m^2/day), inhibition of uric acid production by allopurinol (xanthine oxidase inhibitor), maintain good urine output (100-250 ml/m^2/hour) for at least 24 hours before starting chemotherapy. Diuretic therapy may be required if urine output is suboptimal. Gradual induction of chemotherapy is needed for patients with huge tumour load or with extensive metastasis. In acute leukaemia, a low dose prednisone at 5-10 mg/m^2/day may be started and then gradually increased to full dose in following few days depending on the urine output and tumour response. Similar approach can be applied to non-Hodgkin lymphoma. Frequent monitoring in terms of the fluid intake and output, body weight, blood pressure, serum potassium, calcium, phosphate, uric acid levels and renal function is required.

Management of Hyperuricaemia

Allopurinol is a competitive xanthine oxidase inhibitor and it blocks the conversion of hypoxanthine and xanthine into uric acid. The recommended dosage of allopurinol is 200-400 mg/m^2/day or 10 mg/kg/day for 3-7 days. Since allopurinol does not affect existing uric acid, a period of 2-3 days is needed for the drugs to be effective. Two percent of patients will develop skin rash and hypersensitivity reaction. Nephropathy can still occur because of accumulation and crystallisation of uric acid precursors (xanthine and hypoxanthine) in renal tubules. This is necessary to maintain satisfactory urine output to avoid xanthine crystalluria. The use of sodium bicarbonate to alkalinize the urine has been recommended as part of TLS management. It is now known that alkaline urine increase solubility of uric acid and xanthine and thus promotes its excretion. However alkaline urine also increases the precipitation of phosphate with calcium, and also hypoxanthine when urine pH >7.5. With the presence of allopurinol, this can lead to increase of these metabolites and increase the risk of xanthine-obstructive uropathies.[11] Therefore, urine alkalinisation is not recommended as a part of management of preventing TLS.

Use of Recombinant Urate Oxidase in TLS

Urate oxidase is a natural uricolytic enzyme that catalyses the oxidation of uric acid to hydroxyiosurate and then to allantoin which is 5-10 times more soluble than uric acid. *Aspergillus flavus*-derived urate oxidase (Uricozyme, Sanofi-Synthelabo) has been proven its effectiveness as an uricolytic agent for the past 3 decades. However, it can be complicated with severe allergic reactions (anaphylaxis, bronchospams) in 5% of patients.[12,13] Recombinant urate oxidase (Rasburicase, Fasturtec®, Sanofi-Synthelabo, Inc., Paris, France) is now available which is effective and safe for prophylaxis and treatment of TLS. The primary advantage is its rapid onset of action and rapid decrease serum uric acid level with associated

diuresis.[14-17] A dose of 0.15-0.2 mg/kg iv over 30 minutes can achieve response in 99% of patients with about 88% reduction in uric acid level as early as 4 hours after the first dose. The half life is 16-21 hours, and once daily dose is adequate. The drug may be repeated daily up to 5-7 days. There is no accumulation of xanthine or hypoxanthine and thus avoiding the risk of purine metabolite nephropathy. With the use of recombinant urate oxidase, chemotherapy can be promptly initiated with a significant reduction in the risk of renal dysfunction requiring dialysis. It is also a good alternative for patients who cannot ingest oral allopurinol or are allergic to this drug.[18,19] In one study, rasburicase was administered intravenously at 0.2 mg/kg in 50 ml normal saline over 30 minutes for 5 consecutive days to 36 children with acute lymphoblastic leukaemia and non-Hodgkin lymphoma, serial plasma uric acid, cretonne, phosphate, calcium, lactate dehydrogenase and complete blood picture were measured, the uric acid level was significantly decreased by 4 hours. No patient except 1 steroid-resistant patient who required haemodialysis on day 14. When compared with historic control that was treated with allopurinol, rasburicase achieved significant reduction of uric acid level much earlier than allopurinol (4 hours versus 61 hours). Serum creatinine level of patients remained low while receiving rasburicase whereas 3 out of 14 control patients experienced renal impairment and one of them required haemodialysis.[20-23] Potential serious adverse effects include anaphylaxis, rash, haemolysis, and methoglobulinaemia but they are rare. At room temperature, rasburicase will cause degradation of uric acid within blood samples. Therefore, samples should be immediately transported in ice to laboratory for processing, otherwise falsely low results may occur. Although rasburicase is expensive, it is very effective in reducing number of patients require haemodialysis. This is shown to be a cost-effective measure to prevent complications from tumour lysis syndrome with haematological malignancies.[24-26]

Management of Other Metabolic Abnormalities

Patients with hyperkalaemia should be firstly verified immediately to rule out pseudo-hyperkalaemia due to haemolysis during blood taking procedure. Treatment options of hyperkalaemia are to stabilise cardiac membrane and prevent life threatening cardiac arrhythmias by calcium gluconate (100 mg-200 mg/kg/dose), reducing potassium level by dextrose (25% dextrose 2 ml/kg)-insulin (actrapid 0.1 U/kg) infusion, sodium bicarbonate (1-2 mEq/kg), potassium-binding resins and renal replacement therapy. Concerning hyperphosphataemia, for asymptomatic patients, initial treatment consisted of elimination of phosphate from intravenous fluid, continue hyperhydration and give phosphate binder such as aluminium hydroxide (0.1 g/kg per oral). Severe hyperphosphataemia (phosphorus level >1.62 mmol/L) can be corrected by renal replacement therapy, namely haemodialysis, continuous veno-venous haemofiltration or peritoneal dialysis. Calcium should not be administered as it might precipitate metastatic calcifications. For hypocalcaemia, no intervention is required for asymptomatic patients. If patient develops symptomatic hypocalcaemia, a small dose of intravenous calcium may be given slowly with ECG monitoring for any bradycardia.

Risk Stratification Approach in Management of Tumour Lysis Syndrome

For NHL patients at high risk of developing TLS, namely Burkitt's / Burkitt-like lymphoma with bulky disease, along with hyperhydration, recombinant urate oxidase should be used in initial management. Patients should be admitted to intensive care unit or high-dependency unit for close monitoring. The patient should be prepared with above measures for about 24 hours and then start with gradual stepping up dosage of anti-tumour therapy. For intermediate risk, namely diffuse large B cell lymphoma, allopurinal with hyperhydration can be used as initial treatment. Initial management with a single dose of recombinant urate oxidase can be considered in paediatric population. For low risk patients, namely those with indolent NHL, close monitoring of urine output, renal function and biochemical markers is appropriate.

Patients must be monitored closely especially after start of chemotherapy. At the start, blood test for the metabolites should be checked at every 6-8 hours or more frequent if abnormal results noted. Despite the above efforts, renal replacement therapy should be considered in patients with refractory hyperuricaemia, hyperphosphataemia, hyperkalaemia and oliguria due to acute renal failure to control fluid status and correct metabolic abnormities.

Conclusions

Children with Burkitt's lymphoma with intra-abdominal disease or multiple sites involvement are the highest risk

group of tumour lysis syndrome before or during chemotherapy. Recognition of risk factors, close monitoring with appropriate treatment in at-risk patients are the key to prevent or manage tumour lysis syndrome.

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