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Practical Recommendations for the Management of Children With Endemic Burkitt Lymphoma (BL) in a Resource Limited Setting

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Treatment recommendations for endemic Burkitt lymphoma (BL) in settings with only minimum requirements for curative treatment (PODC setting 1) are described. The reported cure rate for endemic BL is usually <50%. Facilities within setting 1 differ. Three treatment schedules are proposed based on: (1) when accurate staging is not possible, (2) when staging is possible and for (3) relapses and poor responders to primary therapy. A literature review and personal experience were used to formulate the recommendations. Recorded 1-year event free survival was 48% for treatment 1, 61% for treatment 2, and 35% for the rescue treatment. Pediatr Blood Cancer 2013;60:357–362.

Key words: Africa; Burkitt lymphoma; limited resources; treatment

INTRODUCTION

Burkitt lymphoma (BL) accounts for up to 50% of recorded childhood cancers in countries in tropical Africa [1]. The annual incidence in the Northwest Province of Cameroon is 4.54/100,000 children aged <15 years [2]. It mainly occurs in children aged 3–15 years, has a peak incidence between 6 and 8 years and is more common in boys.

Common sites of disease in descending order are the abdomen (lymphoid system, spleen, kidneys, liver, ovaries), face (orbit, mandible, maxilla), paraspinal (presenting as paraplegia), bone marrow, and central nervous system. Lymph nodes, bone, the breast, and testes may be involved. The tumor may double in size within 48 hours, and therefore requires urgent treatment. Historically, the recorded long-term cure rate in Africa using single chemotherapy or low dose combination chemotherapy agents has been <35% compared to >90% cure rate achieved with intensive high dose chemotherapy and optimal supportive care in well resourced centers [3–5]. Recent studies have demonstrated that a >60% cure rate in BL is possible with simple, inexpensive chemotherapy schedules and appropriate matching supportive care [6].

This guideline provides diagnostic and therapeutic recommendations that are affordable and effective, and can be applied safely in a hospital with basic diagnostic and treatment facilities by trained, dedicated nurses, and doctors.

The Pediatric Oncology in Developing Countries group (PODC) has defined settings for the management of BL. In setting 0 the minimal requirements for curative treatment are not met. Palliative care should be provided. In setting 1 the minimal requirements for diagnosis and treatment with curative intent are met. In setting 2 the treatment facilities range between that of settings 1 and 3. In setting 3 all diagnostic and treatment facilities are available. This guideline provides recommendations for setting 1.

MINIMAL REQUIREMENTS FOR SETTING 1

Investigations: The ability to obtain these investigations should be available; fine needle aspirate (FNA), bone marrow aspirate, cerebrospinal fluid cytology, ultrasound scans (USS), full blood count, plain radiography, thick blood films for malaria staining or RDTs (rapid diagnostic tests), stool and urine microscopy, HIV serology, and sickling test.

Chemotherapy agents: These drugs are necessary: cyclophosphamide, methotrexate, vincristine, and hydrocortisone.

For supportive care: IV fluids, antibiotics, anti-fungals, acyclovir, analgesics, anti-vomiting drugs, and nutritional supplementation must be available. Palliative care is essential and financial support to families is required.

DIAGNOSIS

The clinical presentation of BL is usually typical. Other lymphomas, leukemias, Wilms tumor, retinoblastoma, neuroblastoma, and rhabdomyosarcoma, primary bone tumors, and dental pathology need to be considered depending on the site of disease and the age of the patient. BL usually grows faster than the other tumors mentioned in the differential diagnosis. Abdominal masses on USS are hypoechoic in appearance, and the scan may reveal clinically unsuspected tumor [7]. A FNA of the tumor is the standard diagnostic procedure in this setting [8]. Diagnostic procedures can be safely performed with ketamine anesthesia but resuscitation equipment should be available. Examination of cerebrospinal fluid, bone marrow, ascites, or pleural fluid may confirm the diagnosis. In some treatment centers cytology or histopathology is not readily available, or the waiting time for the report is too long to help in the acute management. Treatment should then be started based on the clinical diagnosis.

STAGING OF THE TUMOR

The St Jude (Murphy) staging system for NHL in children is recommended [9]. (Table I). About 15–20% of patients present with stage I or II disease, 65–70% with stage III disease, and 15% with stage IV disease [6]. Staging requires an abdominal

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TABLE I. The St Jude Staging System for NHL in Children

Stage I	A single tumor (extranodal) or anatomic area (nodal) excluding the mediastinum or abdomen
Stage II	A single tumor (extranodal) with regional node involvement
	Two or more nodal areas on the same side of the diaphragm
	Two single (extranodal) tumors ± regional node involvement on the same side of the diaphragm
	A primary gastrointestinal tract tumor ± mesenteric lymph node involvement that is grossly completely resected
Stage III[a]	Two single extranodal tumors on both sides of the diaphragm
	Two or more nodal areas on both sides of the diaphragm
	All primary intrathoracic tumors
	All extensive primary unresectable intra-abdominal disease
	All primary paraspinal or epidural tumors (CNS and CSF not involved)
Stage IV	Any of the above with initial CNS or bone marrow involvement

[a]Elective surgery for presumed abdominal BL is not recommended and abdominal tumors are classified as stage III disease.

ultrasound and cytological examination of the CSF and bone marrow. The intensity of treatment and outcome is related to the stage of disease. If staging is not possible, the same treatment schedule should be considered for all patients [10]. If surgery has been undertaken (though this is not recommended) the tumor is rarely able to be completely resected. All abdominal disease is classified as St Jude stage III. Paraspinal disease presents as paraplegia with or without incontinence. If other CNS signs such as cranial nerve palsies and papiloedema are absent, and the CSF sample does not contain BL cells, this is classified as stage III disease.

TREATMENT

The guardian should be fully informed about the disease and proposed management, including the cost (if any) of treatment. Full contact details and a photograph of the patient and guardian facilitate follow-up. Informed consent must be obtained. Only treatment options with a relative low drug cost, and requiring basic supportive care, are included in this guideline. The potential gain in cure rate with high dose more intensive (and expensive) chemotherapy, was lost from a higher morbidity and mortality rate of treatment complications in a mainly malnourished cohort of patients with BL [11]. Generic medicines are less expensive, and can be procured from many reliable sources. Various low dose combination chemotherapy treatment options containing different combinations of cyclophosphamide (CPM), vincristine, oral and intrathecal methotrexate, prednisone, and arabinoside C were used in East and West Africa. A 25% long-term (>10 years) survival rate was recorded in Uganda. The best survival rate (of 41%) with these combinations was in Ghana. These protocols will not be discussed, because better treatment options are now available [4,12]. Single drug treatment with CPM 40 mg/kg at 2- to 3-week intervals for four to six doses, can result in long-term cures [3,13,14]. Intravenous and oral CPM have comparable pharmacokinetics and can be interchanged at the same dose per kilogram body weight [15]. Tablets are easier to administer and cost less. The routine administration of IT MTX together with CPM induction chemotherapy markedly reduces the risk for a CNS relapse [12]. We recommend a dose of 12.5 mg intrathecal methotrexate and 12.5 mg hydrocortisone. This provides good CNS protection and allows for two doses from one 25 mg vial of methotrexate. High frequency (7 day intervals) CPM at 40 mg/kg + IT MTX 12.5 mg and IT HC 12.5 mg as induction in all patients, followed on Day 28 by three additional pulses of CPM 40 mg/kg at 14-day intervals for patients with stages III and IV disease, resulted in an overall 52% projected 12-month event free survival (EFS) [15].

A 50% EFS rate at 24 months was reported by the French African Pediatric Oncology Group. Patients who had an incomplete response on Day 21 had a further two courses of COPM and two courses of CYM. The cost of investigations, drugs and the need for a higher level of supportive care, are however limiting factors [16].

The response to treatment and the time to assess must be defined. Patients without clinical detectable tumor may still have disease detectable by abdominal USS, bone marrow, and/or CSF examination. We define a complete clinical response as disappearance of all clinical visible or palpable tumor and in patients with abdominal disease, a residual tumor of $\leq$30 ml in volume on abdominal ultrasound, 4 weeks after starting chemotherapy.

Staging classifications have changed with time and must be taken into account when interpreting the outcome of treatment in older publications. The routine use of abdominal USS has made it simpler to identify, monitor, and quantify abdominal disease.

Diagnostic and staging investigations should be performed on admission. The response to treatment is judged on clinical examination and a repeat abdominal USS following three cycles of treatment or after completing induction therapy and before starting consolidation chemotherapy. We accept 12 months disease free survival as a cure, as the risk for a relapse is <5% after 1 year. Therefore a 12-month follow-up period is required to identify relapses, and to confirm the outcome. We recommend the following three treatment schedules:

Higher Dose CPM With IT MTX and IT HC (When Pathology Results Are Not Available and Accurate Staging Is Impossible)

This treatment schedule was designed for use in patients with presumed BL where delay in obtaining pathology results makes diagnosis, and staging, impossible. A similar cumulative total amount of CPM/kg was given as in the Malawi 2002 BL treatment schedule, over a total period of 28 days. The projected 1-year EFS rate 48%, and the toxicity were manageable [10,11]. Figure 1 illustrates the treatment flow sheet.

Risk-Adapted Treatment With CPM, IT MTX, IT HC ± Vincristine, and Methotrexate

Induction treatment with CPM + IT MTX and IT HC was followed by consolidation treatment with CPM, or CPM + vin- vincristine + intravenous MTX. All patients received the same

Fig. 1. Twenty-eight-day treatment protocol for Burkitt lymphoma with cyclophosphamide and intrathecal methotrexate.

induction treatment. On Day 28 patients were allocated to maintenance chemotherapy in Risk Group 1, 2, or 3 according to the initial stage, the clinical response, and the abdominal USS findings (Table II). The overall projected 12-month EFS rate was 61%; 100% for stage I, 85% for stage II, 60% for stage III, and 27% for stage IV. The predictive value of the size of residual abdominal lesions on Day 28 following induction with CPM 40 mg/kg on Days 1, 8, and 15 was confirmed in a separate prospective study [17]. Figure 2 illustrates the treatment flow charts (Table III).

MTX administration and leucovorin rescue (for patients in Risk Group 3): an infusion is started with 5% dextrose water or half strength dextrose/Darrows with 30 ml of 4% $NaHCO_3$ added per liter at a rate of 3 L/m^2/24 hours, 4 hours before starting the MTX infusion, and continue this for another 48 hours. The MTX is reconstituted, added to 200 ml dextrose/water or 0.9% saline, and infused over 3 hours. Leucovorin 15 mg tablets every 6 hours $\times$ 7 doses needs to be started strictly 24 hours after the start of the MTX infusion. A urine output of $\geq$3 ml/kg/hours must be achieved. Methotrexate at this dose can be safely administered in the absence of third space fluid collections, and by adhering to the recommended fluid regime and leucovorin rescue [18].

Second Line Chemotherapy for Recurrent and/or Refractory Disease

This treatment is recommended for patients with refractory or recurrent disease. Patients who relapse following treatment with only CPM and IT MTX, and patients who are not in clinical remission on Day 28 following three courses of CPM and IT MTX + IT HC are offered rescue therapy which includes a higher dose of CPM and vincristine sulfate. Thirty five percent of patients in Malawi and in Cameroon achieved an overall 12-month—EFS [19]. The median time to relapse with the CPM containing protocols is <6 months. Relapses after 1 year (termed late) from end of therapy and very late relapses (up to 4 years) do occur rarely. It is not known (without molecular studies) if late relapses are really a recurrence, or constitute a second, new BL tumor. Our recommendation is to offer this treatment to patients who relapse within 1 year. Patients who have failed Risk Group 3 treatment of the Cameroon 2008 BL protocol, and patients who relapse after presenting with St Jude stage IV disease, are unlikely to benefit from further chemotherapy (available in this setting). Patients with confirmed BL that recurs after 1 year, are treated as patients who present with BL for the first time. The indications for palliative care should be clearly defined. Figure 3 illustrates the treatment schedule.

The different treatment schedules listed above are from non-randomized clinical studies, and provide a base for future randomized multi-center studies. HIV positive patients are treated in the same way [6,10].

TABLE II. Risk Group Allocation on Day 28

Group 1	St Jude stages I and II in clinical remission
Group 2	St Jude stage III or stage uncertain, in clinical remission and largest residual abdominal tumor $\leq$30 ml on ultrasound
Group 3	St Jude stage IV, or patient not in remission, or residual abdominal tumor >30 ml on abdominal ultrasound

SUPPORTIVE CARE

Standardized supportive care guidelines should be included in the protocol. This is important because nurses or doctors with no formal training in pediatric oncology should be taught to safely administer chemotherapy in the PODC setting.

To prevent vomiting, oral metoclopramide, 10 mg given 20 minutes before and 4 hours after CPM administration, is an effective regimen. In patients who require leucovorin rescue, the risk of vomiting (and MTX toxicity) may be further reduced by the IM administration of chlorpromazine 0.5 mg/kg/dose. The use of metoclopramide is prohibited in some countries. Ondansetron IM or IV at 5 mg/dose (or other 5-HT antagonists) is also effective.

As many as 50% of patients may have stunting and/or malnutrition. Malnutrition increases the risk for infections. Nutritional support is recommended and must consist of locally acceptable, available, and affordable components [20–22].

The prevention of tumor lysis syndrome is of critical importance during the first days of treatment. The following strategy has been used successfully in Malawi and Cameroon. Allopurinol 5 mg/kg three times daily 24 hours before the first dose of cyclophosphamide, and continued for a total of 5 days. IV fluids are commenced the day before chemotherapy, and continued for 72 hours at 3 L/m^2/24 hours. Urinary excretion should be $\geq$3 ml/kg/hours. Furosemide is given to increase urinary excretion if needed. Guardians, who normally stay with their child in hospital, can be taught to collect the urine in soft drink bottles, and report the volume to the nursing staff. Serum uric acid,

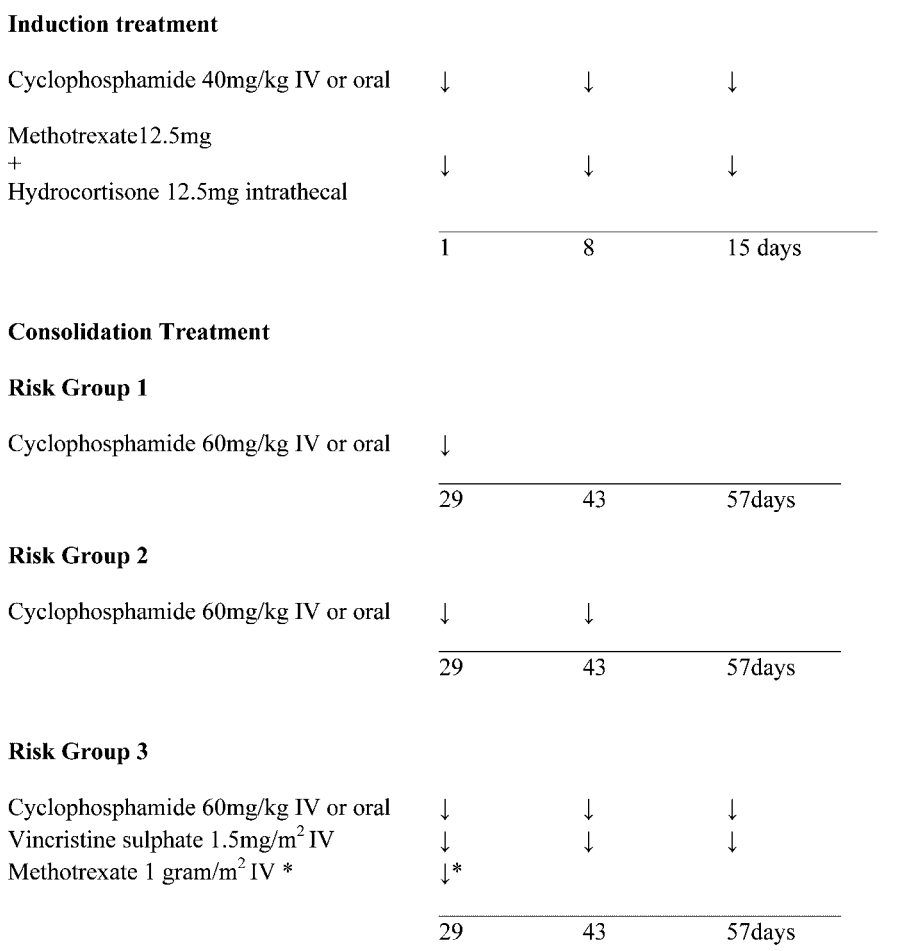

Fig. 2. Risk adapted therapy for Burkitt lymphoma.

electrolytes, and renal function tests are useful, but seldom available. Failure to provide an adequate fluid intake and to achieve the recommended urinary output, may result in metabolic complications, and increase the risk for tumor lysis and early death [6,11].

Fever is a medical emergency. Fever is defined as one recorded temperature of 38.5°C or two recorded temperatures of ≥38.5°C within a 24-hour period. Once malaria has been excluded, empiric broad-spectrum antibiotics which cover Gram positive and Gram negative organisms must be commenced as soon as possible. A broad-spectrum penicillin (e.g., ampicillin) plus an aminoglycoside (e.g., gentamicin) was used successfully in Malawi and Cameroon as first line treatment. Therapy can be modified if a blood culture result is available. If the patient remains febrile for >48 hours, ceftriaxone or another third generation cephalosporin is recommended. Nystatin is prescribed for mucositis. A course of acyclovir is recommended as herpes simplex infection may be present [23] Concomitant analgesics are essential. Morphine provides effective pain relief. Hemorrhagic cystitis is largely prevented by ensuring a fluid intake of 3 L/m^2 in the 48 hours following CPM administration, and by instructing the patient to empty the bladder as frequently as possible [6,10].

MAIN ACUTE SIDE EFFECTS OF CHEMOTHERAPY AGENTS

The healthcare providers should be taught, and the guardians should be informed about the possible side effects of the different chemotherapy agents used.

TABLE III. Practical Notes are Listed

Chemotherapy should be administered on weekdays, when trained staff is on duty to reduce the risk for errors
Chemotherapy must not be given unless the total white cell count is ≥1.0 × 10^9/L
Chemotherapy must be delayed if the patient has fever
Chemotherapy drugs must be mixed in a quiet, separate room with a hood above the mixing surface, and the mixer should wear protective clothing
A clinical photograph provides a record and assists in follow-up
Chemotherapy is also commenced in critically ill patients
Good control of drug stocks prevents shortages and waste
Vincristine sulfate causes irreversible fatal encephalopathy if injected intrathecally inadvertently. The IT MTX and IT HC should not be administered at the same time as the IV vincristine to avoid this
The cost of treatment should be guaranteed when treatment starts

Cyclophosphamide mg/kg (oral or intravenous)	60mg[1] ↓	60mg ↓	60mg ↓
Vincristine 1.5 mg/m^2[†]	↓	↓	↓
Methotrexate intrathecal 12.5mg per dose	↓*	↓*	↓*
Hydrocortisone intrathecal 12mg/dose	↓	↓	↓
Day	1	8	15

[1] Maximum dose of CPM 2.0 gm; [†] Maximum of vincristine sulphate 2.0 mg; * In children with an incomplete response who have already received two or three doses of IT MTX as part of their induction treatment, IT MTX is not given again.

Fig. 3. Rescue chemotherapy schedule.

Co-Morbidities

Infections such as varicella, herpes Zoster, HIV, measles, and parasitic infestations such as malaria and helminths should be identified and treated according to national guidelines. Patients who are HIV positive are given the same chemotherapy, irrespective of whether they are also receiving ARV treatment [6,10].

Palliative Care

This is an essential component of treatment. The palliative care team should be introduced to the patient on first admission, and will provide continued care if curative treatment fails.

SPECIAL CLINICAL PROBLEMS

Respiratory Obstruction

BL involving the neck and upper thorax may cause acute respiratory obstruction. Patients with stridor or signs of upper respiratory obstruction require an emergency, temporary tracheostomy to prevent death. Intravenous corticosteroids may relieve oedema and obstruction.

Paraplegia From Paraspinal Tumor Compression

Weakness/paralysis of the legs and incontinence may resolve completely following chemotherapy. The shorter the delay in starting treatment, the better is the chance of recovery. Patients with unresolved paraplegia and incontinence are at risk of developing progressive decubitus ulcers and infection. The rehabilitation of an incontinent paraplegic child in a poor rural environment is difficult.

Traditional Medicine

This is an integral part of traditional African health care. Some practices are harmful but despite this, traditional healers can be counseled to identify and refer children with tumors to a hospital where treatment is available [24].

Compliance With Treatment and Follow-Up

Failure to complete treatment and poor follow-up is largely preventable. Proper counseling, critical assessment of the parent's resources, support (e.g., food) while in hospital, subsidized transport for hospital visits, contact by mobile phone and, if needed, home visits can achieve 95% compliance with treatment and follow-up. The budget must include these additional costs [25,26].

Advocacy and Parent Support Groups

These are important measures to increase the number of patients who can benefit from treatment. The dedicated nurse at the treatment center is well equipped to provide advocacy and develop parent support groups. The golden standard of care is the best outcome that one can achieve with the available resources.

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