Eur J Cancer, Vol. 27, No. 4, pp. 504–509, 1991.
Printed in Great Britain

0277–5379/91 $3.00 + 0.00

Feature Articles

Burkitt's Lymphoma: a Model for Clinical Oncology

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Burkitt's lymphoma, a pathological entity initially described in Africa, is the most common childhood lymphoma in western countries and represents approximately 5% of all adults lymphomas. This high grade small non-cleaved diffuse lymphoma is a model with which to study the relations between cancer and viruses, the chromosomes and the genes. Burkitt's lymphoma is also a model for clinical research which allows evaluation of the dose effect concept with chemotherapy and the role of megatherapy with autologous bone marrow rescue.
Eur J Cancer, Vol. 27, No. 4, pp. 504–509, 1991

INTRODUCTION

THE STORY of Burkitt's lymphoma (BL) is now a classic part of medical history. The first step was due to an English surgeon, Denis Burkitt, who reported on an unusual childhood tumour in Africa, which now bears his name [1]. The classical picture of a huge jaw tumour remains in the memory of most medical students as the typical manifestation of BL. In fact lymph-nodes and abdominal localisations were, since the first report, part of the same pathological entity [1]. Using a mail enquiry, Burkitt soon discovered the African "lymphoma belt". He then participated in several epidemiological studies throughout Africa leading to the concept of "related disease related cause" [2]. The tumour did not occur in areas where the mean temperature at any time of the year fell below 16°C and where altitude was more than 1800 m, and annual rainfall less than 50 cm. These limiting factors incriminated a biological organism. On 22 March 1961, after the conference "The commonest children's cancer in tropical Africa. A hitherto unrecognised syndrome", a fortuitous discussion occurred between Burkitt and Epstein [3]. The latter was working with chicken tumour viruses, and had received several tumour samples from Burkitt. The first BL cell line "EB1" was issued from one of these samples, and using electron microscopy Epstein, Achong and Barr described a previously unclassified herpes-like virus [3, 4]. Epstein–Barr virus (EBV) was thereafter considered as the specific cause of BL. When serological testing for EBV became available, it was soon obvious that serology was positive in most but not all African BL (97% in tropical Africa, 88% in north Africa) and 20% in non-African cases, that infectious mononucleosis was also due to EBV and that most adult controls had previously been in contact with the virus [3]. In a prospective study of African children, anti-virus capsid antigen (VCA) antibodies were significantly elevated in those who ultimately developed BL [5]. A multi factorial aetiology of BL carcinogenesis was then considered: malaria and various carcinogenetic determinants were suspected as responsible for the disease [5]. Subsequent progress involved pathology (using the International Working Formulation [IWF]), epidemiology (investigating vs. non-endemic BL), immunology (clonal B origin), cytogenetics (non-random chromosomal translocations), and molecular biology (C-*myc*) [6–15]. The disease history, with its coincidences, its fortuitous meetings and its recent discoveries makes BL still a fascinating disease. Most recent steps have concerned advances in chemotherapy, and during the last decade dramatic improvement has been reported leading to cure rates of more than 70% of children with BL [16–22]. Burkitt's name is then related to various achievements that we will summarise in this review.

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Received 14 Jan. 1991; accepted 22 Jan. 1991.

MORPHOLOGY, IMMUNOLOGY, CYTOGENETICS AND MOLECULAR BIOLOGY OF BURKITT'S LYMPHOMA

The initial definition was based on pathology [6]. In the IWF, BL is recognised as a small, non-cleaved, diffuse high grade lymphoma and characterised by a monotonous proliferation of cells, 10 to 25 microns in diameter, with round to oval nuclei, and two to five prominent basophilic nucleoli. The cytoplasm is deeply basophilic, scanty, with several clear vacuoles, some of which contain neutral lipid as recognised by specific stains. Mitotic features are seen in approximately 4% of the neoplastic cells, and in association with this high growth fraction, one often observes numerous pycnotic cells and "starry sky" macrophages containing nuclear debris [7]. Burkitt's lymphoma is a monoclonal proliferation: only one of the two light chains, kappa or lambda, is expressed, and only one single glucose-6-phosphate dehydrogenase (G6PD) isoenzyme is found in heterozygote females [8, 23]. BL is derived from normal B cells at different levels of the antigen independent stage of maturation, and possibly from different cell lineages. The ratio of kappa to lambda tumours is 3:1, similar to the ratio in normal peripheral B cells. Most often, surface IgM is expressed, and is rarely associated with IgD. Cells expressing IgG or IgA with or without IgM are exceptional, and BL cells only express intracytoplasmic IgM in 30% of cases with or without light chain. All BL express HLA DR and most CD 10, but not the terminal

deoxyribonucleotide transferase, clearly differentiating BL from acute common lymphoblastic leukaemia [15, 24–26]. The majority of cell lines derived from African and north African BL express EBV receptors and may derive from the follicular center cell of lymph nodes. In contrast, caucasian BL do not usually express EBV receptors or show a secretory activity, and may originate from medullary lymphocytes [24]. These findings explain the cases with an exclusively leukaemic presentation in some non-endemic BL, and the preferential mucosa-associated lymphoid tissue involvement in endemic BL [25]. The receptors for the constant part of the immunoglobulins, the β_2 microglobulin, and several other markers as B cell antigens including CD 24 and CD 20 are present on the cell surface [24–27]. This heterogeneity of BL phenotyping necessitates complete surface marker evaluation at diagnosis, not only for scientific purposes but also for possible subsequent immunological bone marrow purging procedures [28]. Response to B-cell growth factor (BCGF) or interleukin 2 (IL-2) receptors may help to classify the tumour according to the degree of activation [24].

The best maker of BL is a cytogenetical abnormality found in both endemic and non-endemic disease. This translocation consistently involves chromosome 8q23-q24, and is directed most often (in 70% of cases) to 14:t(8;14) (q24;32), although variants (25%) have been described either to 22:t(8q24;22q11) or to 2:t(2p12;8q24), the former being twice as frequent as the latter [9–12]. 5% of cases have no specific translocation but all bear a 6q marker. Rearrangements of chromosomes 1 and 7 have also been described [13]. The breakpoint on chromsome 14 (14q32) corresponds to the gene of the heavy chain of immunoglobulins. The light chain lambda gene sits on breakpoint 22q12, and the light chain kappa gene on breakpoint 2p12. In 1982, it was demonstrated that BL cells expressed either kappa or lambda light chain if translocation (8;14) was present, but only kappa if chromosome 2, and only lambda if chromosome 22 were involved [8]. Dalla Favera showed that 8q24 corresponds to the oncogene C-*myc* that is involved in chicken lymphomas. C-*myc* is a DNA sequence of 10 000 bases consisting of repeated sequences: 3000 bases code for a conserved sequence transmitted through the human species for a long time. The non-coding sequence of 7000 bases is probably a regulatory sequence [14]. As a consequence of these translocations, the proto-oncogene C-*myc*, or at least its coding position, is joined with the Ig loci. This may lead to the activation of the proliferative role of C-*myc* by deregulating its expression, although the factors involved in this process are still controversial. It may be either transcriptional enhancement leading to a constitutive expression of the C-*myc* gene at elevated levels, or alteration of the gene itself or its presumptive regulatory sequences [29]. The scenario of BL development has been recently reviewed [30]. The chronology of the classical three steps theory [31]—(1) EBV induced immortalisation; (2) proliferation of EBV-carrying B-cells; (3) reciprocal translocation that leads to C-*myc* deregulation—is a matter of debate. Lenoir proposed an alternative model for BL development, where step 1 is the generation of lymphoid cells at high risk for occurrence of a translocation involving the Ig loci, step 2 is the appearance of the translocation involving C-*myc* and the Ig loci, and step 3 is infection by EBV of a B cell carrying the specific translocation (Table 1).

CLINICAL CHARACTERISTICS AND EPIDEMIOLOGY

Burkitt's lymphoma predominantly occurs in childhood. The clinical and epidemiological features will be described separately for endemic and non-endemic cases, although common points may be found [32].

The annual incidence of African BL is 2.2 to 3.8 cases/100 000 inhabitants, and peak incidence is 5–8 years of age in central Africa, and 4–5 years in north Africa. The sex ratio is 2 boys:1 girl [33, 34]. Initial clinical findings include jaw lesion (58% of cases) frequently associated with abdominal disease [34]. The precise site of origin of jaw tumour is unclear, but typically there is involvement of the developing premolar and molar teeth area resulting in the characteristic radiological appearance with early loss of lamina dura, widening of the dental papillar and lytic changes in surrounding bone. The maxillary are involved twice as often as the mandibles. Orbital involvement is also relatively common (18%), probably by direct invasion from maxillary tumour. Abdominal disease is also observed in 58%, involving the retroperitoneum, mesentary and omentum more often than the bowel itself, so that presentation as intussusception, perforation or intestinal obstruction is rare [33, 34]. Ascites is often present due to peritoneal infiltration. Kidney, ovary, pancreas, liver and adrenal are also frequently involved [35]. Peripheral lymph-node involvement is uncommon (less than 1%). Occasionally, breast, pleural, myocardial, pericardial and bone localisations are observed [33]. Bone marrow involvement is initially present in 12% of cases, and central nervous system (CNS) in 30%, the latter being often associated with extra-abdominal tumour, rarely with bone marrow infiltration. CNS involvement is documented by cerebrospinal fluid (CSF) cellularity, cranial nerve palsies, or epidural mass with cord compression. CNS involvement does not share the ominous prognosis described in European series [36]. Data issued from endemic regions in 1984 showed survival rates similar to European results observed between 1970 and 1980. Cure was obtained in 90% of localised and 35% of extensive BL, thus demonstrating identical response to chemotherapy in endemic and non-endemic BL [32, 37, 38]. Relapse occurs early (within 8 months after diagnosis). Late relapse is exceptionally observed in non-endemic regions, raising the hypothesis of an exogenous factor such as EBV and/or malaria persisting and producing a second BL [32].

The annual incidence of non-African BL in children below 16 years in western countries is about 0.1–0.3/100 000, 20–40 times lower than in endemic regions [39]. BL represents 40–45% of non-Hodgkin malignant lymphomas in children [40]. The male to female ratio is 2.3/1 in USA and 3.7/1 in France [41]. There is no clear relation between the incidence of BL, geographical or climatical conditions and/or viral association [40, 41].

The most common initial presentation [15, 39, 40] is rapidly growing, abdominal tumour (70–90%), with a high incidence of abdominal complications: intussusception, gut obstruction and perforation (20%). Peripheral lymph-node presentation is less common (20%) and jaw tumour rare (7–18%). Involvement of the pharynx is reported in approximately 5–10% of the cases [40%], and exclusively leukaemic presentation with circulating tumour cells but without associated mass lesion is specific for non-endemic BL [40].

Bone marrow infiltration associated with other organ involvement is more frequent than in endemic patients (20%). CNS infiltration occurs as meningeal infiltration, cranial nerve palsies or epidural mass with cord compression in 20% of the cases. Two thirds of CNS cases are associated with bone marrow involvement [15, 39, 41].

Table 1. Proposals to explain appearance of BL

	Step		
	1	2	3
G. Klein [31]			
Present scenario for all BL [23]	B-cell immortalisation	Increase in the size of the target-cell population	*myc* deregulation, malignant transformation
African BL scenario	EBV	Malaria	Chromosomal translocation, *myc*/Ig juxtaposition
	Associated with early primary infection	Parasite induced T-cell immunosuppression as well as polyclonal B-cell activation	Probably increased by increased number of cell divisions
G. Lenoir [30]			
Proposed scenario for all BL [22]	Triggering of B-cell	Appearance of competent cells by *myc* deregulation	Autonomously growing malignant cells
African BL scenario	Malaria-induced polyclonal B-cell activation	Chromosomal translocation *myc*/Ig juxtaposition	EBV
	Increases Ig recombinational events per time	Makes B cells responsive to growth signals in the absence of antigenic stimulation	Infection of a cell carrying the infection and outgrowth favored by immune dysfunction

MANAGEMENT OF BURKITT'S LYMPHOMA

Burkitt's lymphoma is one of the most rapidly growing paediatric tumours and requires prompt diagnosis and staging before initiation of a specific treatment.

In any case, initial investigations should include the following procedures. (1) A complete clinical examination searching for any superficial tumour and/or localisation that could easily be biopsied or aspirated, and for any neurological dysfunction, especially facial nerve palsies, skin hypoesthesia and pyramidal symptoms. (2) Rapid and simple imaging, such as abdominal ultrasonography or chest X-ray, avoiding any sophisticated investigation that would delay initiation of therapy. A three dimension measurement tumour should be obtained with ultrasonography. (3) One or two bone marrow smears, with cytogenetical and immunological assessment. Evaluation of the tumour burden should include uric acid level, urea, creatinine, potassium, calcium, phosphorus, lactate dehydrogenase (LDH) and β2 microglobulinaemia. Lumbar puncture and examination of CSF cytospin must be done before initiation of therapy.

Several different clinical situations may occur. In a child with extensive disease BL is immediately suspected, and staging procedures are limited to tumour aspiration, CSF cytology and bone marrow aspiration. Formal histology is not required when cytology is available for diagnosis. Results should be obtained within a few hours, and chemotherapy started immediately. Tumour lysis syndrome is of major concern during induction therapy in such cases and careful monitoring is mandatory [17, 18, 39]. Local disease may be small, sometimes accessible to complete and easy surgical removal. Staging in such cases is not an emergency and should be very extensive since underestimation may lead to suboptimal treatment [39]. The diagnosis may be suspected only at time of surgery for abdominal emergency such as acute intussuseption. Resection of the mass should be considered only if it is likely to be complete, and without to delay initiation of chemotherapy. Aggressive surgery (debulking) is no longer part of the modern treatment of BL [15–17, 39–41].

Early therapy is always essential, but its intensity should be modulated according to the initial staging. Several staging systems have been described. In the 1970s, when surgery was the accepted gold-standard treatment for BL, Ziegler's [42] classification (Table 2) was based on the relation of tumour site and removal procedure, and is still useful. Currently, Murphy's classification [16] is widely used and is based upon a more precise definition of locoregional tumour extension and distant metastasis (Table 3). The role of extensive multiorgan involvement (such as with kidney or liver) as opposed to limited but unresectable disease can improve the clinical usefulness of the Murphy classification in stage III patients [18]. Distinction between stage IV due to CNS or bone marrow invasion is also of value for predicting survival [17, 18].

TREATMENT OF BURKITT'S LYMPHOMA

Ziegler has suggested a role for surgical debulking of tumour [42]. However, due to the extreme chemosensitivity of BL, debuling should be avoided. The potential morbidity associated with surgery is no longer acceptable [42, 43]. Initial surgery should be restricted to 3 well defined situations: (1) biopsy for initial diagnosis when no other means (eg: examination of ascitic fluid, marrow, CSF, pleural effusion) are available; (2) acute

Table 2. Ziegler's classification for Burkitt lymphoma [42]

Stage	
A	Single extra-abdominal site
B	Multiple extra-abdominal sites
C	Intra-abdominal tumour
D	Intra-abdominal tumour with involvement of more than 1 extra-abdominal sites
AR	Stage C but with more than 90% of tumour surgically removed

Table 3. Murphy's classification for childhood non-Hodgkin lymphomas [16]

Stage	
I	Single tumour (extra nodal) or single anatomic area (nodal) apart from mediastinum or abdomen (extra nodal)
II	Single tumour extra nodal with regional node involvement; two or more nodal areas on the same side of the diaphragm; two single (extra nodal) tumours with or without regional node involvement on the same side of the diaphragm; primary gastointestinal tumour (usually ileocaecal) with or without involvement of associated mesenteric nodes only
III	Two single tumours (extranodal) on opposte sides of the diaphragm
	Two or more nodal areas above and below the diaphragm
	All primary intrathoracic tumours (mediastinal, pleural, thymic), all extensive primary intra-abdominal disease; all paraspinal or epidural tumours regardless of other sites
IV	Any of the above with initial CNS or bone marrow involvement

abdominal complications; and (3) complete removal of localised disease but with the exclusion of any heroic surgery.

Secondary surgery is also indicated for patients who still have a residual mass after induction therapy. A necrotic mass is found in two thirds of these patients but residual viable tumour is an indication for intensification of chemotherapy [17].

A role of radiation therapy to prevent local relapse was advocated by the Children's Cancer Study Group in 1984 [45] but has not been confirmed by more recent studies [46]. Moreover, late sequelae may be expected and local radiation is no longer part of treatment, except in some cases of cord compression (although even in this situation chemotherapy is usually effective [47, 48]).

RATIONALE FOR CHEMOTHERAPY

Local control is a minor problem in the treatment of BL, since one third of relapses are local, one third occur in the CNS and the rest are multiorgan. Standard treatment for advanced BL comprises a specific anti-B-cell multiagent chemotherapy, with CNS prophylaxis.

The COMP 4 drug regimen, including vincristine, cyclophosphamide, doxorubicin and prednisone, was the first step in specific treatment of B-cell as opposed to T-cell proliferations [45, 49]. In 1980 such a combination resulted in a 90% cure rate in stage I and II BL, and was accepted as the standard regimen. However, this regimen and other similar combinations [46, 50] gave poor results in advanced disease with only 40% and 32% cure rates, respectively, in stage III and IV [50]. Recently, the objectives have been to minimise the incidence of CNS relapse and to introduce additional agents (cytarabine, etoposide and high dose methotrexate [HDMTX]) in order to overcome drug resistance [50].

The use of cranial irradiation (18–24 Gy) and intrathecal therapy reduced the frequency of isolated CNS relapse to 15% [40, 41]. The secondary endocrine and neurological sequelae induced by cranial radiation prompted the SFOP group to demonstrate that HDMTX without additional radiation was able to reduce CNS relapse to 1% in a group of 114 consecutive stage III–IV BL patients [17]. Long-term follow-up studies are needed to detect possible late effects of HDMTX but chemotherapy alone is now the standard therapy to avoid CNS relapses in BL.

Using intensive pulsed chemotherapy, including HDMTX, several groups are now reporting cure rates of 60–80% in patients with extensive disease [17, 21]. Results are equivalent for patients with stage III or IV without CNS involvement (75% disease-free survival). In these good risk patients, shortening of treatment regimen from 12 months to 4.5 months did not reduce effectiveness [17, 51, 52].

Children with initial CNS disease and bone marrow involvement, have a 20–30% cure rate even with a modern regimen [17, 19, 21]. Craniospinal radiotherapy and consolidation, with pulses of high dose cytarabine was recently reported by the SFOP group with a 75% disease free survival rate [22] which compares favourably with the results achieved by massive therapy (etoposide and melphalan [BACT] or BEAM) with autologous bone marrow rescue [53].

Patients with histologically documented residual tumour after 4 courses of chemotherapy have had their outcome dramatically improved with elective intensification of chemotherapy followed by autologous bone marrow rescue, leading to a 70% cure rate as reported by the SFOP [54].

Studies are underway to assess if the speed of initial response is a predictive factor of subsequent further outcome (SFOP LMB 89 study).

MANAGEMENT OF RELAPSES

During the 1980s, three questions were raised concerning the management of relapsing BL.

(1) May dose effect be used in BL? After the demonstration of a dose response relationship by Appelbaum using the BACT regimen [55], several alternative protocols were proposed either increasing carmustine dose [56, 57], as used in the modified BACT IGR schedule, or incorporating new agents in an attempt to reduce the toxicity of the BACT combination as proposed in the BEAM protocol [58]. The efficacy of total body irradiation has not been demonstrated in BL [53]. Moreover, the short-term toxicity (pneumonitis and encephalopathy) and the expected late sequelae are arguments against this technique for children in whom cure is expected.

(2) Which type of relapse benefits from massive therapy? Resistant relapses (patients who failed to respond to conventional chemotherapy preceding autologous bone marrow transplantation [ABMT]) may show responses but no cure. This category of patients remains an important group in which to consider phase I–II studies. By contrast, at least 25% of patients with sensitive relapses may be cured even when relapsing from modern protocols, provided such a treatment is performed without delay [59, 60].

(3) Which type of marrow rescue should be used? The choice between autologous or allogenic bone marrow transplantation (BMT) is still a matter of debate. The possible contamination of the bone marrow by malignant cells is an argument for allogenic BMT when a donor is available. However, recent reports have demonstrated the efficiency of immunomagnetic depletion to remove tumour cells from bone marrow [61]. The antileukaemic effect of graft vs. host disease as seen in leukaemia is not demonstrated in lymphomas although recent reports from Chicago and Seattle may renew interest in allogenic transplants [62, 63].

One challenge for the 1990s will be to increase salvage rates

in previously heavily treated patients. Trials are under study to evaluate new combination of alkylating agents and the possible value of adjuvant immunotherapy in this setting.

Burkitt's lymphoma in adults, specially in young adults, does not differ from that in children. The use of B-cell type protocols in adults has dramatically increased survival in the past five years [64]. Treatment of adults with the French SFOP pediatric protocol produces a 70% long-term survival in stage III and IV patients (T.P. *et al.*) Future progress in adults will come with a more general acceptance of learning from the paediatric experience.

Burkitt's lymphoma has become a curable disease in more than 80% of the patients. Further advances in management will include avoiding the use of toxic drugs such as alkylating agents in good prognosis groups to prevent sterility and secondary malignancies, and early detection of bad risk patients who may require either high dose chemotherapy with marrow rescue and/or immunotherapy. There is, however, still a gap between the advances made in the basic science of this disease and patient management. Clinical application of fundamental discoveries should come in the near future and we expect BL to continue to be a unique model in clinical oncology.

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