

AIDA PROTOCOL FOR APL

Off-study induction and consolidation treatment of APL

Drugs/Dosage:

Induction:
(a single course)

Idarubicin	12mg/m ²	IV	once daily on Days 2, 4, 6 and 8*
Tretinoin	45mg/m ² /day	PO	starting on Day 1; given as two equally divided doses of 22.5mg/m ² /dose, until haematological CR and for a maximum of 60 days. If haem CR not achieved after 60 days, the patient may be considered high risk and treatment options will need to be reviewed.

*If WBC > 10 x 10⁹/L, all idarubicin doses should be brought forward by one day, with the first dose given within a few hours after starting tretinoin (ATRA).

Once haematological CR achieved, 3 cycles of **consolidation therapy** may begin as below:

Cycle 1:	Idarubicin	5mg/m ²	IV	once daily on days 1, 2, 3 and 4
	Tretinoin	45mg/m ² /day	PO	given as a twice daily dose of 22.5mg/m ² /dose from Day 1 to Day 15
Cycle 2:	Mitoxantrone	10mg/m ²	IV	once daily on days 1, 2, 3, 4 and 5
	Tretinoin	45mg/m ² /day	PO	given as a twice daily dose of 22.5mg/m ² /dose from Day 1 to Day 15
Cycle 3:	Idarubicin	12mg/m ²	IV	a single dose on Day 1 only
	Tretinoin	45mg/m ² /day	PO	given as a twice daily dose of 22.5mg/m ² /dose from Day 1 to Day 15

Administration:

Idarubicin slow IV bolus via fast-running infusion of sodium chloride 0.9%
 Mitoxantrone slow IV bolus via fast-running infusion of sodium chloride 0.9%
 Tretinoin (ATRA) available as 10mg capsules, to be taken with or after a meal
 (N.B. contains soya bean; contra-indicated if allergic to peanut or soya)

Other Drugs:

For patients with potential for tumour lysis syndrome, ensure initiation of prophylactic measures according to Alliance guidelines for management of TLS.
 Posaconazole to be taken during each cycle of chemotherapy, only when neutrophils drop* to < 0.5x10⁹/L and until they are > 0.5x10⁹/L.
 *In the first cycle of treatment, give prophylaxis from the start of the cycle regardless of the initial neutrophil count.
 Consider aciclovir prophylaxis (400mg bd), especially if history of VZV or HSV reactivation

Frequency: each cycle of consolidation therapy may only be given once neutrophils > 1.5 x 10⁹/L and platelets > 100 x 10⁹/L

Main Toxicities: myelosuppression, with high risk of haemorrhage & DIC; alopecia;
 mucositis; cardiomyopathy; differentiation syndrome (see Comments);
 teratogenic (see Comments); headache (may be severe – see Comments);
 bone pain; drying and desquamation of skin and lips; dry eyes;
 ovarian failure; infertility

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Anti- emetics:	Idarubicin: highly emetogenic; Mitoxantrone: moderately emetogenic Tretinoin: mildly emetogenic																
Extravasation:	Idarubicin is a vesicant																
Regular Investigations:	<table border="0"> <tr> <td>FBC</td> <td>twice daily during early stages of treatment (maintain platelets > 50 x 10⁹/l during induction); 2 – 3 times weekly following each consolidation cycle until counts recovered</td> </tr> <tr> <td>U&Es and LFTs</td> <td>D1 of induction, then 3 x wkly; D1 of each consolidation cycle</td> </tr> <tr> <td>Mg²⁺ and Ca²⁺</td> <td>D1 of induction, then weekly; D1 of each consolidation cycle</td> </tr> <tr> <td>Uric acid</td> <td>baseline</td> </tr> <tr> <td>APTT, PT, } Thrombin time }</td> <td>twice daily during early stages of treatment – keep within normal range using FFP</td> </tr> <tr> <td>Fibrinogen</td> <td>twice daily during early stages of treatment - if low, replace with cryoprecipitate, aiming for fibrinogen level 2g/L (avoid elevated fibrinogen levels)</td> </tr> <tr> <td>MUGA/echo</td> <td>see Comments</td> </tr> <tr> <td>Pregnancy test</td> <td>monthly if indicated (see Comments)</td> </tr> </table>	FBC	twice daily during early stages of treatment (maintain platelets > 50 x 10 ⁹ /l during induction); 2 – 3 times weekly following each consolidation cycle until counts recovered	U&Es and LFTs	D1 of induction, then 3 x wkly; D1 of each consolidation cycle	Mg ²⁺ and Ca ²⁺	D1 of induction, then weekly; D1 of each consolidation cycle	Uric acid	baseline	APTT, PT, } Thrombin time }	twice daily during early stages of treatment – keep within normal range using FFP	Fibrinogen	twice daily during early stages of treatment - if low, replace with cryoprecipitate, aiming for fibrinogen level 2g/L (avoid elevated fibrinogen levels)	MUGA/echo	see Comments	Pregnancy test	monthly if indicated (see Comments)
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Comments: Sperm banking if appropriate and time allows.

Check any previous anthracycline exposure, particularly if APL is 2nd malignancy. Maximum cumulative dose of mitoxantrone = 160mg/m². Maximum cumulative dose for IV idarubicin not clearly defined, but 5% cardiomyopathy risk with doses of 150 to 290mg/m².

A baseline MUGA / echo should be performed where the patient is considered at risk of having impaired cardiac function e.g. significant cardiac history, hypertension, obese, smoker, elderly, previous exposure to anthracyclines, previous thoracic radiotherapy. MUGA / echo should be repeated if there is suspicion of cardiac toxicity at any point during treatment, or if cumulative dose of idarubicin, mitoxantrone and any previous anthracyclines approaches maximum.

Tretinoin is highly teratogenic: ensure women of child bearing potential are fully informed of the hazards of becoming pregnant before initiating treatment. These patients must receive both verbal and written information about the teratogenic potential of tretinoin.

Women of child bearing potential must have a negative pregnancy test before starting treatment, and must use reliable contraception while on tretinoin and for one month after. Pregnancy testing should be repeated monthly thereafter until one month after stopping tretinoin. If a woman taking tretinoin thinks she may be pregnant she must stop the drug immediately.

All sexually active men should use a condom whilst on this treatment, and for 3 months after completion.

APL differentiation syndrome (formerly known as retinoic acid syndrome) includes fever, dyspnoea, respiratory distress, hypotension, oedema, pleural or peri-cardial effusion, pulmonary infiltrates, hepatic, renal and multi-organ failure. It is frequently associated with a raised WBC and may be fatal.

If the patient presents with any signs of this syndrome (eg unexplained respiratory distress):

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- i) immediately discontinue tretinoin until clinical condition improves.
- ii) initiate dexamethasone 10mg IV every 12 hours until resolution of the symptoms, and for a minimum of 3 days.
- iii) furosemide may be clinically required
- iv) once symptoms have disappeared, re-introduce tretinoin at 50% of previous dose for the first 4 days. In absence of return of symptoms, full dose may then be resumed. If symptoms do return, tretinoin should be discontinued permanently.

Pseudotumour cerebri, defined as severe headache with nausea, vomiting and visual disorders, may occur with tretinoin. It may be necessary to temporarily discontinue tretinoin and treat with opiates. In such a case, once symptoms disappear, re-introduce tretinoin at 50% dose for the first 4 days, then increase to full dose if symptoms do not return.

This regimen causes significant myelosuppression, which should be supported according to local policies, including neutropenic sepsis policy, along with the use of blood products and isolation.

Dose Modifications

Haematological Toxicity:

Proceed with treatment only if neutrophils $> 1.5 \times 10^9/L$ and platelets $> 100 \times 10^9/L$.
If low counts are thought to be due to disease, discuss with Consultant.

Delay in count recovery after treatment should be managed according to local protocols / practice.

Renal Impairment:

The SPC states that renal impairment can affect the clearance of idarubicin. However, there is no dosing advice according to creatinine clearance. The advice is as follows:

Serum Creatinine ($\mu\text{mol/l}$)	Idarubicin Dose
100 – 175	Give 50% dose
> 175	Clinical decision

NB. A serum creatinine $> 99 \mu\text{mol/L}$ may not correspond to renal impairment, particularly in younger patients. However, if there is evidence of impaired renal function eg reduced creatinine clearance, $\text{Cr}^{51}\text{-EDTA}$, or according to Cockcroft and Gault, then it is reasonable to use the serum creatinine to guide the dose reduction.

Limited information for tretinoin – SPC advises that the daily dose be decreased to $25\text{mg/m}^2/\text{day}$ in patients with renal impairment as a precautionary measure. However, it does not give a cut-off for CrCl or serum creatinine.

Hepatic Impairment:

Bilirubin ($\mu\text{mol/L}$)	Idarubicin Dose
21 – 34	Give 50% dose
> 34	Not recommended

If serum bilirubin, transaminases or ALP $> 5 \times \text{ULN}$, tretinoin should be temporarily withheld. Once serum bilirubin, transaminases or ALP $< 4 \times \text{ULN}$, tretinoin may be resumed at 50% dose. If liver enzymes do not worsen after a trial period at this dose, full dose tretinoin may be resumed. Monitor with care.

If bilirubin $> 60 \mu\text{mol/l}$, maximum daily dose of mitoxantrone is 8mg/m^2 .

Patient Information:

Macmillan leaflets for Idarubicin, Mitoxantrone and ATRA

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References: AML 17 trial, MRC 2008
BCSH AML Guidelines 2006 (now archived)

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