Ministry of Health and Social Welfare

BURKITT'S LYMPHOMA NATIONAL TREATMENT GUIDELINES

ORCI OCEAN ROAD CANCER INSTITUTE

SERVICE TREATMENT
RESEARCH DETECTION
TEACHING PREVENTION

IMA WORLDHEALTH
ADVANCING HEALTH & HEALING THE WORLD OVER

BURKITT'S LYMPHOMA NATIONAL TREATMENT GUIDELINES

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Burkitt's Lymphoma National Treatment Guidelines

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TABLE OF CONTENTS

ABBREVIATIONS AND ACRONYMS

ANC	-	Absolute Neutrophil Count
BL	-	Burkitt's Lymphoma
BUN	-	Blood Urea Nitrogen
CBC	-	Complete Blood Count
CNS	-	Central Nervous System
CSF	-	Cerebral-Spinal Fluid
CXR	-	Chest X-Ray
DDH	-	District Designated Hospital
EBV	-	Epstein Burr Virus
FBP	-	Full Blood Picture
FNA	-	Fine Needle Aspirate
Hb	-	Haemoglobin
HBC	-	Home Based Care
HIV	-	Human Immunodeficiency Virus
IMA	-	IMA World Health
ITMtx	-	Intrathecal Methotrexate
LDH	-	Lactate dehydrogenase
MOHSW	-	Ministry of Health and Social Welfare
Mtx	-	Methotrexate
NGO	-	Non-Governmental Organization
ORCI	-	Ocean Road Cancer Institute
PO	-	Per Oral
TB	-	Tuberculosis
USS	-	Ultra-Sound Scan
WBC	-	White Blood Count

FOREWORD

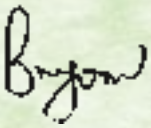
Burkitt's Lymphoma is named after Denis Parsons Burkitt, who in the late 1950's mapped the specific geographic distribution of this disease across Africa. Burkitt's Lymphoma is one of the fastest growing malignancies in humans, with a very high growth fraction which without timely and appropriate treatment, can be life threatening.

In the short history of the description of this tumor, great strides have been made. Between the 1960s and 1990s the work of John Ziegler, Ian Magrath and Dennis H. Wright have pushed forward the boundaries in knowledge of this tumour and greatly improved the patient treatment outcomes. In spite of the advancements in our knowledge about Burkitt's Lymphoma, I would like to stress that, we must not be complacent as there is much still to be done.

Within Tanzania, three (3) out of 100,000 children will be affected by Burkitt's Lymphoma, at any one time. Practicing doctors know that, although chemotherapy regimens have brought great advances in the cure rate of this predominantly childhood cancer, there is more to treatment, than just having the appropriate drugs. Specifically, it is of great importance to make diagnosis at any early stage and institute the appropriate treatment plan, while continually monitoring the patient and their condition, as well as keeping the patient and their relatives informed, about this extremely frightening and distressing condition. Most important is the prevention of tumour re-growth, which can be achieved by administration and completion of combination chemotherapy, given every two weeks.

Since Burkitt's Lymphoma is a curable lymphoma, the use of these treatment guidelines will help improve quality of care and treatment of patients; and in doing so, achieve the best outcome. There is therefore every justification to increase the awareness of this fact and encourage appropriate management, of people suffering from Burkitt's Lymphoma.

The Ministry of Health and Social Welfare, believes that, these guidelines will make a valuable contribution to the fight against BL, and will be a stimulus for more standardized treatment guidelines, for other cancers in the country.



Blandina S. J. Nyoni
Permanent Secretary
Ministry of Health and Social Welfare

ACKNOWLEDGEMENTS

This document is a product of collaborative initiatives of Ocean Road Cancer Institute (ORCI) and IMA World Health in their determination to improve the quality of care, for Burkitt's Lymphoma (BL) patients in Tanzania. The Ministry of Health and Social Welfare, appreciates the technical and financial support of these two Organizations, in making these guidelines a reality. I believe that, this will be a catalyst for developing more standardized treatment guidelines for other cancers in Tanzania, to ensure quality care.

The BL Treatment Program in Tanzania, would not have been where it is now, without the active support of partners, who have supplied resources, and advice, and have been working together in BL clinical work and research. We offer our heartfelt gratitude, to the International Network for Cancer Treatment and Research (INCTR), UICC My Child Matters Project, the United Service Foundation, Walk for Life and American Cancer Society (ACS). These organizations have contributed towards the fight against the cancer, by providing financial and technical support for the program. We extend our thanks to them.

Special thanks go to all hospitals, that have been implementing the Burkitt's Lymphoma Treatment Program, which, through sharing of their experiences in treating BL patients, have provided the basis for the contents in this document.

On behalf of the Ministry of Health and Social Welfare, I would like to acknowledge the following experts, for their participation in developing these guidelines.

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Dr. Gastor Njau	-	Nkinga Hospital
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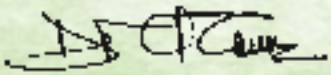
Dr. Maria Lemmo	-	St. Gaspar Hospital, Itigi
Dr. Lulu Chirande	-	ORCI

A lot more have contributed in various ways to make this work successful. It is not easy to mention each one by name, thus the Ministry of Health and Social Welfare want to thank each one of you and confirm that, your contribution is highly valued.



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CLINICAL MANAGEMENT OF BURKITT'S LYMPHOMA IN TANZANIA

Introduction

Development of these National Guidelines for Burkitt's Lymphoma Treatment is a joint effort between ORCI on behalf of the Tanzania Ministry of Health and Social Welfare and IMA World Health. This document is written with a number of concrete objectives in mind.

- Provide easy to follow guidelines for health care personnel/ institutions who care for children suffering from Burkitt's Lymphoma (BL), thereby improving the quality of care for this cancer.

- Make health care personnel/institutions aware of the National Guidelines for Burkitt's Lymphoma Treatment.

- Function as a training manual to promote a standardized management of BL by faith-based and government hospitals.

- Combine the lessons learned from over thirty years of experience by faith-based health care institution to combat BL with the extensive experience of the Ministry of Health and Social Welfare and Ocean Road Cancer Institute (ORCI).

Pathophysiology and Causes

While the exact cause and mechanisms of Burkitt's Lymphoma (BL) are not known it is believed that the Epstein-Barr Virus (EBV) and malaria are contributory factors.

Burkitt's Lymphoma is a monoclonal proliferation of B lymphocytes characterized by small noncleaved cells that are uniform in appearance and that produce a diffuse pattern of tissue involvement. Under the

microscope, BL is characterized by the presence of a "starry sky" appearance (also observed in other highly proliferative lymphomas), imparted by scattered macrophages with phagocytes cell debris.

The African form of BL often involves the maxilla or mandible. The involvement of abdominal organs, such as the kidneys, ovaries, or retroperitoneal structures, is slightly less common. A secondary form of BL - the Sporadic Form, most often involves the abdominal organs with the distal ileum, cecum or mesentery.

The Epstein-Barr Virus has been implicated strongly in the African form of BL, while the relationship is less clear in the Sporadic Form. EBV is associated in approximately 20% of Sporadic cases. Rare adult cases are associated with immunodeficiency, particularly HIV/AIDS. The lymphocytes have receptors for EBV and are its specific target. In the African form of BL, the hosts are believed to be unable to mount an appropriate immune response to primary EBV infection, possibly because of coexistent malaria or another infection that is immunosuppressive. Months to years later, excessive B cell proliferation occurs.[1]

The association of Malaria and BL is based on the fact that it has been shown that during an attack of Plasmodium falciparum malaria, T-cell subpopulations are radically altered so that, in vitro, B lymphocytes infected with EBV proliferate abnormally to secrete large amounts of immunoglobulin and antibody. This phenomenon offers some explanation for the increased incidence of Burkitt's tumour and the high levels of immunoglobulin found in people living in areas where P. falciparum malaria is common."[2]

The association of EBV and BL is based on the findings that most

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[1] Hanxian, H., Aguilar, L. Patturajah A., Burkitt Lymphoma, November 12, 2005, eMedicine & WebMD.

[2] Hilton C., et al. *"T-cell control of Epstein–Barr virus-infected B cells is lost during P. falciparum malaria."* Nature 312, 449 - 450 (1984).

Burkitt's Lymphomas (90%) carry a translocation of the c-myc oncogene from chromosome 8 to either the immunoglobulin (Ig) heavy-chain region on chromosome 14 [t(8;14)] or one of the light-chain loci on chromosome 2 (kappa light chain) [t(8;2)] or chromosome 22 (lambda light chain) [t(8;22)]. These translocations are likely the result of the EB virus action of genomic integration during the process of B cell infection.

These translocations are as follows:

Source	Destination	Map	Immunoglobulin
chromosome 8	chromosome 14	t(8;14)	(lg) heavy chain
chromosome 8	chromosome 2	t(8;2)	kapp light chain
chromosome 8	chromosome 22	t(8;22)	lambda light chain

In every case, c-myc is in a region of vigorous gene transcription. Overproduction of the c-myc product may change the lymphocytes into cancer cells[3].

INTRODUCTION TO BURKITT'S LYMPHOMA DIAGNOSIS & TREATMENT

The clinical appearance of a new BL patient can be dramatic, especially when the tumour has created distortion of the face. Although facial asymmetry is noticed very early by the parents, they may delay presentation by seeking out traditional healers or dental care. Tumours in the abdomen (especially of kidney or ovary) can, on the other hand, grow quite large before coming to the attention of any family member.

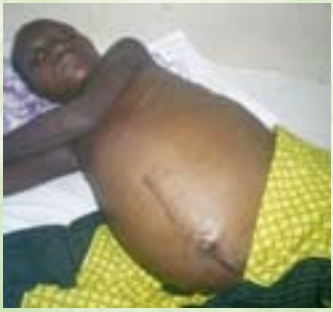
Burkitt's Lymphoma is the fastest growing tumour known to medical science. This means that it is also very amenable and exquisitely sensitive to treatment by chemotherapy alone, with only infrequent indications for surgery or radiation treatment.

[3] Hanxian, H., Aguilar, L. Patturajah A., Burkitt Lymphoma, November 12, 2005, eMedicine & WebMD.

Response to chemotherapy of BL as shown in the treatment response chart below is normally rapid, with noticeable tumour shrinkage within 48 to 72 hours of the first dose of the first cycle. By the beginning of the second treatment cycle, visible or palpable tumour is normally gone. In fact, this rapid response to chemotherapy can become a clinical trial in situations where a firm pathologic diagnosis is not (or not yet) available. With less than complete response to chemotherapy in the first treatment cycle, one should suspect either wrong diagnosis or inactive drug (e.g. expired or spoiled in storage).

Before & After Treatment Result Pictures

Before Treatment After Treatment



Clinical Features

Patient Presentation of BL

A. Typical History

i. Child is between the ages of three (3) and twelve (12) and is of either gender
ii. Progressive swelling in the face or abdomen of 2-8 weeks duration
iii. In case of gingival (gum) swelling, history of tooth extraction after onset of swelling

B. Occasional History

i. Recent onset of gait difficulty or lower limb paralysis
ii. Retention of urine or difficult in passing stools
iii. Progressive swelling of other body part for 2-8 weeks (e.g. Scalp, perineum)
iv. Recent onset of strabismus (crossed eyes) or blindness in one or both eyes

Physical Findings

A. Common physical findings (any combination)

i. Swelling of orbit (eye), maxilla (cheek), mandible (jaw), gingiva (gum) or palate on one or both sides of face
ii. Dental anarchy (loose or disarranged teeth) in area of gingival swelling
iii. Friable (easily bleeding) mouth tumour
iv. Enlarged kidneys (palpable tumour) in costovertebral angle(s)
v. Abdominal mass e.g. enlarged ovary in girls
vi. Ascites

B. Less common physical findings (but still consistent with BL. Any one of these could be the only physical finding).

i. Enlarged testis in boys
ii. Abnormal gait or paralysis of legs
iii. Swelling of any other area of body
iv. Strabismus (crossed eyes) or blindness
v. Edema of legs

Consider other diagnosis if;

i. History more than two (2) months
ii. Tooth extraction that occurred prior to gingival swelling
iii. Teeth not loose or disarranged in spite of gingival swelling
iv. Teeth loose but gingival not swollen
v. Lymph node enlargement
vi. Hepatosplenomegaly
vii. Frequent fevers

Laboratory Investigations:[4]

Optimal Schedule for BL Patient Investigations				
Investigation	**Initial**	**During Chemo**	**F/U Visit**	**Comments**
History & Physical Examination	X	X	X	Basis for diagnosis and prognosis as well as early detection of relapse
FNA/Imprint[5]	X			Either one confirms diagnosis. With accessible tumour, FNA is less invasive but may give false negative results
Full Blood Count ± peripheral smear[6],[7]	X	X	X	Detects anemia, neutropenia, thrombocytopenia and infections.
X-Rays • Chest • Jaw (maxilla & mandible)	X X			Optional. Use for suspected pneumonia, TB, or lung mass
Ultrasound Scan	X	X	X	Screens for and follows abdominal tumours, detects non-palpable tumour and relapse. May also be done for the other tumours e.g. jaw
CSF	X	X		Cytology, Obtain specimen during admin. of ITMTX, repeat until negative x 2.

HIV	X			Recommended for all patients who come for BL treatment.
Bone Marrow	X			Detects abnormal cells (blast cells, tumour cells) indicating bone marrow involvement. Repeat after treatment if it was positive initially.
Electrolytes	X	X		Sodium, Potassium, Chloride
Renal functions	X	X		BUN, Creatinine. Assures that renal function is adequate for chemotherapy
Uric Acid	X	X		Commonly elevated early in chemotherapy, is an index of tumour lysis
Calcium	X	X		Elevated in tumour lysis
Serum proteins	X	X		Total protein and albumin, for nutritional and accurate calcium assessment.
LDH	X	X	X	Non specific but elevated in malignancies. Level correlates with tumour stage at presentation. Normally will reduce to nearly normal with successful treatment.
Urinalysis	X	X		Protein, glucose, microscopy. May detect unsuspected urinary tract infection or haematuria
Stool microscopy	X			For Ova & Parasites. If positive for strongyloides treat for 3 days

[4] Magrath I.T, Ziegler J.L., Templeton A.C. *"A comparison of clinical and histopathological features of childhood malignant lymphoma in Uganda"* Cancer 1974 33(1):285-94.

[5] Choose FNA if tumor is accessible. Imprint if surgical specimen is available. See pages 8-10 for protocol for doing FNA and Imprint

[6] If HB <7gm, give BT until corrected. Do not use Folic Acid during chemotherapy.

[7] If WBC <2,000/mm or absolute neutrophil count <1,000 or platelets <50,000mm, delay chemotherapy until corrected.

Biopsy or Final Needle Aspiration (FNA):[8,9,10]

Tissue sample is removed, fixed in 10% formalin and sent for pathology review with adequate labeling.

Touch preparation: touch a slide to the fresh biopsy sample air dry, fix in formalin and perform urgent H&E stain.

In Burkitt's Lymphoma the slide will reveal

- uniformly immature cells
- cells with vacuolation
- a typical "starry sky" appearance (in an imprint of tissue section)

Detailed Procedure: Fine Needle Aspiration

1. Use a 20-21g needle and a 5-10ml syringe
2. Locate an accessible site containing a palpable tumor mass
3. Swab the area with alcohol
4. Insert the needle to a depth of one (1) to two (2) centimeters
5. Exert negative pressure by pulling on the syringe plunger
6. Withdraw the needle halfway while continuing the negative pressure and insert the needle in another track (optional)
7. Release the negative pressure and remove the needle (this avoids drawing the contents of the needle into the syringe)
8. Disconnect the syringe from the needle
9. Fill syringe with air and reconnect to the needle
10. Place the needle vertically above a clean slide and forcefully push the plunger to expel the contents of the needle onto the slide
11. Immediately spread the droplets on the slide using the tip of the needle (the smear must be very thin)
12. After air drying, fix with a few drops of 95% alcohol
13. Staining method – use your current method of malaria films Leishman, Geimsa or field stain
14. Scan the fields with low power to identify areas with uniform large cells
15. Go to oil immersion to look at the suspicious cells
16. The BL cells should be easily recognized if present (Figure One).
17. The report is simple: "BL cells seen" or "BL cells not seen"
18. Label, Store, & Save

NB: There is a remote possibility of prolonged hidden bleeding from a needle aspirate, but it can usually be avoided by continuing to apply pressure on the site for 15 minutes.

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[8] Burkitt D. *"General features and facial tumours."* In Burkitt's Lymphoma eds. Burkitt D., Wright D. Edinburgh and London, E&S Livingstone, 1970, p 64.

[9] Magrath I.T, Ziegler J.L., Templeton A.C. *"A comparison of clinical and histopathological features of childhood malignant lymphoma in Uganda"* Cancer 1974 33(1):285-94.

[10] Philip T, et al. *"Burkitt's lymphoma in 1985."* Pediatre 1985 Mar; 40(2): 137-60.

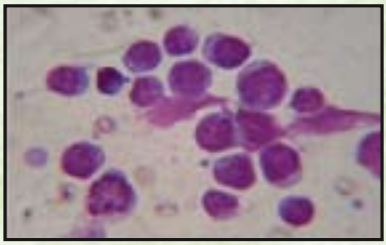


Figure One: FNA Cytology

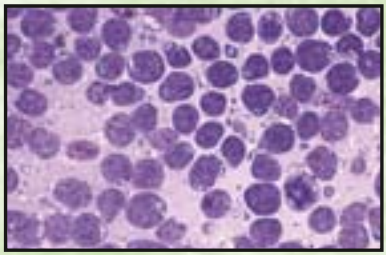


Figure Two: Imprint

Imprinting:

It is sometimes possible that the needle will not be able to actually penetrate the tumour and therefore will give a negative result. In other cases it may be necessary to remove a large tumour, (e.g. ovary), necessitating a tissue specimen examination.

In these instances, the imprinting technique is much more likely to give a definite diagnosis.

Detailed Procedure: Imprinting

1. Take the cut surface of a freshly excised wedge section and lightly blot on a gauze to remove the blood
2. Lightly touch the slide with a freshly cut surface of the specimen
3. Continue to touch it multiple times until you get a uniform thin layer (BL tissue typically continues to leave a residue as you touch it multiple times)
4. After air drying fix the slide with several drops of 95% alcohol
5. Staining method – use your current method of malaria films, Leishman, Geimsa, field stain
6. Scan the fields with low power to identify areas with uniform large cells
7. If there are BL cells the field of uniform cells should show the “starry sky” pattern. The scattered white “stars” are histiocytes (Figure Two)
8. Go to oil immersion to look at the suspicious cells
9. The BL cells should be easily recognized if present (Figure One). You will usually find sheets of uniform cells. The tipoff is the presence of small vacuoles in the periphery of the cell in the thin rim of cytoplasm.
10. Label, Store, & Save.

FACTORS TO BE CONSIDERED WHETHER TO DO FNA OR IMPRINTING:

A decision between using FNA (fine needle aspiration) versus Imprinting for definitive diagnosis of Burkitt's Lymphoma should be based on the following;

FNA

- Accessible Tumour
- Excision/surgery not advisable or planned
- Less invasive

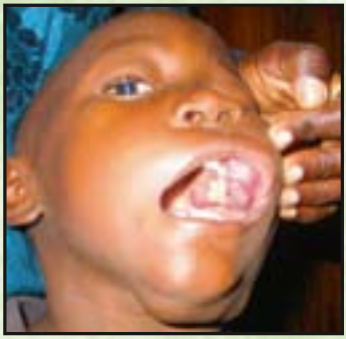
Imprinting

- Tissue specimen available
- Aspiration negative
- Aspiration not feasible

Staging:[11]

This is part of the complete and appropriate management of the patient and gives important prognostic information.

Stage A: Tumour confined to one quadrant of the face, i.e. Right Maxilla, Right Mandibe, Left Maxilla, Left Mandible



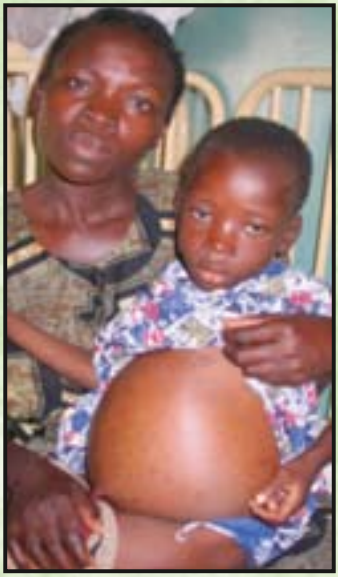
Picture One: Stage A

[11] Magrath I.T, Ziegler J.L., Templeton A.C. *"A comparison of clinical and histopathological features of childhood malignant lymphoma in Uganda"* Cancer 1974 33(1):285-94.

Stage B: Two or more facial quadrants involved

Picture Two: Stage B

Stage C: Intra-abdominal, intra-thoracic or paraspinal mass



Picture Three: Stage C

Stage D: Central Nervous System (CNS), Cerebral Spinal Fluid (CSF) or Bone Marrow involvement

MANAGEMENT AND CHEMOTHERAPY:[12,13, 14]

Standard Burkitt's Lymphoma treatment revolves around a combination of three drugs, Cyclophosphamide, Vincristine, and Methotrexate (systemic and intrathecal). This combination is repeated for a total of six cycles. A chart for calculating body surface area, and a dosing guide, are in appendix B and C.

STANDARD TREATMENT OF CLINICALLY STABLE PATIENT

Cyclophosphamide

To be given for six (6) cycles at an interval of two (2) weeks.
Dose: give 40mg/kg body weight or 1200mg/m² in 250 dextrose 5% within 30 min to 1 hr.

Detailed Procedure: Cyclophosphamide Injection

1. Make sure that the patient is appropriately hydrated
2. Verify the weight and height of the patient, and ascertain body surface area (Appendix C)
3. Calculate the dose of Cyclophosphamide and select the appropriate vials needed
4. Dilute according to the instructions, use sterile water for injection
5. Put the diluted Cyclophosphamide into 250mls of 5% dextrose or normal saline
6. Label the infusion
7. Place butterfly needle or a cannula in an appropriate vein of the forearm
8. Flush with 5cc of sterile saline to ensure proper placement and patency (or use the injection site in an already running IV infusion
9. Infuse over 30 – 60 minutes
10. Continue with hydration

Methotrexate

Intravenous (IV) Methotrexate (50mg/2mls vials)
To be given for 6 cycles at an interval of two weeks.
Dose: 75mg/m² slow push

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[12] Olweny C.L., et. al. *"Long term experience with Burkitt's lymphoma in Uganda."* International Journal of Cancer 1980 Sep. 15:26(3):261-6.
[13] Magrath I.T. *"African Burkitt's lymphoma. History, biology, clinical features and treatment."* American Journal of Pediatric Hematology/Oncology. 1991 Summer; 13(2):222-46.
[14] Philip T, et al. *"Burkitt's lymphoma in 1985."* Pediatre 1985 Mar; 40(2): 137-60.

Intrathecal (IT) Methotrexate (15mg/3ml vials)

Dose according to age:

Below 3 years	– 10mg
3-10 yrs	– 12mg
> 10 yrs	– 15mg

Note:

IT Methotrexate is given weekly.

If there is no CNS involvement – it should be given prophylactically in the first three cycles at weekly interval i.e. 6 doses.

If there is CNS involvement: IT Methotrexate is given in all six cycles i.e. 12 doses at weekly interval.

Remember to take CSF for cytology before giving IT Methotrexate until the result is negative on two successive tests.

Detailed Procedure: Intrathecal Methotrexate

1. Prepare as for a normal spinal tap
2. Calculate the mg dose of Methotrexate based on the patient's age
3. Convert mg dose to number of cc's according to the mg/cc strength of stock Methotrexate solution (see Methotrexate caution note)
4. Fill syringe with calculated number of cc's of Methotrexate
5. Insert a 25g spinal needle in the same location used for a diagnostic spinal tap
6. Collect CSF in a sterile tube, label, and send to lab (omit if prior CSF test results were negative x2 for malignant cells)
7. Connect syringe containing the Methotrexate
8. Slowly inject the entire amount of Methotrexate over one (1) minute
9. Remove the spinal needle
10. Apply pressure with a sterile gauze to site for one (1) minute, then tape

Lab Procedure:

11. Spin CSF specimen down
12. Smear thin layer of sediment on a slide
13. Air dry and fix 95% alcohol solution
14. Stain with Giemsa
15. Analyze for malignant cells
16. Label, Save, & Store

Methotrexate Cautions

Methotrexate comes in *three (3) common concentrations:*

- 2.5 mg/cc
- 5 mg/cc
- 25 mg/cc

The 25 mg/cc concentration is for intravenous (IV) use and may or may not have preservatives

If a patient requires intrathecal injections and only the 25 mg/cc concentration is available make sure that:

- the drug is ***preservative free***
- use a ***tenfold dilution*** (i.e. if a dose is 10mg, then draw up 0.4 cc of to 25 mg/cc Methotrexate and then draw up normal saline reach 4 cc total; 5% dextrose can be used instead of normal saline)

Vincristine

To be given for 6 cycles at an interval of two weeks

Dose: 1.4mg/m^2 slow push for 5 minutes

NB: Vincristine needs to follow the pharmaceutical cold chain

Supportive Treatment

- Ensure hydration- 3liters/m^2 in 24 hrs, starting 12 - 24 hours prior to chemotherapy and continue for 24 - 48 hours post chemotherapy depending on child's condition.
- Tabs Allopurinol 300mg/m^2 as single daily dose to start one (1) day before chemotherapy and continue for 5 days after chemotherapy.
- Monitor vital signs (temperature, respiration and pulse) for at least six (6) hour starting 24 hours prior to chemotherapy.
- Watch for:
    - Anemia (pallor), mucositis, candidiasis;
    - Excessive vomiting or diarrhea;
    - Urine output; and
    - Tumour Lysis Syndrome (See Appendix D).

Management Of Bl Patient During Acute Distress:

- Resuscitate as necessary:
- If Hb <7.0g/dl then transfuse first
- Ensure hydration with IV fluids
- Diagnose and treat co-existing infections; for example sepsis, pneumonia, malaria, and cellulitis
- If airway obstruction is impending
    - Immediately give Cyclophosphamide 40 mg/kg IV bolus as soon as possible (do not wait on arrival of other drugs), with plenty of hydration (i.e. 3liters/m^2 IV normal saline in 24 hours).
    - Commence Allopurinol 300 mg/m^2 a day as soon as the child is able to swallow for 5 days.
    - Always complete standard treatment with three drugs regimen as soon as other drug as are available.
    - Notify anesthetist and have emergency tracheostomy kit at bedside.

Minimizing Side Effects of Treatment:

Antiemetics

Usually children will tolerate chemotherapy with minimal vomiting. If vomiting persists then appropriate anti emetic therapy can be given. Possible regimens Promethazine 6.25-12.5 mg, zofran 2-4mg, metoclopramide 5-l0mg (beware anticholinergic side effects in the young) and dexamethasone (2-4mg) given intravenously. Adjust dose appropriately to child's weight.

Neutropenia and delaying treatment

A FBP (Full Blood Picture) should be done in advance of each standard treatment cycle. If the absolute neutrophil count (ANC) is less than <1,000, the treatment cycle should be postponed by a week. Repeat neutrophil count after one week and give chemotherapy if count > 1,000.

If the neutrophil count is less than <500 then the patient should be admitted in isolation, observed (with four hourly temperature recordings) and placed on a prophylactic oral broad spectrum antibiotic. If the neutropenic patient is pyrexial at any time (above 37.5 ˚C) then cultures should be taken if available and appropriate (Blood x2 sets, urine, throat and wound swabs). The patient should then be started on appropriate triple antibiotic therapy, such as a) Gentamicin, Amoxicillin, Cloxacillin or b) Chloramphenicol or Clindamycin, Amoxicillin and Cloxacillin. An anti-fungal should be considered if cultures are negative and the patient remains pyrexial after one week.

Haematuria

Occasionally with chemotherapy gross haematuria will be noted. This is usually self-limited. Admit and observe these patients until resolution. Ensure adequate hydration preferably intravenously. Delay further chemotherapy until gross haematuria is resolved.

Mouth & Tooth Care

Saline swish and spit can be used to clean visible necrotic tissue and decrease bad breath. Plaque removal can be attempted with a dental scaling instrument. Teeth which are loose and displaced by the BL tumour usually go back into place after the tumour has regressed. Therefore do not remove unless they remain loose after the tumour has shrunk or after five weeks.

Secondary Infection

Tumour necrosis can lead to skin breakdown and predispose to abscess formation. A typical scenario is a tumour which initially regresses in size, but then grows again, becoming erythematous and warm to touch. Abscesses should be treated by incision and drainage, antibiotic coverage, and wet-to-dry dressings.

Cytotoxic Drug Extravasation

Local skin necrosis can occur during the intravenous injection of chemotherapy drugs. Therefore extreme care must be taken to assure safe positioning of the needle inside the vein. Using a butterfly needle or a venocath (as compared to a straight needle) will lessen the chances of needle displacement during administration. Testing the patency and proper positioning can be done with a 5cc saline flush in advance of injecting the chemotherapy drugs.

Tumour Lysis Syndrome

This is best prevented by good hydration and use of Allopurinol during the first chemotherapy treatment. Rapid rise in Uric Acid during chemotherapy increases risk of tumour lysis syndrome. Follow Uric Acid, calcium, and creatinine for 2 to 3 days following chemotherapy. Alkalinization of the urine will also assist in preventing tumour lysis syndrome.

More information on Tumour Lysis Syndrome is found in Appendix E.

RESPONSE, PROGNOSIS AND FOLLOW-UP

ASSESSING RESPONSE

Anything less than complete response i.e. progressive disease during chemotherapy should be referred immediately for further investigations and possible second line chemotherapy.

NB: Any new swelling after chemotherapy in any part of the body should be considered a tumour recurrence until proven otherwise.

In case of relapse after finishing six (6) cycles of chemotherapy, the patient should be referred to specialized institutions such as Ocean Road Cancer Institute or referral hospitals.

PROGNOSIS

The prognosis in children correlates with the bulk of disease at the time of diagnosis. With appropriate management of the metabolic consequences of rapid cell turnover and with combination chemotherapy and CNS prophylaxis, the survival rate has been improved significantly.

Patients with limited (i.e. Stage A) disease have an excellent prognosis, with a survival rate greater than 90%.

Patients with more extensive disease, especially bone marrow and CNS involvement, have a worse prognosis, but long-term survival rates as high as 80% can be achieved with more aggressive chemotherapy regimens.

Adults with Burkitt's Lymphoma, particularly those with advanced stage disease, do more poorly than children with the disease.

FOLLOW-UP SCHEDULE AFTER COMPLETING THE SIX CYCLES TREATMENT

- Monthly for the first 6 months, then
- 3 monthly for the next 18 months, then
- Annually thereafter.

The following should be done during the follow up visits:

- Physical examination
- Growth monitoring (height and weight)
- Ultrasound scan of abdomen
- Counselling (on nutrition and school attendances)
- Advise on nutrition

INDICATIONS FOR REFERRAL

- Lack of medicine
- Treatment failure – progressive disease
- Recurrence within the first three months of treatment
- When there is indication for second line treatment
- When CSF is positive after 12 doses of IT Methotrexate
- Any other lymphomas
- If not sure with the diagnosis

EXPENSES

In Tanzania Cancer patients are **exempted from cost sharing.**

When available, Chemotherapy drugs are to be given free. Burkitt's Lymphoma Treatment Programs, such as those supported by the Ministry of Health and Social Welfare, IMA World Health, and other groups, are designed to distribute the drugs free of charge, so health facilities ought to inquire about enrollment. However, due to financial and logistic constraints, free drugs are not always available, making it necessary for the patients to buy their own drugs. Even in stable patients treatment should not be delayed more than three days, if

possible, and patients must be encouraged to cover the drug costs. According to data from ORCI, the average cost of drugs for full six cycles in 20 Kg child is approximately 300,000/= Tshs

ADHERENCE AND COMMUNITY OUTREACH

Beyond implementing the appropriate medical regimens, a functioning health care facility BL program needs to have a strong community component. Patient mortality and morbidity is associated with two key elements of how patients and their families respond to BL:

1. Delay in seeking treatment - resulting in advanced stage disease at time of seeking care and treatment.
2. Failure to complete all six (6) treatment cycles - resulting in incomplete response to treatment and higher likelihood of recurrence.

Community outreach and education campaigns that address these two prominent factors can help saves lives. The UICC My Child Matters project on Expanding treatment for BL in Tanzania is a good example of an intervention to address the above two problems.

Patients and their families need to be encouraged to seek prompt treatment. Given that only 3/100,000[15] children will be affected by Burkitt's Lymphoma at any one time, the challenge is to promote community awareness of a relatively rare condition. Many factors contribute to a delay in the initial presentation of patients to health facilities. Some of these factors may be addressed through:

1. **Cost**
    a. Enroll additional hospitals in the treatment programs offered by NGOs and the MoHSW, as available.
    b. Inform the public that cancer patients in Tanzania are free of cost sharing including Burkitt's Lymphoma.

[15] Ziegler J.L., et al. *"Cure of Burkitt's lymphoma. Ten-year follow-up of 157 Ugandan patients."* The Lancet 1979 Nov 3; 2(8149):936-8.

2. **Distance**

   Strengthen referral transport systems from lower health facilities to hospitals.

3. **Lack of awareness**

   Distribute IEC materials for prominent display advocating the availability of BL treatment.

Encourage the completion of all six (6) treatment cycles. Some institutions admit patients for (3) three months order to ensure the completion of chemotherapy treatment. Alternatives to three (3) months of in-patient care can include:

1. Develop a "tickler" system to remind appropriate hospital staff of when a patient is due back for follow up. Record detailed contacts including telephone numbers. Contact patients by phone calls.
2. Visit the patient's home if more than a week late for the next scheduled treatment.
3. Encourage integration with other existing health care programs for tracking patients. For example the TB/Leprosy, Malaria and HIV/AIDS.

Even after the regular course of treatment is finished, return visits are necessary (see follow up schedules on page 19) to review the child's condition and check for any sign of relapse.

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APPENDIX A:
DRUG INDEX

CYCLOPHOSPHAMIDE[16]

Cyclophosphamide is a chemotherapy drug that is mainly used in the treatment BL and the following types of cancers.

- Breast cancer
- Non-Hodgkin's lymphoma
- Chronic lymphocytic leukemia
- Ovarian cancer
- Bladder cancer
- Bone and soft tissue sarcoma
- Rabdomyosarcoma
- Neuroblastoma
- Wilm's tumour

Description

Cyclophosphamide is a white colored powder which makes a colorless solution when dissolved. This solution is usually administered through the vein. A central line or a venocath is commonly used to administer cyclophosphamide to the vein.

It is also available as a white colored 25 mg or 50 mg tablet.

Side effects

Side effects associated with cyclophosphamide may vary from person to person. Some patients may experience significant side effects while others may experience very minimal side effects. It is not possible to predict who is going to have more severe side effects. All the side effects described here will not affect everyone. Most patients will have the common side effects like hair loss, while some other side effects may affect few patients, and may not trouble some others.

[16] http://medicineworld.org/cancer/breast/treatment/chemodrugs/cytoxan.html

Bone marrow suppression and lowering of blood counts

Use of cyclophosphamide like many other chemotherapy drugs can cause suppression of the bone marrow resulting in neutropenia. Febrile neutropenia is a significant risk and many times will require admission to the hospital for intravenous antibiotic treatment. Anemia may cause fatigue, lack of energy and tiredness. If platelets go down, increases the risk of bleeding or bruising. The blood counts may start falling in about a week's time after treatment; however the lowest points in the blood counts are usually seen around 10 to 14 days after treatment. Usually from this point onwards the blood count usually recovers and reaches normal values within 21-28 days.

The degree of lowering of the blood counts will depend on the type and dose of chemotherapy. If the red cells or platelets are very low will require have blood or platelet transfusions.

Hair loss

Hair loss is relatively severe with cyclophosphamide. This usually starts 3-4 weeks after the first dose of cyclophosphamide, and may gradually worsen with subsequent doses of cyclophosphamide.

Nausea and vomiting

Cyclophosphamide treatment may cause nausea and vomiting in some patients, and may require medication. Commonly the nausea and vomiting may occur few hours after the administration of chemotherapy and may last one or more days.

Bladder toxicity

Bladder toxicity may present as pain during urination and or increased frequency of urination. This complication can begin within 24 hours of treatment with cyclophosphamide or may be delayed by several weeks. This may be reversed by stopping further drug administration. Rarely will it result in gross haematuria.

Skin and nail color changes
Treatment with cyclophosphamide may result in darkening of the skin. This is due to excess production of pigments. The skin color may return to normal a few months after the treatment has completed.

Stopping of menstrual periods
Amenorrhea is a complication of treatment with cyclophosphamide. This is due to ovarian failure and may be permanent resulting in infertility.

Loss of appetite
Cyclophosphamide treatment may result in loss of appetite.

Mouth ulcers and taste change
Developing soreness in the mouth, or small ulcers in the inner parts of the cheeks, back of throat or tongue. Drinking plenty of fluids and having good mouth care with gentle brush may decrease the chance of developing mouth sores. Change or loss of taste for food may occur during chemotherapy. This problem usually disappears when the treatment is completed and normal taste will come back.

SIADH syndrome
This is a condition in which the body retains excess amounts of water with the production of concentrated urine. This may result in decrease in serum sodium, subsequently causing various complications.

Cardiac toxicity
Cardiac toxicity may be seen with high dose chemotherapy using cyclophosphamide.

Increased risk of other cancer
Treatment with cyclophosphamide may result in increased risk of other caners including leukemia and bladder cancer.

Suppression of immune system

Cyclophosphamide may suppress the immune system making one more susceptible to infection. This occurs independent of the white cell count.

Allergic reactions

Cyclophosphamide treatment may result in allergic reactions like running nose, irritation of the nose and throat. These usually disappear within 2-3 days.

Lung toxicity

Cyclophosphamide treatment may result in lung toxicity, which may result in shortness of breath.

Liver function abnormalities

Cyclophosphamide may interfere with the normal working of liver, causing abnormal liver function tests.

METHOTREXATE (AMETHOPTERIN)[17]

Methotrexate is a chemotherapy drug that is mainly used in the treatment of the following types of cancers.

- Breast cancer
- Head and Neck Cancer
- Osteogenic sarcoma
- Acute lymphoblastic leukemia
- Non-Hodgkin's disease
- Meningial leukemia
- Carcinomatous meningitis
- Bladder cancer
- Colorectal cancer
- Gestational tumours

[17] http://medicineworld.org/cancer/breast/treatment/chemodrugs/methotrexate.html

Description

When reconstituted, Methotrexate appears as a yellow liquid. This solution is usually administered through the vein. However in the treatment of meningeal leukemia and carcinomatous meningitis, this drug is administered directly in to the spinal fluid or brain. Methotrexate may also be available as a 2.5mg or 10 mg tablets. A central line (small catheter into a big vein) or a portocath (similar device which is placed under the skin) is commonly used to administer Methotrexate to the vein.

Side effects

Side effects associated with Methotrexate may vary from person to person. Some patients may experience significant side effects while others may experience very minimal side effects. It is not possible to predict who is going to have more severe side effects. All the side effects described here will not affect everyone. Most patients will have the common side effects like hair loss, while some other side effects may affect few patients, and may not trouble some others.

Bone marrow suppression and lowering of blood counts

Use of Methotrexate like many other chemotherapy drugs can cause suppression of the bone marrow resulting in neutropenia. Febrile neutropenia is a significant risk and many times will require admission to the hospital for intravenous antibiotic treatment. Anemia may cause fatigue, lack of energy and tiredness. As platelets go down, you may be at risk of bleeding or bruising. The blood counts may start falling in about a week's time after treatment; however the lowest points in the blood counts are usually seen around 10 to 14 days after treatment. Usually from this point onwards the blood count usually recover and reaches normal values within 21-28 days.

The degree of lowering of the blood counts will depend on the type and dose of chemotherapy. If the red cells or platelets are very low will require have blood or platelet transfusions.

Nausea and vomiting

Methotrexate treatment may cause nausea and vomiting in some patients, and may require medication. Commonly the nausea and vomiting may occur few hours after the administration of chemotherapy and may last one or more days.

Diarrhea

Treatment with Methotrexate may lead to diarrhea; however diarrhea is usually mild and usually can be relieved by medications like, Imodium.

Mouth ulcers and taste change

You may develop soreness in the mouth, or may notice small ulcers in the inner parts of the cheeks, back of throat or tongue. Drinking plenty of fluids and having good mouth care with gentle brush may decrease the chance of developing mouth sores. If this happens, your physician will give you some lotions to apply to the affected areas. You may also have change or loss of taste for food while undergoing chemotherapy. The food may taste different. This problem usually disappears when the treatment is completed and normal taste will come back.

Skin and nail color changes

Treatment with Methotrexate may result in darkening of the skin. This is due to excess production of pigments. The skin color may return to normal a few months after the treatment has completed.

Fatigue and tiredness

Treatment with Methotrexate may result in fatigue and tiredness. Moderate activity and plenty of rest will help with fatigue and tiredness.

Damage to kidneys

Methotrexate when in given in large doses can cause damage to the

kidney. There is only very low risk for the kidney damage if the standard doses are used. Some times infusion of alkaline fluid may be used with Methotrexate treatment in order to decrease the risk of renal toxicity.

Watering from eyes

Methotrexate when in given in large doses can cause damage irritation and redness in the eye causing inflammation of the conjunctiva. This may occur with lower doses of Methotrexate. Soothing eye drops are sometimes prescribed to these patients.

Hair loss

Hair loss is relatively rare with smaller doses of Methotrexate treatment. However higher doses of Methotrexate can cause significant hair loss. This usually starts 3-4 weeks after the first dose of Methotrexate, and may gradually worsen with subsequent doses of Methotrexate.

Sensitivity to sunlight

The skin may become excessively sensitive to sunlight while you are receiving Methotrexate. This effect may also last for several months after completion of the treatment. You should wear a high protection factor sun cream and protective clothing when going out in the sun.

Liver function abnormalities

Methotrexate may interfere with the normal working of liver causing abnormal liver function tests.

Lung toxicity

Methotrexate treatment may result rarely in lung toxicity. Watch for shortness of breath.

Allergic reactions

Methotrexate treatment may result in allergic reactions like running

nose, irritation of the nose and throat. These usually disappear within 2-3 days.

Skin rash

Methotrexate treatment may result in allergic reactions in the form of a skin rash. These usually disappear within 3-4 days.

Neurological problems

High dose Methotrexate treatment may result in neurological problems like headache, difficulty in speaking, behavioral abnormalities and seizures.

Interaction with other drugs

Methotrexate may interact with other drugs like coumadin, aspirin, penicillins, anti-inflammatory drugs like ibuprofen etc.

VINCRISTINE[18]

WARNING:

If Vincristine extravagates into surrounding tissue, the skin and/or muscle may be severely damaged. Fatalities have occurred when vincristine was injected into the spine. This drug is for intravenous (IV) use only.

How to Use

This is a potent medication. Use it exactly as prescribed. Drink plenty of fluids while taking this medication. Use medication for stomach cramps or constipation.

Side Effects

Nausea, vomiting, loss of weight, diarrhea, rash or bloating are

[18] www.medicinenet.com

common side effects. Not eating before the treatment may help relieve vomiting. Changes in diet such as eating several small meals or limiting activity may help lessen some of these effects. In some cases, drug therapy may be necessary to prevent or relieve nausea and vomiting. Temporary hair loss is another common side effect; normal hair growth should return after treatment has ended. Other symptoms: constipation, stomach cramps, lack of sweating, painful or difficult urination, decrease or increase in urination, bed-wetting, joint pain, lower back or side pain, blurred or double vision, difficulty walking, headache, pain in jaw or testicles, pain or numbness in fingers or toes, nervousness, trouble sleeping, confusion, dizziness, fever or chills, hallucinations, loss of appetite, cough, unusual bleeding or bruising, black, tarry stools, blood in urine or stools, small red spots on the skin. If you notice other effects not listed above, contact your doctor or pharmacist.

Precautions

Contraceptive measures are recommended for use in men and women while taking this medication. Vincristine is not recommended for use during pregnancy. It is not known if this medication passes into breast milk. Do not have immunizations/vaccinations without consent of your doctor, and avoid contact with people who have recently received oral polio vaccine.

Drug Interactions

Phenytoin, digoxin, itraconazole

Overdose

Symptoms of overdose may include seizures

Notes

Avoid touching the eyes or inside the nose without first washing the

hands. Use caution with sharp objects like safety razors or nail cutters and avoid activities such as contact sports in order to lower the chance of getting cut, bruised or injured.

Missed Dose
Do not double dose if missed.

Storage
Refrigerate piggyback or infusion device. Warm to room temperature before infusing, and Check expiration date.

ALLOPURINOL[19]

Drug Class and Mechanism
Allopurinol is used to lower blood uric acid levels. Uric acid is a breakdown product of purines in foods. Uric acid forms crystals in the tissues of the body to cause the inflammation of gout. Elevated blood uric acid levels can also cause kidney disease and stones. Allopurinol can be used to prevent uric acid kidney stones and to prevent recurrent gouty arthritis attacks.

Preparations
Tablets: 100mg, 300mg

Storage
Store at 59-77°F (15-25°C), in a sealed, light- resistant container, avoid moisture.

Prescribed For
Allopurinol is used to treat patients with multiple recurrent gout attacks, erosive destructive gouty joint disease, hard lumps of uric acid deposits in tissues (called tophi), gouty kidney disease, or uric acid stones. Allopurinol is also used to prevent elevation of blood uric acid in patients undergoing chemotherapy for the treatment of certain cancers.

[19] www.medicinenet.com

Dosage

It should be taken with food to avoid stomach irritation. Patients should also drink plenty of fluids while taking Allopurinol.

Drug Interactions

Allopurinol should be avoided by patients with a prior severe reaction to the drug. Allopurinol can cause a flare-up of gouty arthritis while the blood uric acid level is initially adjusted, therefore, Colchicine is often used simultaneously to prevent these flares. Allopurinol is not started during active inflammation because it can worsen and prolong attacks of acute gouty arthritis. Patients taking simultaneous Purinethol or Imuran require reductions of dosages of these drugs. There is an increased risk of skin rash in patients taking ampicillin and amoxicillin (Amoxil). Allopurinol can cause a serious allergic liver toxicity that can be fatal. Appetite loss and itching can be signs of liver toxicity. The risk of this reaction increases in patients with kidney impairment. Patients with kidney impairment require lower doses. Allopurinol is used in children during treatment of cancers or rare diseases of purine metabolism.

Pregnancy

Safety in pregnancy has not been established.

Nursing Mothers

Allopurinol is excreted in breast milk.

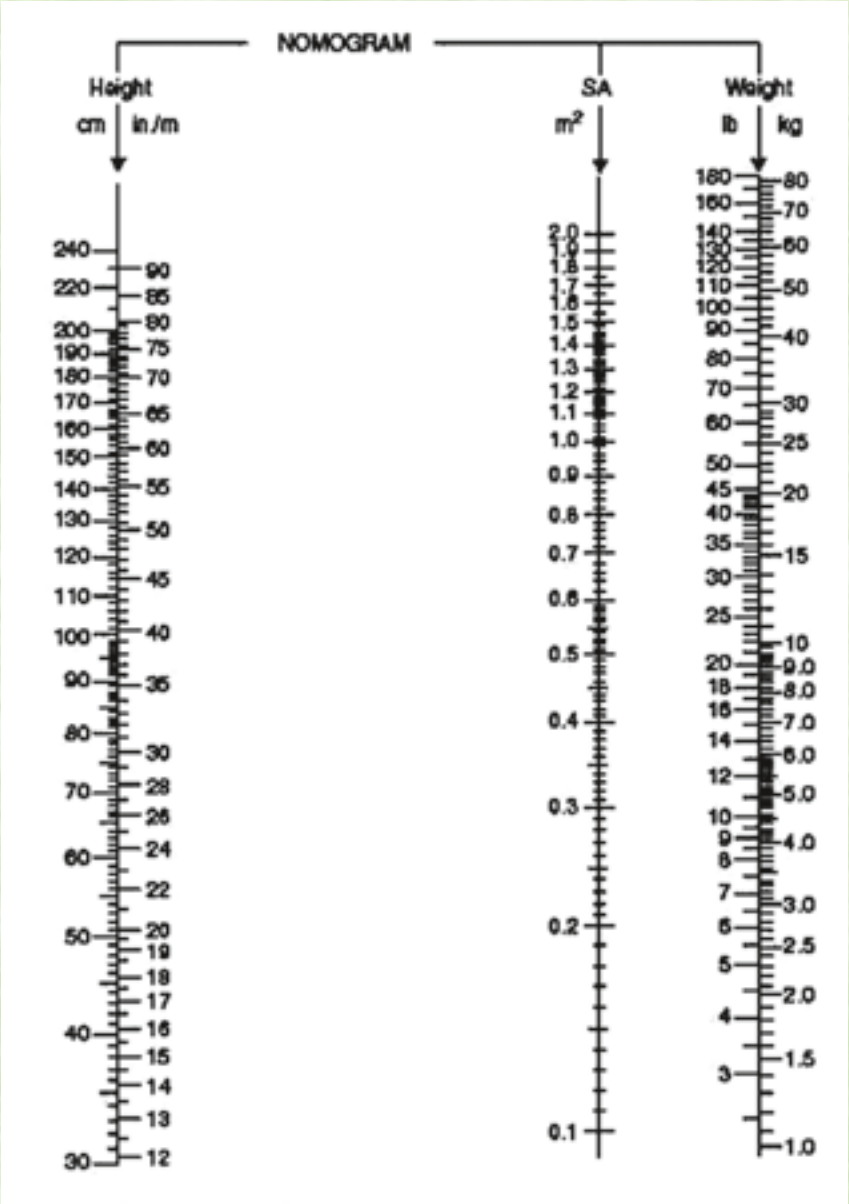
Side Effects

The most frequent adverse reaction to Allopurinol is skin rash. Allopurinol should be discontinued immediately at the first appearance of rash, painful urination, blood in the urine, eye irritation, or swelling of the mouth or lips, because these can be a signs of impending severe allergic reaction, which can be fatal. Rarely, Allopurinol can cause nerve, kidney, and bone marrow damage.

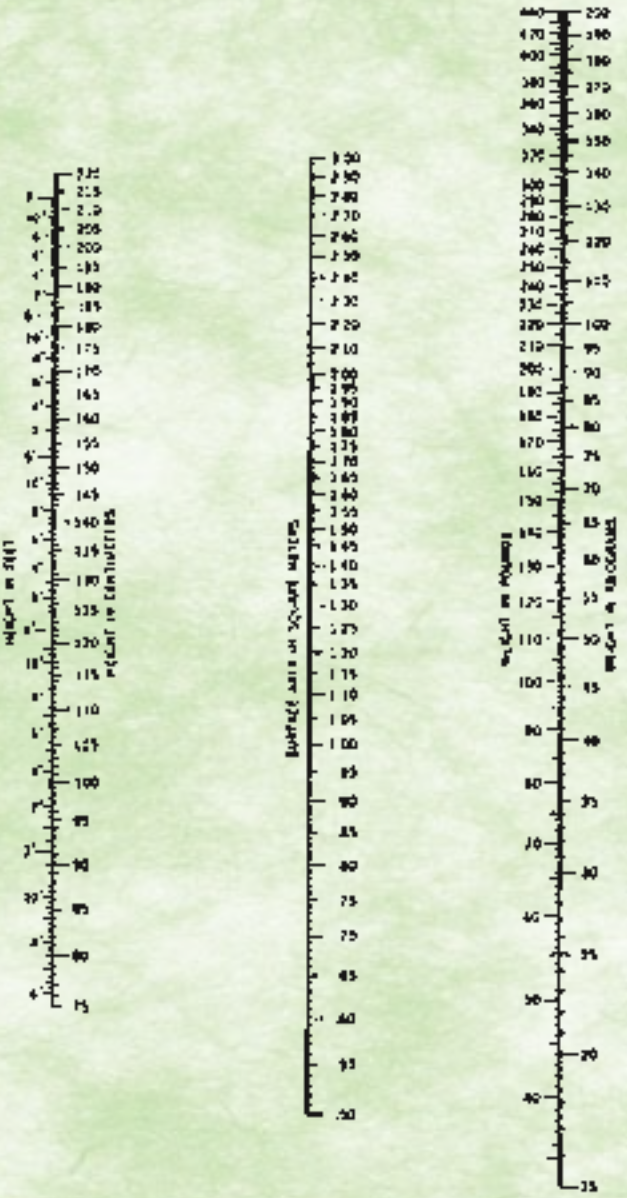
APPENDIX B:
CHEMOTHERAPY DOSAGE SCHEDULE

BL Chemotherapy Dosage Schedule				
		Cyclophosphamide IV	Vincristine IV	Methotrexate IV
Weight Kg	Body Area m^2	40mg/Kg mg	1.4mg/m^2 mg	75mg/m^2 mg
4	0.26	160	0.4	19.5
5	0.3	200	0.4	22.5
6	0.34	240	0.5	25.5
7	0.38	280	0.5	28.5
8	0.42	320	0.6	31.5
9	0.46	360	0.6	34.5
10	0.49	400	0.7	36.8
11	0.53	440	0.7	39.8
12	0.56	480	0.8	42
13	0.59	520	0.8	44.3
14	0.62	560	0.9	46.5
15	0.65	600	0.9	48.8
16	0.68	640	1	51
17	0.71	680	1	53.3
18	0.74	720	1	55.5
19	0.77	760	1.1	57.8
20	0.79	800	1.1	59.3
21	0.82	840	1.1	61.5
22	0.85	880	1.2	63.8
23	0.87	920	1.2	65.3
24	0.9	960	1.3	67.5
25	0.92	1000	1.3	69
27	0.97	1080	1.4	72.8
32	1.1	1280	1.5	82.5
36	1.2	1440	1.7	90
40	1.3	1600	1.8	97.5

APPENDIX C:
NORMOGRAM FOR ESTIMATION OF BODY SURFACE AREA (CHILDREN)



APPENDIX D:
NORMOGRAM FOR ESTIMATION OF BODY SURFACE AREA (ADULT)



APPENDIX E:
TUMOUR LYSIS SYNDROME

Tumour Lysis syndrome (TLS) refers to the constellation of metabolic disturbances that may be seen after initiation of cancer treatment[20]. Tumour Lysis syndrome usually occurs in patients with bulky, rapidly proliferating, and treatment-responsive tumours. Tumour Lysis syndrome is typically associated with acute leukemias and high-grade non-Hodgkin lymphomas, such as Burkitt's Lymphom.

CLINICAL FEATURES

A constellation of clinical symptoms, such as;

- nausea
- vomiting
- lethargy
- edema
- fluid overload
- congestive heart failure
- cardiac dysrhythmias
- seizures
- muscle cramps
- tetany
- syncope
- sudden death

These issues may develop prior to initiation of chemotherapy or more commonly within 72 hours after administration of cytotoxic therapy.

Differentials

Acute Renal Failure; Exclude pre-renal and renal causes

Lab Studies

High-risk patients should have laboratory monitoring (BUN, creatinine,

[20] Burkitt D. *"A sarcoma involving the jaws in African children."* British Journal of Surgery. 1958 Nov; 46 (197):218-23.

phosphate, uric acid, LDH, and calcium) prior to therapy and for 48-72 hours after treatment induction.

MANAGEMENT OF TUMOUR LYSIS SYNDROME

1. **Early identification** of patients at risk by assessing the extent of tumour burden, histopathologic findings, and renal is the most important aspect of management function.

2. Initiate **prophylactic measures** before the initiation of therapy. This entails Allopurinol and hydration

3. **Prompt initiation of supportive care** for patients who develop acute tumor lysis syndrome during treatment, withholding cancer therapy if possible until all parameters are corrected through Allopurinol and hydration

   a) Allopurinol is a xanthine oxidase inhibitor and is given to reduce the conversion of nucleic acid byproducts to uric acid in order to prevent urate nephropathy and subsequent oliguric renal failure.

   Patients unable to take oral medications can be given intravenous Allopurinol.

PEDIATRIC DOSE	• <6 years: 150 mg/d PO divided bid/tid, not to exceed 800 mg/d • 6-10 years: 300 mg/d PO • IV: 200 mg/m^2/d • >10 years: Administer as in adults
ADULT DOSE	• 600-800 mg/d PO, not to exceed 800 mg/d; alternatively, 200-400 mg/m^2/d IV; not to exceed 600 mg/d

b) Hydration:

Volume depletion is a major risk factor for tumor lysis syndrome and must be corrected vigorously.

Ideally, intravenous hydration in high-risk patients should begin 24-48 hours prior to initiation of cancer therapy and continue for 48-72 hours after completion of chemotherapy.

Continuous infusion rates as high as 4-5 L/d (or 3 $L/m^2/d$) yielding urine volumes of at least 3 L/d should be given unless the patient's cardiovascular status indicates impending volume overload.

NOTES:

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