Thames Valley
Strategic Clinical Network

ETOPOSIDE (ORAL)

INDICATION

Second-line palliative care protocol for patients with myeloid malignancy (Acute Myeloid Leukaemia - AML, Myeloproliferative Disease – MPD and overlap MPD and Myelodysplastic Syndromes).

Licensed for relapsed/refractory AML.

Available as 50mg and 100mg capsules

Oral etoposide should not be used interchangeably with injectable etoposide due to differences in exposure, dose, schedule of treatment and indication.

TREATMENT INTENT

Palliative

PRE-ASSESSMENT

1. Blood tests - FBC, coagulation screen, U&Es, LDH, ESR, urate, calcium, magnesium, creatinine, eGFR, serum bicarbonate, LFTs, glucose, Hepatitis B core antibody and Hepatitis BsAg, Hepatitis C antibody
2. Ensure histology is confirmed prior to administration of chemotherapy and document in notes
3. Record clinical impact of disease, blood film, bone marrow aspirate and trephine, immunophenotype, cytogenetic results and calculate IPSS score
4. Urine pregnancy test - before cycle 1 of each new chemotherapy course in women with reproductive potential
5. ECG
6. Record performance status (WHO/ECOG)
7. Record height and weight
8. Obtain informed 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
9. Ensure fertility advice given (see fertility guidelines). **For women of childbearing potential:** 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. Women of childbearing potential should be advised to use effective contraception during and up to 6 months after treatment. **For men:** Advise to use effective contraception during and up to 6 months after treatment.
10. Consider dental assessment / consider dental check is carried out by patient's own dental practitioner before treatment starts
11. Treatment should be agreed in the relevant MDT.
12. Ensure pre-treatment counselling in line with national recommendations for oral systemic anti-cancer therapy (SACT).

DRUG REGIMEN / CYCLE FREQUENCY

Ensure ANC > 1 x 10^9/L and Platelets > 50 x 10^9/L before starting etoposide (unless counts are low due to disease).

Week	ETOPOSIDE Oral dose
1-2	150mg / week e.g. 50mg OD on Monday, Wednesday, Friday
Review every 2 weeks, and dose escalate (as below) if there is either no reduction in, OR reduction of < 20% of WCC	
3-4	300mg / week e.g. 50mg OD on Monday-Saturday (Sunday off)
5-6	450mg / week e.g. 50mg OD on Monday, Wednesday, Friday, Saturday, Sunday, 100mg on Tuesday & Thursday.
7-8	600mg / week e.g. 50mg OD on Monday and Friday, 100mg OD on Tuesday, Wednesday, Thursday, Saturday & Sunday

Capsules should be taken on an empty stomach

Dose adjust to maintain WCC 5-10 x 10^9/L, ANC > 1 x 10^9/L, Platelet ≥ 50 x 10^9/L and Hb > 100g/L

Continue as long as the patient has clinical benefit.

DOSE MODIFICATIONS

In cases of renal or hepatic impairment that is marginally above the thresholds indicated it may be clinically reasonable to proceed without dose reduction; in such cases it is vital to monitor biochemical status prior to each chemotherapy dose.

Renal / Hepatic Impairment

Renal impairment	Hepatic impairment
GFR >50ml/min: 100% dose GFR <50ml/min: 75% dose Subsequent doses should be based on clinical response.	Bilirubin ≤50micromol/L with normal albumin and renal function: 100% dose Bilirubin >50 micromol/L or decreased albumin levels: Consider 50% dose, increase if tolerated

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SPECIAL WARNINGS / PRECAUTIONS / MONITORING

- Dose limiting bone marrow suppression.
- Prior radiotherapy and/or chemotherapy, and bone marrow recovery.
- Low serum albumin may increase the risk of toxicities. Patients with impaired hepatic and renal function should also be regularly monitored.
- Mutagenic potential, and possible decrease in male fertility.
- Rare occurrence of acute leukaemia, in association with other anti-neoplastic drugs.
- Secondary leukaemia - unknown cumulative risk or predisposing factors. An 11q23 chromosome abnormality is observed in some patients who received both epipodophyllotoxins regimens and non - epipodophyllotoxins regimens, as well as *de novo* leukaemia.
- Tumour lysis syndrome.

INVESTIGATIONS

- FBC at baseline and at the start of every cycle
- U&E & LFT as clinically indicated.

CONCURRENT MEDICATION

ALLOPURINOL	300mg PO once daily for 7 days only if WCC > 50 x 10^9/L and continue until white cell count is within range
ACICLOVIR	200mg PO three times a day if ANC < 1 x 10^9/L
FLUCONAZOLE	50mg PO once daily if ANC < 1 x 10^9/L
PPI	Daily if clinically indicated
TRANEXAMIC ACID	1.5g PO three times a day if clinical evidence of "wet" mucosal bleeding and Platelet < 50 x 10^9/L

EMETIC RISK

Low to Low-Moderate

INTERACTIONS

Concomitant high doses of **Ciclosporin** (resulting in concentrations > 2000 ng/ml) has led to an 80% increase in etoposide exposure (AUC). Total body clearance of etoposide decreased by 38% compared to etoposide alone.

Concomitant **Phenytoin** is associated with increased Etoposide clearance and reduced efficacy.

Concomitant **anti-epileptic drugs** may lead to decreased seizure control due to pharmacokinetic interactions between the drugs.

Concomitant **Warfarin** may result in elevated INR - monitor INR closely.

Phenylbutazone, Sodium salicylate, and **Aspirin** may displace Etoposide from plasma protein binding, which in vitro demonstrates 97% plasma protein binding.

Anthracyclines and Etoposide cross resistance has been reported.

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS

Very commonly reported:
Myelosuppression, leukopenia, thrombocytopenia, neutropenia, anaemia, abdominal pain, constipation, nausea, vomiting, anorexia, hepatotoxicity, alopecia, hypertension, pigmentation, asthenia, malaise

For all other adverse effects, refer to SPC.

MORTALITY

Therapy related mortality in this setting is likely to be less than 1%

REFERENCES

1. Wattel et al (1996) A randomized trial of hydroxyurea versus VP16 in adult chronic myelomonocytic leukemia. Groupe Français des Myélodysplasies and European CMML Group. Blood 88(7):2480-7.
2. Neon Healthcare Ltd. Etoposide (Vepesid) capsules. Summary of Product Characteristics. Updated on 9/6/2022. Accessed on 5/10/22 via https://www.medicines.org.uk/emc
3. Krens S D et al (2019). Dose recommendations for anticancer drugs in patients with renal or hepatic impairment. *Lancet Oncol*; **20:** e201–08

REVIEW

Name	Revision	Date	Version	Review date
Julia Wong	New Document	March 2017	1.0	March 2019
Cheuk-kie Cheung	General formatting	May 2017	1.1	March 2019
Dr Lynn Quek	Annual Protocol meeting	October 2019	1.2	October 2021
Yen Lim, Haematology Pharmacist. NSSG Myeloid Group	Renal/hepatic dosing updated. Dosing schedule clarified. Annual protocol meeting.	November 2022	2.0	November 2024