DA

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. Pregnancy Test - for all women with childbearing potential before each new chemotherapy course.
3. ECG and Echo at baseline.
4. Record performance status (WHO/ECOG).
5. Record height and weight.
6. 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.
7. Fertility - it is very important the patient understands the potential risk of infertility, all patients should be offered fertility advice (see fertility guidelines).
8. Hydration and tumour lysis prevention; refer to tumour lysis protocol.
9. Consider dental assessment.
10. Treatment should be agreed in the relevant MDT
11. **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.**

ALLOCATION OF PATIENTS ACCORDING TO RISK GROUP

Patients are allocated therapy on the basis of risk groups:

Good risk

Any patient with favorable genetic abnormalities [t(8;21), inv(16)/t(16;16)] including those detected using RT-PCR irrespective of marrow status after Course 1 or the presence of other genetic abnormalities. Patients with acute promyelocytic leukaemia [t(15;17)] should usually be treated according to the Spanish protocol.

Standard risk

Any patient not in either good risk or poor risk groups. This includes patients with neither favourable nor adverse genetic abnormalities and not more than 15% blasts in the bone marrow after Course 1.

Poor risk

Any patient with more than 15% blasts in the bone marrow performed after Course 1 or with adverse genetic abnormalities [-5, -7, del(5q), abn(3q), complex] and without favourable genetic abnormalities.

1. If the patient is defined as good- or standard-risk they should progress to Course 2 when neutrophils recover to 1.0 x 10^9/L and platelets to 100 x 10^9/L.
2. If the patient is defined as poor-risk they can either progress to Course 2 DA 3+8, or receive an alternative induction protocol. It is recommended that such patients are discussed at the Leukaemia MDT.

DRUG REGIMEN

Course 1 - DA 3+10

Days 1 to 10	**CYTARABINE** 100 mg/m^2 12 hourly slow intravenous bolus (20 doses)
Days 1, 3 and 5	**DAUNORUBICIN** 60 mg/m^2 od intravenous infusion in 250 mL sodium chloride 0.9% over 1 hour (3 doses)

Course 2 - DA 3+8

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 od intravenous infusion in 250 mL sodium chloride 0.9% over 1 hour (3 doses)

CYCLE FREQUENCY/ CYCLE NUMBERS

2 cycles, with the second cycle given only if neutrophils ≥ 1.0 x 10^9/L and platelets ≥ 100 x 10^9/L.

DOSE MODIFICATION - discuss with consultant.

Cytarabine:

Renal impairment	Hepatic impairment
No dose reduction necessary normally as doses not considered high dose	Bilirubin > 34 micromol/L: give 50% dose Escalate doses in subsequent cycles in the absence of toxicity

Daunorubicin:

Renal impairment	Hepatic impairment
Cr < 105 micromol/L: give 100% dose Cr 105-265 micromol/L: give 75% dose Cr > 265 micromol/L: give 50% dose	Bilirubin 20-50 micromol/L: give 75% dose Bilirubin 51-85 micromol/L: give 50% dose Bilirubin > 85 micromol/L: omit

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, Coagulation screen.
- U&E, LFT.
- 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)
Fungal prophylaxis	As per local protocol
Aciclovir	200 mg three times a day for duration of treatment and for 3 months after completion
Proton pump inhibitor	As per local formulary

EMETIC RISK

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

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS

Daunorubicin	Nausea, alopecia, chronic and acute cardiac failure and dysrhythmias. There is a recommended maximum cumulative lifetime dose of daunorubicin of 600 mg/m^2.
Cytarabine	Nausea, 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.

Others: myelosuppression, infections, mucositis.

EXTRAVASATION RISK

Cytarabine: neutral
Daunorubicin: vesicant

TREATMENT RELATED MORTALITY

AML induction therapy is associated with a relatively high mortality risk of generally between 5-10%. This should be discussed with the patient at the time of consent. This risk is not only due to the chemotherapy but also consequent on the fact that patients treated with AML induction are already unwell as a consequence of having uncontrolled / untreated AML

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).

REVIEW

Name	Revision	Date	Version	Review date
Dr Peniket, Dr H Eagleton, Prof Vyas	Mortality risk added, pre-assessment review	Feb 2016	4.0	
Cheuk-kie Jackie Cheung, Haematology Pharmacist. NSSG Myeloid Group	Annual protocol meeting. Formatting, daunorubicin diluent volume changed.	Oct 2019	4.1	Oct 2021