Thames Valley
Strategic Clinical Network

ADE (CYTARABINE + DAUNORUBICIN + ETOPOSIDE)

INDICATION

Induction chemotherapy for patients with acute myeloid leukaemia (AML). Its use is particularly for patients under 60 years of age but it can be applied to older patients according to clinicians' assessment.

TREATMENT INTENT

Curative

PRE-ASSESSMENT

1. Confirm diagnosis
2. Blood tests - FBC, DCT, U&Es, LDH, ESR, urate, calcium, magnesium, creatinine, LFTs, glucose, Igs, hepatitis B core antibody and hepatitis B surface antigen, hepatitis C antibody, EBV, CMV, VZV, HIV 1+2 after consent, group and save.
3. ECG +/- Echo - *if clinically indicated*.
4. Record performance status (WHO/ECOG).
5. Record height and weight.
6. Pregnancy Test - for all women with childbearing potential before each new chemotherapy course.
7. 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.
8. Fertility - it is very important the patient understands the potential risk of infertility, all patients should be offered fertility advice (see fertility guidelines).
9. Hydration and tumour lysis prevention in patients with bulk disease (refer to tumour lysis protocol)
10. Consider dental assessment / Advise dental check is carried out by patient's own dental practitioner before treatment starts in practical.
11. Treatment should be agreed in the relevant MDT.
12. **Central venous access should be used, e.g. Hickman line or PICC. In urgent cases it may be necessary to start chemotherapy via a peripheral cannula.**

DRUG REGIMEN

Cycle 1 - ADE 10+3+5

Days 1 to 10	**CYTARABINE** 100 mg/m^2 12 hourly slow intravenous bolus (20 doses)
Days 1, 3 and 5	**DAUNORUBICIN** 50 mg/m^2 once daily in 250 mL sodium chloride 0.9% intravenous infusion over 1 hour (3 doses)
Days 1 to 5	**ETOPOSIDE** 100 mg/m^2 once daily in 500-1000 mL sodium chloride 0.9% intravenous infusion over 1 hour (5 doses)

Cycle 2 - ADE 8+3+5

Days 1 to 8	**CYTARABINE** 100 mg/m^2 12 hourly slow intravenous bolus (16 doses)
Days 1, 3 and 5	**DAUNORUBICIN** 50 mg/m^2 once daily in 250 mL sodium chloride 0.9%intravenous infusion over 1 hour (3 doses)
Days 1 to 5	**ETOPOSIDE** 100 mg/m^2 once daily in 500-1000 mL sodium chloride 0.9% intravenous infusion over 1 hour (5 doses)

CYCLE FREQUENCY

2 cycles, with the second cycle given only if neutrophils ≥ 1 x 10^9/L and platelets ≥ 100 x 10^9/L.

DOSE MODIFICATIONS

Discuss with consultant.

Cytarabine

Renal impairment	Hepatic impairment
No dose reduction necessary normally as doses not considered high dose	Mild/moderate impairment: no dose adjustment necessary Severe impairment: 25-50% dose and increase as tolerated

Etoposide

Renal impairment	Hepatic impairment
GFR >50ml/min: 100% dose GFR <50ml/min: 75% dose	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
Subsequent doses should be based on clinical response.	

Daunorubicin:

Renal impairment	Hepatic impairment
GFR 30-50 mL/min or Cr 105-265 micromol/L: give 75% dose GFR <30 mL/min or Cr > 266 micromol/L: give 50% dose Haemodialysis: give 50% dose	Bilirubin 20-50 micromol/L: give 75% dose Bilirubin > 50 micromol/L: give 50% dose

Maximum cumulative dose = 600 mg/m^2 (in normal cardiac function)
= 400 mg/m^2 (in patients with cardiac dysfunction or exposed to mediastinal irradiation).

INVESTIGATIONS

- FBC, U&E, LFT, Coagulation screen.
- Recent bone marrow aspirate – this should be evaluated cytologically before proceeding with Course 2.

CONCURRENT MEDICATION

Drug	Dose and duration
Allopurinol	300 mg daily for first 14 days of initial induction chemotherapy. (If a remission is attained the subsequent use of allopurinol is not required)
Aciclovir	200 mg three times a day for duration of treatment and for 3 months after completion
Proton pump inhibitor	Daily if clinically indicated, as per local formulary
Fungal prophylaxis	As per local protocol

EMETIC RISK

Days 1 to 5: Moderate
Days 6 to 10: Low

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS

Daunorubicin	Alopecia, chronic and acute cardiac failure and dysrhythmias. There is a recommended maximum cumulative lifetime dose of daunorubicin of 600 mg/m^2.
Cytarabine	Diarrhoea, oral ulceration, hepatic dysfunction. A cytarabine syndrome is also recognised in which patients suffer from fever, myalgia, bone pain, occasional chest pains, maculopapular rash, conjunctivitis and malaise. It usually occurs 6 to 12 hours following administration.
Etoposide	Alopecia, hypertension, transient systolic hypotension following rapid IV administration. Anaphylactic reactions have been reported rarely and have responded to stopping the infusion and the administration of an antihistamine and hydrocortisone.

Others: myelosuppression, infections, mucositis, nausea

EXTRAVASATION RISK

Cytarabine: neutral
Daunorubicin: vesicant
Etoposide: irritant

TREATMENT RELATED MORTALITY

2% to 5% (under 60s) but higher in older patients

REFERENCES

1. Hann IM, Stevens RF, Goldstone AH, Rees JK, Wheatley K, Gray RG, Burnett AK. Randomized comparison of DAT versus ADE as induction chemotherapy in children and younger adults with acute myeloid leukemia. Results of the Medical Research Council's 10th AML trial (MRC AML10). Adult and Childhood Leukaemia Working Parties of the Medical Research Council. Blood. 1997 Apr 1;89(7):2311-8.
2. Grimwade D, Walker H, Oliver F, Wheatley K, Harrison C, Harrison G, Rees J, Hann I, Stevens R, Burnett A, Goldstone A. The importance of diagnostic cytogenetics on outcome in AML: analysis of 1,612 patients entered into the MRC AML 10 trial. The Medical Research Council Adult and Children's Leukaemia Working Parties. Blood. 1998 Oct 1;92(7):2322-33.
3. Medical Research Council AML15 Protocol. MRC Working Parties on leukaemia in adults and children (2007)
4. 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
Prof Vyas	Changes in the concurrent medication and pre-assessment section, adding mortality risk	Feb 2016	4.0	
Cheuk-kie Jackie Cheung, Haematology Pharmacist. NSSG Myeloid Group	Annual protocol meeting	Oct 2019	4.1	Oct 2021
Yen Lim, Haematology Pharmacist. NSSG Myeloid Group	Annual protocol meeting. Renal/hepatic dosing updated.	Nov 2021	4.2	Nov 2023