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|  | **Issue date: July 2016**  **Review date: July 2018** |
|  | 1. Follow protocol guidelines at all times 2. Administer Chemotherapy safely.   3. Detect and treat side effects promptly. |

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| 1. | Actinomycin D |
| Also known as | Dactinomycin |
| Type of chemotherapy | Antitumour antibiotic: Inhibits DNA and RNA synthesis. Cell cycle non phase specific. |
| Pre-constitution storage | Below 25 degrees in chemotherapy cupboard. Protect from light. Stable for 5 years. |
| Compatibility | Normal saline, Dextrose 5%w/v - Maximum conc. 10microg/ml |
| Post reconstitution storage | Stable for 7 days when refrigerated. Also stable when frozen. |
| Clinical Uses: | Wilms tumour, rhabdomyosarcoma |
| Administration | Intravenous: bolus |
| When to delay | ANC <1.0; Platelets < 100 |
| When to reduce | 1. Hematologic: If there is repeated delayed adequate bone marrow recovery from the last 2 doses reduce by 25%; reduce by weight and age as per protocols 2. Liver toxicity:      1. Sinisoidal Obstruction Syndrome |
| When to discontinue | Hypersensitivity; prolonged myleosuppression |
| Interactions | Erythromycin, doxorubicin, hydroxyurea, use together but with caution. Tranexamic acid, hepatotoxic and gastrotoxic drugs (e.g., NSAIDs) need to be considered (can give ranitidine as pre-treatment prophylaxis if needed). |
| Special Considerations | Drug is a vesicant (giving in 5%Dextrose preferred) Ensure good IV access before giving to prevent extravasation. |
| Potential Side Effects | * Nausea & Vomiting, Diarrhoea * Stomatitis, mucositis * Gastric and Oesophogeal Ulceration * Bone Marrow Depression (Nadir Day 7-14) * Neurotoxic: Malaise, Fatigue, Fever, Mental Depression * Hepatotoxic (esp. Wilms with tumour) * Sinusoidal Obstruction Syndrome (AKA Veno-occlusive disease of the liver (VOD) * Alopecia * Facial flushing * **Radiation recall phenomenon: Omit Dactinomycin when receiving radiotherapy** |
|  | **Nursing Intervention** |
|  | Explain chemotherapy given as a bolus. Make sure to flush with normal saline to ensure IV access is patent and thus prevent extravasation. |
|  | Administer Anti-emetics and ranitidine as prescribed. |
|  | Adhere to safe handling of Cytotoxic Drugs guidelines. |
|  | Ensure FBP is adequate i.e Hb >7, ANC> 1.0, Plts >100. |
|  | Monitor closely for signs of extravasation and other S/E’s mentioned above. |

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| 2. | Asparaginase |
| Also known as: | Colaspas, Elaspar, Erwinase |
| Type of chemotherapy | Bacterial enzyme protein from Erwinia chrysanthemi or more commonly, E. Coli. which catalyzes the conversion of L-asparagine to aspartic acid and ammonia. Some cells, e.g. acute lymphoblastic leukaemia cells, cannot synthesise this amino acid and so die if circulating asparagine is removed. |
| Pre-constitution storage | Between 2-8 degrees stable for 3 years from date of manufacture. |
| Compatibility | Normal saline |
| Post reconstitution storage | Stable for 8 hours at room temperature. |
| Clinical Uses: | Acute lymphoblastic leukaemia |
| Administration | Administer intradermal test dose of 1000 units 1 hour prior to IM dose.  Intramuscular route – preferred as less risk of anaphylaxis  Intravenous – slow bolus – Risk of severe anaphylaxis 10-40%. |
| Special Considerations | Risk of anaphylaxis – please ensure antihistamine, adrenaline and steroids available prior to giving injection. |
| When to delay | If actively bleeding do not give IM |
| When to reduce | Severe hepatic impairment – clinical decision – clotting/bleeding risk may also be increased. |
| When to discontinue | If anaphylaxis to E.Coli Asparaginase develops (30% of patients) erwinia may be cautiously tried instead.  Coagulopathy: If symptomatic, hold asparaginase until symptoms resolve, then resume with the next scheduled dose. Consider factor replacement if fibrinogen <0.8g/L (FFP, cryoprecipitate, factor VIIa). Do not withhold dose for abnormal laboratory findings without clinical symptoms.  Pancreatitis (Grade 3-4): Discontinue asparaginase in the presence of hemorrhagic pancreatitis or severe pancreatitis (abdominal pain >72 hours and > Grade 3 amylase elevation (> 2.0x ULN). In the case of mild pancreatitis, asparaginase should be held until symptoms and signs subside, and amylase levels return to normal and then resumed. Severe pancreatitis is a contraindication to additional asparaginase administration. |
| Interactions | Caution with hepatotoxic and anticoagulant drugs. Methotrexate, Vincristine and G-CSF – Separate from these medications by minimum 24hrs (3 hours for Vincristine). Also steroids – increased risk side effects (e.g., hyperglycaemia, thrombosis and UGI bleed) can be used together in regimen but offer ranitidine cover and try to avoid Tranexamic acid if not bleeding. |
| Potential Side Effects | * Hypersensitivity reactions and anaphylaxis – urticarial (itch), angio-oedema (swelling), bronchospasm (difficulty breathing), abdominal pain, hypotension. * Pancreatitis – consider for acute abdominal pain * Coagulopathy – leading to bleeding and thrombotic events (measure baseline fibrinogen and/or APTT prior to each phase) * Hyperglycaemia – measure CBG prior to each dose. * Hypoalbuminaemia – monitor closely as very common and pre-disposes to oedema and increased exposure of protein-bound drugs (e.g., Methotrexate). |
|  | **Nursing Intervention** |
|  | Administer Anti-emetics as prescribed. Measure CBG prior to each dose. |
|  | Adhere to safe handling of Cytotoxic Drugs guidelines. |
|  | Ensure antihistamine, adrenaline and steroids are available and nearby in case of emergency. |
|  | Give as IM injection preferably. Administer intradermal test dose of 1000 units 1 hour prior to IM dose. |
|  | Monitor closely for signs of hypersensitivity reaction and other S/E’s mentioned above. If present call for help immediately. |

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| 3. | Bleomycin |
| Also known as: | More than 12 trade names |
| Type of chemotherapy | Antitumour Antibiotic: Cell cycle specific. Inhibits DNA synthesis and may inhibit RNA and protein synthesis. |
| Pre-constitution storage | Below 25 degrees in chemotherapy cupboard. Protect from light at all times. |
| Compatibility | **For Administration**: Normal saline or Dextrose 5%w/v protected from light. (conc. 3000-15000 units/ml)  **For storage post reconstitution**: only.  I.E. if you do not use the entire vial reconstitute with Normal Saline for subsequent storage. |
| Post reconstitution storage | Store in refrigerator, protected from light, in Normal saline.  Duration: 28 days. |
| Clinical Uses: | Hodgkins Lymphoma, Kaposi’s Sarcoma, germ cell tumours, malignant palliative pleural effusions. |
| Administration | Intravenous: Slow Bolus (minimum 5ml NS or D5). Can also be given IM (make up to 5ml with a 1% lidocaine solution as diluent)  Intracavitary: Ensure pleural effusion drained completely. Then mix 60iu with 50-100mls of Normal Saline and inject through chest drain. Clamp drain immediately. |
| When to delay | Myelosuppression |
| When to reduce | If Creatinine Clearance 10-50mls/minute give 25% dose reduction, if <10ml/min give 50% dose reduction. No dose adjustment required in hepatic impairment. |
| When to discontinue | Maximum cumulative lifetime dose = 350000units (250000units in KS?)  Idiosyncratic reaction – hypotension, fever, chills, wheezing, mental confusion |
| Interactions | Cisplatin and O2 therapy – increases the risk of lung toxicity. Phenytoin (reduced absorption). Caution with other nephrotoxic drugs (e.g., NSAID’s, Aminoglycosides) as may pre-dispose to drug accumulation. |
| Special Considerations | Dose dependent pulmonary fibrosis.  Avoid single IV boluses more than 30000units. |
| Potential Side Effects | * Fever (50% after 48 hours, 25% if given IM) * Nausea & Vomiting, Stomatitis, Mucositis * Pulmonary Toxicity: Pneumonitis (see above) – perform baseline CXR at point of diagnosis and avoid oxygen concentrations of above 30-40% unless absolutely necessary. Monitor for dyspnea and fine rales. * Alopecia * Skin changes: Striae, Pruritis, Skin Peeling, Hyperpigmentation * Decreases pharmacological effects of Phenytoin * Anaphylaxis: Wheezing, Flushing, Hypotension, Tachycardia |
|  | **Nursing Intervention** |
|  | Explain to parents that chemotherapy given as a bolus. |
|  | Administer Anti-emetics as prescribed. |
|  | Adhere to safe handling of Cytotoxic Drugs guidelines. |
|  | Ensure FBP is adequate i.e Hb >7, ANC> 1.0, Plts >100. |
|  | Monitor closely for signs of anaphylaxis and other S/E’s mentioned above. |

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| 4. | Carboplatin |
| Also known as | More than 20 trade names |
| Type of chemotherapy | Alkylating agent: Cell cycle non phase specific. Inhibits DNA synthesis. |
| Pre-constitution storage | Below 25 degrees in chemotherapy cupboard. Stable for 18-24 months. Protect from light at all times |
| Compatibility | **For Administration**: Dextrose 5%w/v (Normal Saline may be used if there is no alternative but D5%w/v is preferred). Final concentration 0.5-4mg/ml. |
| Post reconstitution storage | **For storage post reconstitution**: Stable for 8 hours at room temperature or 24hours when refrigerated in D5%w/v. |
| Clinical Uses: | Retinoblastoma, Wilms tumour, hepatoblastoma. |
| Administration | Intravenous: Infused over 1 hour |
| When to delay | 1. Myelosuppression: ANC< 1000, plt <100  2. Hepatic Toxicity: For SGOT (AST) or SGPT (ALT) > 4 x ULN for age, hold start of chemotherapy cycle until under 4 x ULN  for age |
| When to reduce | 1. Renal: If creatinine clearance less than 60ml/min; To trial dosing as per Calvert Formula – this takes creatinine clearance into account. Alternatively (if not using Calvert) – if CrCl 20-60ml/min – reduce by 25%, if CrCl 10-20ml/min – reduce by 50%, if CrCl <10ml/min reduce by 75%. However, clinical judgment needs to be applied for all severities of renal impairment with platinum compounds.  2. Marrow Suppression: If there is repeated delayed adequate bone marrow recovery from the last 2 doses reduce by 25%; reduce by weight and age as per protocols  3. Hearing  For 20 dB loss from baseline hearing at < 2000 Hz, decrease dose intravenous carboplatin by 50% for subsequent cycles. For > 20 dB loss at < 2000 Hz delete intravenous carboplatin from subsequent cycles.  4. Allergic Reaction  With the exception of anaphylaxis (see below), if an allergic reaction occurs, it is recommended to treat with:  1) diphenhydramine 1 mg/kg/dose (max dose 50 mg) IV slow push over 10-15 minutes or equivalent H1-receptor antagonist.  2) hydrocortisone 2 mg/kg/dose (max dose 200 mg) IV or equivalent steroid, if not responsive to diphenhydramine  3) ranitidine 1 mg/kg/dose IV (max dose 50 mg) over 15 minutes or equivalent H2-receptor antagonist, if unresponsive to diphenhydramine and hydrocortisone.  4) epinephrine 0.01 mg/kg/dose of a 1 mg/mL solution (max dose 0.3 mg) subcutaneously, if not responsive to diphenhydramine, hydrocortisone, and ranitidine, or if airway/breathing problem present.  In subsequent cycles of Carboplatin, it is recommended to infuse Carboplatin over 2 hours and premedicate with diphenhydramine 1mg/kg (max dose 50 mg) and steroids (if reaction is more than a mild reaction), and ranitidine 1 mg/kg/dose IV (max dose 50 mg) or equivalent H2-receptor antagonist if unresponsive to diphenhydramine and steroid. |
| When to discontinue | Anaphylaxis, severe renal impairment, |
| Interactions | Avoid giving with other renal or ototoxic medications, absorption of phenytoin reduced. |
| Special Considerations | Renal toxicity/ Ototoxicity |
| Potential Side Effects | * Nausea & Vomiting (moderate-severe), Stomatitis, Diarrhoea * Bone Marrow Depression (dose limiting) Thrombocytopaenia particularly (Nadir Day 14-21) * Nephrotoxicity * Neurotoxicity: Seizures, Peripheral Neuropathies * Hepatotoxicity * Ototoxicity * Skin Changes: Rash * Alopecia * Anaphylaxis: Wheezing, Flushing, Hypotension, Tachycardia |
|  | **Nursing Intervention** |
|  | Explain chemotherapy given as a one hour infusion – parents to call nurse if too fast or too slow. |
|  | Administer Anti-emetics as prescribed. |
|  | Adhere to safe handling of Cytotoxic Drugs guidelines. |
|  | Ensure FBP is adequate i.e Hb >7, ANC> 1.0, Plts >100. |
|  | Monitor closely for signs of anaphylaxis and other S/E’s mentioned above. |

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| 5. | Cisplatin |
| Also known as | CDDP |
| Type of chemotherapy | Alkylating agent: Cell cycle non phase specific. DNA breaks and causes cross linkage. |
| Pre-constitution storage | Between 15-25 degrees in chemotherapy cupboard. Stable for 24 months. Protect from light at all times |
| Compatibility | **For Administration**: Normal Saline (Mannitol concentration must not exceed 18.75mg/ml in normal saline if it is added) |
| Post reconstitution storage | **For storage post reconstitution**: Stable for 20 hours at 25 degrees. Do not refrigerate. |
| Clinical Uses: | Hepatoblastoma, osteosarcoma, medulloblastoma. |
| Administration | Intravenous: Infused over 6 hours |
| When to delay | Myelosuppression |
| When to reduce | 1. Renal Toxicity   * If the calculated creatinine clearance using the Schwartz formula is < 70 mL/min/1.73 m2 hold cisplatin for 1 week. * If renal function does not improve, omit cisplatin. * If the calculated creatinine clearance using the Schwartz formula is > 70 mL/min/1.73 m2 prior to the next course, cisplatin can be resumed at a 25% dose reduction. * If it remains < 70 mL/min/1.73 m2, omit cisplatin.   Schwartz formula:  - Creatinine clearance or radioisotope GFR  70ml/min/1.73 m2 or  - A serum creatinine based on age/gender as follows:    2. Bone Marrow Suppression: If there is repeated delayed adequate bone marrow recovery from the last 2 doses reduce by 25%; reduce by weight and age as per protocols |
| When to discontinue | Severe Ototoxicity; severe renal toxicity |
| Interactions | Tenofavir – try to avoid and all other renal or ototoxic medications - Can use Ciprofloxacin/Tazocin in place of Aminoglycosides. Also be aware that some drugs which can induce electrolyte abnormalities (especially hypomagnesaemia and hypokalaemia (Diuretics and Caffeine/Theophylline)), mannitol can be used for forced diuresis. |
| Special Considerations | Renal toxicity: Pre hydration for 3 hours is essential, followed by continuing hydration to continue for 24 hours after infusion is complete  Ototoxicity: Prior to each infusion ask parents if hearing has reduced since last dose. |
| Potential Side Effects | * Nausea & Vomiting: May be severe (1-72 hours), May be delayed * Taste Alteration * Diarrhoea * Bone Marrow Depression (Nadir Day 10-21) * Neurotoxic: Loss of Motor Function, Seizures * Nephrotoxic (Dose Limiting): Electrolyte Disturbance - Hypokalaemia, hypomagnesaemia, hypophosphataemia, and hypocalcaemia * Ototoxic: Tinnitus, High frequency Deafness – perform baseline audiometry where possible using Brock scale as outlined in GCT protocol. * Anaphylaxis: Wheezing, Flushing, Hypotension, Tachycardia |
|  | **Nursing Intervention** |
|  | Explain chemotherapy given as a six hour infusion – parents to call nurse if too fast or too slow. |
|  | Give 3 hours of pre-hydration DNS 200ml/m2/hr |
|  | Administer Anti-emetics as prescribed. |
|  | Adhere to safe handling of Cytotoxic Drugs guidelines. |
|  | Ensure FBP is adequate i.e Hb >7, ANC> 1.0, Plts >100. Ask about hearing. Check CCP. |
|  | Give hydration both during and until 24 hours after cisplatin infusion: 500mls DNS + 6grms mannitol infused at 125ml/m2/hr for 24hours. |
|  | Give calcium, potassium and magnesium IV or oral supplements |
|  | Monitor closely for signs of anaphylaxis and other S/E’s mentioned above. |

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| 6. | Cyclophosphamide |
| Also known as: | Cytoxan, Neosar |
| Type of chemotherapy | Alkylating agent: Cell cycle non phase specific. DNA breaks and causes cross linkage. |
| Pre-constitution storage | Below 25 degrees in chemotherapy cupboard. Protect from light. Stable for at least 5 years from date of manufacture. |
| Compatibility | Normal saline, Dextrose 5%w/v. Do not use water for injection containing benzyl alcohol. Needs to be shaken vigorously. (doses <1g – 100ml NS, doses >1g – 250ml NS) |
| Post reconstitution storage | Stable for 6 days at room temperature when reconstituted in Normal saline and 48hrs if D5%w/v is used. But as there is no preservative unless strict aseptic conditions should be used within 8 hours. |
| Clinical Uses: | Lymphoma, Soft tissue sarcoma, leukaemia |
| Administration | Intravenous: Infuse over 30-60 minutes. |
| When to delay | Serum Na below 130mEq |
| When to reduce | 1. Renal Toxicity   * If GFR is greater than 50 mL/min/1.73 m2, give full dose cyclophosphamide. * If 10 to 50 mL/min/1.73 m2 give 75% dose; * if less than 10 mL/min/1.73 m2, give 50% dose of cyclophosphamide.   2. Gross Hematuria  No dose modification of Cyclophosphamide for microscopic hematuria should be made. If microscopic hematuria present, it is recommended to give fluid bolus of 10 ml/kg of 0.9 NS and increase hydration rate by 50%.  A. Transient gross hematuria during or following a cycle of therapy (only one episode, which clears to less than gross hematuria):  a) Do not modify the cyclophosphamide dose.  b) Use continuous infusion MESNA, as below.  B. Persistent gross hematuria after completion of a cycle of therapy:  a) Hold subsequent cyclophosphamide until the urine clears to less than gross hematuria.  b) Reinstitute cyclophosphamide at full dose, with the MESNA changed to a continuous infusion:  C. Persistent gross hematuria occurring during a cycle of ifosfamide/cyclophosphamide:  a) Interrupt the cyclophosphamide.  b) Withhold further cyclophosphamide until the next cycle of therapy or until urine clears.  c) increase hydration to 3500-4000 ml/m2/day and daily MESNA dose to 100% of the cyclophosphamide dose.  D. Occurrence of a second episode of gross hematuria or persistence of microscopic hematuria on the continuous infusion regimen:  a) Continue the cyclophosphamide when the urine clears to less than gross hematuria.  b) Double the loading and infusion doses of MESNA.  c) Continue to give MESNA by continuous infusion for 48 hours after the last dose of cyclophosphamide.  E. Persistent gross hematuria in the face of this "double dose, continuous infusion regimen discontinue cyclophosphamide.  3. Cardiac Abnormalities   * For symptomatic CHF or other cardiac disorders, decrease the next dose of cyclophosphamide by 25%. * If this dose of cyclophosphamide is tolerated without recurrence or worsening of the CHF or other cardiac disorders, then escalate the cyclophosphamide back to full dose in subsequent cycles and monitor cardiac function with each cycle.   4. SIADH   * Monitoring of fluid intake and serum sodium concentration is indicated. * If the SIADH is severe enough to result in seizures, reduce the doses of whichever drug (or both) were given by 25% on subsequent cycle and escalate them back to 100% if tolerated.   5.  Bone Marrow Suppression: If there is repeated delayed adequate bone marrow recovery from the last 2 doses reduce by 25%; reduce by weight and age as per protocols.  **6.** Hepatic Impairment: Adequate liver function is required for metabolism to the active compound and although this is the case, increased toxicity has been noted in patients with severe hepatic impairment. A 25% dose reduction is recommended but clinical judgment must also be used in patients with any form of hepatic impairment. |
| When to discontinue | Frank haematuria despite appropriate maximal MESNA administration |
| Interactions | Naladixic Acid – try to avoid, Drug is activated via the CYP450 system (particularly 3A4) therefore caution is advised in patients taking enzyme inhibitors or inducers. Also be aware of drugs which may increase the risk of SIADH. Avoid Tranexamic acid if haematuria – increased risk of clot retention and dysuria. |
| Special Considerations | **Doses higher than 1.2grm/m2 require MESNA** (MESNA dose either given as continuous infusion or divided over 4 doses per day) |
| Potential Side Effects | * Nausea & Vomiting, Diarrhoea, Anorexia * Stomatitis * Poor wound healing * Easy bruising/bleeding * Alopecia * Bone Marrow Depression (Nadir Day 10-14) * Nephrotoxic: Haemorrhagic Cystitis: Bladder Fibrosis/transitional cell Ca of bladder * Rarely – sterility * If high dose used – 1-2% chance of secondary AML |
|  | **Nursing Intervention** |
|  | Explain chemotherapy given over 30-60 minutes.  Tell parents to inform you if infusion too fast or too slow. |
|  | Make sure there is MESNA available before starting infusion if using doses higher than 1.2grms/m2. Perform urinalysis in all patients prior to administration and afterward, record any abnormalities in the notes. |
|  | Administer Anti-emetics as prescribed. |
|  | Adhere to safe handling of Cytotoxic Drugs guidelines. |
|  | Ensure FBP is adequate i.e Hb >7, ANC> 1.0, Plts >100. |
|  | Monitor closely for S/E’s mentioned above – even at low doses – if patient experiences pain passing urine or haematuria – start MESNA. |

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| 7. | Cytarabine |
| Also known as | Cytosar, Tarabine |
| Type of chemotherapy | Antimetabolite: S Phase specific. Inhibits DNA, RNA and Protein synthesis |
| Pre-constitution storage | Below 25 degrees in chemotherapy cupboard. Stable for 3 years. |
| Compatibility | Normal saline, Dextrose 5%w/v (conc. range – 0.1-37.5mg/ml), IT route must use preservative free given in 5-10ml. |
| Post reconstitution storage | Stable for 1 month when refrigerated. |
| Clinical Uses: | Leukaemia, Lymphoma |
| Administration | Intravenous: Low dose – bolus  Intravenous: High Dose – infusion over 4 hours. (Give steroid eye drops)  Intrathecal – bolus. |
| When to delay | 1. Bone marrow suppression  2. For rash or conjunctivitis, withhold for Grade 3-4 toxicity until resolved. Make up missed doses and consider concurrent treatment with hydrocortisone or dexamethasone, and/or with dexamethasone ophthalmic drops for conjunctivitis. |
| When to reduce | Severe liver and renal impairment; For low dose regimens no dose reduction is required in renal impairment. For high dose regimens the risk of neurotoxicity increases with reduced renal function, in this case; CrCl 45-60ml/min – 40% dose reduction, 30-45ml/min – 50% dose reduction, <30ml/min – avoid. In hepatic impairment, both high and low dose regimens should have doses reduced by 50% if bilirubin >34micromol/L. The dose can then be re-escalated in subsequent cycles in the absence of toxicity. |
| When to discontinue | Hypersensitivity to this drug |
| Interactions | Ciprofloxacin – need to increase dose of Antibiotic, Fluorouracil should not be given alongside cytarabine as this will reduce the effectiveness of fluorouracil. Avoid IV cytarabine alongside IT Methotrexate – serious neurological consequences may incur. |
| Special Considerations | Fever.  If child develops a fever post cytarabine dose recheck FBP on each day of fever. If ANC>1.0 and no signs of infection assume cytarabine induced fever. If ANC<1.0 assume febrile neutropenia and start FN protocol antibiotics and stop chemotherapy. |
| Intra-thecal procedure | Preparing the injection:   1. Using a sterile and aseptic technique the cytarabine is drawn very gently through a 2micron filter. 2. If the cytarabine concentration is 100mg/5ml and no further dilution is required. 3. The correct age based dose (see the table below) is drawn aseptically through the 2 micron filter, capped and then given to the child. 4. Each syringe with cytarabine must be immediately capped and labeled clearly with the child’s name, the mg dose and name of chemotherapy contained and the date it was prepared. 5. As there is no preservative in Intrathecal preparations of chemotherapy, any syringes prepared and all chemotherapy remaining in vials opened must be discarded at the end of each day. Otherwise there will be a serious risk of causing a CNS bacterial infection with subsequent use. |
| Potential Side Effects | * Nausea & Vomiting, Diarrhoea, Anorexia * Stomatitis * Bone Marrow Depression (Nadir Day 7-14) * Neurotoxic: Ataxia / Dysarthria (High dose) * Hepatotoxic * Flu-like symptoms: Fever, Arthralgia, * Conjunctivitis – for high dose, give 0.1% dexamethasone or 1% prednisolone eye drops, 1 drop 2 hourly immediately before treatment and up to 24 hours after. Can use artificial tears if cannot tolerate/ unavailable. * Skin Changes: Rash to soles of feet and palms with high dose * Pulmonary Oedema can occur in high dose. * **Drug Interactions: Drug incompatible with Gentamycin – must never be given at the same time.** |
|  | **Nursing Intervention** |
|  | Explain chemotherapy given as a bolus or 4 hour infusion – parents to call nurse if too fast or too slow. |
|  | Ask parents to report any fevers. If fever – call doctor and order repeat FBP. |
|  | Administer Anti-emetics as prescribed. |
|  | Adhere to safe handling of Cytotoxic Drugs guidelines. |
|  | Ensure FBP is adequate i.e Hb >7, ANC> 1.0, Plts >100. |
|  | If giving HD cytarabine infusion ensure parents have steroid eye drops. |
|  | Monitor closely for signs of anaphylaxis and other S/E’s mentioned above. |

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| 8. | Dacarbazine |
| Type of chemotherapy | Alkylating agent |
| Pre-constitution storage | Between 2-8 degrees stable for 3 years from date of manufacture. Protect from the light |
| Compatibility | Normal saline, dextrose 5%w/v |
| Post reconstitution storage | Stable for 4 days at 4 degrees and protected from sunlight. This drug is very light sensitive. |
| Clinical Uses: | Hodgkins lymphoma, germ cell tumours. |
| Administration | Intravenous – slow bolus, protect from light. |
| When to delay | Myelosuppression |
| When to reduce | If there is repeated delayed adequate bone marrow recovery from the last 2 doses reduce by 25%; reduce by weight and age as per protocols. Renal impairment: CrCl 45-60ml/min – 20% reduction, 30-45ml/min - 25% reduction, <30ml/min – 30% reduction. In severe hepatic impairment – extensively metabolized in the liver and dose reductions may be necessary in severe hepatic impairment but this would be a clinical decision. |
| When to discontinue | Documented hypersensitivity to this drug |
| Interactions | Naladixic acid – try to avoid. Caution with tranexamic acid- increased risk of hepatic veno-occlusive disease. Hepatotoxic drugs or CYP450 (2A1) inducers/inhibitors. |
| Special Considerations | Highly emetogenic |
| Potential Side Effects | * Highly emetogenic * Rare but life threatening hepatic necrosis * Diarrhoea, Anorexia * Headache * Fatigue * Stomatitis * Bone Marrow Depression (Nadir Day 10-14) * Sterility and teratogenic |
|  | **Nursing Intervention** |
|  | Administer Anti-emetics as prescribed. |
|  | Adhere to safe handling of Cytotoxic Drugs guidelines. |
|  | Protect vials from the light. |
|  | Ensure FBP is adequate i.e Hb >7, ANC> 1.0, Plts >100. |
|  | Monitor closely for S/E’s mentioned above. |

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| 9. | Daunorubicin |
| Type of chemotherapy | Anthracycline antibiotic: Inhibits DNA replication. Cell cycle non phase specific. Maximum effect in S Phase. |
| Pre-constitution storage | Below 25 degrees in chemotherapy cupboard. Protect from light. Stable for 5 years. |
| Compatibility | Normal saline, Dextrose 5%w/v (conc. 5mg/ml) |
| Post reconstitution storage | Stable for 28 days when refrigerated. Protect from light. |
| Clinical Uses: | Leukaemia, lymphoma |
| Administration | Intravenous: fast infusion over 30 minutes |
| When to delay | Febrile neutropenia; neutropenia alone if beginning a new cycle of treatment; reversible cardiac insufficiency |
| When to reduce | Renal impairment: Creatinine 105-265micromol/L – reduce by 25%, if creatinine >265micromol/L – reduce by 50%. Hepatic impairment: bilirubin 20-50micromol/L – reduce by 25%, if bilirubin >50micromol/L reduce by 50%, if bilirubin >85micromol/L – avoid. Only dose reduce with raised transaminases if signs of toxicity are observed. |
| When to discontinue | No more than 400mg/m2 (except for Osteosarcoma protocol); cardiotoxicity. |
| Interactions | G-CSF should not be given within 24hrs. Caution with other cardiotoxic drugs or those which may prolong the QTc. |
| Special Considerations | Drug is a vesicant. Ensure good IV access before giving to prevent extravasation.  Cardiomyopathy – Maximum lifetime dose of all combined anthracyclines added together (e.g. doxorubicin, epirubicin etc) should never exceed 400mg/m2 in total. Perform baseline echo and ECG. |
| Potential Side Effects | * Nausea & Vomiting * Discolour urine – red (for up to 48 hours) * Bone Marrow Depression (Nadir Day 7-14) * Stomatitis * Alopecia * Cardiomyopathy (Dose Limiting) * **Radiation recall phenomenon: Omit Daunorubicin when receiving radiotherapy** * **NB: This drug is a vesicant** |
|  | **Nursing Intervention** |
|  | Explain chemotherapy given over 30 minutes. Make sure to flush with normal saline to ensure IV access is patent and thus prevent extravasation.  Tell parents to inform you if infusion too fast or too slow. |
|  | Count total number of doses of anthrcyclines ever given to patient do not exceed 400mg/m2 |
|  | Administer Anti-emetics as prescribed. |
|  | Adhere to safe handling of Cytotoxic Drugs guidelines. |
|  | Ensure FBP is adequate i.e Hb >7, ANC> 1.0, Plts >100. |
|  | Monitor closely for signs of extravasation and other S/E’s mentioned above. |

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| 10. | Doxorubicin |
| Type of chemotherapy | Anthracycline antibiotic: Inhibits RNA / DNA synthesis. Cell cycle non phase specific. Maximum effect in the S Phase. |
| Pre-constitution storage | Below 25 degrees in chemotherapy cupboard. Protect from light. Stable for 2-4 years depending on manufacturer. |
| Compatibility | Normal saline, Dextrose 5%w/v (max conc. 2mg/ml) |
| Post reconstitution storage | Stable for 28 days when refrigerated.  Out of fridge and protected from the light – stable for 48 hours. |
| Clinical Uses: | Leukaemia, lymphoma, osteosarcoma |
| Administration | Intravenous: Infuse over 3 hours unless otherwise stated. |
| When to delay | If child has neutropenia (<1 or thrombocytopenia <100); omit during radiotherapy. |
| When to reduce | 1. Bone Marrow Suppression:If child has a second pancytopenia delaying chemotherapy reduce the subsequent doses by 25%  2. Mucositis  Mucositis that interferes with oral fluid intake necessitating IV fluids or NG fluids should result in a 25% decrease in the next dose. The dosage may be escalated back to 100% if subsequent doses are not associated with significant mucositis.  3. Change In Ejection/Shortening Fraction   * If the cardiac ejection fraction falls below 47% or shortening fraction below 27%, prolongation of the QTc interval (> 0.44 sec), and the patient is asymptomatic repeat the study in 1 week. * If the ejection fraction or shortening fraction remains abnormal 1 week later, omit doxorubicin. * If doxorubicin is held from a cycle of therapy, repeat the study prior to the next cycle. If the cardiac ejection fraction returns to normal and is ≥ 47% and shortening fraction is ≥ 27%, resume doxorubicin at full dose.  1. Hepatotoxicity:     No dose adjustment needed in renal impairment but may be more sensitive to the side effects (e.g., cardiomyopathy and long QTc interval) |
| When to discontinue | Do not exceed 400mg/m2 life time total dose. If possible keep below 300mg/m2 |
| Interactions | G-CSF give 24 hours apart; ondansetron and other drugs which can prolong the QTc may cause life threatening cardiac arrythmia; |
| Special Considerations | Drug is a vesicant. Ensure good IV access before giving to prevent extravasation.  Cardiomyopathy – Maximum lifetime dose of all combined anthracyclines added together (e.g. daunorubicin, doxorubicin, epirubicin etc) should never exceed 400mg/m2 in total. Perform baseline echo and ECG. |
| Potential Side Effects | * Nausea & Vomiting (moderate to severe) * Discolour urine – red (for up to 48 hours) * Bone Marrow Depression (Nadir Day 7-14) * Stomatitis * Alopecia * Cardiac Toxicity (dose limiting) * **Radiation recall phenomenon: Omit Doxorubicin when receiving radiotherapy** * **NB: This drug is a vesicant** |
|  | **Nursing Intervention** |
|  | Explain chemotherapy given over 3 hours. Make sure to flush with normal saline to ensure IV access is patent and thus prevent extravasation.  Tell parents to inform you if infusion too fast or too slow. |
|  | Count total number of doses of anthracyclines (see above) ever given to patient do not exceed 400mg/m2 |
|  | Administer Anti-emetics as prescribed. |
|  | Adhere to safe handling of Cytotoxic Drugs guidelines. |
|  | Ensure FBP is adequate i.e Hb >7, ANC> 1.0, Plts >100. |
|  | Monitor closely for signs of extravasation and other S/E’s mentioned above. |

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| 11. | Etoposide |
| Also known as | VP16 |
| Type of chemotherapy | Plant Alkaloid (Semi-synthetic podophyllotoxin): Single, double strand breaks in DNA. G2 phase specific. |
| Pre-constitution storage | Below 25 degrees in chemotherapy cupboard. Protect from light. Stable for 5 years from date of manufacture. |
| Compatibility | Normal saline, Dextrose 5%w/v (0.4mg/ml max concentration (0.2mg/ml minimum), any higher requires an in-line filter) |
| Post reconstitution storage | Stable for 4 days at room temperature.  Protect from the light. |
| Clinical Uses: | Retinoblastoma, Leukaemia, lymphoma, osteosarcoma, Neuroblastoma |
| Administration | Intravenous: Infuse over 4 hours. Protect from the light.  Oral daily dosage usually: 50mg/m2/d (oral bioavailability 50%) taken with or without food. The injection can be used for oral administration if needed. |
| When to delay | If child has neutropenia (<1 or thrombocytopenia <100); |
| When to reduce | 1. Bone Marrow Suppression: If child has a second pancytopenia delaying chemotherapy reduce the subsequent doses by 25%   2. Hypersensitivity Reaction to Etoposide   * If with any dose, patient exhibits signs/symptoms of hypersensitivity reaction (HSR) in relation to administration of etoposide the infusion should be discontinued and appropriate treatment per institutional guidelines initiated. * In subsequent cycles of Etoposide, it is recommended to slow Etoposide administration to over 3 hours, and premedicate with diphenhydramine 1 mg/kg IV, hydrocortisone 2mg/kg IV, and ranitidine 1 mg/kg IV, as above. * Appropriate monitoring for HSR signs/symptoms should be instituted during the Etoposide infusion with emergency anaphylactic treatment available. * If anaphylaxis, drug administration should be discontinued and appropriate treatment instituted   3. Liver Toxicity    **OR** if ALT 2x ULN – 50% dose reduction  If ALT >2x ULN – clinical decision  4. Renal Toxicity   * If there is evidence of renal toxicity, adjust the dose of etoposide as follows: * If the creatinine clearance is between 10 to 50 mL/minute, administer 75% of the dose. * If the creatinine clearance is less than 10 mL/minute, administer 50% of the dose. |
| When to discontinue | Do not exceed 2000mg/m2 |
| Interactions | G-CSF do not give within 24hours, Phenytoin increases etoposide clearance and reduces its efficacy. |
| Special Considerations | Etoposide causes hypotensive crisis when given as a bolus.  **I.E. NEVER give as a BOLUS**  Risk of secondary malignancy (usually AML within 2-3 years) with cumulative doses of above 2grms/m2. |
| Potential Side Effects | * Nausea & Vomiting * Bone Marrow Depression (Nadir Day 7-14) * Alopecia * Fatigue * Anaphylaxis: Bronchospasm, Fever, Lumbar Pains * Hypotension ( on rapid infusion) |
|  | **Nursing Intervention** |
|  | Explain chemotherapy given over 4 hours.  Tell parents to inform you if infusion **too fast** or too slow. |
|  | Count total number of doses of etoposide ever given to patient do not exceed 2000mg/m2 |
|  | Administer Anti-emetics as prescribed. |
|  | Adhere to safe handling of Cytotoxic Drugs guidelines. |
|  | Ensure FBP is adequate i.e Hb >7, ANC> 1.0, Plts >100. |
|  | Monitor closely for signs of extravasation and other S/E’s mentioned above. Check vital signs and blood pressure prior to and during infusion ½ hourly. |

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| 12. | 5 Fluorouracil |
| Type of chemotherapy | Antimetabolite: Pyramidine analogue. S Phase specific. Irreversibly inhibits thymidylate synthase. Inhibits DNA, RNA and Protein synthesis |
| Pre-constitution storage | Below 25 degrees in chemotherapy cupboard protected from the light. Stable for 2 years. |
| Compatibility | Normal saline, Dextrose 5%w/v (recommended conc. 2mg/ml, but can otherwise be diluted in 500ml) |
| Post reconstitution storage | Stable for 42 days at room temperature. |
| Clinical Uses: | Colorectal, pancreatic ca and NPC, SCC and BCC |
| Administration | Intravenous: Low dose – bolus  Intravenous: High Dose – infusion over 4 to 24 hours.  Topically |
| When to delay | If child has neutropenia (<1 or thrombocytopenia <100); |
| When to reduce | If child has a second pancytopenia delaying chemotherapy reduce the subsequent doses by 25%, in moderate hepatic impairment reduce dose by 1/3rd, in severe impairment reduce by 2/3rd, if bilirubin >85micromol/L – avoid. No dose reduction needed in renal impairment but beware that cardiotoxicity may be more likely to occur in renal failure. |
| When to discontinue | Nil |
| Interactions | G-CSF should not be given within 24hours. Cytarabine – reduces the efficacy of fluorouracil. Drugs which may cause coronary vasospasm (e.g., sumatriptan) |
| Special Considerations | Leucovorin potentiates its effect and is therefore given concurrently when used IV. |
| Potential Side Effects | * Nausea & Vomiting, Diarrhoea, Anorexia * Stomatitis * Bone Marrow Depression (Nadir Day 7-14) * Palmar-plantar erythrodysesthesia – benign - treat with simple emollients (aqueous cream or E45) * Conjunctivitis and Blepharitis – Mild: NS eye drops, Severe – may need dose reduction * Cardiac toxicity – chest pain – uncommon in children but be aware. |
|  | **Nursing Intervention** |
|  | Explain chemotherapy given as a 4-24 hour infusion (check doctor’s prescription) – parents to call nurse if too fast or too slow. |
|  | Administer Anti-emetics as prescribed. |
|  | Adhere to safe handling of Cytotoxic Drugs guidelines. |
|  | Ensure FBP is adequate i.e Hb >7, ANC> 1.0, Plts >100. |
|  | Monitor closely for S/E’s mentioned above. |

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| 13. | Ifosfamide |
| Type of chemotherapy | Alkylating agent: Cell cycle non phase specific. DNA breaks and causes cross linkage. |
| Pre-constitution storage | Below 25 degrees in chemotherapy cupboard. Protect from light. Stable for at least 5 years from date of manufacture. |
| Compatibility | Normal saline, Dextrose 5%w/v. Do not use water for injection containing benzyl alcohol. (max conc. 40mg/ml). |
| Post reconstitution storage | Stable for 7 days at room temperature or 6 weeks when refrigerated. |
| Clinical Uses: | Lymphoma, Rhabdomyosarcoma, osteosarcoma |
| Administration | Intravenous: Infuse over 3 hours. |
| When to delay | If child has neutropenia (<1 or thrombocytopenia <100). |
| When to reduce | 1. Bone marrow suppression: If child has a second pancytopenia delaying chemotherapy reduce the subsequent doses by 25%  Thrombocytopenia   * If platelet recovery (≥ 75,000/μL) does not occur by the time of a scheduled ifosfamide cycle, delay chemotherapy administration until the platelet count is >75,000/μL and decrease the dose of ifosfamide by 25%. * If platelet recovery to >75,000/μL occurs by the time of the next scheduled chemotherapy cycle following the ifosfamide dose reduction, subsequent cycles should be at the same reduced dose of ifosfamide. * If platelet recovery to 75,000/μL does not occur by the time of the next scheduled chemotherapy cycle despite reduction of the ifosfamide dose, the ifosfamide dose should be further decreased to 50% in the next cycle.   2. Gross Hematuria  **(see under cyclophosphamide)**  3. Renal Toxicity  The renal injury produced by ifosfamide is permanent, and in some cases progressive. Renal irradiation, young age (< 3 years of age), and absence of one kidney are risk factors for severe renal toxicity. ALL PATIENTS MUST BE CAREFULLY MONITORED FOR FANCONI SYNDROME.  Elements of Fanconi Syndrome include:  1. Renal phosphorus wasting with hypophosphatemia.  2. Renal bicarbonate wasting with acidosis.  3. Renal potassium wasting with hypokalemia (< 3.0 mEq/L).  4. 1+ glycosuria with serum glucose < 150 mg/dl.  5. Proteinuria: a ratio of urine protein:urine creatinine > .2 occurring in the absence of significant malnutrition and acidosis due to sepsis/infection.  If CrCl 15-60ml/min – reduce dose by 20%, if CrCl <15ml/min – reduce dose by 40%.  4. Neurotoxicity  This is an organic brain syndrome which ranges from mild confusion and disorientation to seizures, ataxia, and coma. It may be aggravated by impaired renal function. It usually, but does not always, resolve spontaneously, and it may or may not recur with subsequent doses.   1. Hepatic impairment.   Adequate liver function is required for metabolism to the active compound and although this is the case, increased toxicity has been noted in patients with severe hepatic impairment. A 25% dose reduction is recommended but clinical judgment must also be used in patients with any form of hepatic impairment. |
| When to discontinue | If child develops ifosfamide neurotoxicity |
| Interactions | Metoclopramide increases the risk and severity of neurotoxicity; do not give G-CSF within 24hours. Caution with drugs known to cause SIADH. Avoid with Tranexamic Acid in haematuria due to the risk of clot retention and dysuria. |
| Special Considerations | **NEVER EVER give without MESNA** (MESNA dose either given as continuous infusion or divided over 4 doses per day) May use oral Mesna – solution for infusion may be administered orally, diluted in equal volume with orange juice or cola. The oral bioavailability of mesna is 50-75% (100% if given IV) and this must be taken into account when dosing orally. There is also a delay in urinary clearance of oral mesna by 2 hours and this should be accounted for when administering via this route. |
| Potential Side Effects | * Nausea & Vomiting, Diarrhoea, Anorexia * Stomatitis * Bone Marrow Depression (Nadir Day 10-14) * Nephrotoxic: Haemorrhagic Cystitis: Bladder Fibrosis * Cardiotoxic (in high dose) * Alopecia * Inappropriate ADH secretion * Reversible encephalopathy with confusion and lethargy – treat with Methylene Blue 50mg boluses |
|  | **Nursing Intervention** |
|  | Explain chemotherapy given over 3 hours.  Tell parents to inform you if infusion too fast or too slow. |
|  | Make sure there is MESNA available before starting infusion. Perform urinalysis in all patients prior to administration and afterward, record any abnormalities in the notes. |
|  | Administer Anti-emetics as prescribed. |
|  | Adhere to safe handling of Cytotoxic Drugs guidelines. |
|  | Ensure FBP is adequate i.e Hb >7, ANC> 1.0, Plts >100. |
|  | Monitor closely for S/E’s mentioned above. |

# 14. Methylene Blue – Also see separate guidelines for Ifosfamide encephalopathy.

**Novel treatment for the management of ifosfamide neurotoxicity: Rationale for the use of methylene blue**

1. [Sarah Donegan](http://opp.sagepub.com/search?author1=Sarah+Donegan&sortspec=date&submit=Submit), PharmD, BCOP
   1. *Investigational Drug Service, Boston Medical Center, Boston, Massachusetts*

**Abstract**

**Objective.** To provide an overview of the proposed pathophysiology of ifosfamide encephalopathy and the role of methylene blue for the treatment and prevention of this toxicity.

**Data Source.** A Medline search using the terms ‘‘ifosfamide encephalopathy’’ and ‘‘methylene blue’’ was conducted for the period of 1990-2001. The reference lists from retrieved articles were reviewed

**Data Extraction.** The author reviewed the retrieved material and included animal and pharmacokinetic data related to ifosfamide and the pathophysiology of ifosfamide neurotoxicity. Additionally, preclinical data and case reports describing the clinical use and rationale for methylene blue were included.

**Data Synthesis.** Encephalopathy is a unique toxicity described with ifosfamide, but not with cyclophosphamide. Ifosfamide undergoes a secondary ‘‘deactivation’’ metabolic pathway to yield dechloroethylated metabolites and chloroacetalde-hyde. Chloroacetaldehyde is a metabolite that contributes to both the nephrotoxicity and neurotoxicity described with ifosfamide. Chloroacetaldehyde (or a dechloroethylated metabolite) may exert neurotoxic effects by one or more of the following mechanisms: (a) direct neurotoxic damage, (b) depletion of central nervous system (CNS) glutathione level, or (c) inhibition of mitochondrial oxidative phosphorylation resulting in impaired fatty acid metabolism. The biochemical derangements described with this acute toxicity appear to mimic a neonatal mitochondrial disorder, for which methylene blue has been used. Methylene blue has been shown to restore and maintain mitochondrial respiration and therefore can be used to correct or prevent acute neurotoxic effects. Methylene blue has been used to treat moderate to severe cases of ifosfamide neurotoxicity and has also been used prophylactically to prevent encephalopathy in high-risk conditions with the use of oral and bolus iv ifosfamide regimens. Methylene blue may be useful in the treatment of grade III or IV neurotoxicity or in those patients with recurrent neurological symptoms associated with ifosfamide administration. The use of prophylactic or concurrent administration of methylene blue with ifosfamide requires further clinical evaluation.

Neurotoxicity was assessed based on M. D. Anderson scores [[19](http://annonc.oxfordjournals.org/content/17/4/646.full#ref-19)]. On obtaining scores of ≥2, an attempt was made not to decrease the dose of ifosfamide. Any neurotoxicity was managed by administering methylene blue as an intravenous bolus of 50 mg repeated at the same dose every 2 h until the neurotoxic event resolved, or as continuous infusion at 200 mg/day diluted in 5%w/v dextrose [[20](http://annonc.oxfordjournals.org/content/17/4/646.full#ref-20)].

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| 15. | MESNA |
| Chemotherapy aduvant (Not cytotoxic). | Mesna reduces the incidence of haemorrhagic cystitis and haematuria when a patient receives ifosfamide or cyclophosphamide. These two agents may be converted to urotoxic metabolites such as acrolein and 4-hydroxy-ifosphamide.  Mesna assists to detoxify these metabolites by reaction which binds its sulfhydryl group with the vinyl group in the toxic metabolites. It also increases urinary excretion of cysteine. |
| Pre-constitution storage | Below 30 degrees for 5 years from date of manufacture. |
| Compatibility | Normal saline or Dextrose 5%w/v |
| Post reconstitution storage | Stable for 24 hours at room temperature. |
| Clinical Uses: | Always given when Ifosphamide is used and given when doses of cyclophosphamide exceed 1.2grms/m2 |
| Administration | Intravenous – slow bolus over 15 minutes or given concurrent in the chemotherapy infusion (i.e. in the bag with the ifo or cyclo). |
| When to delay | Never give ifosfamide without giving MESNA |
| When to reduce | Never |
| When to discontinue | Only if discontinuing ifosfamide/cyclophosphamide or if documented hypersensitivity |
| Interactions | No known serious interactions |
| Special Considerations | Should be given 4 times per day for each day of ifosphamide or cyclophosphamide infusion. |
| Potential Side Effects | * Headache * Nausea/vomiting * Rarely – severe allergic reaction |
|  | **Nursing Intervention** |
|  | Ensure sufficient amounts of MESNA are available to complete 4 doses per day before starting a course of Ifosphamide or high dose cyclophosphamide. |
|  | Monitor closely for signs of S/E’s mentioned above. |

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| 16. | Methotrexate – High dose (more than 100mg/m2) |
| Type of chemotherapy | Antimetabolite – S Phase specific, arrests DNA, RNA, Protein synthesis, dihydrofolate reductase inhibitor. |
| Pre-constitution storage | Between 15-30 degrees in chemotherapy cupboard. Protect from light. Stable for 2 years from date of manufacture. |
| Compatibility | Normal saline, Dextrose 5%w/v. Do not use water for injection containing benzyl alcohol. (max conc. 20mg/ml) |
| Post reconstitution storage | Stable for 1 month when refrigerated. Protect from the light. |
| Clinical Uses: | Leukaemia, lymphoma, osteosarcoma. |
| Administration | Intravenous: Protect from the light  For Osteosarcoma infuse over 4 hour.  For lymphoma infuse as prescribed (usually longer than for osteosarcoma) |
| When to delay | 1. Marrow Suppression: If ANC <1, Plts <100.  2. Liver Dysfunction:  Samples for the determination of ALT value must be drawn immediately prior to a course of intravenous MTX. Blood samples for ALT should not be drawn immediately following the MTX infusions as 100% of patients are expected to have significant elevations at that time.   * Hold IV MTX for direct hyperbilirubinemia of > 2.0 mg/dL. |
| When to reduce | If myelosuppression delays chemotherapy date more than one time then reduce the dose by 25% for subsequent doses |
| When to discontinue | Withhold for elevated serum creatinine for age or above 1.4mg/dl (124micromols/L); Or dose reduce if CrCl 20-50ml/min – 25% reduction, 10-20ml/min – 50% reduction, <10ml/min – contraindicated. Be aware that co-trimoxazole can increase creatinine through competitive tubular secretion so this may give a falsely raised creatinine value – watch for additional signs of renal impairment with creatinine increases. withhold for serum transaminases more than 5 times per normal. It is considered normal for transaminases and bilirubin to rise in patients on high dose methotrexate for up to 2 weeks. However, if this persists (>3 weeks) or the bilirubin >50micrmol/L, withhold and continue when bilirubin <20micromol/L at half of the previous dose. Escalate the dose from 50%, 75% and 100% at 10 day intervals. Co-trimoxazole should also be discontinued when bili >50micromol/L. Also, plasma albumin should be monitored closely in patients with hepatic impairment as this may reduce protein binding. |
| Interactions | Do not give concomitant NSAID’s; an hepatotoxins – use with caution; penicillins reduce renal clearance (Use meropenem if possible as opposed to Tazocin for treating infections following methotrexate infusion). Drugs which may displace methotrexate from albumin (e.g., NSAIDs, sulphonamides). Co-trimoxazole co-administration should be avoided and the dose omitted on the day of methotrexate. Also caution with nephrotoxics and this will reduce clearance. Omeprazole can reduce methotrexate clearance, use ranitidine instead. |
| Antiemetic usage | Give prophylaxtically |
| Special Considerations | Prior to starting chemotherapy, urinary pH must be alkaline i.e. between pH7-8. To achieve this, sodium bicarbonate infusion is given before during and for a full 5 days after methotrexate infusion. The urine is tested each time to ensure adequate alkalinasation. **At hour 42 post MXT** infusion **folinic acid rescue** is commenced. **If this is forgotten the child will die.** Folinic acid is given PO or IV every 6 hours (15mg/m2/dose) for 3 days. |
| Potential Side Effects | * Nausea & Vomiting (Dose dependant), Diarrhoea, Anorexia * Stomatitis, Mucositis * Bone Marrow Depression (Nadir Day 7-14) * Neurologic : Dizziness, Malaise, Blurred Vision, Raised CSF Pressure, Seizures, Headache, Fever * Renal : Risk of Renal failure, Acute Renal Tubular Necrosis. * Hepatotoxicity : Can lead to Fibrosis * Skin Changes: Photosensitivity, Dry skin, Alopecia * Respiratory: Pulmonary Toxicity * **Refrain from Folic acid & derivatives (including fruit and juices) while on treatment** |
|  | **Nursing Intervention** |
|  | Teach the parents to test the urinary pH each time the child passes urine. Ensure adequate supply of pH sticks/paper for 6 full days testing. |
|  | Ask the parents to collect all urine each day so the doctors can calculate ml/kg/hr rate daily. |
|  | Commence sodium bicarbonate infusion (25mmol/500ml DNS) – ensure there is enough to continue for a full 6 days of infusion. |
|  | Ensure FBP is adequate i.e Hb >7, ANC> 1.0, Plts >100. |
|  | Administer Anti-emetics as prescribed. |
|  | Adhere to safe handling of Cytotoxic Drugs guidelines. |
|  | Explain chemotherapy given over 4 hour. Document time infusion finished.  Tell parents to inform you if infusion too fast or **too slow**. |
|  | Monitor closely for S/E’s mentioned above. |
|  | Start folinic Acid rescue (15mg/m2/dose - 6hrly) 42 hours following the completion of the methotrexate infusion. |

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| 17. | Methotrexate (low dose = less than 100mg/m2) |
| Type of chemotherapy | Antimetabolite – S Phase specific, arrests DNA, RNA, Protein synthesis, dihydrofolate reductase inhibitor. |
| Pre-constitution storage | Between 15-30 degrees in chemotherapy cupboard. Protect from light. Stable for 2 years from date of manufacture. |
| Compatibility | Normal saline, Dextrose 5%w/v. Do not use water for injection containing benzyl alcohol. (max conc. 20mg/ml). |
| Post reconstitution storage | Stable for 1 month when refrigerated. Protect from the light. |
| Clinical Uses: | Leukaemia, lymphoma, osteosarcoma. |
| Administration | Intravenous – slow bolus or short 30 minute infusion.  Intrathecal – bolus injection (maximum dose 12mg) |
| When to delay | If ANC <1, Plts <100. |
| When to reduce | (see above)  If myelosuppression delays chemotherapy date more than one time then reduce the dose by 25%/50% for subsequent doses or as per protocol |
| When to discontinue | Withhold for elevated serum creatinine for age or above 1.4mg/dl (124micromols/L); withhold for serum transaminases more than 5 times per normal |
| Interactions | Do not give concomitant NSAID’s; an hepatotoxins – use with caution; penicillins reduce renal clearance (Use meropenem if possible as opposed to Tazocin for treating infections following methotrexate infusion). Drugs which may displace methotrexate from albumin (e.g., NSAIDs, sulphonamides). Co-trimoxazole co-administration should be avoided and the dose omitted on the day of methotrexate. Also caution with nephrotoxics and this will reduce clearance. Omeprazole can reduce methotrexate clearance, use ranitidine instead. Oral antibiotics decrease intestinal absorption of PO methotrexate. |
| Intrathecal procedure | Preparing the injection:   1. Using a sterile and aseptic technique the methotrexate is drawn very gently through a 2micron filter. 2. If the methotrexate concentration available is 5mg in 2ml, then no further dilution is required and the correct age based dose (see the table below) is drawn aseptically through the 2 micron filter, capped and then given to the child. 3. If the methotrexate concentration available is 50mg in 2ml then this will require further dilution as follows:  * 18ml of sterile water for injection or preservative free 0.9% w/v NaCl. is drawn up into a 20ml syringe. * 2ml of (50mg/2ml)methotrexate is added. * The 2 micron filter is connected to the 20ml syringe * A 5ml syringe is connected to the other side of the 2micron filter and the correct dose for age of this diluted methotrexate is gently drawn through the filter into this 5 ml syringe.  1. Each syringe with methotrexate must be immediately capped and labeled clearly with the child’s name, the mg dose and name of chemotherapy contained and the date it was prepared. 2. As there is no preservative in Intrathecal preparations of chemotherapy, any syringes prepared and all chemotherapy remaining in vials opened must be discarded at the end of each day. Otherwise there will be a serious risk of causing a CNS bacterial infection with subsequent use. |
| Special Considerations | * Should not be given with milk |
| Potential Side Effects | * Nausea & Vomiting (Dose dependant), Diarrhoea, Anorexia * Stomatitis, Mucositis * Bone Marrow Depression (Nadir Day 7-14) * Neurologic : Dizziness, Malaise, Blurred Vision, Raised CSF Pressure, Seizures, Headache, Fever * Renal : Risk of Renal failure, Acute Renal Tubular Necrosis. * Hepatotoxicity : Can lead to Fibrosis * Skin Changes: Photosensitivity, Dry skin, Alopecia * Respiratory: Pulmonary Toxicity * Refrain from Folic acid & derivatives (including fruit and juices) while on treatment |
|  | **Nursing Intervention** |
|  | Check recent comprehensive chemistry panel – see above in special considerations. |
|  | Ensure IT dose is no more than 12mg total. |
|  | Administer Anti-emetics as prescribed. |
|  | Adhere to safe handling of Cytotoxic Drugs guidelines. |
|  | Ensure FBP is adequate i.e Hb >7, ANC> 1.0, Plts >100. |
|  | Monitor closely for S/E’s mentioned above. |

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| 18. | Vinblastine |
| Type of chemotherapy | Plant Alkaloid (Mitotic Inhibitor): Arrests mitosis, M phase specific. Inhibits RNA / DNA synthesis. |
| Pre-constitution storage | Stable for 3 years from date of manufacture when refrigerated. |
| Compatibility | Normal saline, Dextrose 5%w/v. (May be preferably given in 5% dextrose) |
| Post reconstitution storage | Stable for 1 month when refrigerated. If stored at 37 degrees and protected from the light – stable for 14 days. |
| Clinical Uses: | Kaposi’s sarcoma, hodgkins lymphoma, neuroblastoma, germ cell tumours |
| Administration | Intravenous – slow bolus. |
| When to delay | If ANC <1, Plts <100. |
| When to reduce | If myelosuppression delays chemotherapy date more than one time then reduce the dose by 25% for subsequent doses. If bilirubin 26-51micromol/L OR ALT 60-180units/L – 50% dose reduction, if bilirubin >51micromol/L and ALT normal – 50% dose reduction, if bilirubin>51micromol/L and ALT >180units/L – omit. No dose adjustment necessary in renal impairment but may be more sensitive to side effects (e.g., neuropathy and SIADH). |
| When to discontinue | Active bleeding. |
| Interactions | Dexamethasone may decrease the levels; Less potent interactions with cyclosporine, ritonavir, nifedipine and isoniazid – give but cautiously. Do not give G-CSF either within 14 days before or 24 hours after. Concomitant use of Bleomycin may cause Raynauds. Caution with drugs which may increase the risk of SIADH. Caution with constipating drugs (opioids and ondansetron). |
| Special Considerations | **Intravenous only – FATAL by all other routes.** |
| Potential Side Effects | * Nausea & Vomiting, Constipation, Anorexia, Abdominal Pain * Stomatitis * Bone Marrow Depression (Nadir Day 5-10) * Neurotoxic: Peripheral Neuritis, Paralytic Ileus, Jaw pain * Respiratory: Shortness of breath, Bronchospasm * Inappropriate ADH secretion. * Skin Changes: Alopecia, Rash, Photosensitivity * **NB: This drug is a vesicant** |
|  | **Nursing Intervention** |
|  | Administer Anti-emetics as prescribed. |
|  | Adhere to safe handling of Cytotoxic Drugs guidelines. |
|  | Ensure good blood return from venous access device. Monitor closely for signs of extravasation. Act promptly if extravasation occurs. |
|  | Monitor closely for S/E’s mentioned above. |
|  | Check for constipation. Administer laxatives as prescribed |

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| 19. | Vincristine |
| Type of chemotherapy | Plant Alkaloid (Mitotic Inhibitor): Arrests mitosis, M phase specific. Inhibits RNA / DNA synthesis. |
| Pre-constitution storage | Stable for 2 years from date of manufacture when refrigerated. |
| Compatibility | Normal saline, Dextrose w/v. (5% dextrose may be preferable) |
| Post reconstitution storage | Stable for 1 month when refrigerated. |
| Clinical Uses: | Leukaemia, lymphoma, solid tumours. |
| Administration | Intravenous – slow bolus – please dilute to final volume of 10ml for each injection with D5%w/v or Normal Saline. |
| When to delay | Severe ileus or constipation, cranial nerve palsies until they reverse; until complete resolution of foot drop; in the case of seizures believed to be due to vincristine full dose administration may be resumed if started on an anti-convulsant and clinically stable; delay if serum bilirubin >3mg/dl or 50mmol/L; SIADH - Monitoring of fluid intake and serum sodium concentration is indicated. If the SIADH is severe enough to result in seizures, reduce the doses by 25% on subsequent cycle and escalate them back to 100% if tolerated |
| When to reduce | Reduce by 50% for sensory or motor weakness not interfering with function, or parasthesias interfering with function but not with activities of daily living (ADL); reduce by 50% for serum bilirubin between > 2mg/dl (35mmol/L) and < 3mg/dl (50mmol/l)  If bilirubin 26-51micromol/L OR ALT 60-180units/L – 50% dose reduction, if bilirubin >51micromol/L and ALT normal – 50% dose reduction, if bilirubin>51micromol/L and ALT >180units/L – omit. No dose adjustment necessary in renal impairment but may be more sensitive to side effects (e.g., neuropathy and SIADH). |
| When to discontinue | Significant profound motor or sensory neuropathy interfering with ADL |
| Interactions | Azole antifungals, protease inhibitors, macrolide antibiotics (erythromycin, clarithromycin etc) – **do not give** within 24 hours as they potentiate the side effects of vincristine. Less potent interactions with cyclosporine, ritonavir, nifedipine and isoniazid – give but cautiously. Caution with drugs which may increase the risk of SIADH. Caution with constipating drugs (opioids and ondansetron). Use of Isoniazid may increase the risk of bone marrow depression. |
| Special Considerations | **Intravenous only – FATAL by all other routes.**  **Never** give **more** than **2mg** as a **single dose.** |
| Potential Side Effects | * Constipation, Paralytic Ileus, Anorexia * Neurotoxic: Peripheral Neuritis (Progressive), Jaw pain (high dose), ptosis, ataxia and vocal cord palsy * Fever, Headache, Fatigue * Respiratory: Shortness of breath, Bronchospasm * Alopecia * Inappropriate secretion of anti diuretic hormone * **NB: This drug is a vesicant** |
|  | **Nursing Intervention** |
|  | Administer Anti-emetics as prescribed. |
|  | Adhere to safe handling of Cytotoxic Drugs guidelines. |
|  | Check for presence of numbness, tingling fingertips or toes, foot drop, clumsiness. Observe for any hoarseness, stridor or coughing induced by swallowing which may indicate a vocal cord palsy. Record and report immediately. If present DO NOT give drug. Report same to medical staff. |
|  | Ensure good blood return from venous access device. Flush line. Dilute vincristine to a final volume of 10ml with D5%w/v or Normal Saline. Monitor closely for signs of extravasation. Act promptly if extravasation occurs. |
|  | Check for constipation. Administer laxatives as prescribed |

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| 20. | 6-Mercoptopurine |
| Also known as: | 6-MP, Xaluprine, Purinethol |
| Type of chemotherapy | Antimetabolite – pro-drug intracellularly converted to thio-nucleotide metabolites which inhibit de-novo purine synthesis through multiple enzymatic steps and incorporates into DNA. Targets S-phase. |
| Pre-constitution storage | Do not store above 25 °C. |
| Compatibility | Dispersed tablet can be given with orange juice. |
| Post reconstitution storage | If dispersing in syringe give immediately once dissolved. |
| Clinical Uses: | ALL, inflammatory bowel disease. |
| Administration | PO (or NG) |
| When to delay | As per ALL protocol |
| When to reduce | In renal impairment: if CrCl 10-50ml/min: give on alternate days, if CrCl <10ml/min – avoid. In hepatic impairment: If the bilirubin >50micrmol/L, withhold and continue when bilirubin <20micromol/L at half of the previous dose. Escalate the dose from 50%, 75% and 100% at 10 day intervals. |
| When to discontinue | Severe hepatic impairment. |
| Interactions | ALLOPURINOL – major interaction – increases mercaptopurine level 4-5-fold. If on allopurinol reduce dose of 6-MP by 75% (i.e., 25% of original dose). Ribavirin – reduces efficacy of 6-MP at cellular level. Co-trimoxazole reduces absorption, give at different times of the day. Caution with other hepatotoxic drugs. |
| Special Considerations | Must be taken in the evening (better response) 1 hour after food and NOT with milk or dairy products. |
| Potential Side Effects | * Bone Marrow Depression – Anaemia, leucopenia and thrombocytompenia (all in >10% and nadir 14 days) * GI – abdominal cramps, diarrhea and nausea, stomatitis (common) * Hepatotoxicity – 30% - dose reduce as per above instruction. * Metabolic – hyperuricaemia (10%) * Secondary malignancy. |
|  | **Nursing Intervention** |
|  | Available as tablet form – For children unable to swallow or with NG tube - remove plunger from oral syringe, place tablet in syringe barrel, replace syringe plunger against the dose, cap syringe. When dose is to be given, draw approximately 2 mL of water into syringe. Allow tablets to disintegrate over 1-3 min. The dose can be given directly via an NG tube (followed by flush) or added to juice to be given orally. |