

SMILE (Etoposide, Ifosfamide, Methotrexate and Dexamethasone)

INDICATION

Natural Killer/T-cell lymphoma

TREATMENT INTENT

Curative

SPECIAL PRECAUTIONS

This protocol causes marked myelosuppression despite G-CSF. All patients will require hospitalisation for supportive care. Grade 3/4 neutropenia reported in ~70% of patients. Grade 3/4 thrombocytopenia reported in 42% of patients. L-asparaginase associated liver toxicity is common.

PRE-ASSESSMENT

1. Ensure histology is confirmed and documented in the notes.
2. Record stage of disease – MRI of head (if indicated), PET-CT scan (including head) or contrast enhanced CT (neck, chest, abdomen and pelvis), presence or absence of B symptoms, clinical extent of disease, bone marrow aspirate and trephine.
3. Blood tests - FBC, U&Es, LDH, ESR, urate, calcium, magnesium, creatinine, LFTs, glucose, Igs, hepatitis B core antibody and hepatitis B surface Ag, hepatitis C antibody, EBV, CMV, VZV, HIV 1+2 after consent, group and save.
4. EBV PCR baseline should be measured – this can be used as an early marker of response
5. Consider lumbar puncture to ascertain the presence of leptomeningeal involvement and CSF protein.
6. ECG +/- Echo - *if clinically indicated*.
7. Record performance status (WHO/ECOG).
8. Record height and weight.
9. Consent - ensure patient has received adequate verbal and written information regarding their disease, treatment and potential side effects. Document in medical notes all information that has been given. Obtain written consent on the day of treatment.
10. Fertility - it is very important the patient understands the potential risk of infertility. All patients should be offered fertility advice by referring to the Oxford Fertility Unit.
11. Ensure patient has a **creatinine clearance** of > 50 mL/min.
12. Patients **MUST NOT** receive co-trimoxazole in the week before the first methotrexate infusion.
13. A number of drugs can interfere with tubular secretion of methotrexate. These include penicillins, aspirin and NSAIDs. Tazocin should NOT be used during high dose methotrexate administration or rescue. Consider using meropenem or other alternative. Review indications for aspirin and NSAIDs and consider stopping during methotrexate treatment.
14. T = 0 is the time of the start of the methotrexate infusion.
15. Start oral sodium bicarbonate capsules at T = -12 hours. Administer 1.5 g four times a day +

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1.5 g prn for 36 hours, then review. Review regular sodium bicarbonate requirements at the end of the methotrexate infusion, and continue as appropriate until methotrexate level is less than 0.1 micromol/L.

16. Dipstick urine every 2 hours to check pH > 7. **If pH < 7, give additional bicarbonate as in point 15.**
17. Methotrexate infusion must aim to be given over 6 hours, although may be continued for longer if technical problems restrict flow rate.
18. FBC, creatinine and liver function should be monitored carefully during every course.
19. Urine pregnancy test before cycle 1 of each new chemotherapy course for women of child-bearing age unless they are post-menopausal, have been sterilised or have undergone a hysterectomy.
20. Treatment should be agreed in the relevant MDT.
21. Arrange insertion of double lumen central line (or a PICC line).

DRUG REGIMEN / CYCLE FREQUENCY

Day 0	Hydration / Alkalinisation - Pre methotrexate (starting T= -12 hours; see below). PENTAMIDINE 4mg/kg IV (max 300mg) in 100mL sodium chloride 0.9% over 1 hour.
Day 1 (T=0)	METHOTREXATE 2g/m ² IV infusion in 1000 mL sodium chloride 0.9% over 6 hours.
Day 2 (T=+24hrs)	Calcium folinate (Folinic acid) post methotrexate (starting 24 hours after the start of methotrexate). Continue with fluids and folinic acid rescues until methotrexate level < 0.1 micromol/L.
Days 2 to 4	ETOPOSIDE 100 mg/m ² IV infusion daily in 500-1000mL of sodium chloride 0.9% over 1 hour. DEXAMETHASONE 40mg PO or IV MESNA 300 mg/m ² IV infusion pre- ifosfamide in 50 mL sodium chloride 0.9% over 15 minutes IFOSFAMIDE 1500 mg/m ² + MESNA 900mg/m ² IV infusion daily in 1000mL sodium chloride 0.9% over 1 hour MESNA 300 mg/m ² IV infusion at 3, 6 and 9 hours post-ifosfamide in 50 mL sodium chloride 0.9% over 15 minutes
Day 8, 10, 12, 14, 16, 18, 20	ASPARAGINASE (E coli) medac 6000 units/m ² IM*. <i>No more than 5000 Units in 2 mL should be administered per injection site. If more than 5000 Units in 2 mL per single dose is required, several injection sites should be chosen.</i> A TEST DOSE of 1000 Units should be given intradermally before treatment commences.
Day 6	GCSF as per local policy until WBC >5x10 ⁹ /L

***Note:** ASPARAGINASE (E coli) can be administered via intravenous infusion in selected patients if bleeding risk precludes intramuscular administration:

ASPARAGINASE TEST DOSE: 1000 Units IV infusion in 250mL sodium chloride 0.9% over 30 minutes 1 hour before administration of treatment dose.

Observe patient for 1 hour post dose for any signs of reaction. Only proceed to give the remaining full treatment dose if no reaction.

ASPARAGINASE (E coli) medac 6000 Units/m² minus 1000units (given in the test dose) IV infusion in 250mL sodium chloride 0.9% over 2 hours.

Intravenous hydration:

Start: T = -12 hours.

Fluid: 1000 mL glucose 2.5%, sodium chloride 0.45% with potassium chloride 20 mmol and sodium bicarbonate 100 mmol added. Following completion of methotrexate infusion, decrease amount of sodium bicarbonate in fluids to 50 mmol/L.

Flow rate: 200 mL/hour (or 150 mL/hour if less than 1.6 m²).

Duration: Continue fluids during methotrexate infusion. Administer fluids until methotrexate level is less than 0.1 micromol/L.

Methotrexate intravenous infusion:

Start: T = 0 (aim to start at 10.00 am)

Run infusion over 6 hours if possible. May run for longer if technical reasons limit flow rate.

Levels: Check 48 hours after the start of the methotrexate infusion, and every 24 hours thereafter until methotrexate level is less than 0.1 micromol/L.

Urine output:

Check: Every 4 hours.

Aim: 400 mL/m²/4 hours (approx. 700 mL over 4 hours).

Furosemide: Administer 20-40 mg to maintain urine output.

Folinic acid rescue:

Start: 24 hours after **the start** of methotrexate infusion.

Dose: 30 mg every 3 hours for 5 doses, then every 6 hours until methotrexate level is less than 0.1 micromol/L.

Administration: Give intravenous boluses for at least the first 4 doses then change to oral if the patient is compliant and not vomiting.

CYCLE FREQUENCY AND RESTAGING

Cycles repeated every 28 days. Re-stage after 2 cycles.

Patients in CR or CRu, judged to have localized disease amenable to radiotherapy should be discussed in the MDT. Responding patients may benefit from IFRT before proceeding to complete 6 courses.

Alternatively, consider consolidating an early response with a stem cell transplant.

DOSE MODIFICATIONS

Neutrophils must be $>1 \times 10^9/L$ and Plts $>100 \times 10^9/L$ prior to each cycle.

Methotrexate

Fluid in a third space, e.g. pleural effusion or ascites, is potentially very dangerous as methotrexate can accumulate and cause prolonged toxicity. High dose methotrexate should not be given in such cases.

Renal impairment		Hepatic impairment	
CrCl (mL/min)	Dose	Bilirubin micromol/L	AST Dose
>80	100%	<50	and <180 100%
60	65%	51-85	Or >180 75%
45	50%	>85	Contra-indicated
<30	Contra-indicated	It is expected that patients receiving high dose methotrexate will develop hypertransaminasemia and occasionally hyperbilirubinemia. These elevations can last up to 2 weeks following the methotrexate infusion and are not considered toxicity requiring discontinuation of repeated administration of methotrexate. Persistent hyperbilirubinemia and/or grade 3-4 hypertransaminasemia for longer than 3 weeks should result in discontinuation of the drug. Dose reduce, particularly in patients with concomitantly impaired renal function. Severe hepatic impairment – Contra-indicated	

Etoposide

Renal impairment		Hepatic impairment
CrCl (mL/min)	Dose	Consider
>50	100%	Bilirubin 26-51 micromol/L or AST 60-180 u/L 50% dose
15-50	75%	Bilirubin > 51 micromol/L or AST > 180 u/L - clinical decision.
<15	50%	
Subsequent doses should be based on clinical response.		

Patients with raised bilirubin and/or decreased albumin may have an increase in free etoposide and hence greater myelosuppression.

Ifosfamide

Renal impairment		Hepatic impairment - discuss with consultant
GFR (mL/min)	Dose	SPC: Not recommended in patients with a bilirubin > 17 micromol/L, or serum transaminases or ALP > 2.5 x ULN. Clinical decision.
> 60	100%	
40-59	70%	
<40	Clinical decision.	

INVESTIGATIONS

FBC, U&E, Creatinine, LFTs.

During asparaginase treatment, monitor: glucose, LFTs, PT, APTT and fibrinogen.

CONCURRENT MEDICATION

Refer to tumour lysis protocol	
Ranitidine (or PPI if specifically indicated - discuss with consultant)	150mg twice daily for the duration of treatment
Fluconazole	50 mg daily for the duration of treatment
Aciclovir	200 mg three times a day for duration of treatment and for 3 months after completion
Pentamidine	4mg/kg IV, max 300mg. To be given on Day 0 of each cycle
G-CSF	from day 6 as per local policy until WBC >5x10 ⁹ /L
Co-trimoxazole	After the last cycle, start co-trimoxazole 480 mg daily on Monday / Wednesday / Friday for 3 months.

A number of drugs can interfere with tubular secretion of methotrexate. These include penicillins, aspirin and NSAIDs. Tazocin should NOT be used during high dose methotrexate administration or rescue. Consider using meropenem or other alternative. Review indications for aspirin and NSAIDs and consider stopping during methotrexate treatment.

EMETIC RISK

High risk

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS**Methotrexate**

- Renal damage
- Stomatitis, mucositis, interstitial pneumonitis
- Sterile cellulitis, skin changes and increased skin sensitivity to sun.
- Neurotoxicity

Asparaginase

Allergy/anaphylaxis: Asparaginase –test dose advised before administration (1000 Units)

Asparaginase should be discontinued in the presence of:

1. Pancreatitis (identified by raised amylase and low insulin).
2. Severe liver dysfunction.
3. Life-threatening allergic reaction.
4. Thrombosis: There is a concern over L-asparaginase-induced thrombophilia. During the period of treatment with asparaginase, levels of antithrombin, fibrinogen and the APTT should be monitored at least twice a week. If the level of fibrinogen is < 0.8 g/l or the level of antithrombin is < 70% and / or APTT is > 2x upper limit of normal at any time then replace with antithrombin concentrate and/or fibrinogen concentrate. Discuss with Haematology consultant.

Ifosfamide-induced encephalopathy

Refer to [nomogram](#) to assess risk. If patient develops neurotoxicity, **STOP** ifosfamide and administer:

Methylthioninium chloride (methylene blue) can be given as prophylaxis against, or treatment of ifosfamide induced encephalopathy. This should be started on the day of ifosfamide administration and continued for 24 hours after administration or until neurotoxic symptoms subside.

Dose: 50 mg TDS IV or PO. NB: 50 mg = 5 mL of 1% solution.

IV: Administer 50 mg in 50 to 100 mL sodium chloride 0.9% or glucose 5%, over 15 to 30 minutes.

Orally: Use injection for oral administration. Dilute one ampoule in 100 mL water before taking orally to minimise GI effects. Drink through a straw to avoid staining teeth. 53-97% oral absorption.

Glucarpidase

NHS England will fund Glucarpidase (unlicensed in UK) for adults receiving high-dose methotrexate chemotherapy (doses >1g/m²)

- Who develop significant deterioration in renal function (>1.5x ULN and rising, or the presence of oliguria) OR
- Have toxic plasma methotrexate level AND
- Have been treated with all standard rescue and supportive measures AND
- At risk of life-threatening methotrexate-induced toxicities

The recommended dose is one single intravenous injection of 50units/kg.

EXTRAVASATION RISK

Asparaginase: neutral
 Etoposide: irritant
 Ifosfamide: neutral
 Methotrexate: inflammatory agent

TREATMENT RELATED MORTALITY

1-5%

REFERENCES

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2. Motoko Yamaguchi 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):4410-6.
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4. UCLH - Dosage Adjustment for Cytotoxics in Renal Impairment (Version 3 - updated January 2009).
5. Medac. Summary of Product Characteristics Spectrila (asparaginase). Updated 28/08/2018. Accessed via <http://www.medicines.org.uk/emc> on 21/04/2019.

Review

Name	Revision	Date	Version	Review date
Cheuk-kie Jackie Cheung (Haematology Pharmacist)	Update methotrexate level time and addition of extravasation section	Jul 2018	1.2	
NSSG Lymphoma Group	Annual protocol review	May 2019	1.3	May 2021