Chemotherapy Protocol

LYMPHOMA

PEGAPARGASE-DEXAMETHASONE-ETOPOSIDE-IFOSFAMIDE-METHOTREXATE

(SMILE)

Inpatient Regimen

Regimen

Lymphoma – InP-SMILE-Pegasparagase-Dexamethasone-Etoposide-Ifosfamide-Methotrexate

Indication

- Newly diagnosed, relapsed, or refractory extranodal natural killer (NK) T-cell lymphoma
- WHO performance status 0, 1, 2

Toxicity

Drug	Adverse Effect
Pegasparagase	Liver toxicity, hypersensitivity reactions, coagulation abnormalities, thrombosis, raised lipase and amylase, lethargy, somnolence, confusion, dizziness, convulsions, headache, diarrhoea, pancreatitis, pyrexia, chills, swelling of limbs, pain, injection site reactions
Dexamethasone	Weight gain, gastrointestinal disturbances, hyperglycaemia, CNS disturbances, cushingoid changes, glucose intolerance
Etoposide	Hypotension on rapid infusion, hyperbilirubinaemia
Ifosfamide	Haemorrragic cystitis, encephalopathy, nephrotoxicity
Methotrexate	Stomatitis, conjunctivitis, renal toxicity

This regimen often causes marked myelosuppression despite the use of growth factors. A large proportion of patients will require hospitalisation for supportive care. NCI-CTC grade 3 or above neutropenia is reported in approximately 70% of patients. NCI-CTC grade 3 or above thrombocytopenia is reported in 42% of patients.

The adverse effects listed are not exhaustive. Please refer to the relevant Summary of Product Characteristics for full details.

Monitoring

Drugs

- FBC, LFTs (including albumin) and U&Es prior to day one of treatment and each Pegasparagase dose.

- EDTA or calculated creatinine clearance prior to day one of treatment

- Urine dip test for proteinuria and haematuria every four hours the day of and the day after ifosfamide administration. The patient should be instructed to report any signs or symptoms of cystitis.

- Fluid balance monitoring every four hours the day of and the day after ifosfamide administration. Urine output should be maintained above 100ml/hour.

- A fluid space, e.g. pleural effusion or ascites, is potentially very dangerous as methotrexate can accumulate and cause prolonged toxicity. Methotrexate should not be given in such cases.

- Methotrexate levels taken every 24 hours starting 48 hours after the end of the infusion until the level is below 0.1micromol/L

- Urinary pH every two hours as a minimum until the methotrexate level is below 0.1micromol/L. The pH should be maintained above 7.

- Strict fluid balance chart to be maintained throughout methotrexate administration with appropriate action taken if positive by more than 2kg/L.

- During the period of treatment with Pegasparagase, twice weekly blood tests with a coagulation screen including fibrinogen, full blood count, liver function tests and amylase. The antithrombin level should also be checked and if evidence of thrombosis then replace.

Dose Modifications

The dose modifications listed are for haematological, liver and renal function and drug specific toxicities only. Dose adjustments may be necessary for other toxicities as well.

In principle all dose reductions due to adverse drug reactions should not be re-escalated in subsequent cycles without consultant approval. It is also a general rule for chemotherapy that if a third dose reduction is necessary treatment should be stopped.

Please discuss all dose reductions / delays with the relevant consultant before prescribing, if appropriate. The approach may be different depending on the clinical circumstances.

Haematological

There are no dose modifications for NCI-CTC grade 3 or below haematological toxicity on day one of each cycle. Instead treatment should be delayed until the minimum criteria, described in the table below, are reached.

Criteria	Eligible Level
Neutrophil	equal to or more than $1x10^9$/L
Platelets	equal to or more than $100x10^9$/L

If an NCI-CTC grade 4 thrombocytopenia (platelets less than $25x10^9$/L) occurs in cycle one reduce the dose of the etoposide, ifosfamide and methotrexate by 25% in the next cycle.

The platelets must be above $25x10^9$/L prior to the administration of Pegasparagase.

Consider blood transfusion if patient symptomatic of anaemia or has a haemoglobin of less than 8g/dL (80g/L).

Liver Impairment

Transient increases in bilirubin and transaminases lasting up to two weeks are likely following methotrexate infusion and should not be considered an indication to stop treatment. Persistent hyperbilirubinaemia and/or NCI-CTC grade 3/4 hypertransaminasemia for longer than three weeks should result in discontinuation of the drug.

Drug	Bilirubin µmol/L		AST/ALT units	Dose (% of original dose)
Pegasparagase	more than 3xULN		more than 5xULN	Clinical decision
Etoposide	30-51	or	60-180	Consider dose reducing to 50%
	more than 51	or	more than180	Clinical decision
Ifosfamide	more than 20	or	more than 2.5xULN	Not recommended
	or ALP more than 2.5xULN			
Methotrexate	less than 50	and	less than 180	100%
	51-85	or	More than 180	75%
	more than 85		N/A	omit

Renal Impairment

Drug	Creatinine Clearance (ml/min)	Dose (% of original dose)
Pegasparagase	No dose adjustment required	
Etoposide	more than 50	100%
	15-50	75%
	less than15	50%
Ifosfamide	more than 60	100%
	40-59	70%
	less than 40	Clinical decision
Methotrexate	80 or greater	100%
	60-79	65%
	45-59	50%
	less than 45	Do not administer

Other

Dose reductions or interruptions in therapy are not necessary for those toxicities that are considered unlikely to be serious or life threatening. For example, alopecia, altered taste or nail changes.

Peg-Pegasparagase

Discontinue Pegasparagase in the presence of;

- pancreatitis (raised amylase or low serum insulin)
- thrombosis
- NCI CTC grade 3 or 4 hypersensitivity reaction
- any grade 3 non-haematological toxicity

Hypersensitivity

Patients should be monitored for hypersensitivity reactions for an hour post dose in accordance with local practice

There is a risk of hypersensitivity reactions with Pegasparagase, pre medication with paracetamol, chlorphenamine and a H2 antagonist such as famotidine is recommended.

Reduce the Pegasparagase dose to 50% if a previous NCI-CTC grade 1 or 2 hypersensitivity reaction has occurred. In this case, consider the use of prednisolone 1mg/kg/day.

Pancreatitis

Impairment of pancreatic function occurs frequently and may be caused by decreased insulin synthesis or necrosis and inflammation of the cells of the pancreas. Pancreatitis can occur despite normal serum amylase and can be fatal. Pancreatic function, including blood glucose, should be determined prior to and regularly monitored during therapy.

Etoposide

Where significant reductions in albumin levels occur consider reducing the dose of etoposide.

Ifosfamide

Haemorrhagic Cystitis

Urine should be dipstick tested for signs of haematuria every four hours on the day of and the day after ifosfamide administration.

If microscopic haematuria is present, an increase in hydration can be used to facilitate the elimination of ifosfamide and its metabolites. Additional mesna appears to have little benefit as its role is in prevention rather than treatment. However, owing to its low toxicity consideration should be given to increasing the dose of mesna (although arbitrary, consider doubling the dose).

In the case of frank haematuria, a urological opinion should be sought. Mesna is of little

value at this point as it's role is to prevent haemorrhagic cystitis and not for its treatment.

Neurological

In the case of a NCI-CTC grade 1 neurological toxicity, the dose of ifosfamide may be reduced for the next cycle. If a NCI-CTC grade 2 neurological toxicity appears or neurological toxicity worsens despite dose reduction, the ifosfamide should be stopped.

Risk factors for CNS toxicity include a low albumin, renal impairment, prior administration of cisplatin, poor performance status, CNS tumour, bulky pelvic disease, concomitant psychotropic drugs and younger age. Methylene blue 50mg four times a day intravenous infusion in 100ml sodium chloride 0.9% can be used to prevent or treat ifosfamide encephalopathy.

Regimen

28 day cycle for 2 cycles

Drug	Dose	Days	Administration
Methotrexate	2000mg/m^2	1	Intravenous infusion in 1000ml sodium chloride 0.9% over 360 minutes
Dexamethasone	40mg	2, 3, 4	Oral or intravenous
Etoposide	100mg/m^2	2,3,4	Intravenous infusion in 500ml sodium chloride 0.9% over 60 minutes
Mesna	300mg/m^2	2,3,4	Intravenous infusion in sodium chloride 0.9% 100ml over 15 minutes
Ifosfamide	1500mg/m^2	2,3,4	Intravenous infusion in sodium chloride 0.9% 1000ml over 60 minutes (the ifosfamide and mesna are mixed in the same bag)
Mesna	1500mg/m^2		
Mesna	900mg/m^2	2,3,4	Intravenous infusion in sodium chloride 0.9% 1000ml over 12 hours
Pegaspargase	1500units/m^2	7	Intramuscular injection (IM)

Dose Information

- Etoposide will be dose banded according to the nationally agreed bands (20mg/ml)
- Ifosfamide will be dose banded according to the nationally agreed bands (80mg/ml)
- Mesna will be dose banded according to the nationally agreed bands (100mg/ml)
- Methotrexate will be dose banded according to the nationally agreed bands (methotrexate high dose)
- The Pegaspargase can be given between days 5-10, if the dose falls on a weekend or if it is given as an outpatient or ambulatory.

Administration Information

Extravasation

- Etoposide – irritant
- Ifosfamide – neutral
- Mesna – neutral
- Methotrexate – inflamitant
- Pegasparagase - neutral

Other

- Pegasparagase - For smaller volumes the preferred route of administration is intramuscular. When given IM the volume injected at each site should not exceed 3mL in adults. If a higher volume is given the dose should be divided and given at multiple injection sites.
- Intravenous Pegasparagase is usually given over a period of 1-2 hours in 100mL Sodium Chloride 0.9%
- The methotrexate infusion must not be started until the urinary pH is above 7. This urinary pH must be maintained throughout the methotrexate infusion and until the methotrexate level is 0.1micromol/L or below

Additional Therapy

This is an inpatient regimen please ensure all supportive and take home medication are prescribed on the inpatient chart or general electronic prescribing system.

The peg-Pegasparagase may be administered as an out-patient or in ambulatory care.

- Antiemetics

  Starting 15-30 minutes prior to chemotherapy

  - dexamethasone 8mg oral or intravenous on day one only prior to methotrexate
  - metoclopramide 10mg three times a day for 7 days then when required oral or intravenous bolus
  - ondansetron 8mg twice a day for 7 days oral or intravenous bolus

- Methotrexate hydration

  The following fluid regimen is recommended as hydration. Fluid hydration should start at least six hours prior to methotrexate. This schedule should be repeated every 12 hours until the methotrexate level is below 0.1 micromol/L

  - Furosemide 40mg once only dose when required for the treatment of fluid overload or to maintain urine output oral or intravenous

  - Sodium chloride 0.9% with 20mmol potassium chloride 1000ml intravenous infusion over 240 minutes with 50-100mmol sodium bicarbonate adjusted to maintain urinary pH above 7

  - Sodium chloride 0.9% with 20mmol potassium chloride 1000ml intravenous infusion over 240 minutes with 50-100mmol sodium bicarbonate adjusted to maintain urinary pH above 7

  - Glucose 5% (with or without 20-27mmol potassium chloride) 1000ml intravenous infusion over 240 minutes with 50-100mmol sodium bicarbonate adjusted to maintain urinary pH above 7

- Post-treatment starting 24 hours after the start of the intravenous methotrexate infusion, folinic acid 30mg every 3 hours intravenous beginning 24 hours after the start of the methotrexate infusion and continued until the methotrexate levels are below 0.1micromol/L. This may be given orally from dose 5 onwards if the patient is able to tolerate oral therapy. If levels of methotrexate are above 2micromol/L additional folinic acid may be necessary. Seek advice from a senior member of staff.

- Pegasparagase treatment dose infusion reactions

  - chlorphenamine 10mg intravenous when required for treatment Pegasparagase infusion related reactions
  - hydrocortisone 100mg intravenous bolus when required for treatment Pegasparagase infusion related reactions
  - paracetamol 1000mg when required for treatment Pegasparagase infusion related reactions

- Growth factors starting on day 6 and continued until the neutrophil count is above $1x10^9$/L. For example:

  - filgrastim or bioequivalent 300microgram once a day from day 6 subcutaneous
  - lenograstim or bioequivalent 263microgram once a day from day 6 subcutaneous

- Mouthcare for the prophylaxis or treatment of mucositis in accordance with local guidelines

- Gastric protection with a H_2 antagonist may be considered in patients considered at high risk of GI ulceration or bleed (Proton pump inhibitors should be avoided whilst receiving high dose methotrexate).

- In female patients consider norethisterone 5mg three times a day oral to delay menstruation – this is to be used with caution due to increased theoretical risk of thrombosis when combined with asaparaginase.

- Anti-infective prophylaxis as follows:

    - aciclovir 400mg twice a day oral
    - Fluconazole 50mg once a day
    - Pentamidine 300mg once every 28 days, nebulised

Additional Information

- A significant number of drugs interact with intravenous methotrexate. At the doses used in this protocol this can lead to significant toxicity or reduction in efficacy. Always check for drug interactions before prescribing any additional medication

References
1. Yamaguchi M, Kwong YL, Kim WS et al. Phase II Study of SMILE Chemotherapy for Newly Diagnosed Stage IV, Relapsed, or Refractory Extranodal Natural Killer (NK)/T-Cell Lymphoma, Nasal Type: The NK-Cell Tumor Study Group Study. J Clin Oncol 2011; 29 (33): 4410-4416

REGIMEN SUMMARY

InP-SMILE-Pegasparagase-Dexamethasone-Etoposide-Ifosfamide-Methotrexate

Other than those listed below, supportive medication for this regimen will not appear in Aria as prescribed agents. The administration instructions for each warning describes the agents which must be prescribed on the in-patient chart or general electronic prescribing system

Day 1

1. Warning – Check supportive medication prescribed

   Administration instructions
   1. Dexamethasone 8mg oral or intravenous on day 1 only
   2. Metoclopramide 10mg three times a day, days 1 to 7 days then as required oral or intravenous bolus
   3. Ondansetron 8mg twice a day, days 1 to 7 oral or intravenous bolus
   4. Furosemide 40mg when required oral or intravenous
   1. Fluids repeated on a 12 hourly cycle to maintain fluid balance, urine output and pH above 7 until methotrexate level is below 0.1micromol/L
      - sodium chloride 0.9% with potassium chloride 20mmol 1000ml intravenous infusion over 240 minutes with 50-100mmol sodium bicarbonate adjusted to maintain urinary pH above 7
      - sodium chloride 0.9% with potassium chloride 20mmol 1000ml intravenous infusion over 240 minutes with 50-100mmol sodium bicarbonate adjusted to maintain urinary pH above 7
      - glucose 5% 1000ml (with or without potassium chloride 20-27mmol) intravenous infusion over 240 minutes with 50-100mmol sodium bicarbonate adjusted to maintain urinary ph above 7
   5. Folinic acid 30mg every 3 hours intravenous beginning 24 hours after the start of the methotrexate infusion and continued until the methotrexate levels are below 0.1micromol/L. This may be given orally from dose 5 onwards
   6. Growth factor continued until the neutrophil count is above $1x10^9$/L
      - filgrastim or bioequivalent 300microgram once a day from day 6 subcutaneous
      - lenograstim or bioequivalent 263microgram once a day from day 6 subcutaneous
   7. Aciclovir 400mg oral twice a day
   8. Fluconazole 50mg once a day
   9. Pentamidine 300mg nebulised once every 28 days
   10. Consider gastric protection (PPI should be avoided whilst on methotrexate)
   11. Consider mouthwashes
   12. Consider norethisterone for menstruating women

2. Methotrexate 2000mg/m^2 intravenous infusion in 1000ml sodium chloride 0.9% over 360 minutes

   Administration Instructions
   Monitor fluid balance, urine output, weight and urinary pH

   The methotrexate infusion must not be started until the urinary pH is above 7. This urinary pH must be maintained throughout the methotrexate infusion and until the methotrexate level is 0.1micromol/L or below. Ensure folinic acid is prescribed starting 24 hours after the start of the methotrexate infusion.

Days 2, 3, 4

3. Warning – Check supportive medication prescribed

   Administration instructions
1. Dexamethasone 8mg oral or intravenous once on day 1
2. Metoclopramide 10mg three times a day, days 1 to 7 days then as required oral or intravenous bolus
3. Ondansetron 8mg twice a day, days 1 to 7 oral or intravenous bolus
4. Furosemide 40mg when required oral or intravenous
   2. Fluids repeated on a 12 hourly cycle to maintain fluid balance, urine output and pH above 7 until methotrexate level is below 0.1micromol/L
      - sodium chloride 0.9% with potassium chloride 20mmol 1000ml intravenous infusion over 240 minutes with 50-100mmol sodium bicarbonate adjusted to maintain urinary pH above 7
      - sodium chloride 0.9% with potassium chloride 20mmol 1000ml intravenous infusion over 240 minutes with 50-100mmol sodium bicarbonate adjusted to maintain urinary pH above 7
      - glucose 5% 1000ml (with or without potassium chloride 20-27mmol) intravenous infusion over 240 minutes with 50-100mmol sodium bicarbonate adjusted to maintain urinary ph above 7
5. Folinic acid 30mg every 3 hours intravenous beginning 24 hours after the start of the methotrexate infusion and continued until the methotrexate levels are below 0.1micromol/L. This may be given orally from dose 5 onwards
6. Growth factor continued until the neutrophil count is above $1x10^9$/L
   - filgrastim or bioequivalent 300microgram once a day from day 6 subcutaneous
   - lenograstim or bioequivalent 263microgram once a day from day 6 subcutaneous
7. Aciclovir 400mg oral twice a day
8. Pentamidine 300mg once every 28 days nebulised

9. Fluconazole 50mg once a day
10. Consider gastric protection (PPI should be avoided whilst on methotrexate)
11. Consider mouthwashes
12. Consider norethisterone for menstruating women

4. Dexamethasone 40 mg oral
   Administration Instructions
   May be administered as dexamethasone 40mg intravenous

5. Etoposide 100mg/m^2 intravenous infusion in 500ml sodium chloride 0.9% over 60 minutes

6. Mesna 300mg/m^2 intravenous infusion in 100ml sodium chloride 0.9% over 15 minutes

7. Ifosfamide 1500mg/m^2 and mesna 1500mg/m^2 intravenous infusion in 1000ml sodium chloride 0.9% over 60 minutes
   Administration Instructions
   The ifosfamide and mesna are mixed in the same infusion bag of 1000ml sodium chloride 0.9%.

8. Mesna 900mg/m^2 intravenous infusion in 1000ml sodium chloride 0.9% over 12 hours
   Administration instructions
   Starting immediately after the ifosfamide/mesna**.** On day four this infusion may be replaced with oral mesna at a dose of 320mg/m^2 rounded upwards to the nearest 400mg tablet, at 0, 2 and 6 hours post ifosfamide

Days 7

9. Chlorphenamine 10mg intravenous

10. Dexamethasone 10mg intravenous

11. Paracetamol 1000mg tablet

12. H_2 antagonist according to local formulary choice and availability
    Administration Instructions:
    Administer according to local formulary choice and availability one of the following 30 minutes prior to SACT;

    - famotidine 20mg oral once only
    - nizatidine 150mg oral once only

    Please be aware that the patient may already be taking a regular H_2 antagonist and will not need to take another in this instance

    If there is no stock of these products due to national shortages treatment may proceed without the H_2 antagonist provided there is no instruction in the ARIA journal indication the patient **must have** H_2 antagonist treatment.

    All infusion related reactions must be recorded in the ARIA journal and reported to the appropriate consultant

13. Pegasparagase 1500units/m^2 intramuscular injection
    Administration Instructions
    For smaller volumes the preferred route of administration is intramuscular. When given IM the volume injected at each site should not exceed 3mL in adults. If a higher volume is given the dose should be divided and given at multiple injection sites.

14. Chlorphenamine 10mg intravenous once only when required for the relief of treatment Pegasparagase infusion related reactions

15. Hydrocortisone 100mg intravenous bolus once only when required for the relief of treatment Pegasparagase infusion related reactions

16. Paracetamol 1000mg oral once only when required for the relief of treatment Pegasparagase infusion related reactions

DOCUMENT CONTROL

Version	Date	Amendment	Written By	Approved By
1	Feb 2024	None	Nanda Basker Pharmacist	Dr Katie Smith Consultant