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INVITED REVIEW ARTICLE

Burkitt Lymphoma: A potentially curable childhood tumour: Experience in Ile-Ife, Nigeria (1986-2014)

Durosinmi MA*

Department of Haematology and Immunology, Obafemi Awolowo University Teaching Hospitals Complex (OAUTHC), Ile-Ife, Nigeria

Abstract

Background: Burkitt lymphoma (BL) is the commonest tumour among Nigerian children. It is reported to be highly responsive to readily available cytotoxic drugs; yet, the outcome of therapy remains abysmal.
Objectives: To review the epidemiology of BL in terms of risk factors, age incidence, regional distribution, disease sub-types, examine the available treatment regimens locally and internationally and report on the outcome of treatment in Nigeria under different conditions.
Methods: A comprehensive literature review on the epidemiology of BL was undertaken and results of publications and clinical trials of BL were evaluated.
Results: Three major sub-types of Burkitt lymphoma are recognised in the world literature; the classic endemic BL (eBL) in sub-Saharan Africa, EBV-independent sporadic BL (sBL) found in population outside the endemic areas and the HIV-related BL (HIV-BL), which is found in regions with high incidence of HIV infection. All the sub-types have common cytogenetic abnormalities: t (8, 14), t (8, 22), and t (2, 8). The COM regimen incorporating cyclophosphamide, oncovin and methotrexate (with the intrathecal cytarabine and methotrexate), was found to be very effective for eBL. Treatment outcome was dismal for the self-financed patients treated with COM regimen between 1986 and 2000 (Group A) compared to the internationally sponsored patients treated between 2000 and 2014 (Group B). While 16.8% of Group A patients had no chemotherapy, 9.8% were lost to toxic deaths and 88% defaulted; most of the patients in group B had full chemotherapy; the Event-Free Survival (EFS) rates at 12 and 24 months were 58.3% and 53.4%, respectively.
Conclusions: COM regimen with intrathecal cytarabine and methotrexate is very effective for eBL.

Keywords: *Burkitt lymphoma, Cyclophosphamide, Intrathecal, Methotrexate, Oncovin*

Introduction

Burkitt lymphoma (BL) was first reported by Denis Burkitt, as a sarcoma of the jaws among 38 Ugandan children who presented with an invariably fatal tumour with distinct clinical features in 1958; the children were aged 2-14 years with 79% between 2 and 7. [1] BL is the fastest growing tumour known to man, with a doubling time of about 24 hours and a growth potential of 100%. The tumour is executively sensitive to chemotherapy and it has been found to be potentially curable with combination cytotoxic agents incorporating non-cross resistant drugs

*
Correspondence
Department of Haematology and Immunology
Obafemi Awolowo University
Ile-Ife, Nigeria.
Telephone: +2348033298205
Email: **mdurosin@gmail.com**

Epidemiology

There are two major subtypes of BL; the African or endemic BL (eBL), which is typically found in malaria-holoendemic sub-Saharan equatorial Africa and Papua New Guinea and the sporadic BL (sBL) found in other populations. The emergence of HIV/AIDS pandemic in the early 1980s brought

with it the 3rd subtype, AIDS-related BL (HIV-BL), which is very rare in childhood eBL. [2] BL is considered an AIDS-defining malignancy in the non-endemic zones of Europe and North America, where it accounts for about 20% of AIDS-related lymphomas, compared to less than 5% in the eBL zone of equatorial Africa. [3 - 5] The clinical features of AIDS-related BL are similar to those of sporadic BL: peripheral lymphadenopathy, abdominal disease and bone marrow involvement. The higher incidence of HIV/AIDS in the BL endemic zones of tropical Africa has not translated to a higher incidence of the tumour in the population, [6] probably because BL is not normally associated with immunosuppression. [5] The incidence of BL associated HIV/AIDS in Ile-Ife, Nigeria, since the routine screening of BL for AIDS viruses started in 2004, was only 0.9%. That was a 2-year old boy whose mother was found to be seropositive for the virus in his pregnancy (unpublished).

Risk Factors

Early exposure to the ubiquitous Epstein-Barr virus (EBV), a DNA herpesvirus is believed to be a major risk factor in the pathogenesis of eBL, where over 95% of cases are EBV-related. EBV is less common in the other subtypes of the tumour, 40-50% and 10-20% in HIV-BL and sBL cases respectively. [4, 7, 8] The tumour cells in all EBV-associated BL express Epstein-Barr virus nuclear antigens (EBNA1) and some other non- coding viral RNAs. [4, 7] In African BL, chronic lymphocytic proliferation by the persistent *P. falciparum* challenge and early exposure to EBV infection play significant roles in the pathogenesis of the tumour. [2]

In all subtypes of BL, with or without EBV antigen, lymphomagenesis is driven by similar chromosomal translocations, in which the c-myc proto-oncogene on the long arm of chromosome 8 is translocated to one or other of the regulatory immunoglobulin genes, such as the heavy chain locus on chromosome 14 (IGH) [t(8;14)(q24;q32)] in over 80% of cases., Less commonly, kappa light chain gene on chromosome 2 [t(2;8)(p11;q21)] is involved in 15% or the lambda light chain on chromosome 22 [t(8;22)(q24;q11.2)] in about 5% of cases. [2, 9, 10] There is deregulation of the c-myc protein, the tumour cells are activated and remain permanently in the cycle, such that all the living tumour cells can be labelled with a proliferation marker such as Ki67, giving a labelling index of 100%. [11] Lenze and colleagues recently showed that the three BL sub-types share very similar microRNA (miRNA) profile that is totally different from the miRNA signature for diffuse large B-cell lymphoma (DLBCL). [12] Rare familial cases of BL affecting first-degree relatives have been reported in sub-Saharan Africa. [13]

Incidence

The highest incidence of BL, 10 per 100,000 children aged less than 15 years of age, is found in tropical rain forest of Africa. BL is uncommon in children from high socio-economic class living in endemic areas and it is rare in people living in highland areas more than 1550m above sea level. [14] Endemic BL is typically a disease of children, where it accounts for 30-60% of childhood malignancies. [15 - 17] The age incidence of this tumour in Nigeria is 3 to 45 (median, 9) years. Endemic BL is rare in children below age two years and above 15 years. [2, 14, 16 - 19] Outside the endemic zones, the incidence of the disease is much lower; only about 0.2/100,000 in the western world. [19]

Older children and younger adults are the targets for sporadic disease seen in the Western world, with a median age of 33 years (range: 18–76); [19] the oldest in the Ile-Ife series was a 45-year old female nursing officer, who was successfully treated with the common COM regimen and she remains disease free since 1988. [21] Rare cases of BL have been documented in patients in their 7th decade of life. [19] The male-to-female ratio in BL is 2-3 to 1 in both endemic and sporadic cases. [18,19]

Clinical features

Clinically, childhood eBL presents with tumours involving essentially the jaws, abdomen, pelvis, and the orbit at relative frequencies of 60.7%, 55.6% and 20.8%, respectively. [15, 19] Other uncommonly affected sites include the central nervous system (CNS), peripheral nodes (20.8%), kidneys and bone marrow (20.2%). As high as 90.9% of the patients had BL affecting multiple sites at presentation. [22] Jaw tumours are rarely seen among children over 15 years and adults (Table I). [15, 22] Bone marrow,

intestinal tract and leptomeningeal disease occur commonly in both eBL and sBL. [18, 20, 22] BL-related orbital tumours are major causes of childhood blindness and 6th and 7th cranial nerve palsies. [23]
The majority of BL patients present with swellings of the affected jaw or other facial bones, with the loosening of the teeth and distortion of dental anatomy; abdominal mass, CNS disease, notably cranial nerve palsies and paraplegia. BL affects virtually any organ with the exception of the lungs. Very rarely, BL presents as acute lymphoblastic leukaemia (L3-ALL), a very notorious leukaemia with poor response to conventional anti-ALL medications.
Immunophenotypically, BL cells express B-cell associated surface antigens such as CD19, CD20 and CD77. The tumour cells are uniformly negative for Terminal deoxynucleotidyl transferase (TdT) and CD34, but there is moderate to strong expression of kappa specific surface membrane IgM, confirming the maturity of the B-lymphocytes. There is a strong expression of germinal centre markers such as BCL-6 and CD10 but BCL2 is absent or only weakly positive. Almost 100% of the BL cells express the proliferative antigen, Ki67/MIB1. [24]

Tumour Diagnosis

Correct diagnosis of BL is mandatory for cost effective treatment outcome. Tumour cell morphology is central to disease confirmation:

(a) With fine needle aspiration cytology biopsy (FNACB) of the easily accessible tumour stained with Romanowsky stains, such as Leishman's, Burkitt cells would show as large monomorphic lymphoblasts with distinct nucleoli, abundant deeply basophilic and vacuolated cytoplasm.

(b) Histopathology slides of tumour biopsy (and touch preparation or tumour imprint) stained with Haematoxylin and Eosin (H & E) would typically show homogeneous sheets of lymphoblasts, with the round to oval nuclei, slightly coarse chromatin, multiple nucleoli, and intensely basophilic vacuolated cytoplasm containing neutral fat. The homogenous appearance is interspersed with scattered macrophages, with ingested apoptotic and necrotic tumour cells, giving the characteristic "starry sky" appearance (at low magnification). There are frequent mitotic figures.

(c) FNACB is most frequently employed in our practice because of its low cost and simplicity as well as the tendency to engender immediate disease confirmation (under 1 hour) and facilitate early commencement of therapy. [15, 18] Morphology can be complemented with *Ki67, BCL6 and BCL2* histochemistry. ***P***ositive cytology with at least 90% Ki67 and negative BCL2 staining reaction is confirmatory. [25] When available, tumour cell karyotyping for the characteristic cytogenetic abnormalities and microarray profiling are more advanced complementary diagnostics. [19]

Cerebral Spinal Fluid Examination

A number of BL patients present with asymptomatic CNS disease manifesting as malignant CSF pleocytosis, which is confirmed from the CSF usually obtained when administering the first dose of intrathecal cytotoxic therapy. However, clinically evident CNS complications manifest more often in relapse. CSF tumour cells are best demonstrated by cytologic examination of CSF in a cytospin, cell count should be performed and the CSF protein and glucose should be quantified.

Pre-therapy Physical and Laboratory Assessment of Patients

Successful treatment of BL is driven by an accurate assessment of presenting physical abnormalities based on physical examination, including accurate measurement of patient's height, weight and the sizes of all palpable tumours. The results of laboratory tests and radiological investigations must be noted for tumour evaluation.

Laboratory evaluation

These should include:

(I) Complete blood count (CBC), incorporating

the leucocytes and differentials, platelet count, Hb concentration and PCV

(ii) Blood chemistry which includes electrolytes with calcium and phosphates, uric acid, the renal panel including creatinine and blood urea nitrogen and the liver function tests with alkaline phosphatase, transaminases (SGOT/SGPT) and total bilirubin.

(iii) Serum lactic acid dehydrogenase (LDH), an important measurement of tumour load and prognosis

(iv) Total protein and serum albumin

(v) Transmissible viral screening (with consent) including hepatitis and HIV/AIDS viruses

(vi) Blood group type and Haemoglobin electrophoresis, and

(vii) Urinalysis

(viii) Bone Marrow examination for the confirmation of bone marrow disease which was recorded in about 20% of the Ile-Ife series (Table I)

Table I: Burkitt lymphoma and Patients Characteristics by Period of Enrolment

Characteristics	*Group I [1986-2000; n = 214]*	*Group II [2004-2014; n = 88]*	χ^2	*p-values*
Age range (y; median)		2 – 30; 8		
< 15years (n; %)	186; 86.9	81; 92		
≥15 years (n; %)	28; 13.1	7; 8	1.60	0.206
Gender (n; %)				
Female	77 (36)	31 (36)		
Male	137 (63)	57 (64.8)	0.02	0.901
M:F	1.8:1	1.8:1		
Tumour Stage (n; %)				
A	28 (13.1)	5 (5.7)		
B	24 (11.2)	2 (2.3)		
C	92 (43.0)	45 (51.1)		
D	70 (32.7)	36 (40.9)	11.025	0.012
Drug Cycles (n; %)				
0-2	112 (52.3)	20 (22.7)		
3	21 (9.8)	12 (13.6)		
4-6	73 (34.1)	55 (62.5)		
≥6	08 (3.7)	01 (1.1)	26.61	0.000
Tumour sites				
Abdomen	95 (44.4)	47 (53.4)		
Jaw	71 (33.2)	17 (19.3		
Abdomen + Jaw	43 (20.1)	17 (19.3)		
Orbit	11 (5.1)	06 (6.8)		
Kidneys	24 (11.2)	13 (14.8)		
	55 (25.7)	13 (14.8)	9.22	0.101
Bone Marrows	11 of 57 (19.3)	22 of 84 (26.2)	0.56	0.454
Ovaries	10 of 137 (5.8)	4 of 31 (12.9)		0.271
Testes	8 of 137 (5.8)	8 of 57 (14)		0.079
Breast	2 of 77 (2.6)	1 of 31 (3.2)		1.000

$p < 0.05$ is statistically significant

Radiological and Imaging Tests

The required imaging studies include the following:

(i) Plain X-ray of the skull (Postero-anterior [PA] and lateral views) for the demonstration of jaw and orbit lesions and loss of lamina dura

(ii) Chest X-ray (PA and lateral views)

(iii) Complete abdominal and pelvic ultrasound for the demonstration of the integrity of the liver, spleen, ovaries and identification of any other abdominal structures.

Disease Staging at Diagnosis

Tumour stage is, by far, the most important determinant of disease prognosis in BL. Other prognostic factors include chemotherapy regimen, relapse type and quality of supportive therapy, poor performance status, bulky tumour, high LDH, CNS and /or bone marrow disease. [26, 27] The number of chemotherapy courses administered to each patient is based on the tumour load (clinical stage) as shown in Table II.

Table II: Staging of Burkitt lymphoma

	Staging Description
A	Single extra-abdominal tumour
AR	Intra-abdominal tumour with > 90% of tumour surgically resected
B	Multiple extra-abdominal tumours, excluding bone marrow (BM) and /or CNS disease
C	Unrespectable abdominal tumours without BM and CNS disease, but regardless of other sites
D	Any of the above with BM and/or CNS disease

Patients may be simply stratified into two risk groups: (a) Low-Risk: A single extra abdominal tumour less than 10 cm in its widest diameter and (b) High-Risk: Disease stage beyond the definition of low-risk disease. [15]

Differential diagnoses

BL needs to be differentiated from other childhood tumours with similar histologic appearance under H & E sections including the small, blue, round cell tumours or small, round-cell tumours such as acute lymphoblastic leukaemia (ALL), granulocytic sarcomas in acute

myeloblastic leukaemia (AML), diffuse large cell lymphomas and lymphoblastic lymphoma. Childhood abdominal tumours (such as rhabdomyosarcoma, neuroblastoma and nephroblastoma [Wilms tumour]) and some jaw tumours such as ameloblastoma and dentigenous cysts may also mimic BL.

Treatment

The biologic characteristics of BL cells require sequential administration of regimen incorporating non-cross resistant, short-duration cytotoxic drugs such as cyclophosphamide (CPM) and the cell cycle phase-specific drugs such as methotrexate (MTX), cytarabine (ara-C) and vincristine (VCR). The use of these drugs in the treatment of BL has been associated with considerable success, even as single agents. [19] Intrathecal methotrexate and cytarabine with or without hydrocortisone are administered as prophylaxis or for the treatment of CNS disease. At the Makerere University in Uganda, John Ziegler and his group pioneered the early clinical trials on the treatment of eBL starting with CMP alone. [28] In that series, complete response (CR) rate of 81% was achieved among the 186 patients enroled and those that relapsed were successfully re-induced with additional CMP, or a combination of MTX, ara-C and VCR.

However, cytoxan, oncovin and methotrexate combination, the COM regimen, was noted to be better associated with durable remission than any single agent. This observation led to its recognition and adoption, especially when administered together with intrathecal MTX and ara-C for CNS disease, as the foremost initial therapy for eBL. [19, 26 – 28]
The pioneering trial of Williams and colleagues, at the UCH, Ibadan Nigeria, in the early eighties supported the efficacy of COM regimen as a clinical remission (CR) rate of 67% was achieve and the projected 12-month survival was 44%. [29] Subsequent rather disappointing reports on COM regimen from across the country, including Fasola and colleagues in Ibadan, obtaining a CR of 22.8% in 2002, [30] Oguonu and colleagues in Enugu reporting CR of 48%, [31] and Kagu and group in Ife who obtained CR of only 23.9% [18] with none of the patients in the reports living up to 12 months post-therapy. [18, 30, 31]

The poorer treatment outcome with COM regimen obtained in the published studies from Nigeria, [18, 29 – 32] compared to earlier publications from East Africa, [19, 26 – 28] could possibly be attributable to inadequate exposure of patients to chemotherapy and supportive care rather than

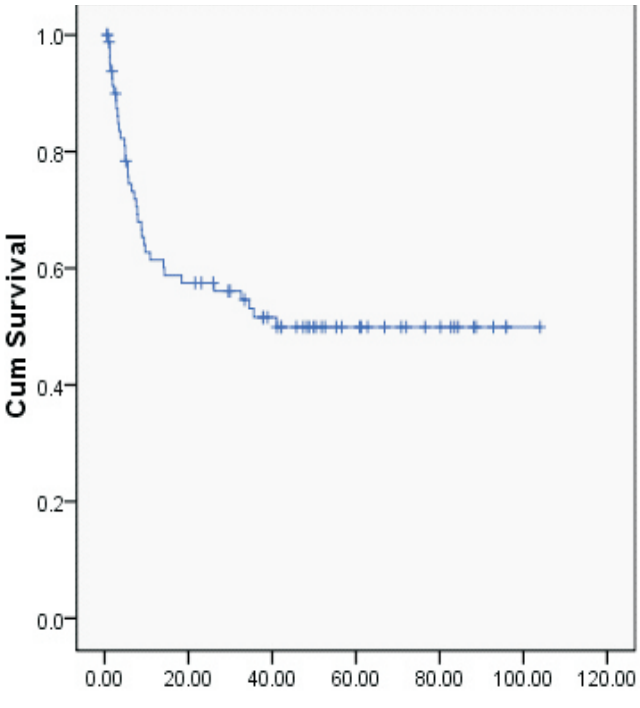

Figure 1: Endemic Burkitt Lymphoma Treatment in Ile-Ife OS for Group II Patients in Months since Commencement of Chemotherapy

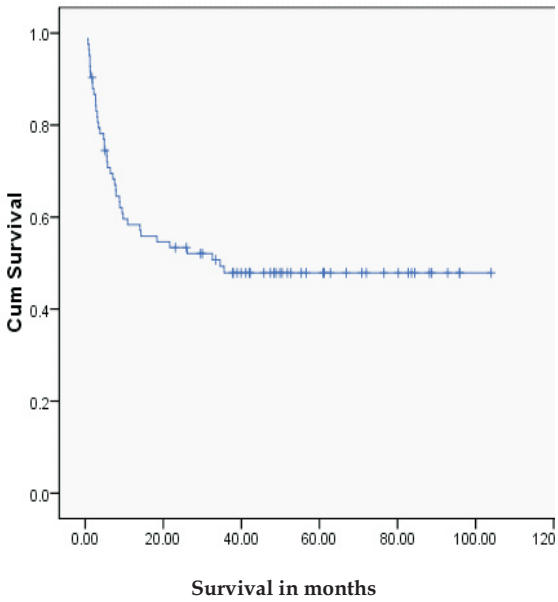

Figure 2: Endemic Burkitt Lymphoma Treatment in Ile-Ife EFS for Group II Patients in Months since Commencement of Chemotherapy

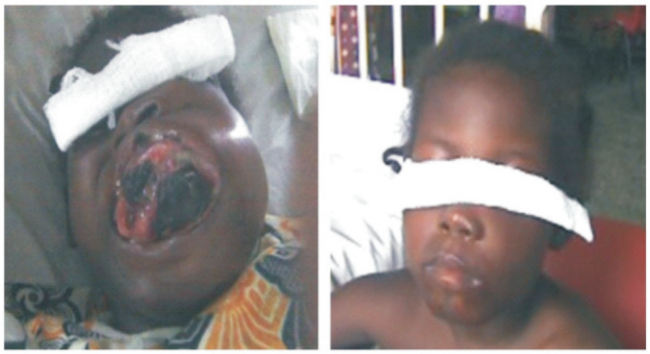

Figure 3: A female child with facial Burkitt Lymphoma before and 14 days after Chemotherapy

the ineffectiveness of the medications. This hypothesis was confirmed when the survival reports of the two groups of Nigerian patients with eBL who had similar clinical presenting features (Groups I & II) (Table I) exposed to COM induction as primary therapy under different conditions, were compared. The self-sponsored Group I patients (n = 214, median age of 9 years and male-to-female ratio of 1.8:1) managed between 1986 and 2000 had a CR of 31.7% with default rate of 88% after a median follow-up period of 2.4 (0.1-66.8) months and only 4 survivals after a median follow-up period of 61 (6-164) months post therapy. Computation of the Overall Survival (OS) was not feasible in this group because of the high default rate. The details of these findings had earlier been reported. [18]

Group II patients (n = 88, a median age of 8 years

Table III: Burkitt Lymphoma Treatment Regimens for Group I (19862000)

Drug	*Dosage*	*Route*	*Days*		*Number of Patients (%)*
CTX	1 g/m²	IV	1	COM	117 (54.7)
VCR	1.4mg/ m²	IV	1		
MTX	45mg/ m²	IV	1		
Plus				COM	59 (27.6)
Prednisolone	40mg/ m²	PO	1-5		
Intrathecal (IT) Prophylaxis					
MTX, Or	12.5mg/ m²	IT	1 & 5		
Ara-C	50mg	IT	1 & 5		
Patients with confirmed CNS Disease					
MTX	12.5mg/ m²	IT	1 & 5		
Ara-C	50mg	IT	1 & 5		
Hydrocortisone	25mg	IT	1 & 5		
Second-Line Treatment, 4-6 cycles of 29-day APO Regimen					
A	**75mg/m²**	IV	1 & 29		
P	**40mg/m²**	PO	1-29		
O	**1.4 mg/m²**	IV	**1, 8, 15, 22 & 29**		

Key: Adriamycin -A, Prednisolone -P, Oncovin -O

Table IV: Burkitt Lymphoma Treatment Regimens for Group II 2004-2014

Drug	*Dosage*	*Route*	*Days*
CTX	1 g/m²	IV	1
VCR	1.4mg/ m²	IV	1
MTX	75mg/ m²	IV	1
Low-risk: **3 cycles of 14-day Regimen, each with IT Prophylaxis**			
High-risk: **No CNS disease, 6 treatment cycles, first 3 with IT therapy. Plus CNS disease, 6 treatment cycles All with IT therapy.**			
MTX, Or	12.5mg/ m²	IT	1 & 5
Ara-C	50mg	IT	1 & 5
Patients with confirmed CNS Disease			
MTX	**10 mg (≥ 2 < 3 yr); 12 mg (≥ 3 yr)**	IT	1 & 8
Ara-C	40 mg (≥ 2 < 3 yr); 50 mg (≥ 3 yr)	IT	4
Second-Line Treatment, 4 cycles of 21-day Regimen			
ETOP	60 mg/m²	IV	1-3
IFOS	1500 mg/m²	IV	1-3
Mesna	300 mg/m² x 4	IV	**1-3**
Ara-C	100 mg/m²	IV	1-3
IT Therapy			
MTX	Per First-Line	IT	1 & 8
Ara-C	Per First-Line	IT	1 & 8

and a male-to-female ratio of 1.8:1) managed under an internationally sponsored multicenter clinical trial gave an impressive CR of 80.7%. The OS of this cohort of patients was 61.4%, 57.5% and 51.6% at 12, 24 and 36 months respectively (Figure 1). The Event-Free Survival rates were also encouraging with 58.3%, 53.4% and 47.9% at 12, 24 and 36 months respectively (Figure 2). Patients surviving two years were assumed to be cured, because BL relapse is unusual after 12 months of disease-free survival. [33] The full details of these observations had previously been reported. [15] Figure 3 shows a girl child with facial eBL before and at day-14 of the first cycle of COM Regimen.

The major reasons for the very poor survival of the patients in the Ile-Ife series include inadequate exposure to chemotherapy, [18, 29-32, 34] adulterated or substandard medications, [30] very high default rate, [18] and drug resistance and the involvement of the sanctuary disease sites including the CNS and testicles. [35] Group I fell into the latter class; not only were the regimen components unstandardised (Table III), the drugs were given only when available.

The impressive treatment outcome obtained for Group II patients, was due to a combination of positive factors including the standardisation of chemotherapy (Table III), as compared to Group I (Table III), ready availability of chemotherapy, availability of appropriate supportive care and availability of facilities for efficient patient follow-up (Table I). [15]

Tumour Lysis Syndrome (TLS)

Tumour lysis syndrome is a major life-threatening metabolic complication of chemotherapy for BL due to the rapid destruction of tumour cells. It is characterised by hyperuricaemia, hyperkalaemia, hyperphosphataemia, hypocalcaemia and acute renal failure. TLS is preventable using strategies such as pre-therapy hydration and allopurinol therapy, at least 24 to 48 hours before initiating chemotherapy. These measures are continued until the tumour load reduces to 75% or less. Urine flow should be maintained at 1.5 $L/m^2/24$ hours. BL cases who present with primary renal disease should be carefully managed to prevent TLS-related fatal acute kidney injury. [36]

Salvage Therapy for Unresponsive or Relapsed cases

For patients unresponsive to the traditional COM regimen, (such as occurs in primary resistance), relapse occurring within the first 3 months of achieving initial CR and patients presenting with multiple relapses, the more apparently highly aggressive drugs are employed as salvage therapy with good treatment outcome. Such medications are usually used as the primary therapy for adult BL commonly seen in the Western world. Unfortunately, these medications are not very suitable for cases in the tropics because of the associated risk of drug-related morbidity and mortality. Williams at the UCH, Ibadan, in the early eighties prior to the era of Growth factors, tried the use of high-dose cytarabine for eBL with some degree of success. [32] In the Ile-Ife series, the second line regimen used for Group II patients included ifosfamide (and mesna) and etoposide (Table IV). [15] A very effective regimen developed for adult BL therapy is CODOX-M/IVAC regimen (cyclophosphamide, vincristine, doxorubicin and high-dose methotrexate alternating with ifosfamide, etoposide and high-dose cytarabine, along with intrathecal methotrexate and cytarabine), which is associated with 90% cure rate. [35] Addition of rituximab to therapy has been shown to further improve the survival of cases. [35] Highly aggressive cytotoxic medications should be used with great caution in our clime; the provision of adequate supportive care including growth factors would need to be guaranteed.

Conclusion

Endemic BL is now a potentially curable tumour, with careful use of combination COM regimen and intrathecal methotrexate and cytarabine. Genuine and cheaper generic formulations of the chemotherapeutic drugs are available. There is no place for single agent use as primary induction therapy for eBL. It is conceivable to conclude that with political will and efficient supportive therapy, BL is no longer life-threatening cancer as it was some few years ago.

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