

were alive and significantly more had died or defaulted than the non-KS patients.

Between 1 January and 31 March 2005, 4580 patients started ART-326 (7%) with a diagnosis of KS and 4254 with another non-KS diagnosis. The 12-month cohort outcomes of KS and non-KS patients censored on 31 March 2006 are also shown in Table 1. At 12 months, significantly fewer KS patients were alive and significantly more had died or defaulted compared to non-KS patients.

Discussion

In both quarters, between 5–10% of patients starting ART were placed on treatment because they had KS. The proportion of KS patients alive at six-months and 12-months was significantly lower compared to other non-KS patients: this was due to higher death rates and default rates. Default means loss to follow-up, and unpublished data suggest that a large percentage of defaulters are, in fact, patients who have died. Despite these inferior results, over half the patients with KS and on ART were still alive one year after commencing treatment.

This was an operational study conducted within the routine system and therefore has all the limitations of this type of research. Data were not collected on the demographic characteristics of patients, the extent of disease (which has been shown to influence prognosis),³ or HIV – or drug-related morbidity or causes of death. We also have no information about how many KS patients received their vincristine. There was a general shortage of the drug in country during the latter half of 2005, with 35% of ART facilities having completely run out of stock of vincristine between July and September 2005 (source: HIV Unit, Ministry of Health, Malawi). However, the strengths of the study were that it was countrywide, the routine systems for monitoring patients using master cards and registers are robust and regularly checked by supervising teams, and we believe that the results are reliable and representative. The use of six-month and 12-month quarterly cohort analysis is now well established and enables survival analyses to be carried out as part of the routine system. For busy ART facilities and supervising teams with scarce human resources, individual patient survival outcomes are too time-consuming to carry out. Cohort survival analysis, however, is quick and reliable provided the registers are regularly updated.

There are many aspects that require further assessment. In particular, treatment outcomes in the routine setting need to be analysed in relation to (1) the staging of AIDS-KS, particularly bulk of the disease, pulmonary involvement and systemic illness and (2) the usefulness of prior and continuation treatment with cytotoxic chemotherapy with either vincristine or bleomycin (the latter given by intramuscular injection which is easier to administer). However, in resource-poor countries there are always going to be difficulties in procuring and accessing cytotoxic drugs. It is therefore necessary to identify KS patients earlier in the disease when ART on its own is likely to provide significant benefits in terms of reducing the bulk of disease and improving long-term survival.

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Current investigations and treatment of Burkitt's lymphoma in Africa

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SUMMARY We reviewed the scientific literature on Burkitt's lymphoma (BL) in Africa in order to provide information on the current status of clinical care and the existing research challenges. BL epidemiology led to the discovery of the Epstein Barr virus, an important cause of several viral illnesses and malignancies. The incidence of BL

has increased in the endemic areas of Africa, overlapping with the epidemic of HIV and increase of malaria. The impact of this on the clinical care of BL in the region is therefore of interest, especially in HIV-infected children. Rapid methods must be developed which enable the correct diagnosis to be made. It is important to improve supportive care to allow fairly aggressive treatment, to research into salvage therapy for those who fail first-line treatment, and to develop less toxic drug combinations for HIV-infected patients. Documentation of HIV status through counselling should be offered to all patients.

Introduction

Burkitt's lymphoma (BL) was described more than five decades ago by Dr Denis Burkitt, a British surgeon at Mulago Hospital in Kampala.¹ Over recent years the incidence of BL has increased in endemic areas of Africa, overlapping with the HIV epidemic and malaria in the region.^{2,3} This review aims to describe the current status of the clinical care of patients suffering from the disease in the region focusing on diagnostic investigations and on the treatments which are available. We also try to identify new areas of research and interventions to address the challenges.

Over view of variants of BL

BL clinical variants

There are several forms of BL described according to geographic distribution, risk factors, immunology and molecular markers (Table 1). Endemic BL (eBL), the disease originally described by Burkitt, is largely found in Africa. Sporadic BL (sBL) is the form subsequently described outside Africa, but it is morphologically similar to eBL. A third subtype of BL is found in association with HIV infection. Although the disease has been well described in the developed world and is known to occur in HIV-positive adults in Africa, not much has been published about the characteristics of the form of this disease, which is found in HIV-positive children in Africa.

Clinical characteristics

The unifying characteristic in all patients with BL is the unique morphology and the chromosomal translocation involving the Myc oncogene, irrespective of geographical location and immunodeficiency status. In this region eBL is the predominant subtype of BL, presenting as jaw swelling in 72%, abdominal tumours in 56% and as central nervous system tumours as a primary presentation in 30% of cases. Children aged between two and nine years typically have the characteristic facial skeleton shown in Figure 1.

Presentation with lymphadenopathy is common, and systemic presentation has been described. Acute leukaemia, unusual tumour sites and dissemination are often seen.⁴

Diagnosis of BL in Africa

BL is the fastest growing tumour known, with the tumour doubling in size within 24 h (the hallmark of an aggressive disease). This calls for an accurate and reliable diagnostic process. Despite the typical clinical features exhibited by the disease in Africa (Figure 1), accurate diagnosis still rests with tissue examination as standard for the diagnosis of non-Hodgkin's lymphomas.⁵ The methods commonly employed in obtaining tissue for diagnostic purposes include:

- Excisional biopsy;
- Cytological methods such as touch preparation, fine needle aspiration (FNA);
- Centrifuge of body cavity fluids.^{6,7}

Each of these procedures has its advantages and disadvantages depending on the circumstances which are often dictated by the clinical setting. Excisional biopsy has the merit of providing sizeable tissue samples for histology and allowing for further advance tests such as immunohistostaining. It also allows for the storage of pathological material which may be useful for a later review.⁵ The disadvantage is that there is a need for surgery, which may take time to organize and which requires skills that may not be available. Further, patients must present early and in very good general

Table 1 An overview of clinical features of BL clinical variants

| Characteristics | eBL | sBL | HIV associated BL |
|-------------------------------|--|---|---|
| Clinical presentation | Facial skeleton (50%) Central nervous system (33%) Other organs also affected | Abdominal, ileo-caecal (80%) Bone marrow (20%) Other organs also affected | Organ and nodal presentation |
| Pathology/morphology | Germinal centre B-cell Monomorphic medium sized B-cells with basophilic cytoplasm and multiple mitotic figures | | |
| Chromosomal translocations | t(8; 14) (q24; q32), 60–70%; t(8; 22) (q24; q11), 10–15%; t(2; 8) (p12; q24), 2–5% | | |
| Ig region involved | Ig heavy chain joining region (early B-cell) | Ig switch region (late stage B-cell) | Ig switch region (late stage B-cell) |
| Epstein Bar virus association | 100% | 30% | 30–50% |
| Chemotherapy | Ideally, short intensive chemotherapy should be given but currently in Africa low dose combinations are given due to lack of supportive care | Short intensive chemotherapy | Short intensive chemotherapy ^a HAART |
| PROGNOSIS ^b | Potentially very good prognosis but compromised by poor health system in Africa, Socioeconomic factors ^{16–18,20} | Very good | Poor ^c |

^aUnknown benefit

^bDependent on treatment with chemotherapy (not always available in Africa)

^cDepends on HIV not on Burkitt's itself
HAART, highly active antiretroviral therapy



Figure 1 Five-year-old boy with BL (Source: Ugandan Cancer Institute, Kampala, Uganda with permission from guardians)

health. Cytological investigations, on the other hand, can lead to diagnosis using body cavity fluids or aspirate samples from an accessible tumour mass. The accuracy of FNA in African BL has been highlighted; it has a high degree of correlation with tissue biopsy. Many centres are currently using FNA for diagnostic purposes and treatment initiation.⁸ In patients with a rapidly progressive disease, a cytological sample could be obtained by needle biopsy of an accessible mass for confirmatory diagnosis. This may be useful in HIV-associated BL, which can present as a systemic disease. In contrast, in patients presenting early, with limited disease, fewer complications and a stable general condition, an excision biopsy should be advised if the medical expertise is available. The tissue obtained from an excision biopsy is then used for touch preparation providing a guide on the initiation of therapy required while awaiting a conclusive diagnosis.⁵ In the absence of surgical expertise, the use of FNA or other cytological methods is recommended in order to reach a diagnosis.

Diagnosis based on tissue samples therefore remains the ideal. It should be the goal for future improvement in the accuracy of diagnosis together with access to advanced tests such as immunohistochemistry, flow cytometry and molecular methods. Recent studies have shown the usefulness of molecular markers and micro array technology in further refining the diagnosis of BL.⁹

Staging of BL

Another management challenge in BL in Africa is that of staging. The basic evaluation of BL for staging should include clinical evaluation with medical history, physical examination and tumour measurements, supplemented by imaging studies (X-rays of the jaw, chest X-ray) and abdominal ultrasound. For staging purposes laboratory investigations should include complete blood counts, bone marrow aspirate with or without biopsy, cerebrospinal fluid analysis, blood chemistry (liver function tests, renal function tests), lactate dehydrogenase and uric acid and electrolytes. Routine stool and urine examinations should also be done. Voluntary counselling and testing for HIV is advisable for all patients. The

determination of the degree of immunosuppression as shown by CD4 count should also be included where feasible. The staging system designed by Zeigler has stood the test of time and is widely used in the eBL areas of Africa, despite its limitations which have been highlighted in the review by Magrath.¹⁰ The staging system has some merit: it is very easy to apply in resource-poor settings since the basic assumption is that the primary site involved in BL is the face. Challenges to the applicability of the staging system still remain, particularly in low-incidence areas such as North Africa, where the disease presents mainly with abdominal features. A new challenge to the staging system is its usefulness in diagnosis HIV BL, which may present as systemic disease.¹¹ Any new staging system would need to take these challenges into consideration.

Treatment of eBL

Initial successful clinical trials in Africa of the treatment of BL were fundamental to the rapid strides in treatment of malignancies using chemotherapy.¹² The conclusion of over 20 y of studies was mainly that BL is a curable disease with a favourable long-term outcome. The disease is highly sensitive to chemotherapy as single agents or in combination. The favourable response in African patients was also achievable in BL outside Africa. Finally, the presence of central nervous systemic disease does not necessarily lead to a poor outcome even in late stage disease, since intrathecal therapy and prophylaxis are effective in improving outcome.^{13,14} In a long-term follow-up study by Olweny a complete response rate of 81% was observed after a 10-year follow-up: factors influencing remission duration and survival were the stage at which the disease was presented and the protocol used.¹²

These findings have been the backbone of practice in Africa for over 30 years. However, the outcome of cancer treatment in children in general in Africa has worsened.¹⁵ The reason for this has been political instability and socio-economic changes, which have affected most countries in the region. Scant resources are allocated to health care, resulting in limited access to quality health care. Late disease presentation is prevalent due to a lack of anticancer drugs and poor compliance.^{15–18} Treatment options by the end of the 1980s with proven benefit were the single agent cyclophosphamide in multiple dosages, combination chemotherapy consisting of cyclophosphamide, vincristine and methotrexate or cyclophosphamide, vincristine and cytosine arabinoside. Intrathecal prophylaxis improves outcome when the disease has reached an advanced stage, especially in patients with malignant pleocytosis.¹⁴

The recent replication of the Ugandan experience with the cyclophosphamide monotherapy in a field situation in Malawi has led to the relaunching of studies aimed at improving the outcome of the treatment of childhood BL in Africa.¹⁹ This study has shown the long-term survival benefits of cyclophosphamide as a single agent in children with BL. Ninety-two children with a confirmed diagnosis of BL and a known disease site were treated with cyclophosphamide monotherapy over a six-year period (1991–1997). Seventy-three could be traced and 40 were alive after 59 months of initial treatment. A better survival rate was observed (63.5%) for children with facial BL compared to those with a more disseminated disease (33.3%). Survivors received, on average, six courses of treatment compared to four for non-survivors. These results validate the early findings from Uganda, further confirming that eBL remains very responsive to chemotherapy and that cyclophosphamide

monotherapy may lead to good remission induction and long-term remission in early stage disease.¹²

Overall, more than 70% of childhood cancers are now curable in developed countries when using intensive therapy combined with good supportive care. Children in Africa with cancer in general and BL in particular have not been beneficiaries of this modern treatment paradigm. This is despite evidence in earlier studies from Africa suggesting that higher dosages of treatment could achieve better responses than so far observed.¹⁴

The feasibility of using such a less intensive treatment was studied in Malawi.²⁰ A modification of the LMB89 protocol was made by reducing the dosage to an intermediate level, albeit higher than that which is the current standard combination for BL COM (cyclophosphamide, vincristine and methotrexate) combination. The end points were event-free survival at one year and marrow and gastro intestinal toxicity and risk of infection. Of 44 BL children, 34% presented with stage I and II, 66% with stage III. Event-free survival was 90% for those with early-stage disease and 52% for late-stage disease. Death during the study occurred mainly due to drug toxicity and lack of supportive care. The trend of high morbidity and mortality related to chemotherapy in this setting continued when the duration of the treatment was shortened.²¹ Dose modification may therefore lead to a good response but the high rate of relapse, high morbidity and mortality reduce the prospects of the widespread use of this approach.²⁰

Challenges of chemotherapy for BL in Africa

In Nigeria socioeconomic factors are significantly responsible for the poor outcome for children with eBL combined with late-stage disease presentation, lack of access to laboratory facilities and chemotherapy. The lack of progress in achieving a higher response rate and greater survival rates in the last 30 years has been due to an inability to administer treatment in higher doses caused by poor support systems.¹⁰ In Africa there is therefore no salvage option for patients who fail the initial therapy, especially in those with early relapse and a suspected resistance to the drugs. So far there is no appropriate protocol for the treatment of HIV-associated BL in the eBL setting. This is compounded by an absence of clear documentation of the magnitude of the problem, i.e. the incidence, clinical characteristics and treatment outcome of HIV-associated BL in African children.²² Reported observations of children with HIV treated with good outcomes should provide examples.²³ In Malawi 4% of BL patients are HIV-positive. The incidence could be higher in countries with higher rates of HIV infection. New trials are required for patients with BL who are HIV infected.²⁴

Conclusion and future direction

The increasing burden of BL in Africa combined with the epidemic of HIV requires an improvement in the level of care in the region. Though the disease presentation has not changed, a significant care gap has emerged between Africa and developed countries.

Socioeconomic factors seem to be mainly responsible for the poor outcome in Africa. It is necessary to improve diagnostic and treatment options in the region. Quick methods for diagnosis need to be developed, which do not compromise their validity. They must be based on clinical circumstances and the available expertise. There should be a concerted effort to shift the treatment of BL in Africa towards combinations that translate into clear benefit for most of BL

patients. This requires improved supportive care allowing for the use of fairly aggressive regimens in order to improve response and survival rates, and which provide for salvage therapy and the prevention of the emergence of drug resistance. Finally, documentation of HIV status with appropriate counselling should be part of the workup of patients with BL in Africa. This is more possible with the extended use of highly active antiretroviral therapy.

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Critical care management of eclamptics: challenges in an African setting

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SUMMARY We conducted a retrospective study of the management and outcome for eclampsia patients in the intensive care unit (ICU) of National hospital, Abuja between November 2001 and April 2005 (42 months). The patients' case files and ICU records were used to extract the necessary data. During the study period, there were a total of 4857 deliveries, with 5051 total births (including multiple births) and 4854 live births. Forty eclamptics were admitted to the ICU, giving an ICU admission rate of 8.2/1000 live births. The records of two patients were incomplete. The average age of the patients was 28.4 years (range 17–4 years). Six patients (15.8%) were booked and 32 (84.2%) were not. The average duration of stay in ICU was 5 days. Twenty patients (52.6%) had antepartum eclampsia, 12 (31.6%) had postpartum eclampsia and six (15.8%) presented with intrapartum eclampsia. Twenty-nine (76.3%) gave birth via caesarean section and nine (23.7%) delivered per vagina augmented by oxytocin infusion. Seventeen (45%) received mechanical ventilation; 20 (53%) received oxygen via nasal prongs, nasal catheters or variable performance facemask. One patient (2%) did not receive oxygen therapy. All the patients were admitted postpartum. There were 11 maternal deaths, giving a case fatality

rate of 29%. There were five (45.4%) deaths due to haemolysis, elevated liver enzymes and low platelet count syndrome and two (18.2%) due to disseminated intravascular coagulation. The remaining deaths were due to cerebrovascular accident (9.1%), lobar pneumonia (9.1%), acute renal failure (9.1%) and multiple organ failure (9.1%). All patients were admitted postpartum. This fatality rate is higher than that detailed in the reports reviewed in this study. Early referral of eclamptics or at risk patients to a tertiary care institution may help reduce morbidity and mortality. In addition, early referral to a facility providing basic essential obstetric care or comprehensive essential obstetric care is also important. Another important factor is the correct diagnosis of pre-eclampsia during antenatal and postpartum care by screening, noting blood pressure levels, performing urinalysis for protein and asking about warning signs such as headache, blurred vision, epigastric pain, etc.

Introduction

Eclampsia is reported to occur in about one in 2000 deliveries in the developed world.^{1,2} This varies widely in the developing world, from one in 100 to one in 1700 deliveries.³

Pre-eclampsia is defined as proteinuric hypertension developing after the 20th week of pregnancy and regressing after delivery. Eclampsia is a major complication of pre-eclampsia. Hypertension is commonly defined as blood pressure higher than 140/90.

The incidence of eclampsia in Nigeria depends on socio-demographic factors. It is a leading cause of maternal death in parts of northern Nigeria^{4,5} and a significant cause in southern Nigeria.^{6–8}

In Gombe, northern Nigeria (24.2%), eclampsia is a major cause of maternal mortality, second to obstetric haemorrhage (27.1%).⁹ In Sokoto, northern Nigeria, eclampsia and obstetric haemorrhage were responsible for 76% of adolescent maternal deaths.¹⁰ In Nnewi, in southern Nigeria, eclampsia contributed 21% to the maternal deaths.¹¹

The incidence of eclampsia has an inverse relationship to good antenatal care, improved standard of living and literacy. Eclamptics often require intensive care unit (ICU) management for organ support and higher medical care.

We undertook this study because we could find no published reviews of ICU management of this major cause of maternal mortality in West Africa (a region made up of 19 countries).

Materials and methods

We carried out a retrospective study of eclamptic patients admitted to the general ICU of the National Hospital, Abuja, Nigeria, from November 2001 to April 2005. The National Hospital, Abuja is the top tertiary care centre in the federal capital territory of Nigeria, Africa's most populous country. It is a referral centre for hospitals in the Abuja metropolis and its suburbs. Though 40 eclamptics presented during the study period, the hospitals records of two patients were incomplete. They were therefore not included in the study except when calculating the ICU admission rate.

The patients' case files and ICU records were used to extract the necessary data. Their demographics, booking status, parity, gestational age at delivery and time of the fits (antepartum, intrapartum and postpartum) were documented. Also noted were the total number of deliveries and live births.