Thames Valley
Strategic Clinical Network

Nelarabine/Cyclophosphamide/Etoposide (Nel-Cyc-Etop)

INDICATION

Salvage therapy for Refractory T-cell acute lymphoblastic leukaemia or T-cell lymphoblastic non-Hodgkin's lymphoma

Nelarabine is accessed via the Cancer Drugs Fund- requires Blueteq application.

TREATMENT INTENT

Curative

PRE-ASSESSMENT

1. Blood tests - FBC, coagulation screen, U&Es, LDH, ESR, urate, calcium, magnesium, creatinine, LFTs, glucose, Igs, $\beta_2$microglobulin, hepatitis B core antibody, hepatitis BsAg, hepatitis C antibody, EBV, CMV, VZV, HIV 1+2 after consent
2. **Send a "group and save" sample to transfusion and inform patient and transfusion laboratory that they will require irradiated blood products for all future transfusions**. Ensure irradiation card is attached to the patient's notes and copy given to the patient.
3. Ensure histology and diagnosis are confirmed prior to administration of chemotherapy and document in notes
4. Assess for CNS involvement.
5. Nelarabine can be associated with neurological complications so be cautious in patients with other neurological problems prior to therapy.
6. Record stage of disease
7. Urine pregnancy test - before cycle 1 of each new chemotherapy course in women aged 12 – 55 years of age unless they have been sterilised or undergone a hysterectomy
8. Record performance status (WHO/ECOG)
9. Record height and weight (also needed to calculate CrCl)
10. 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
11. Fertility - it is very important the patient understands the potential risk of infertility, all patients should be offered fertility advice (see Fertility Guidelines)
12. Hydration - refer to Tumour Lysis protocol

DRUG REGIMEN

Encourage 3L oral fluids daily

Days 1 to 5 **ETOPOSIDE** 100mg/m^2 daily in 1000ml Sodium Chloride 0.9% IVI over 1 hour

CYCLOPHOSPHAMIDE 440mg/m^2 daily in 250ml Sodium Chloride 0.9% IVI over 30 minutes

Days 7 to 11* **NELARABINE** 650mg/m^2 daily intravenous infusion over 1 hour

***The second part of the regimen with Nelarabine can be given on Days 8 to12. Nelarabine has 8 hours expiry

Note on regimen schedule: This treatment can be given in reverse sequential order of the two parts of the regimen (i.e. Nelarabine on Days 1-5, and Cyclo/Etop on Days 7-11 or 8-12). There must always be 1 or 2 days gap separating administration of the two parts of the regimen.

INTRATHECAL administration if indicated **MUST BE** given **NO LESS** than 6 days prior to starting nelarabine or 2 days following completion of nelarabine due to increased risk of neurotoxicity.

CYCLE FREQUENCY

Every 21 days. Usually only 1 – 2 cycles will be given. If partial response, a 2nd cycle may be given

DOSE MODIFICATIONS

Haematological Toxicity

Before each cycle, neutrophils should be >0.75 x10^9/L and platelets should be >75 x10^9/L unless low counts are due to bone marrow disease. Please note that in the series of Commander et al.,from the start of therapy median neutrophil recovery was 25 days and median platelet recovery was 21 days.

Neurological Toxicity

Nelarabine must be discontinued at the first sign of neurological events of National Cancer Institute Common Terminology Criteria Adverse Event (NCI CTCAE) grade 2 or greater. Discuss with consultant.

Renal / Hepatic Impairment

Nelarabine- discuss with consultant

Renal impairment	Hepatic impairment
Not studied. Nelarabine and its active metabolite are partially renally excreted. Monitor closely for toxicity if CrCl <50mL/min.	Not studied. Use with caution.

Etoposide- discuss with consultant

Renal impairment	Hepatic impairment
CrCl >50ml/min 100% dose CrCl 15-50ml/min 25% dose reduction CrCl<15 ml/min 50% dose reduction Subsequent doses should be based on clinical response	Bilirubin 26-51 micromol/l or AST 60-180 u/l 50% dose reduction Bilirubin > 51 micromol/l or AST > 180 u/l – clinical decision

Cyclophosphamide- discuss with consultant

Renal impairment		Hepatic impairment
GFR (mL/min)	Dose	Clinical decision. Exposure to active metabolites may not be increased, suggesting dose reduction may not be necessary
>20	100%	
10-20	75%	
<10	50%	
Clinical decision – consider whether patient is being treated with high dose treatment		

INVESTIGATIONS

- FBC, Coagulation screen.
- U&E, LFT.
- Calculated creatinine clearance.
- Recent bone marrow aspirate/trephine.
- CT scan if appropriate.
- Neurological assessment with nelarabine therapy

CONCURRENT MEDICATION

Tumour Lysis Prophylaxis Risk stratify as per local policy	Allopurinol 300mg PO once daily (cycle 1 only). Start 24 hours prior to chemotherapy and continue for 14 days OR Rasburicase if WCC > 100 x 10^9/L or patient has bulky disease e.g. Large mediastinal mass or elevated urate at diagnosis. As per local policy
Aciclovir	200mg PO three times a day
PPI	Daily if clinically indicated
Antifungal Prophylaxis	Refer to local antifungal policy.
Co-trimoxazole	480mg OD on Monday, Wednesday and Friday if neutrophils > 1 x 10^9/L and platelets > 100 x 10^9/L.
Mesna (only in patients pre-existing bladder disorders and at risk of haemorrhagic cystitis)	The oral dose of mesna is 40% of the dose of the cyclophosphamide given on 3 occasions at intervals of 4 hours beginning 2 hours before the cyclophosphamide injection; thus a total dose of mesna equivalentto 120% of the cyclophosphamide is given. In patients at high-risk of urothelial toxicity a shorter interval may be left between oral mesna doses, or the number of doses increased, or both. Alternatively, the initial dose of mesna (20% of the dose of the Cyclophosphamide) may be given intravenously at the same time as cyclosphophamide, followed by two oral doses (each 40% of the dose of the Cyclophosphamide) given 2 and 6 hours after the intravenous dose

ANTI-EMETICS

Days 1-5: Moderate-High
Days 7-11: Low risk

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS

Neurotoxicity
Severe neurological reactions have been reported with the use of nelarabine. These reactions have included altered mental states including severe somnolence, central nervous system effects including convulsions, and peripheral neuropathy ranging from numbness and paresthesias to motor weakness and paralysis. There have also been reports of reactions associated with demyelination, and ascending peripheral neuropathies similar in appearance to Guillain-Barré Syndrome.

Patients treated previously or concurrently with intrathecal chemotherapy or previously with craniospinal irradiations are potentially at increased risk for neurological adverse events and therefore concomitant intrathecal therapy and/or craniospinal irradiation is not recommended.
Full recovery from these reactions has not always occurred with cessation of nelarabine.

Therefore, close monitoring for neurological reactions is strongly recommended, and nelarabine must be discontinued at the first sign of neurological reactions of NCI CTCAE Grade 2 or greater.

Commonly reported toxicities; G2 and 3 sensory and motor neurotoxicity, febrile neutropenia, ataxia, G3/4 leukopenia, thrombocytopenia.
Other toxicities include: musculoskeletal pain, fever, infections, nausea/vomiting, anorexia, fatigue and rashes, hemorrhagic cystitis.

TREATMENT RELATED MORTALITY

5-10%

REFERENCES

1. Commander et al. Salvage therapy with nelarabine, etoposide, and cyclophosphamide in relapsed/refractory paediatric T-cell lymphoblastic leukaemia and lymphoma. British Journal of Haematology, 2010, 150, 345–351
2. Whitlock et al. Nelarabine in Combination with Etoposide and Cyclophosphamide Is Active in First Relapse of Childhood T-Acute Lymphocytic Leukemia (T-ALL) and T-Lymphoblastic Lymphoma (T-LL). [Abstract]. Blood 2014 124:795;
3. Luskin et al. Nelarabine, cyclosphosphamide and etoposide for adults with relapsed T-cell acute lymphoblastic leukaemia and lymphoma. [Abstract]. British Journal of Haematology, 2016, 174, 321–334
4. Novartis (2015) Nelarabine Atriance® Summary of Product Characteristics. Last updated on eMC 21 May 2018 accessed via http://www.medicines.org.uk
5. UCLH - Dosage Adjustment for Cytotoxics in Hepatic Impairment (Version 3 - updated January 2009).
6. UCLH - Dosage Adjustment for Cytotoxics in Renal Impairment (Version 3 - updated January2009).

REVIEW

Name	Revision	Date	Version	Review date
Nadjoua Maouche (Lead Pharmacist)	New protocol	January 2018	1.0	January 2020
Jon Barrett Haematology Pharmacist. NSSG Myeloid Group	Annual Protocol meeting	October 2019	1.1	October 2021