Irish Medical Journal
Established 1867

Issue: Ir Med J; Vol 113; No. 1; P6

Burkitt Lymphoma/Leukaemia in Children & Young Adolescents

E. O'Rourke[1,4], A. Malone[1,4], A. O'Marcaigh[1], L. Storey[1], D. Betts[2], M. McDermott[3], O.P. Smith[1,4]

1. Department of Haematology, Our Lady's Children's Hospital Crumlin
2. Department of Cytogenetics, Our Lady's Children's Hospital Crumlin
3. Department of Pathology, Our Lady's Children's Hospital Crumlin
4. UCD School of Medicine, University College Dublin

Abstract

Aims
Burkitt Lymphoma (BL) accounts for approximately 40% of childhood non-Hodgkin Lymphoma (NHL) in the developed world. Survival rates have improved dramatically in recent years, a success attributed to better use of poly-chemotherapy and targeted immunotherapy. Nevertheless, relapse is unpredictable and carries a dismal prognosis. We report on event-free survival (EFS) and overall survival (OS) rates in the Republic of Ireland (ROI) during 2000-2017, and evaluate novel predictors of outcome.

Methods
Data was collected by retrospective review of patient medical records.

Results
Thirty-three patients were identified (twenty-five [76%] males, eight [24%] females), fourteen [42%] having stage III disease at presentation. Six [18%] had stage IV disease. Five [15%] had refractory disease; one salvaged with allogeneic stem cell transplantation. Of the four [12%] who died; two [50%] had weights >99th centile, one [25%] >90th centile. One died during induction from refractory lactic acidosis, one from early relapse.

Discussion
EFS and OS was 85% and 89% respectively; in keeping with the best international standards. Obesity appears to be a poor predictor of outcome in our cohort.

Introduction

Burkitt Lymphoma (BL) was first described by Irish physician-scientist Denis Parsons Burkitt. Working in Uganda in the 1950s, Burkitt noticed conspicuous swellings in the jaws of African children; these transpired to be common tumours in Africa and were invariably associated with additional tumours in other unusual sites. It became apparent that a proportion of childhood lymphomas described in Europe and the USA were indistinguishable from BL as first described in Africa - although the characteristic features of a jaw tumour excluding bone marrow involvement, were absent[1]. This important distinction lead to the classification of BL into two major subtypes - endemic (African) and sporadic. Endemic BL has an incidence far higher (10 /100,000) than sporadic BL (0.4/ 100,000),[2] and whilst endemic BL most commonly involves the jaw, abdomen and CNS, sporadic BL invariably involves the abdomen and/or bone marrow. The role of EBV in the pathogenesis of BL remains unclear - endemic BL cells demonstrate 90% positivity for the EBV genome whilst the sporadic demonstrates only 20% positivity[3].

BL expresses a characteristic chromosomal translocation; usually t(8;14) and more rarely t(8;22) or t(2;8). Each of these translocations juxtapose the *c-myc* oncogene and immunoglobulin locus regulatory elements resulting in the inappropriate overexpression of *c-myc*. The malignant cells show a mature B-Cell immunophenotype and are negative for terminal deoxynucleotidyl transferase. Furthermore, these malignant cells usually express a clonal surface immunoglobulin M with either kappa or lambda light chain restriction. A rapidly growing tumour, BL cells display a proliferation fraction (measured by Ki-67 immunohistochemsitry) approaching 100%.

Although Diffuse Large B cell Lymphomas (DLBCL) is a distinct entity morphologically and immunophenotypically, distinguishing between BL and DLBCL is not as clear cut clinically or histologically. Aggressive B- cell NHLs are encountered in practice that display some but not all features of classic BL, referred to as Burkitt-like Lymphoma, and whether these cases are closer to BL or DLBCL has not yet been established[4]. As they are assigned the same treatment protocols we review patients from all three cohorts.

Children with sporadic Burkitt/Burkitt-like lymphoma present with an abdominal mass in approximately 80% of cases[5]. There are two variations of primary abdominal BL - the first is diffuse involvement of the mesentery and omentum, and the second are tumours localised to the bowel wall thought to arise from Peyer's patches. Less common presentations involve the mediastinum, nasopharynx or Waldeyer's ring. Burkitt Leukemia (B-AL) is diagnosed when more than 25% of bone marrow (BM) cells are constituted by tumour cells.

BL exhibits an aggressive clinical course; recognised as the fastest growing human cancer, it can double in size in 24 hours. Despite notoriety for its aggressive nature, outcome has improved significantly over the past two decades, a success that can largely be attributed to the introduction of combination chemo-immunotherapy. Historically, paediatric patients in ROI were treated according to the FAB/LMB 96 Protocol[6] which stratified patients into treatment arms according to stage, site and Central Nervous System(CNS)/BM involvement. Whilst EFS was approximately 90% using this protocol, EFS of stage III with a lactate dehydrogenase (LDH) greater than two times the upper limit of normal (>Nx2) and of stages IV and B-AL was around 84% in the early 2000s, indicating a need for therapeutic improvement and identifying a higher risk population in which to evaluate the potential benefit of Rituximab[7]. The introduction of Rituximab for high-risk patients according to the COG-Inter B-NHL 2010 protocol[8] in our institution has resulted in BL representing one of the most treatable childhood malignancies. However, relapse consistently carries a poor prognosis, with salvage chemotherapy invariably proving futile.

Although bearing the name of an Irishman, there has been no evaluation of the ROI's experience of paediatric and adolescent BL. In this retrospective study, we aimed to determine the incidence and outcomes of BL in the paediatric/adolescent population of Ireland. With special attention to patients who relapsed or failed to achieve remission, this study aimed to evaluate novel predictors of outcome.

Methods

Clinical and laboratory data were retrieved by retrospective review of patient medical records. All paediatriac/adolescent cases of BL (<16 yrs) in the Republic of Ireland during 2000-2017 inclusive were identified from patient records in Our Lady's Children's Hospital, Crumlin (OLCHC). A number of variables were identified, including specific parameters at presentation, cytogenetics, treatment protocol and outcome. These variables were captured for each patient and entered into a database that enabled analysis for this study .

OLCHC represents the national tertiary referral centre for children's cancer in Ireland – thus, all BL patients in the ROI have been diagnosed, treated and followed up at Crumlin. Patient information was de-identified and protected for confidentiality.

Results

Every paediatric/adolescent case of BL in the Republic of Ireland has had their diagnosis established or confirmed in our institution. Diagnosis of BL required central review of clinical, morphologic, immunophenotypic, genetic and histological findings. Every patient underwent a full history and physical examination, and was staged with bilateral BM examinations, CSF analysis and radiological investigations.

Table 1: Clinical Characteristics of Patients

	Number	Percent
Patients	33	100
Gender:		
Male	25	76
Female	8	24
Subtype:		
Burkitt Lymphoma	21	64
Burkitt Leukemia	5	15
Burkitt-Like Lymphoma	3	9
DLBCL	4	12
Stage		
II	5	15
III	14	42
IV	6	18
N/A	8	24
Abdominal Involvement	17	51
Bone Marrow Involvement	7	21
CNS Involvement	1	3
Rasburicase Prescribed	15	45
Treatment Protocol		
EICNHL-COG-InterB NHL 2010	25	76
FAB/LMB 96	7	21
Relapse	5	15
Complete Remission	29	88

Thirty-three patients were identified (twenty-five [76%] males, eight [24%] females), the majority having abdominal symptoms and stage III disease at presentation (see Table 1). Cases were classified: classic BL or B-cell lymphoma unclassifiable (with features intermediate between DLBCL and BL). Six [18%] had stage IV (five B-AL and one CNS involvement) disease at presentation. BL generally displays a propensity to occur in males – this was evident in our cohort with a male: female ratio of approximately 3:1. The EFS and OS for the total cohort was 85% and 89% respectively which is in keeping with the best results worldwide. Looking at the survival curve – all events happen very early i.e. within 3 months of finishing chemotherapy. (see Fig. 1a & 1b)

Fig. 1a: Event Free Survival

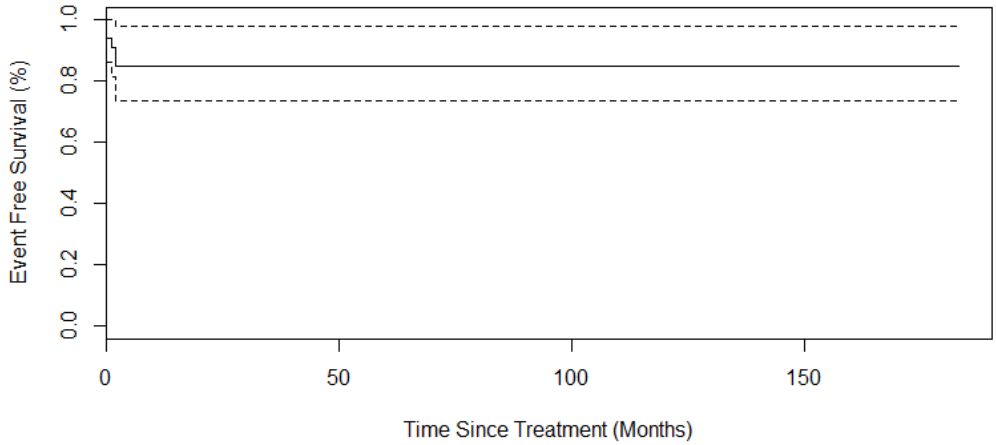
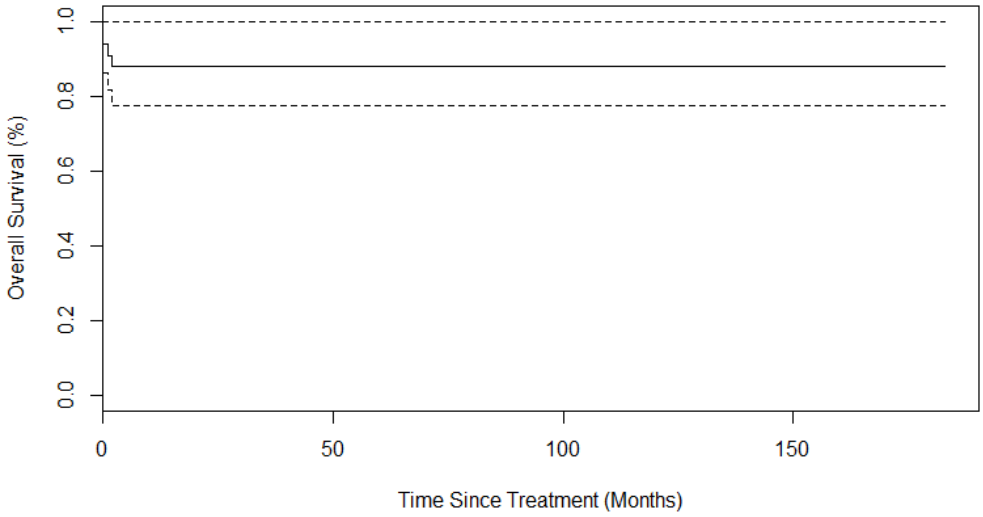


Fig. 1a: Overall Survival



All patient received first line therapy according to either the FAB/LMB 96 Protocol (seven [21%]), or the EICNHL COG-INTER B 2010 Protocol (twenty-five [76%]). Patients were stratified by stage, risk and CNS involvement, thus the specific chemotherapy regime varied accordingly. Unfortunately one of the patients in this cohort died secondary to an anaphylactic reaction to Rituximab infusion. Urate levels were used to stratify patients into risk of tumour lysis syndrome; namely urate ≥ 450 mmol/L – fifteen [45%] above this threshold were administered recombinant xanthine oxidase (Rasburicase).

Five [15%] had refractory or relapsed disease, one of whom was salvaged with allogeneic stem cell transplantation (see Table 2). Of the four [12%] who died; two [50%] had B-AL; of these one died during induction from refractory lactic acidosis and hypoglycaemia (LDH 40,000 IU/l at diagnosis) and one from early relapsed disease (LDH 13,572 IU/L at diagnosis). The two [50%] remaining had primary refractory disease and both patients were obese, with weights > 99th percentile. One of these patients had a Burkitt-Like Lymphoma. Although BMI could not be ascertained as height was not available for all patients, a linear model to determine the difference in weight after adjusting for age indicates that those that relapse are significantly heavier (p=0.009) by 18.4 kg on average (see Table 3).

Cytogenetics were not obtained for the entire cohort, however the majority (eighteen [55%]) of the tumours expressed the characteristic t(8;14) chromosomal translocation. Although all of the relapsed patients possessed the characteristic t(8;14) translocation, of these two possessed extra genetic abnormalities: one a partial trisomy 1q, and one expressed gain of BCL6 and loss of tp53.

Table 2: Clinical Characteristics of Patients That Relapsed

Sex	Age (years)	Weight at Diagnosis(kg)	Weight Centile	Diagnosis	Genetics	Time to Relapse	Outcome
M	7	57.5	99th	Burkitt-Like Lymphoma	t(8;14)	2 months post EOT	RIP – Refractory BL
M	13	60.5	90th	Burkitt Leukaemia Ig-ve	t(8;14), partial trisomy 1q		RIP – Lactic Acidosis
F	14	37	3rd	Burkitt Leukaemia	t(8;14)	1 month post EOT	RIP – Acute Renal Failure
M	15	110	99th	Burkitt Lymphoma	t(8;14), Gain Bcl6, Loss tp53	During last cycle	RIP – Refractory BL
M	7	27.4	84th	Burkitt Lymphoma	t(8;14)	2 months post EOT	Complete remission

Table 3: Weight of Patients

	Relapse	Remission	Total
Mean	58.5	26.8	31.8
Standard Deviation	31.96	12.82	20.15
Median	57.5	24.9	26.6
Min, Max	27.4, 110.0	8.0, 65.0	8.0, 110.0
1Q, 3Q	37.0, 60.5	18.2, 31.2	19.8, 37.7

Discussion

Staging was established using St. Jude's classification[9]. Stage does not appear to have a direct effect on outcome – the vast majority presented in late stage disease and the only patient that presented with stage II disease subsequently relapsed. Hence, it seems that stage is more helpful in guiding therapy rather than serving as a prognostic indicator, and that other patient and tumour factors influence outcome. Patients were further stratified into high or low risk by accounting for LDH levels. It is worth nothing that after comparing mean LDH levels in patients who relapsed against those that achieved full remission, there was no significant difference. In general, bulky disease correlated with grossly elevated LDH levels, but did not confer a risk of poor response to treatment.

Incomplete response to standardised treatment and/or relapse remains almost impossible to predict, and escalation of chemotherapy alone is invariably ineffective. To date, no parameters are published to predict the response of patients to chemotherapy. Furthermore, chemotherapy is tenuously administered in high-risk patients with bulky tumours as the consequences of tumour lysis syndrome can be devastating, as seen in our cohort. The introduction of recombinant xanthine oxidase for patients with elevated urate levels above the standardised threshold will undoubtedly lessen risk, however our cohort is too small to determine its effectiveness. For patients that require escalation of treatment, Rituximab could be the key to overcoming these problems.

Three out of the four [75%] relapsed patients were significantly overweight at diagnosis, two with weights >99th centile, one on the 90th centile. Furthermore, the only patient that relapsed and subsequently achieved remission had a weight most appropriate for their age. Our results show that relapsed patients were heavier by 18.4kg on average - a staggering statistic despite the small sample size. In the adult NHL population obesity represents a long-recognized poor prognostic indicator; analysis of advanced-stage NHL patients treated at the University Division of Hematology of Turin concluded that the risk of death among overweight patients was 2.9 (CI, 1.3–6.2) times that of the reference group[10]. Similar conclusions have been drawn in paediatric ALL patients. A retrospective analysis of 4,260 patients with newly diagnosed ALL enrolled from 1988 to 1995 onto five concurrent Children's Cancer Group studies concluded that obesity at diagnosis independently predicts likelihood of relapse and cure in preteenagers and adolescents[11]. Furthermore, this study found that the effect of obesity on outcome appears unrelated to alterations in chemotherapy doses, intervals between cycles, or therapy-related toxicity. Similar results were seen in the CALGB 10403 study, which hypothesised that this association is likely multifactorial in nature[12]. Hepatic, hyperglycemic, and thrombotic toxicities occurred more frequently during induction in CALGB 10403, when the combination of high leukemia burden and obesity may have heightened pro-inflammatory and pro-coagulant states. Similarly, there is limited evidence that adipocytes attract leukemia cells and may shelter lymphoblasts during chemotherapy thus conferring resistance[13]. The data reflects no such avenues of research in BL patients, nor is there any published data supporting a similar negative effect, but it appears to represent a potential fruitful approach.

Indeterminate tumour genetics and/or additional mutations appears to represent another poor prognostic indicator in our cohort. Two of the relapsed patients possessed extra genetic abnormalities: one had a partial trisomy 1q whilst another expressed gain of BCL6 and loss of *tp53*. Trisomy 1q is a rare secondary karyotypic event in various hematologic malignancies, and whilst the gene involved is unknown, some hypothesize that the most common region of duplication habors genes associated with tumor cell invasiveness[14]. Gains or amplifications of 1q (present in approximately 20% of patients with classical BL) and an increasing genetic complexity have been associated with poor clinical outcomes[15]. These abnormalities were not present in any of the other remitted patients.

As our patient cohort is small and events are rare, median time to event results cannot be discussed. However looking at the survival curve, it appears that if an event is going to happen, it will happen very early – those that relapsed in this cohort did so within the first 3 months of finishing chemotherapy. This is in keeping with the current thinking in

BL – if a relapse is going to happen, it will likely happen early. This provides specialists with some confidence in ascertaining that their patient has achieved complete remission.

Declaration of Conflicts of Interest:
The authors declare they have no conflict of interest.

Corresponding Author:
Professor Owen Smith
Department of Haematology, Our Lady's Children's Hospital Crumlin
UCD School of Medicine, University College Dublin
Email: owen.smith@OLCHC.ie

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