# The evolving management of Burkitt's lymphoma at Red Cross Children's Hospital

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*Background.* Treatment for Burkitt's lymphoma at Red Cross Children's Hospital has evolved from the use of aggressive surgery and less intensive chemotherapy to a conservative surgical approach with more intensive chemotherapy.

*Methods.* The study was a retrospective folder review of patients diagnosed with Burkitt's lymphoma at RCCH between 1984 and 2004.

*Results.* Ninety-two children were treated for Burkitt's lymphoma at RCCH between 1984 and 2004. There were 10 patients with group A or fully resected disease, 52 with group B or extensive localised disease, and 30 with dissemination to the bone marrow and/or central nervous system or group C disease. Protocol 1 (less intensive chemotherapy based on the COMP regimen) was used from 1984, with protocol 2 (more intensive chemotherapy based on the LMB regimen) introduced in 1988 for group C disease, 1991 for group B disease and 1996 for group A disease. Overall 5-year survival increased from 20% with protocol 1 to 66% with protocol 2 for group C disease, and from 76.5% with protocol 1 to 88.2% with protocol 2 for group B disease. There were more admissions for neutropenic fever in patients on protocol 2 and more episodes of mucositis, and these patients required more red cell and platelet transfusions. With a more conservative surgical approach, biopsy largely replaced attempts to partially resect the tumour at primary surgery, and there was a consequent decline in surgical complications.

*Conclusions.* Intensive chemotherapy with protocol 2 has resulted in improved survival for group C and group B patients, but with more morbidity. Protocol 1, which is less intensive with less morbidity, remains a viable strategy for group A and group B disease in resource-poor settings.

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Burkitt's lymphoma (BL) is the third most common solid tumour occurring in children in Africa, being exceeded only by brain tumours and Wilms' tumour. This is due to the high incidence of endemic BL (estimated at 40 - 100 per million per year in children under 15)[1] in the 'lymphoma belt', an area from 10° north to 10° south of the equator, which corresponds roughly with the malaria belt. The ability of the Epstein-Barr virus (EBV) to transform lymphocytes by inducing the translocations typically found in BL appears to be augmented by malarial parasitaemia. These translocations involve the c-Myc oncogene on chromosome 8 and one of the immunoglobulin heavy or light chain loci on chromosomes 2, 14 and 22.

The endemic form found in these areas is characterised by a jaw mass (58%), with or without abdominal disease (58%). Bone marrow involvement is rare (7%) but central nervous system involvement is more common (19%). The sporadic form found throughout the Western world typically presents as an abdominal mass (88%). Bone marrow involvement is more common than in the endemic form (21%) while jaw masses (14%) and central nervous system involvement (11%) are less common.[2] In South Africa most cases fall into the sporadic group.

This review examines the evolution in treatment for BL at Red Cross War Memorial Children's Hospital (RCCH) between 1984 and 2004. With the use of protocol 1 (P1) and aggressive surgery during the 1980s, excellent results were being achieved for patients with extensive localised disease. This was however at the cost of considerable surgical morbidity, and the outcomes of patients with bone marrow and central nervous system involvement remained dismal. A more intensive regimen, protocol 2 (P2), was introduced during the late 1980s, first for those with disseminated disease, and then for localised disease. At the same time a consensus was emerging internationally that with more intensive chemotherapy, debulking of large abdominal tumours was no longer necessary.[3] In addition, relook surgery to assess disease response after induction chemotherapy could be reserved for patients where residual disease was suspected.

We undertook this review of patients treated for BL at RCCH in order to establish whether our patients with disseminated disease have a superior survival with P2 and

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whether the outcome for extensive localised disease improved despite the increased toxicity associated with more intensive chemotherapy.

## Methods

The study was a retrospective folder review of patients diagnosed with BL at RCCH between 1984 and 2004. Patients were identified from the Oncology Registry of the RCCH Haematology-Oncology Service. Data on each patient were collected from the hospital notes. Four HIV-positive patients presented with BL between 2003 and 2004. These patients were treated with antiretroviral therapy and an alternative protocol, and were excluded from this study.

The diagnosis of BL was made on histological examination. Upon diagnosis, staging for each patient involved bilateral bone marrow biopsy, and examination of the cerebrospinal fluid (CSF). Chest X-ray and ultrasound of the abdomen were mandatory, and CT scans of the head, chest or abdomen were obtained where indicated.

During the early years of the study, tumours were partially or completely resected where possible. More recently this was gradually superseded by biopsy (via laparotomy or laparoscopy) for all but small localised intra-abdominal tumours. Definitive surgery was performed in patients presenting with intraluminal complications such as intussusception. When the diagnosis could be made from the bone marrow, or cerebrospinal, pleural or ascitic fluid, surgical biopsy was not performed.

The patients were divided into groups according to the risk stratification devised by the French Paediatric Oncology Society[4] (Table I).

Two chemotherapy protocols were used, P1 based on the COMP arm of United States Children's Cancer Group protocol CCG-551,[5] and P2 based on the French Paediatric Oncology Society protocol LMB-89 (Fig. 1).[6] P2 was introduced for group C patients in 1988, for group B patients in 1991, and for group A patients in 1996.

All patients were treated with allopurinol, hyperhydration and urinary alkalinisation at the commencement of induction chemotherapy to prevent tumour lysis syndrome. Granulocyte colony stimulating factor at a dose of 5 µg/kg per day for 14 days was used in an attempt to shorten the period of neutropenia following intensive chemotherapy in P2.

Originally, second-look laparotomy was often performed as part of the review of advanced abdominal disease after induction chemotherapy. Later, it was reserved for cases where there was clinical or radiological suspicion of residual disease.

Relapse-free and overall survival were estimated by the method of Kaplan and Meier. Survival analysis was performed using Statistica 6.1 (Statsoft, Inc. 1984 - 2003).

**Table I. Risk stratification for Burkitt's lymphoma (devised by the French Pediatric Oncology Society)**

| | |
|---|---|
| Group A | Complete surgical resection of stage I or abdominal stage II |
| Group B | All patients not eligible for group A or group C |
| Group C | Any tumour with CNS involvement<br>Any tumour with more than 25% blasts in the bone marrow |

## Results

Ninety-two HIV-negative patients with BL were admitted to RCCH between January 1988 and December 2004. There were 64 males and 28 females, with a male/female ratio of 2.3:1. The patients ranged in age from 1.6 to 13.95 years, with a median age of 5.53 years. The two treatment cohorts had an almost identical demographic profile.

Seventy patients (76%) presented with symptoms related to abdominal disease, including pain, distension and vomiting. Nine patients presented with a jaw mass, and 6 with a neck mass. Four presented with generalised adenopathy and bone pain, and 3 with paresis due to paraspinal masses.

At diagnosis 77 (83.6%) were found to have abdominal disease. Fifty-nine had bowel involvement, including 10 with intussusception. Twenty patients had disease involving the liver and 10 had renal involvement. Thirteen patients had involvement of the uterus, ovary or bladder and 1 patient had involvement of the testes. Twenty-five patients had ascites. Nine patients (9.8%) had jaw masses and 12 patients had pleural effusions.

Fifteen patients (16.3%) had central nervous system involvement at diagnosis. Three had paraspinal masses, 4 had central nervous system masses with cranial nerve palsies, and 11 had blasts in the cerebrospinal fluid. Twenty-five patients (27.2%) had more than 25% blasts in the bone marrow. Ten of these patients also had central nervous system involvement.

In all, 30 patients (32.6%) had group C disease; 15 with leukaemia, 5 with central nervous system involvement and 10 with both. Ten patients (10.9%) had group A disease; 9 had fully resected localised abdominal lymphomas and 1 cervical adenopathy. The other 52 patients (56.5%), including 6 with less than 25% blasts in the bone marrow, had group B disease.

There were more group C patients in the P2 cohort (40% for P2 v. 17% for P1), and less group A patients (5% v. 23%), due to the staggered introduction of this protocol. Both cohorts had a similar percentage of group B patients (55% v. 60%).

All group A patients had complete resection. Thirteen (61.9%) of the abdominal group B and C patients treated with P1 but only 8 (15.7%) of those treated with P2 had partial resection. Second-look laparotomy was performed for 10

## BURKITT LYMPHOMA PROTOCOL ONE

(based on the COMP arm of United States Children's Cancer Group protocol CCG-551)

| INDUCTION | MAINTENANCE (monthly for 6 cycles) |
|---|---|
| Cyclophosphamide 1 200 mg/m$^2$ IV | Cyclophosphamide 1 000 mg/m$^2$ IV |
| Prednisone 60 mg/m$^2$ PO daily for 28 days | Prednisone 60 mg/m$^2$ PO daily for 5 days |
| Vincristine 2 mg/m$^2$ IV weekly x 4 | Vincristine 1.5 mg/m$^2$ IV x 2 |
| Methotrexate IT | Methotrexate IT |
| Methotrexate 300 mg/m$^2$ IV | Methotrexate 300 mg/m$^2$ IV |

## BURKITT LYMPHOMA PROTOCOL TWO

(based on the French Paediatric Oncology Society protocol LMB-89)

| | | | |
|---|---|---|---|
| GROUP A | 1. | Cyclophosphamide 250 mg/m$^2$ IV 12-hourly x 6<br>Vincristine 2 mg/m$^2$ IV x 2<br>Prednisone 60 mg/m$^2$ PO/day x 5 days<br>Doxorubicin 30 mg/m$^2$ IV daily x 2 | 2 cycles |
| GROUP B | 1. | Cyclophosphamide 300 mg/m$^2$ IV<br>Vincristine 1 mg/m$^2$ IV<br>Methotrexate + Hydrocortisone IT<br>Prednisone 60 mg/m$^2$ PO daily for 7 days | 1 - 2 cycles |
| | 2. | Vincristine 2 mg/m$^2$ IV<br>Methotrexate 3 g/m$^2$ IV over 3 hours<br>Prednisone 60 mg/m$^2$ PO daily for 5 days<br>Cyclophosphamide 250 mg/m$^2$ IV 12-hourly x 6<br>Doxorubicin 30 mg/m$^2$ IV daily x 2<br>Methotrexate + Hydrocortisone IT x 2 | 2 cycles |
| | 3. | Methotrexate 3 g/m$^2$ IV over 3 hours<br>Cytarabine 100 mg/m$^2$ IV daily x 5<br>Methotrexate/Cytarabine + Hydrocortisone IT x 2 | 2 cycles |
| | 4. | Repeat 2 … but …<br>Cyclophosphamide 500 mg/m$^2$ IV daily x 2<br>Methotrexate + Hydrocortisone IT x 1 | 1 cycle |
| GROUP C | 1. | As for Group B … but …<br>Methotrexate + Hydrocortisone + Cytarabine IT x 3 | 1 - 2 cycles |
| | 2. | As for Group B … but …<br>Methotrexate 8 g/m$^2$ IV over 4 hours<br>Methotrexate + Hydrocortisone + Cytarabine IT x 3<br>Cyclophosphamide 500 mg/m$^2$ IV 12 hourly x 6 for 2nd cycle | 2 cycles |
| | 3. | Cytarabine 50 mg/m$^2$ IV x 5<br>Cytarabine 2000 mg/m$^2$ IV x 4<br>Etoposide 100 mg/m$^2$ IV x 5<br>Methotrexate + Hydrocortisone IT x 1 for CNS disease<br>Methotrexate 8 g/m$^2$ IV and triple IT therapy between cycles for CNS disease | 2 cycles |
| | 4. | Repeat 2 … but …<br>Cyclophosphamide 500 mg/m$^2$ IV daily x 2<br>Methotrexate + Hydrocortisone + Cytarabine IT x 1 | 1 cycle |

*Fig. 1. Protocols used for Burkitt's lymphoma at RCCH, 1984 - 2004.*

(33.3%) patients treated with P1 – in all but 1 case as a routine procedure. Fourteen (22.5%) of those treated with P2 underwent relook laparotomy – all had a residual mass on clinical examination or imaging. In only 4 of these 24 cases was there histological evidence of lymphoma, and in all cases this was strongly suspected on clinical examination and imaging.

All group A patients on both protocols survived. The estimated 5-year overall survival for group B patients was 76.5% with P1, and 88.2% with P2 ($p = 0.35$) (Fig. 2). There were 5 deaths with P1, 4 from recurrent lymphoma and 1 in remission as a result of varicella encephalitis. Five of those treated with P2 died: 2 had recurrent lymphoma, 1 developed bowel infarction and peritonitis following surgery for tumour-related intestinal obstruction, and 2 deaths were treatment-related – 1 during induction with haemorrhagic oesophagitis, and 1 in remission with cerebral aspergillosis.

The estimated 5-year overall survival for group C patients was 20.0% with P1, and 66.0% with P2 ($p = 0.04$) (Fig. 3). All 4 deaths with P1 were the result of BL recurrence. Of those treated with P2, 6 died of recurrent disease, and 2 deaths were treatment-related. Both of these occurred during induction – 1 as a result of Gram-negative septicaemia and 1 due to mucormycosis.

Twenty-eight patients (30.4%) developed tumour lysis syndrome requiring some form of medical intervention. Three of these patients were treated with P1 and none required dialysis, whereas 25 were treated with P2 and 12 of them required either peritoneal or haemodialysis. All patients requiring dialysis had high tumour burdens with extensive abdominal disease (2), leukaemia (7) or large pleural effusions (3).

Twelve of the 49 abdominal group B and C patients who had laparotomy with biopsy or partial resection had surgical complications. These included adhesive small-bowel obstruction (6), anastomotic leaks or perforations (6), volvulus (1) and jejunal obstruction (1). Of the 13 in the P1 cohort who had partial resection, 5 patients (38.5%) experienced complications – mainly anastomotic leaks. Two of the 8 patients (25%) in the P2 cohort who underwent partial resection suffered adhesive small-bowel obstruction.

There were 26 episodes of neutropenic fever with P1 (0.9 episodes per patient) compared with 192 in the group treated with P2 (3.1 episodes per patient). There were also more positive blood cultures in the P2 cohort (0.94 per patient) compared with the P1 cohort (0.27 per patient). Transfusion requirements were higher for the P2 cohort. These patients required 4.1 red cell transfusions and 4.0 platelet transfusions per patient compared with 1.4 and 0.6 respectively for those treated with P1. Severe mucositis was more frequent with P2 (1.9 episodes per patient) compared with P1 (0.3 episodes per patient).

Among group B patients treated with P2, 88% required at least one red cell transfusion and 62% at least one platelet transfusion. Ninety-one per cent of patients suffered an episode of febrile neutropenia, and 97% suffered severe mucositis. Frequency of episodes

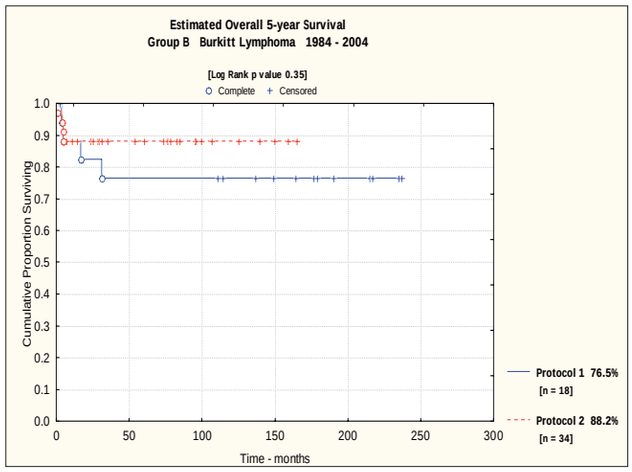


*Fig. 2. Estimated overall 5-year survival for group B Burkitt's lymphoma, 1984 - 2004.*

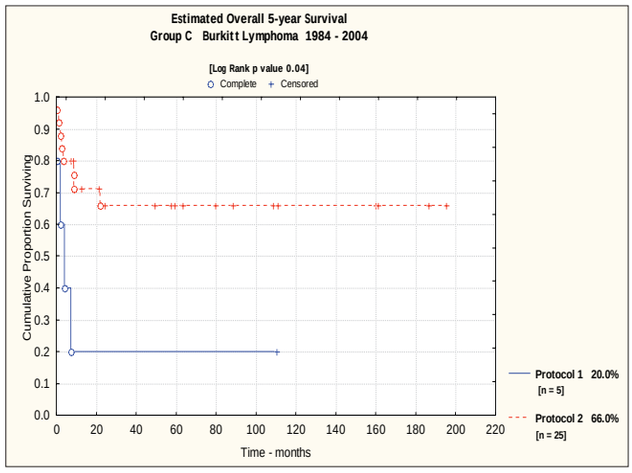


*Fig. 3. Estimated overall 5-year survival for group C Burkitt's lymphoma, 1984 - 2004.*

of neutropenic fever and severe mucositis, as well as red cell and platelet requirements, were particularly high for group C patients treated with P2.

## Discussion

BL was first described by Dennis Burkitt in Uganda in 1958 as a 'sarcoma involving the jaw in African children'.[7] He observed its dramatic response to chemotherapy, demonstrating a number of long-term remissions with one or two doses of cyclophosphamide.[8] Further evaluation showed that this endemic variant was clinically related, and histologically identical, to the abdominal form[9] that constitutes the sporadic variant. Initially treatment consisted of surgical cytoreduction where possible and chemotherapy.[10]

The subsequent evolution of BL treatment has seen the use of increasingly intensive chemotherapy and a reduction in the role of surgery. Early work demonstrated increased survival where complete resection could be achieved,[11] and advocated an aggressive surgical approach to BL.[12] As the efficacy of chemotherapy regimens improved, it became obvious that aggressive attempts at surgical cytoreduction delayed the administration of chemotherapy, and were associated with an increase in complications requiring surgical intervention.[13,14] Debulking surgery to reduce tumour bulk no longer appears to be necessary. Surgery is now only required for diagnostic purposes, or in the event of surgical complications of the lymphoma such as intestinal obstruction.

While regimens such as COMP,[15] on which P1 was based, proved very effective for patients with localised disease, cure for those with dissemination to the bone marrow or central nervous system remained elusive. Successive studies by groups in France[16,17] and the USA[18] showed that high cure rates could be obtained with more intensive chemotherapy. The French reported a 5-year overall survival of 100% for group A, 94% for group B and 85% for group C.[6]

Our patients fitted the profile of the sporadic type of BL. Abdominal disease predominated (83.6%) with few jaw masses (9.8%), and bone marrow involvement (27.2%) was more common than central nervous system involvement (16.3%). As in all other series males predominated but the median age (5.53 years) is younger than that reported in the French study (8 years). This is presumably the result of almost universal exposure to EBV at a young age. The high rate of dissemination to the bone marrow and/or central nervous system (32.6%) illustrates the ongoing problem of late diagnosis of childhood malignancy in South Africa. There were only 21.9% group C patients in the French study.[6]

The introduction of P2 improved the estimated 5-year overall survival for group C patients from 20.0% for those treated with P1 to 66.0% for those treated with P2 ($p = 0.04$). There is a trend for improved survival among group B patients with an increase in the estimated 5-year overall survival from 76.5% with P1 to 88.2% with P2 ($p = 0.35$). The group B results are comparable to the 94% reported by the French, but the group C results are still disappointing compared with the 85% reported in the French study.[6]

Side-effects of chemotherapy have increased with the introduction of P2. Group B and C patients had more episodes of neutropenic fever and severe mucositis, and higher blood product requirements. There were 4 treatment-related deaths with P2 – 2 in group B and 2 in group C – and there was a high rate of tumour lysis requiring dialysis.

Our patients appear to have experienced more side-effects than those treated in the French study. Treatment-related mortality was higher among both our group B patients (5.9% v. 0.8%) and our group C patients (8% v. 4.1%). Our group B patients required more red cell transfusions (88% v. 58%) and platelet transfusions (62% v. 17%), and suffered more episodes

of febrile neutropenia (91% v. 82%) and severe mucositis (97% v. 38%).[6]

Partial tumour resection among group B and C patients declined from 61.9% with P1 to 15.7% with P2. At the same time the surgical complication rate following complete or partial resection declined from 38.5% with P1 (more than half of them anastomotic leaks) to 25% with P2 (both adhesive small-bowel obstruction). Second-look laparotomy rates also decreased from 33.3% on P1 to 22.5% on P2. Laparoscopy has been increasingly used for diagnosis in place of laparotomy, with the aim of minimising adhesions and consequent bowel obstructions.

In conclusion, the introduction of more intensive chemotherapy for the treatment of BL at RCCH has resulted in a marked increase in survival for patients with disseminated disease. Survival has improved more modestly for extensive localised disease, but this has been accompanied by increased morbidity, which appears to exceed that reported in the French study. A more conservative surgical approach to BL has decreased the surgical complication rate.

In our unit patients with extensive localised disease treated with P1 attained a 76.5% estimated 5-year overall survival. This compares favourably to the 62% failure-free survival reported in the original USA study,[4] and the 77.4% event-free survival reported in Lebanon for locally advanced disease.[19] Only one death in our P1 cohort was treatment-related, and toxicity was mainly limited to neutropenic fever and anaemia requiring red cell transfusion.

While regimens similar to P2 (also based on the French LMB protocol) are used in other South African centres,[20] less intensive regimens such as P1 are still used in the developing world. These regimens with their low side-effect profile and minimal transfusion requirements are ideal for African centres with limited resources, and are recommended for children with group B BL in these settings.

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