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

Alan Davidson, Farieda Desai, Marc Hendricks, Patricia Hartley, Alastair Millar, Alp Numanoglu, Heinz Rode

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

Haematology Oncology Service, School of Child and Adolescent Health, Red Cross War Memorial Children's Hospital and University of Cape Town

Alan Davidson, MB ChB, FCPaed (SA)
Farieda Desai, MB ChB, FCPaed (SA)
Marc Hendricks, MB ChB, FCPaed (SA)
Patricia Hartley, *MB ChB, FCPaed (SA)*

Department of Paediatric Surgery, School of Child and Adolescent Health, Red Cross War Memorial Children's Hospital and University of Cape Town

Alastair Millar, MB ChB, FRCS, FRACS
Alp Numanoglu, MB ChB, FCS (SA)
Heinz Rode, MB ChB, MMed, FCS (SA), FRCS

Corresponding author: *A Davidson (davidson@ich.uct.ac.za)*

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 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

Infectious complications

TB represents a significant problem. During the period 1996 - 2004, the incidence of TB was 7/72 (9.7%) in our transplant patients. Presentation was 10 months to 8 years post transplant with symptoms of fever and cough in all and weight loss in most. No patients were on prophylaxis. With the exception of one renal case, the rest all had pulmonary TB with pericardial involvement in 2 cases. Immunosuppression at the time of diagnosis consisted of cyclosporin, azathioprine and prednisone. Diagnosis was made on finding acid-fast bacilli using a combination of sputum, nasogastric aspirate and bronchial lavage. In one case, a fine-needle aspirate of the lung produced the acid-fast bacilli. All the cases were typically mycobacterium TB and fully sensitive to rifampicin and INH. Three cases had had an increased dose of steroids in the preceding 3 months. An increased cyclosporin dose (up to 5 times) was required once starting the rifampicin. All cases were successfully treated with no loss of patient or graft.

Fatal CMV infection was seen in a 13-year-old girl with renal dysplasia and Fanconi's anaemia who received a CMV-mismatched organ (donor CMV positive: recipient CMV negative) in February 2001. Prophylactic intravenous ganciclovir was given for 2 weeks, but unfortunately she developed a pneumonia requiring ventilation 11 months later and died of CMV pneumonia.

EBV-driven post-transplant lymphoproliferative disorder (PTLD) was seen in 1 renal transplant who presented with a nodal mass in his inguinal region. Immunosuppression was reduced and ganciclovir and rituximab (anti-CD 20 agent) were given together with chemotherapy. Therapy remains successful together with preserved renal function.

Other serious infections in this group of patients have included disseminated varicella with transverse myelitis, *Pneumocystis jiroveci* pneumonia and cat scratch disease (*Bartonella henselae*). All were treated successfully and retained their grafts.

Vaccinations

Audit of vaccination status in a group of 32 cases with age range 93 - 225 months (mean 148 months) reviewed post transplant found protective immunity to hepatitis A (53% patients), hepatitis B (19% patients) and varicella (72% patients).

Adolescent transplant transition

We have had difficulty with transition of adolescents to adult units in the last 10 years with 5 adolescents having lost their grafts and 2 dying within 1 year of transfer despite adequate renal function at time of transfer. We have good 1- and 5-year graft and patient survival but our long-term outcome in the adolescent age group is significantly worse than in younger transplant recipients, as is reported universally.

Discussion

Paediatric transplantation poses numerous challenges, not only the conventional problems of acute rejection and infection, but also technically creative surgery to accommodate the significant size range (our group ranged from 8 kg to 63 kg) of paediatric patients. There may be further challenges in a developing country including difficult social circumstances, poor HLA matching (68% of our patients had 5 or more mismatches) as well as a limited number of donors exacerbated by the high incidence of HIV infection. In order to try and increase our donor pool, we may need to expand the current pool of living related donors (24%) beyond just the parents and potentially also consider non-heart-beating donors.

Whereas previously acute rejection was our biggest concern, this has now become easier to manage, by using the newer immunosuppressant agents including induction with IL2 receptor blockers. Our acute rejection rate has reduced to 18.8% using 2 initial doses of IL2 receptor blockers (both basiliximab and daclizumab used in 2-dosing regimen). Despite the initial cost of this form of therapy, these agents have allowed us to use an overall cheaper immunosuppressive protocol (such as cyclosporin and azathioprine) in our setting where cost containment is important.

However, the consequences of increased immunosuppression and reduced rejection are increased infection; this is highlighted by problems such as CMV infection or EBV-driven PTLD. This is particularly a problem in the young patient with no previous CMV or EBV exposure who receives a donor organ-recipient mismatch. The advent of qualitative and, more recently, quantitative polymerase chain reaction (PRC) testing will have a significant impact on both monitoring and management of these viruses. Intravenous ganciclovir is costly and inconvenient and hopefully prophylaxis will be made easier with the introduction of the oral valganciclovir form. As yet no vaccines are available for these two viruses.

TB is endemic in our region – our rate of TB in paediatric transplant patients was 9.7% – and together with HIV infection, raises issues of drug resistance, choice and duration of prophylactic agents.[6] Our patients developed TB 10 months to 8 years post transplant and it would thus be futile using prophylaxis for TB in the first 6 months only. Drug interactions between anti-TB drugs and immunosuppressants are also a concern.

On review of the vaccination status in a small group of our patients, hepatitis B levels were low post transplant with *Varicella* rates best overall. Paediatric studies have shown loss of antibodies to vaccinations within 6 months post-transplant.[7] Awareness of adequate vaccination pre-transplant, specifically live-attenuated vaccines, with regular post-transplant monitoring, is important in reducing complications from these infections.

In an established paediatric programme, with 1- and 5-year results which are satisfactory by international paediatric standards, despite all the problems of a developing country, emphasis on long-term graft and patient survival becomes an important focus. In view of this, we have tried to limit nephrotoxicity often caused by calcineurin inhibitors by using renal-sparing immunosuppressants. MMF has been useful in reducing dosing or even ceasing calcineurin inhibitors completely in those with chronic allograft nephropathy[8] and we have managed to use MMF and steroids as dual therapy only, with stable renal function so far in 3 of our patients.

Sirolimus has also been well described as a renal-sparing agent,[9] but we have seen a significant number of drug-related side-effects including interstitial pneumonitis and thrombocytopenia with purpura. In 2 cases we have noticed unexplained new-onset proteinuria, which has been described by a few centres as a concern.

In those patients on calcineurin inhibitors, cyclosporin has been responsible for significant cosmetic effects (hirsuitism and gum hypertrophy). These patients have usually been changed to tacrolimus therapy but this has also had problems of diabetes in 6% of our renal transplant in which 50% were black paediatric patients (relatively higher incidence than that of the total programme which consists of 31% black patients).

Children's growth in paediatric transplantation has received much attention recently and this is particularly important at a centre where growth hormone is not easily available. Steroids as immunosuppression have attracted negative press recently. In response to this, there have been three main approaches: (*i*) steroid elimination or avoidance in the first place[12] with use of heavier immunosuppression such as a prolonged course of daclizumab; (*ii*) steroid withdrawal in those who had steroids at time of transplant;[13] or (*iii*) steroid preservation at low dosing. We use the last approach using low-dose (0.05 mg/kg/day) alternate-day steroids. A recent review by Marks and Trompeter[14] also encouraged steroid preservation to prevent exchanging acute rejection for infection including EBV/PTLD. They suggest that steroids remain superior to many other immunosuppressive drugs in terms of cost and past experience, suggesting that it may be more sensible to remove calcineurin inhibition.

Long-term outcomes are greatly affected by adolescent issues and this is clearly seen by our results at 1 and 5 years compared with the group more than 7 years post transplant (Figs 4 and 5). This is notoriously the most difficult group of patients to follow up, a problem for colleagues in both paediatric and adult units alike, and we have this in common with the rest of the world.[15] This is particularly problematic where resources are limited, with adolescent issues similar to those in developed countries, but different economic constraints resulting in patients not being offered repeat dialysis or transplant.

In response to our poor long-term graft survival in adolescence, we have set up a combined transplant clinic with our adult and paediatric team based at the adult unit. This includes social support in the form of psychiatrists, nurses and social workers.

Challenges in the transition period include overcoming the fear of an unknown hospital, adjusting to a different patient/doctor ratio and increased independence in terms of their own health care. The move is preceded by psychological input in the form of workshops and one-to-one interviews prior to transfer to the adult unit.

We also delay the transfer to at least 16 years of age and often even older until patients are mature enough to do the transition with their independence established. Preparation of our younger adolescents, involving them in their own renal function results and medication adjustments, is also important with a positive goal of seeing transition to an adult unit as a successful 'graduation' process. A 'champion' on the adult service is required – be that a nurse or a doctor – so that the patients feel comfortable at the time of transfer by identifying a familiar face involved with them throughout the transition period.

Other factors affecting long-term outcome also depend on decreasing cardiovascular risk factors by reduction of steroid dosing, careful attention to body mass index to prevent obesity and inclusion of statins where necessary.

Despite all the challenges of a developing country, a successful paediatric transplant programme is possible, provided one is aware of all the pitfalls including infection, nephrotoxic drugs and adolescent transition.

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