

GENERAL GUIDELINES FOR MAINTENANCE CHEMOTHERAPY IN CHILDREN WITH ACUTE LYMPHOBLASTIC LEUKAEMIA

General considerations

- check height, weight and calculate surface area (m^2) every 3 months and adjust drug dosages accordingly. In the absence of a Normogram to calculate the surface area, use the following formula:

$$\text{SURFACE AREA} = \text{SQUARE ROOT of } [\text{Height (cm)} \times \text{Weight (kg)} / 3600]$$

- check full blood picture every 2 weeks for the next 1-2 months after starting maintenance chemotherapy and monthly thereafter if stable.
- bone marrow aspiration should be considered if counts are repeatedly low or if there is clinical suspicion of relapse. The majority of relapse ($>2/3$) would occur within the first year of diagnosis.
- central nervous system disease usually presents with headache, vomiting, altered sensorium or hypothalamic symptoms (e.g. hyperphagia, excessive weight gain)

Managing blood counts

- adjust chemotherapy to maintain absolute neutrophil count (ANC) $\geq 1 \times 10^9$ /dL.
 - if ANC is $0.75 - 1.0 \times 10^9$ /L ($500 - 1000/mm^3$) or platelet count $50-100 \times 10^9$ /L, reduce 6-mercaptopurine (6MP) and methotrexate (MTX) dose by 50%.
 - keep at this dose until counts are above those levels.
 - then increase 6MP and MTX to 75% recommended dose and review in 1 week.
 - if counts are acceptable, then continue at 100% dose,
 - if neutrophil count $< 0.5 \times 10^9$ /L or platelets $< 50 \times 10^9$ /L, stop both drugs.
 - restart drugs at 50% dose when ANC $> 1.0 \times 10^9$ /L, then increase to 75% and 100% as above.
- normally Hb would remain stable but repeated falls in haemoglobin alone may be due to 6MP intolerance; hence reduce dose as above and attempt to increase dose gradually again. MTX should stay at top dose. If counts take longer to recover, consider performing bone marrow aspiration after 2-3 weeks.
- Anaemia occurring early in the course of continuing therapy should be treated with transfusion and the dose of 6MP and MTX maintained. If persistent anaemia occurs (i.e. Hb < 8 gm/dl) despite reducing the dose of 6MP, the MTX dose should be reduced appropriately.
- if counts are persistently low and dose of 6MP/MTX are suboptimal, consider withholding cotrimoxazole. Re-introduce once 6MP or MTX are at $> 75\%$ of protocol dosage. If neutropenia recurs or if child cannot tolerate at least 75% drug dosage, cotrimoxazole should be stopped. The maintenance of adequate drug dose should take priority over continuing cotrimoxazole. If cotrimoxazole is stopped, it must be remembered that the child is at increased risk of pneumocystis pneumonia and there should be a low threshold for treatment of suspected interstitial pneumonitis.

Other complications

- in severe diarrhoea and vomiting, stop both drugs. Restart at 50% protocol when better and return to full dose when tolerated.
- severe MTX mucositis; withhold MTX until improvement and restart at full dose.
- initiate supportive treatment with mouthwash, antifungal treatment (Nystatin / Daktarin oral gel) and local anaesthetic e.g. viscous xylocaine.

- in clinically significant liver dysfunction (e.g. jaundice); oral MTX should be stopped until improvement occurs. Restart at reduced dose and increase as tolerated. Investigate for causes of liver dysfunction. Monitor LFT.

Infections

- *Pneumocystis carinii* pneumonia (PCP) prophylaxis
Cotrimoxazole is routinely used as prophylaxis against PCP and continued until the end of therapy. In the event of chronic cough or unexplained tachypnoea, a chest X-ray is required. If there is evidence of interstitial pneumonitis, then send off nasopharyngeal secretions for PCP IFT and treat empirically with high dose cotrimoxazole (Bactrim/Septim) (20 mg/kg/day in divided doses) for 2 weeks.
- *Febrile neutropaenia* (ANC < 1 x 10⁹ /dL)
 - if there is significant fever (temperature ≥ 38.5 °C x 1 or ≥ 38 °C x 2, one hour apart), stop all drugs and admit to hospital for IV antibiotics.
 - take appropriate cultures and chest X-rays as indicated; start IV antibiotics immediately, without waiting for specific bacteriological confirmation. Use an aminoglycoside - cephalosporin combination to treat both gram negative and gram positive organisms.
 - if nosocomial infection is suspected, use the appropriate antibiotics according to your hospital's culture-sensitivity pattern. Assume multiresistant bacterial sepsis when dealing with patients presenting with septic shock.
 - early and aggressive therapy will save lives.
- *Antifungal therapy* may be indicated in prolonged neutropenia or if there is no response to antibiotics, or if fungal infection is suspected.
- *Vancomycin* may be indicated if there is a long line in situ or if MRSA or coagulase negative *Staphylococcus* infections are suspected.
- *Chicken Pox/Measles infection*
 - these are life-threatening infections in ill immunocompromised children.
 - always reinforce this information on parents when they come for follow-up.
 - if a patient is significantly/directly exposed (in the same room > 1 hour), including the 3 days prior to clinical presentation, to sibling, classroom contact, enclosed playmate contact or other significant contact, they are at increased risk of developing these infections. **GIVE:**
 - **Measles:** Human broad-spectrum immune globulin IM 0.5ml/kg divided into 2 separate injection sites on the same day.
 - **Chickenpox:** There is no Zoster immune globulin readily *available locally*.
exposed patients: oral Acyclovir 200mg 3 x/day for 5 days (< age 6 years) and 400 mg 3 x/day if > 6 years for 5 days.
These patients must be monitored for signs of infections. If a patient develops chickenpox, admit, isolate and treat immediately with IV acyclovir 500 mg/m²/dose every 8 hours until no new lesions are noted, followed by oral acyclovir 400mg 5x daily (children < 2 years old) until the lesions are healed, usually in 10 days. If > 2 years old, 800mg 5x daily.
 - Chemotherapy must be stopped on suspicion of exposure; and if infected and treated: commence chemotherapy at 2-3 weeks after last vesicle has dried up.

Vaccinations

Children on chemotherapy should not receive any vaccinations until 12 months after cessation of chemotherapy. They may then recommence their immunisation programme continuing from where they left off.

References

Approach to anaemia

1. Lileyman JS, Hann IM. Paediatric Haematology. London, Churchill Livingstone, 1992.

Immune Thrombocytopenic purpura

1. George J, et al. (1996) Idiopathic thrombocytopenic purpura: a practice guideline developed by explicit methods for the American Society of Hematology. *Blood* 1996; 88: 3-40.
2. Lilleyman J. Management of Childhood Idiopathic Thrombocytopenic Purpura. *Brit J Haematol* 1997; 105: 871-875
3. James J. Treatment Dilemma in Childhood Idiopathic Thrombocytopenic Purpura. *Lancet* 305: 602
4. Nathan D, Orkin S, Ginsburg D, Look A. *Nathan and Oski's Hematology of Infancy and Childhood. 6th ed 2003. W.B. Saunders Company.*

Haemophilia

1. Malaysian CPG for Management of Haemophilia..

Oncology emergencies

1. Pizzo, Poplack: *Principles and Practice of Paediatric Oncology. 4th Ed, 2002*
2. Pinkerton, Plowman: *Paediatric Oncology. 2nd Ed. 1997*
3. Paediatric clinics of North America, Aug 1997.