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# Acute renal failure in Children with pre-chemotherapy advanced stage Burkitt's lymphoma

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## Abstract

*Background:* Outcome of treatment of Burkitt's lymphoma - associated acute renal failure (BLARF) without dialysis is rather poor. This was a retrospective comparative study aimed at determining the outcome of two different treatment protocols tried on children with BLARF in two separate eras.

*Methods:* One group of patients was assigned to treatment protocol A (TPA) and the other to treatment protocol B (TPB). TPA consisted of oral allopurinol, intravenous (IV) cyclophosphamide, vincristine, methotrexate, frusemide, 8.4% sodium bicarbonate and intrathecal (IT) methotrexate. TPB consisted of oral allopurinol, alternate days IV infusion of low dose cyclosphosphamide (125mg/m$^2$x4doses), IT methotrexate, oral calcium lactate, IV calcium gluconate, salbutamol, insulin and IV infusion of frusemide, sodium bicarbonate and glucose.

Results: There were 16 BLARF patients (12 boys) aged 6-14 years. Nine of 16 underwent TPA while 7 underwent TPB. Three of 9 TPA patients had stage C Burkitt's lymphoma (BL) while 6 had stage D BL. Five and 2 patients in TPB had stages C and D BL, respectively (P=0.1371). All the 16 patients had post-chemotherapy tumour lysis syndrome (TLS). Six of 9 patients in TPA died from TLS while the other 3 died from other causes. The 2 deaths in TPB were due to causes other than TLS. Risk of mortality from TLS was 30 times higher with TPA than TPB (P=0.0048). Hypertension, seizures, congestive heart failure, bleeding diathesis, severe anaemia, uraemia, proteinuria and microhaematuria were common co-morbidities in the patients.

*Conclusion:* Present data suggest that slow IV infusion of low dose cyclophosphamide given on alternate days in addition to pre-emptive anti-TLS measures were associated with better survival rate (71.4%) in BLARF patients assigned to TPB.

**Keywords:** Cyclophosphamide infusion; oligoanuria; tumour lysis syndrome

## Introduction

While acute lymphoblastic leukaemia (ALL) is the commonest childhood malignancy in the United States of America [1] and United Kingdom [2], Burkitt's lymphoma (BL) remains the leading childhood malignancy in Nigeria [3]. The advanced stage form of BL (Stage C or D) is often associated with heavy tumour burden with potential for either pre-or post-chemotherapy tumour lysis syndrome (TLS) and acute renal failure (ARF). Biochemical perturbations of tumour cell lysis (known as TLS) which also occur in ARF encompass hyperkalaemia, hyperuricaemia, hyperphosphataemia and hypocalcaemia [4,5,6]. The high morbidity and mortality that are frequently associated with advanced stage BL (ASBL) are the consequences of these complications (TLS and ARF) and other co-morbidities [4,5,6].

Burkitt's lymphoma – associated ARF (BLARF) is not uncommon [4,5]. It is in fact the major primary aetiology of ARF in our center [7] and outcome of treatment has been very dismal. This rather gloomy outcome has stimulated series of management strategies aimed at improving outcome in a centre where facilities for dialysis are grossly inadequate and beyond the reach of majority of our patients [8].

This retrospective study was therefore an attempt at determining which of two treatment protocols tried on children with BLARF between January, 1994 and December, 2003 was associated with a better outcome.

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**Material and methods**

*Patients reviewed:* Clinical charts of BL patients managed from January 1994 through December 2003 were retrospectively reviewed. Two treatment protocols A and B were tried on the patients with BLARF. Treatment protocol A (TPA) was tried between January 1994 and August 1999 while treatment protocol B (TPB) was tried between September 1999 and December 2003.

All patients underwent lumbar puncture (for cerebrospinal fluid sample), fine needle aspiration of tumour mass and bone marrow aspiration for cytologic confirmation of clinical diagnosis of BL and staging.

*Analysed clinical and laboratory data:* Only data of patients who presented with pre chemotherapy BLARF and underwent either TPA or TPB were analyzed. Post chemotherapy BLARF, and ARF cases whose aetiology was diagnosed only at autopsy to be BL were excluded. Analysed data were age, gender, height, weight, admission and discharge vital signs, duration of illness before presentation (whether early or late), BL stage, type of treatment protocol and number of courses received, type of remission achieved (partial or complete), ARF type (whether oliguric, non-oliguric or anuric), number of times transfused, admission duration, presence or absence of TLS, co-morbidities and complications, mortality risk factors, whether or not the patient survived and duration of follow-up of each survivor.

Analysed laboratory data included pre and post chemotherapy plasma biochemical parameters, creatinine clearance determined by the Schwartz formula [9], fractional excretion of filtered sodium (FeNa %), pre and post treatment 24-hour urinary protein level. Others included urinalysis especially for microhaematuria, urine and blood cultures, thin and thick blood films for malaria parasites, white blood cell counts (WBC), platelets counts and haematocrits.

*Definitions:*

Stage C BL: intra-abdominal tumour [10].

- Stage D BL: intra-abdominal tumour with involvement of one or more extra-abdominal sites, for example bone marrow and central nervous system [10].
- Complete remission: defined as resolution of all clinical and laboratory evidence of the tumour [4].
- Tumour lysis syndrome: Because hyperkalaemia, hyperuricaemia, hyperphosphataemia and hypocalcaemia which characterize TLS also occur in ARF irrespective of aetiology, it became necessary to define the criteria for determining TLS in post chemotherapy BLARF patients within the context of this study. Post chemotherapy TLS in BLARF was regarded to have occurred if (a) plasma potassium level was $\geq$1mmol/L above the pre-treatment value in the hyperkalaemic patient or $\geq$1mmol/L above the upper limit of normal in BLARF patients with normal pre-treatment level, (b) plasma uric acid and phosphate levels were $\geq$0.1mmol/L above the baseline values in patients with hyperuricaemia and hyperphosphataemia or $\geq$0.1mmol/L above the upper limits of normal in BLARF patients with normal pre-treatment values, and (c) plasma calcium level $\geq$0.1mmol/L below the baseline value in BLARF patient with hypocalcaemia or $\geq$0.1mmol/L below the lower limit of normal in patients with normal pre-treatment levels.
- Acute renal failure: defined as admission plasma creatinine level $\geq$120µmol/L or creatinine clearance <80ml/min/1.73m$^2$. ARF was further subdefined as oliguric ARF (daily urine volume <250ml/m$^2$), nonoliguric ARF (daily urine volume ranging between 250 and 900ml/m$^2$) and anuric ARF (daily urine volume <20ml/m$^2$).
- Hypertension: defined as blood pressure (BP) >95th percentile for age and gender according to the report of the Second Task Force on BP control in children [11].
- Significant proteinuria: urinary protein level >60mg/m$^2$/day [12].
- Significant microhaematuria: pressure of $\geq$5 red blood cells (rbc)/high power field (hpf) in a spun urine specimen.
- Early presentation: defined as patients who presented within 2 weeks of parents noticing the tumour mass.
- Late presentation: defined as patients who presented > 2 weeks of parents noticing the tumour mass.

*General treatment:*

- Daily fluid intake: restricted to insensible fluid loss (300 – 400ml/m$^2$/day) plus volume of fluid equivalent to previous 24hours urine volume; this was usually given as 5% or 10% dextrose water infusion [7].
- Salt and protein intakes were restricted to 0.5 – 1mmol of sodium/kg/day and 0.5 – 1g/kg/day, respectively [7].
- Hypertension [7] was treated with intravenous (IV) frusemide (2-4mg/kg/day) in combination with IV hydralazine (0.2 – 0.5mg/kg) repeated 6 hourly till BP has dropped to the upper limit of normal for age; normotension was thereafter maintained with either oral α-methyldopa (25-50mg/kg/day), captopril (0.25-0.6mg/kg/day), amilodipine (0.15-0.3mg/kg/day) or lacidipine (0.06-0.12mg/kg/day).
- Heart failure was treated with digoxin, 0.02mg/kg intramuscularly (IM) stat, followed by 0.01mg/kg IM 8 hourly x 2 doses.
- Seizures were controlled with IV diazepam, 0.2-0.4mg/kg bolus, repeated when necessary.

*Specific treatment:*

1. Treatment protocol A (TPA):
   a) Oral allopurinol, 300mg/m$^2$/day in 3 divided doses for at least 24-48 hours before chemotherapy and throughout chemotherapy period.

b) Induction chemotherapy (ICT).
- Cyclophosphamide, 250mg/m$^2$ (1/4 of standard dose) IV bolus days 1 and 2.
- Vincristine, 0.7mg/m$^2$ (1/2 of standard dose) IV bolus day 1 only.
- Methotrexate, 18.75mg/m$^2$ (1/2 of standard dose) IV bolus day 1 only.
- Intrathecal (IT) methotrexate, 12.5 mg/m$^2$ (normal dose) days 1 and 5.

In the absence of methotrexate, cytosine arabinoside, 50mg/m$^2$(1/2 of standard dose) was given subcutaneously on days 1, 2 and 3 and IT (50mg/m$^2$) days 1 and 5.

c) Frusemide, 2-4mg/kg IV bolus x 1 dose simultaneously with ICT.

d) 8.4% sodium bicarbonate, 0.5-1mmol/kg IV bolus x 1 dose simultaneously with ICT.

Treatment of TLS following TPA: 8.4% sodium bicarbonate (1mmol/kg IV stat, repeated daily), and 10% calcium gluconate 0.2-0.5ml/kg (0.045-0.1135mmol/kg) IV slowly, repeated daily and soluble insulin IV/glucose infusion were given for correction of hyperkalaemia and hypocalcaemia. IV soluble insulin was given 6 hourly (0.25unit/kg) while glucose (4g/kg) was infused slowly over 24hours. We tried to achieve this by adding 8ml/kg of 50% dextrose water to 5% dextrose water infusion after decanting an appropriate volume of the latter. The entire volume received was not more than the total daily fluid requirement per day.

2. Treatment protocol B (TPB):

a) Oral allopurinol as in TPA

b) Induction chemotherapy (ICT)
- Cyclophosphamide, 125mg/m$^2$ (1/8 of standard dose) given slowly over 24hours to deliver approximately 0.0866mg/m$^2$/minute as IV infusion on days 1, 3, 5 and 7.
- IT methotrexate, 12.5mg/m$^2$ days 1 and 5 or cytosine arabinoside as in TPA.

c) Calcium lactate tablet, 150-300mg thrice daily from the day of admission till normalization of plasma calcium level.

d) Salbutamol, 0.125 – 0.25mg IV 6 hourly in patients with admission hyperkalaemia and throughout the duration of ICT. In normokalaemic patients, it was given simultaneously with and throughout ICT.

e) Frusemide, 2-4mg/kg added to IV fluid on commencement of ICT to run slowly for 24hours. Usually we stop frusemide infusion as soon as diuresis is achieved.

f) 8.4% sodium bicarbonate, 0.5-1mmol/kg added to IV fluid on commencement of ICT to run slowly for 24hours and throughout ICT duration.

g) 10% calcium gluconate, 0.2-0.5ml/kg IV slowly 2 hours post ICT and repeated when indicated.

h) IV soluble insulin/glucose infusion therapy: same as for the treatment of TLS in TPA but usually commences 2-4 hours post ICT in TPB. All patients receiving IV soluble insulin/glucose infusion had their plasma electrolytes, urea, uric acid, phosphate, calcium and glucose checked 2-4 hourly when possible.

Maintenance of remission: following the first course of chemotherapy which ICT in both TPA and TPB represented, patients were given 3 to 5 more courses of chemotherapy at 2 to 3 weeks intervals depending on the clinical and biochemical status of the patients, to maintain remission. The maintenance chemotherapy usually consisted of standard doses of IV cyclophosphamide 1000mg/m$^2$, IV vincristine 1.4mg/m$^2$ and IV methotrexate 37.5mg/m$^2$ given as bolus doses on the first day of each course. IT methotrexate, 12.5mg/m$^2$ was given on days 1 and 5. To cut cost, some of the patients received their maintenance chemothepray as out-patients.

*Follow up:* After they have been regularly discharged, all patients were seen initially in the clinic after 2 weeks and subsequently, every month. Those who lived more than 100km away from the hospital, were seen 2-3 monthly.

*Data analysis:* Student's t test was used in comparing statistical means while $X^2$ and Fisher's exact tests were carried out to compare proportions where indicated, for statistical significance. $P<0.05$ was regarded as statistically significant. Risk of mortality from a given factor was tested by determining the odds ratio (OR) from the 2 x 2 $X^2$ test table; the 95% confidence interval (CI) was determined from Miettinen's test-based approximation using the $X^2$. CI = OR $^{(1\pm1.96/x)}$ where X equals $\sqrt{X^2}$ [13].

## Results

Over a period of 10years, 214 new cases (144 boys, 70 girls, M:F = 2.1:1) of BL were seen. Of these, 23 (10.75%) were new cases of BLARF thus giving an incidence of 2.3 new BLARF cases/year. Sixteen of 23 BLARF patients presented pre-chemotherapy while 5 occurred post-chemotherapy; aetiology of 2 cases of BLARF was diagnosed to be BL, only at autopsy. Only the data of 16 pre-chemotherapy BLARF patients who underwent either TPA or TPB were analysed. 9 of 16 BLARF patients (8males, 1 female) received TPA (mean age, 9.6±3.3years) while 7 (4 males, 3 females) received TPB (mean age, 9.9±2.2years). Gender difference between TPA and TPB was not statistically significant (P=0.1731). Similarly, the mean ages were similar in both TPA and TPB, P>0.5. TPA versus (VS) TPB with regards to mean ± SD admission height (128.2±19.4 VS 128.6 ±10.46cm, P>0.5), weight (22.1±8.34 VS 25.1± 6.75kg, P>0.2), systolic blood pressure (SBP) (133.3±20.62 VS 141.43± 19.52mmHg, P>0.2), diastolic blood pressure (DBP) (89.4±21.6 VS 100±8.16mmHg, p>0.1), pulse rate (120±23.1 VS 108.6±15.4 pulsations/min, P>0.2) and respiratory rate (36.2±10.7 VS 45.14±11.42 cycles/min P>0.1) were similar in both treatment groups 7 of 9 (78%) patients who received TPA and all 7 patients who received TPB

were hypertensive. Mean duration of illness before presentation in hospital were 4.72 ±2.6 (2.5-10) weeks and 2.78±0.8 (2-4) weeks in TPA (all presented late) and TPB (3 presented at exactly 2 weeks of illness), respectively (P>0.5). Three of 9 who received TPA had stage C BL while 6 had stage D BL; five and 2 patients who received TPB had stages C and D BL, respectively. Number of patients with stages C and D BL in both TPA and TPB were similar, P=0.1371. Tables 1 and 2 respectively, summarize the clinical characteristics of each patient in TPA and TPB. Four patients each in TPA (patients 1,4,5 and 7) and TPB (patients 1,2,3, and 4) were febrile (Temperature, $37.8^0$ to $38.6^0$C) on admission (pre-chemotherapy). There were no malaria parasites found in their thin and thick blood films. Similarly, blood and urine cultures were sterile in all patients. Three TPA patients (patients 2,8 and 9) and 2 TPB patients (5 and 7) who were afebrile on admission, eventually became febrile post-chemotherapy with positive blood cultures (E. coli x 2, Klebsiella species x 2 and Staphylococcus aureus x 1).

The mean urine volume/day ± SD in the 2 nonoliguric and 7 oligoanuric patients in TPA were 600±71ml/$m^2$/day and 59.54 ±47.76ml/$m^2$/day, respectively. All 7 patients in TPB were oligoanuric with a mean urine volume of 75.43±59.08ml/$m^2$/day. Urine volumes in the oligoanuric patients in both TPA and TPB were similar, P>0.5. Pre-chemotherapy quantitative proteinuria data were available in only 7 patients (TPA x 2, TPB x 5). All had significant proteinuria with a mean ±SD of 718.4±472.1 (111.1-1,500) mg/$m^2$/day. All proteinuric patients were hypertensive (mean SBP 141.43± 15.74mmHg; mean DBP 100±13mmHg); they were aged 7 – 14 (10.93±2.6) years. 9 of 16 patients (TPA x 3, TPB x 6) including the 7 proteinuric patients had pre-chemotherapy significant microhaematuria; none of them showed clinical evidence of urinary tract infection (UTI). Urine cultures were sterile and urinalysis revealed no significant pyuria. Pre-chemotherapy urinalysis revealed significant microhaematuria in the 3rd (6-13rbc/hpf), 5th (5-9rbc/hpf) and 6th (12-17rbc/hpf) patient of the TPA group. Similarly, 13-19 rbc/hpf, 6-8rbc/hpf, 15-18 rbc/hpf, 8-10 rbc/hpf, 5-8 rbc/hpf and 7-9 rbc/hpf, were respectively present in the urines of patients 1,2,3, 4,5,and 6 of the TPB group.

Table 3 shows the haematologic data of patients in the two treatment protocols. Comparisons of pre and post-chemotherapy white blood cell counts (TPA, P<0.001; TPB, P<0.05), haematocrits (TPA, P<0.001; TPB, P<0.001) and platelets counts (TPA, P<0.05; TPB, P<0.05) in each of the two treatment groups showed statistically significant differences. Cytologic examination of the cerebrospinal fluids (csf) of all patients, revealed BL cells in patients 1,2,4 and 7 only (TPA, table 1). BL cells were found only in the bone marrows of patients 6 and 7 of the TPB group. Table 4 shows the various drug treatments received by the patients.

Tables 5 and 6 summarize the pre and post-chemotherapy plasma biochemistry data of patients who received TPA and TPB, respectively. Analysed post-chemotherapy data in Tables 5 and 6 were those obtained 4to 6 hours post ICT, because some of the TPA patients died within 6 hours of chemotherapy. Post ICT plasma levels of sodium (P>0.2), potassium (P>0.05), phosphate (P>0.5), calcium (P>0.2), uric acid (P>0.2) urea (P>0.5), and creatinine (P>0.05) were similar in both TPA and TPB. However, plasma level of bicarbonate (P<0.05) was significantly higher in TPB than in TPA. Pre-ICT plasma albumin levels in both TPA and TPB were similar (P>0.5). Also, there was similarity between the mean creatinine clearances ± SD for TPA (21.1±13.23ml/min/1.73$m^2$) and TPB (20.95±9.4ml/min/1.73$m_2$), P>0.05. For TPB, mean ± SD FeNa was 12.04±8.71%; incomplete data precluded FeNa determination in TPA.

**Table 1.** Clinical characteristics of acute renal failure (ARF) patients who received treatment protocol A

| *Patient number* | *Age / gender* | *Clinical stage/ presentation* | *Renal failure type* | *Required dialysis* | *Number of chemotherapy courses received* | *Complications* | *Transfused* | *Outcome* | *Probable cause(s) of death* |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 13yrs/M | Stage D/Fever, headache, toothache, bone pains, proptosis, poor speech, defective hearing in the left ear, neck stiffness, left facial nerve palsy, BP 150/100mmHg dyspnoea, abdominal masses, ascites, and bilateral renomegaly, | Nonoliguric ARF (NARF) | Yes but not dialysed | 1 but incomplete | Hypertension, congestive cardiac failure and TLS | | Spent 4 days on admission but died 14 hours post chemotherapy | Tumour lysis syndrome (TLS) |
| 2 | 13yrs/F | Stage D/ Headache, neck stiffness and severe palor. BP 140/110mmHg. Craggy abdominal | NARF | No | 1 | Hypertension, Klebsiella septicaemia, fluid and electrolyte imbalance, TLS | Once | Spent 14 days on admission but died 1 week post chemotherapy | Septicaemia and severe dehydration following |

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|---|---|---|---|---|---|---|---|---|---|
| | | masses, ascites, bilateral renomegaly, and bipedal oedema, | | | | | | | onset of diuresis |
| 3 | 5yr/M | Stage C/ Facial swelling, severe palor, dyspnoea, BP 130/80mmHg, reduced urinary output, craggy abdominal masses, ascites, bilateral renomagaly, bipedal oedema. | Oliguric ARF (OARF) | Yes but not dialysed | 1 but incomplete | Hypertension, congestive cardiac failure, gingivostoma-titis and severe hyperkalaemia (7.5mmol/L) | Once | Spent 8 days on admission but died 4 days post chemotherapy. | Hyperka-laemia from TLS |
| 4 | 10yr/M | Stage D/ Fever, severe palor, BP 120/60mmHg, abdominal pain and distension, craggy abdominal masses, ascites, enlarged kidneys, right facial nerve palsy, bilateral proptosis, neck stiffness, flaccid paraplegia, faecal and urinary incontinence. | Anuric ARF (ANARF) | Yes but not dialysed | 1 but incomplete | TLS, Bleeding diathesis, and severe anaemia | Twice | Spent 6 days on admission but died 36hours post chemothe-rapy | Uraemia, TLS |
| 5 | 6yr/M | Stage C/ Fever, jaw mass, BP 90/50mmHg,abdo minal masses, ascites, renomegaly, bipedal oedema, failure to produce urine. | ANARF | Yes but not dialysed | 1 but incomplete | Bleeding diathesis, hyperphospha-taemia (1.8mmol /L), hypocalcaemia (1.7mmol /L), tetany, vomiting | | Spent 3 days on admission but died 6 hours post chemothe-rapy. | TLS, Uraemia |
| 6 | 14yr/M | Stage C/ Vomiting pallor, dyspnoea, seizures, BP 150/100mmHg, reduced urinary output, jaw and abdominal masses, hepatospleno-megaly, left renomegaly and ascites, | OARF | No | 1 but incomplete | Severe anaemia, hypertension, seizures, congestive cardiac failure | Once | Spent 4 days on admission but died 12 hours post chemothe-rapy | TLS |
| 7 | 8yr/M | Stage D/ Fever, jaw mass, dyspnoea, severe palor, seizures, coma, neck stiffness, BP 160/110mmHg, abdominal masses, bilateral renomegaly, ascites and reduced urinary output, | ANARF | Yes but not dialysed | 1 but incomplete | Severe anaemia, hypertension, seizures, coma, bleeding diathesis, congestive cardiac failure, TLS | Once | Spent 2 days on admission but died 5 hours post chemothe-rapy | TLS, Uraemia and conges-tive cardiac failure |
| 8 | 10yr/M | Stage D/ Dyspnoea, BP 130/95mmHg, bone pains, jaw mass, hepato-splenomegaly, abdominal masses, bilateral renomegaly, ascites, bipedal oedema, paraplegia and reduced urinary output. | OARF | No | 1 | Hypertension, congestive cardiac failure, septicaemia, TLS | Twice | Spent 12 days on admission but died 9 days post chemotherapy | Septi-caemia |
| 9 | 7yr/M | Stage D/ Dysuria, dyspnoea, BP 130/100mmHg, neck stiffness, coma, abdominal masses, ascites, tender | OARF | Yes but not dialysed | 1 | Hypertension, urinary tract infection, severe anaemia, congestive heart failure, TLS | Once | Spent 13 days on admission but died 1 week post chemothe-rapy | Septicae-mia, conges-tive heart failure. |

hepatomegaly, bilateral renomegaly and oliguria.

**Table 2.** Clinical characteristics of acute renal failure (ARF) patients who received treatment protocol B

| *Patient Number* | *Age/ gender* | *Clinical stage/presentation* | *Renal failure type* | *Required dialysis* | *Number of chemotherapy courses received* | *Complications* | *Transfused* | *Outcome* | *Probable cause(s) of death* |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 11yr/M | Stage C/ Fever, facial puffiness, pallor, BP 140/100mmHg, diminished urinary output, axillary, submental and inguiral lymphadenopathy, craggy abdominal masses, ascites, hepatosplenomegaly, bipedal oedema, | OARF | No | 5 | Hypertension, tumour lysis syndrome (TLS) | - | Survived Admitted Initially for 27 days | - |
| 2 | 9yr/F | Stage C/ Fever, severe pallor, vomiting, headache, seizures, BP 170/120mmHg, dyspnoea, reduced urinary output, submental, cervical, axillary and inguiral lymphadenopathy. Facial puffiness, abdominal masses, hepatosplenomegaly, bilateral renomegaly and ascites. | OARF | No | 3 | Hypertensive encephalo-pathy, severe anaemia, congestive heart failure, TLS | Once | Survived. Admitted initially for 20 days | - |
| 3 | 14yr/F | Stage C/ Fever, severe pallor, facial puffiness, dyspnoea, BP 140/100mmHg, diminished urinary output, bilateral renomegaly, abdominal masses, hepatosplenomegaly, ascites, bipedal oedema. | ANARF | Yes but not dialysed | 2 | Hypertension, severe anaemia, congestive heart failure, TLS | Once | Survived. Was admitted initially for 23 days | - |
| 4 | 7yr/M | Stage C/ Pallor, fever, reduced urinary output, facial puffiness, dyspnoea, BP 130/90mmHg, abdominal masses, bilateral renomegaly, ascites, bipedal oedema, | ANARF | No | 1 | Hypertension, congestive heart failure, severe anaemia, TLS | - | Spent 10 days on admission but died 1 week post chemotherapy | Fluid and electrolyte imbalance. |
| 5 | 10yr/F | Stage C/ Pallor, reduced urinary output, drowsiness, seizures, headache, dyspnoea, BP 170/110 mmHg abdominal masses, bilateral renomegaly, ascites, bipedal oedema. | OARF | Yes but not dialysed | 4 | Hypertensive encephalopathy, pulmonary oedema, septicaemia, bleeding diathesis, TLS | Once | Survived. Admitted initially for 27 days | - |
| 6 | 8.5yr/M | Stage D/ Headache, BP 110/90mmHg, jaw mass, loose teeth, slurred speech, | OARF | No | 2 | Upper gastro-intestinal bleeding, Diastolic | Once | Survived. Admitted initially for 30 days | - |

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|---|---|---|---|---|---|---|---|---|---|
| | | right facial and hypoglossal nerves palsies, cervical and submandibular lymphdenopathy. Reduced urine volume, abdominal masses, bilateral renomagaly, ascites, bipedal oedema, | | | | hypertension, severe anaemia, TLS | | | |
| 7 | 9.7yr/M | Stage D/ Cough, dyspnoea, pallor, facial puffiness, proptosis, BP 140/100mmHg, abdominal masses, ascites, bipedal oedema, paraplegia, | OARF | Yes but not dialysed | 1 | Septicaemia, disseminated intravascular coagulopathy, pulmonary, oedema, hypertension, TLS | Once | Spent 15 days on admission but died 12 days post chemotherapy. | Septicaemia Bleeding diathesis |

**Table 3.** Haematologic data of patients in the two treatment groups

| | *Protocol A Mean ± SD* | *Protocol B Mean ± SD* | *P-value* |
|---|---|---|---|
| *White Blood Cell counts, /cmm* | | | |
| a. Pre-chemotherapy | 10,467 ± 2,684 (n = 9) | 9,886 ± 3301 n =7) | > 0.5 |
| b. Post-chemotherapy | 3,410 ± 1,767 (n = 7) | 5,670 ± 2,829 (n= 7) | > 0.05 |
| *Haematocrit, %* | | | |
| a. Pre-chemotherapy | 23.3 ± 2.6 (n = 9) | 26.5 ± 2.9 (n = 7) | < 0.05 |
| b. Post-chemotherapy | 15.6 ± 1.85 (n = 8) | 18 ± 2.1 (n= 7) | < 0.05 |
| *Platelets counts, / cmm* | | | |
| a. Pre-chemotherapy | 348,964.4 ± 133,075( n=9) | 412,286 ± 157,761 (n = 7) | > 0.5 |
| b. Post-chemotherapy. | 204,000 ± 101,917 (n = 7) | 224,246 ± 121,931.5 (n = 7) | > 0.5 |

**Table 4.** Drugs received by patients in both treatment protocols

| Drugs | *Treatment protocol A (TPA)* | | | | *Treatment protocol B (TPB)* | | | |
|---|---|---|---|---|---|---|---|---|
| | Mean number of doses | Duration of drug administration | Frequency of drug administration Overall mean dosage | Cummulative mean dosage | Mean number of doses | Duration of drug administration | Frequency of drug administration | Cummulative mean dosage |
| Oral allopurinol | 9.4 ± 5.8 (3-18) | 3.3 ± 1.73 (1 – 6) days | 3 ÷ doses per day | 757 ± 469.5 (192 – 1515) mg | 25.3 ± 7.1 (15 – 36) | 8.43 ± 2.4 (5 – 12) days | 3 ÷ doses/day | 2369.3 ± 779 (1245 – 3456) mg |
| IV cyclophosphamide | 1 dose | IV bolus | stat dose | 275± 115.01 (160 – 505) mg | X 4 doses | 4 days | Alternate days | 465 ± 73.5 (415 – 625) mg |
| IV vincristine | 1 dose | IV bolus | stat dose | 0.59+/- 0.16 (0.43-0.84) mg | - | - | - | - |
| IV methotrexate[a] | 1 dose | IV bolus | stat dose | 17.22 ± 4.23 (12 – 22.5) mg | - | - | - | - |
| IT methotrexate[a] | 1 dose | IV bolus | stat dose | 13.59 ± 6.4 (8 – 25.3) mg | 2 | IT bolus | Days 1 and 5 | 23.54 ± 4.2 (20.8 – 31.75) mg |
| Subcutaneous cytosine arabinoside[b] | 2.3 ± 1.15 (1 –3) | 2.3 ± 1.15 (1 – 3) days | Once daily | 79.17 ± 42.37 (32 - 114) mg | - | - | - | - |
| IT cytosine arabinoside[b] | 1.7 ± 0.6 (1 – 2) | 1.7 ± 0.6 (1 – 2) days | Days 1 and 5 | 56.33 ± 22.4 (32 – 76) mg | X 2 doses | 2 days | Days 1 and 5 | 88 mg |
| IV frusemide | 1 | IV bolus | Stat dose | 61 ± 8.5 (45 – 74) mg | 3.3 ± 1 (2 – 5) | 3.3 ± 1 (2 – 5) days | IV infusion alternate days | 183 ± 48.21 (130 – 260) mg |
| IV sodium bicarbonate[c] | 2.8 ± 2.2 (1 – 7) | IV bolus | Once daily | 58.0 ± 46.60 (15 – 140) mmol | X 4 doses | 4 days | IV infusion alternate days | 50.3 ± 13.5 (38 – 79) mmol |
| IV soluble insulin[d] | 6 ± 4.3 (2 – 14) | IV bolus | 6 hourly | 33.04 ± 29.4 16 – 98) units | 6.71 ± 2.21 (4 – 10) | IV bolus | 6 hourly | 40.2 ± 9.04 (25 – 49.4)units |
| Glucose infusion[d] | 1.57 ± 0.79 | 30 ± 25.7 (6 – 78) hours | Slowly as IV infusion daily | 138.3 ± 94.8 (56 – 136) g | X 4 doses | 4 days | IV infusion alternate days | 402 ± 108.1 (304 – 632)g |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | (1 – 3) | | | | | | | |
| IV calcium gluconate[d] | 3.14 ± 2 (1 –6) | 3.14 ± 2 (1 – 6) days | daily | 5.96 ± 5.78 (2.03 – 18.9) mmol | 1.71 ± 0.76 (1 – 3) | 1.71 ± 0.76 (1 – 3) days | Daily; IV slowly | 3.47 ± 3.6 (0.86 – 8.9) mmol |
| Calcium lactate tablet | - | - | - | - | X 63 doses | 25 ± 8.83 (10 – 33) days | 8 hourly per oral | 17.7 ± 9.2 (9 – 29.7) g |
| IV salbutamol | - | - | - | - | 16 doses per patient | 4 days | 6 hourly alternate days | 2.86 ± 1.1 (2 – 4) mg |

[a]Given to 6 of 9 TPA and 6 of 7 TPB patients.
[b]Given to 3 of 9 TPA and 1 of 7 TPB patients.
[c]Data for TPA are those for the management of tumour lysis syndrome (TLS); TPA patients received a mean bicarbonate dose of 15.13 ± 2.5 (12 – 19.2) mmol during induction chemotherapy.
[d]Received by 7 of 9 TPA patients during TLS management.

**Table 5.** Pre and Post Chemotherapy plasma chemistry data in patients who received protocol A

| | *Pre-chemotherapy Mean ± SD* | *Post-chemotherapy[a] Mean ± SD* | *P Value* |
|---|---|---|---|
| Sodium, m mol/L | 130.9±3.1 (n=9) | 128.0+6.8 (n=6) | >0.5 |
| Potassium, m mol/L | 4.9±1.2 (n=9) | 6.35±1.2 (n=6) | <0.05 |
| Bicarbonate m mol/L | 19.33±2.1 (n=9) | 17.5±2.2 (n=6) | >0.1 |
| Phosphate m mol/L | 1.5±0.4 (n=9) | 1.9±0.4 (n=6) | <0.05 |
| Calcium m mol/L | 1.92±0.33 (n=9) | 1.25±0.42 (n=9) | <0.002 |
| Uric acid, m mol/L | 0.54±0.18 (n=9) | 0.83±0.42 (n=7) | >0.05 |
| Urea, m mol/L | 20.5±8.7 (n=9) | 29.3±10.2 (n=7) | >0.05 |
| Creatinine, u mol/L | 359±182.1 (n=9) | 356.3±178 (n=5) | >0.5 |
| Albumin, g / L[b] | 33.6±2.6 (n=9) | NA | |

[a]Mean random blood glucose level following glucose infusion was 10± 2.53 m mol/ L
[b]NA = not available

**Table 6.** Pre and post chemotherapy plasma chemistry data in patients who received protocol B

| | *Pre-chemotherapy Mean ± SD (n=7)* | *Post-chemotherapy[a] Mean + SD (n=7)* | *P Value* |
|---|---|---|---|
| Sodium, m mol/L | 131.14 ± 1.46 | 131 ±4.32 | >0.5 |
| Potassium, m mol/L | 3.98 ± 0.49 | 5.2±0.72 | <0.002 |
| Bicarbonate m mol/L | 19 ±2.24 | 20.43±1.72 | >0.2 |
| Phosphate m mol/L | 1.35 ± 0.21 | 1.92±0.3 | <0.002 |
| Calcium m mol/L | 2.03 ± 0.26 | 1.0 ± 0.5 | <0.001 |
| Uric acid, m mol/L | 0.48 ± 0.24 | 25.6±3 | >0.5 |
| Urea, m mol/L | 23.43 ±6.2 | 25.6±3 | >0.5 |
| Creatinine, u mol/L | 322± 97.24 | 364.21±80.4 | >0.5 |
| Albumin, g /L[b] | 33.3 ± 3.8 | 38±3 | >0.05 |

[a]Mean random blood glucose level following glucose infusion was 9.2 ± 2.05 m mol/ L
[b]Post-chemotherapy sample size for albumin = 3

*Treatment outcome:* None of TPA patients received more than 1 course of chemotherapy; this was due to early death. However, in the TPB group 5 of 7 received <4 courses; two on account of death and 3 due to financial constraints. Three of 7 TPB patients achieved partial clinical remission with the first course and complete remission with subsequent courses. Two achieved complete remission with first course and were maintained with subsequent courses. The mean time interval between commencement of ICT and onset of diuresis in all TPB patients was 2.14±1.21 (1-4) days. Mean urine volume at onset of diuresis was 351.43±69 (267-483) ml/m$^2$/day. However, in TPA only 3 of 9 achieved diuresis (patients, 1, 8 and 9) with a mean onset time of 1.7+0.6 (1-2) days. Their mean urine volume at onset of diuresis was 1,008.7±1,227.3 (259-2,425) ml/m$^2$/ day. The other 6 patients were oligoanuric till death. By TLS definition (according to this study), all the 16 BLARF patients had post-chemotherapy TLS. 6 of 9 TPA patients died from TLS while the remaining 3 patients died from other causes (table 1). Deaths from TLS occurred within 5-36 (mean,

14.6±12.6) hours of post ICT in the TPA group. However, in TPB 5 of 7 survived the TLS while 2 of 7 died from causes other than TLS. The risk of dying from TLS was 30 times higher with TPA than with TPB (OR: 30, 95% CI = 4.03 – 223.2; P=0.0022). Mortality rate was 100% in TPA and 28.6% in TPB. The risk of mortality from TPA was 45 times higher than TPB (OR: 45, 95% CI = 3.94 – 514.4; P=0.0048). TPA patients spent an average of 7.3±4.6 (2-14) days on admission before demising while the 2 non-survivors among the TPB patients spent 12.5±3.5 (10-15) days, P>0.1. The 5 survivors spent 20-30 (mean, 25.4±3.91) days on admission before they were regularly discharged after the second course of chemotherapy; subsequent courses were received as out-patient due to financial constraints. Mean vital signs at discharge were respiratory rate 23.6±3 cycles/min, pulse rate 71.6±7.5 pulsations/min, SBP100±10mmHg and DBP 66±8.90mmHg. None of the patients received anti-hypertensive drugs beyond the first 24hours of ICT because their BPs crashed to normal levels.

Mean plasma biochemical data obtained 2-3 days before discharge, were sodium 135.4±3mmol/L, potassium 3.94±0.43mmol/L, bicarbonate 27.4±1.94mmol/L, phosphate 1.0±0.26mmol/L, calcium 2.34±0.36mmol/L, Uric acid 0.18±0.08mmol/L, urea 6.74±2mmol/L, creatinine 83.2±11.4umol/L, random blood glucose (4.23±1.14mmol/L) and albumin 39.4±3.05g/L. Discharge plasma albumin was significantly higher (P<0.01) than admission level, 33.3±3.8g/L. Quantitative discharge proteiuria data were available in 3 patients only (mean ± SD, 164±108mg/m$^2$/day). This was significantly lower than the pre-ICT mean proteinuria (539.04± 371.52mg/m$^2$/day, P<0.05) level in the 5 survivors. Discharge microhaematuria in the survivors ranged from 0-3 rbc/hpf. Mean discharge FeNa for the survivors was 1.16±0.63%. This was significantly lower than their pre-ICT value, 14.7±9.1% (P<0.01). Discharge haematocrit ranged between 24 and 31% (mean, 26.6±3.4). The patients were followed up for a mean period of 3.8 ±1.64 (2-6) months. All were still in remission with normal renal function when they were last seen in the clinic.

**Discussion**

Unlike post-chemotherapy BLARF which occurs quite commonly [4,14,15], pre-chemotherapy BLARF is infrequent [5,15]. BLARF remains a potential threat to survival in children with ASBL [4,5]. The pathophysiology of ARF in lymphoma appears to be multifactorial. Earlier studies indicated that it could occur as a result of TLS, lymphomatous infiltration of the kidneys, renal tubular destruction, glomerular compression, ureteric, renal artery and vein obstruction [5,16,17,18]. Intense renal vasoconstriction following massive release of adenosine by lysed tumour cells in the kidneys has also been postulated to cause BLARF [19]. The massive lymphomatous involvement of the kidneys in all our patients strongly suggest the possibility of compressive nephropathy as the cause of BLARF. Hypertension is not an uncommon co-morbidity in BL especially when the kidneys are involved [5,15]. It was present in 87.5% of the patients. Its pathophysiology has earlier been speculated to be due to overstimulation of the renin-angiotensin-aldosterone system (RAAS) provoked by reduced renal perfusion sequel to renal artery and pre-glomerular vascular compression by the tumour mass [5]. The rapid onset of diuresis (within 1-4 days) and drop in BP to normal following ICT and tumour lysis in the TPB group lend credence to the compression theory.

The tachycardia and tachypnoea which were recorded in the patients, reflected the congestive heart failure and pulmonary oedema which most of the patients had (tables 1 and 2). The cardiopulmonary problem was the resultant effect of hypertension, severe anaemia and vascular congestion due to oligoanuria.

Pre-chemotherapy fever was observed in 8 of 16 BLARF patients in the absence of clinical and laboratory evidence of infection. There were no malaria parasites in the blood of the patients and blood and urine cultures were sterile. The fever was possibly immune mediated. Burkitt's tumour antigen-antibody immune complexes formed either in the circulation, or the kidney or both possibly initiated this acute phase reaction. Malignancy and immune complexes, like infections, may cause fever by stimulating the leukocytes and other immunologically active cells to produce and release pro-inflammatory cytokines (PICs) into the circulation. The PICs include interleukin (IL) – I, IL-6 and tumour necrosis factor - α(TNF-α)[20]. PICs increase sympathetic activity by stimulating the vasomotor centre either directly or indirectly via the hypothalamus. Reduced heat dissipation due to intense vasoconstriction caused by increased sympathetic activity often results in fever [20].

The significant pre-chemotherapy proteinuria and microhaematuria in 7 of 16 patients suggest acute glomerulonephritis which like the fever, was probably immune mediated. The glomerulonephritis must have contributed significantly to the hypertension and biochemical perturbations in the BLARF patients. The proteinuria could also have been made severer by the hypertension. Hypertension increases glomerular capillary pressure thereby increasing transglomerular protein losses [21]. This in the experience of the authors, is a rare feature of BL. However, a review of the work of Hyman et al by James [22] revealed an association between nephrotic syndrome and Hodgkin's disease and other lymphomatous tumours. Recently, microhaematuria and nephrotic proteinuria were reported in a child with acute lymphoblastic leukaemia – induced haemolytic uraemic syndrome [23]. The significant improvement in the nephritic features following ICT in the 5 survivors is highly suggestive of an association between BL and the nephritis.

Apart from the nephritic features, some of the patients also presented with some other rare features that are not commonly seen in endemic BL; these are namely bone

marrow and lymph node involvements [24]. These are commonly seen in the non-endemic type of BL [25]. As seen in this study, the CNS is, however, not uncommonly involved in endemic BL [5,24].

Clearly, TLS was a common accompaniment of ICT in our BLARF patients; all patients had TLS. Some studies have shown that BLARF and ASBL patients need not die from TLS if pre and post chemotherapy dialysis, and continous veno-venous haemofiltration are offered [4,26]. These forms of renal replacement therapy are presently not readily available to majority of our patients due to a number of factors including financial constraints on patients' part [8]. In this centre, only one of six patients who could afford dialysis would eventually get dialysed [8]. These problems informed the need to design a treatment protocol that would significantly reduce the need for dialysis in BLARF patients. This requirement was met by TPB. TPB promises to be the treatment of choice in a center where pre and post chemotherapy dialysis are not readily feasible, given the better outcome of the patients who received this form of treatment compared with TPA. The mortality risk was 45 times higher in TPA than TPB (P=0.0045) notwithstanding the fact that all the patients hold TLS post-chemotherapy. The only plausible reason for the poor outcome in TPA patients is that the cytotoxic drugs given were many, and they were also given IV as bolus doses without pre-emptive anti-TLS measures. This regimen possibly caused rapid and massive tumour lysis and biochemical perturbations with sudden onset of TLS and the attendant systemic chaos that led to sudden death in the patients within hours of ICT. This syndrome of sudden death within hours of ICT has been attributed to biochemical perturbation of rapid tumour-cell lysis and renal malfunction [6,14]. Cardiac arrest from rapid changes in serum potassium, calcium and phosphate is a recognized complication of rapid tumour cell lysis [27]. On the contrary, outcome was much better in TPB because of slow infusion of low-dose cyclophosphamide over a 24-hour period, repeated on a altermate days times 4 doses. Furthermore, pre-emptive anti-TLS measures which encompass calcium (oral and IV), IV salbutamol, IV insulin, and IV infusions of glucose, frusemide and bicarbonate contributed significantly to better outcome in TPB. This regimen allows for slower tumour-cell lysis rate and less chaotic biochemical derangement as well as smooth and continous extra-renal disposal of high plasma potassium by salbutamol, bicharbonate, insulin and glucose. These drugs promote cellular ingress of potassium thereby preventing severe hyperkalaemia [28,29]. Calcium, apart from antagonizing hyperkalaemic cardiotoxicity, also helps in correcting hyperphosphataemia- induced hypocalcaemia of both ARF and TLS. Calcium lactate also binds dietary phosphate thereby reducing its plasma level. Forced alkaline diuresis (frusemide and bicarbonate infusion) was carried out to promote excretion of metabolic products of tumour-cell lysis and prevention of uric acid and phosphate nephropathy. Alkalinization of the urine with bicarbonate infusion to prevent uric acid and hyperphosphataemic nephropathy, is considered the standard treatment by some authors [30]. The non-significant rise (P>0.05) in the plasma level of uric acid post ICT in both TPA and TPB, underlined the therapeutic efficacy of allopurinol (a xanthine oxidase inhibitor) which the patients received before, during and after ICT. As part of measures to reduce morbidity and mortality from ICT in ASBL with ARF, cyclophosphamide is administered routinely over a two-day period with or without low dose methotrexate in addition to a first induction course haemodialysis in a centre in the United States of America [4].

Age and stage of BL did not affect outcome in these patients, age and number of BLARF patients with stages C and D Burkitt's lymphoma were similar in both TPA and TPB. Similarly, late hospital presentation which has been reported a significant risk factor for mortality in renal failure [7,31] did not affect outcome in our patients. Majority of patients in both treatment groups presented late (P>0.5). The type of induction chemotherapy given (TPA Vs TPB) was the most significant factor that affected outcome in this study. Hypertension, seizures, congestive heart failure, bleeding diathesis, severe anaemia and uraemia were common co-morbidities (tables 1 and 2) that also influenced outcome in the patients.

Data from the present study suggest that hypertension, proteinuria and microhaematuria that are responsive to cytotoxic drug therapy could complicate advanced stage BL. Furthermore, the study shows that TLS is a common accompaniment of post – ICT in BLARF patients; slow IV infusion of low dose cyclophosphamide (125mg/m$^2$) given on alternate days times 4 doses in addition to pre-emptive anti-TLS measures are associated with better survival rate (71.4%) when compared with patients in TPA group (no survivor) who had multiple IV bolus doses of cytotoxic drugs.

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