TRETINOIN (ALL TRANS RETINOIC ACID)

Induction of remission in acute promyelocytic leukaemia.
For patients not suitable for anthracycline based treatment.

Drugs/Dosage: **Tretinoin** 45mg/m^2/day, given as a twice daily dose of 22.5mg/m^2/dose until complete remission or a maximum of 90 days continuous treatment

Administration: Available as 10mg capsules, to be taken with or after a meal

Other Drugs: If patient presents with WBC > 10 x 10^9/L, give dexamethasone 10mg IV every 12 hours for first 5 days as prophylaxis against retinoic acid syndrome – see Comments

When tretinoin is initiated without concurrent chemotherapy, use the following guidelines:
If WBC is < 5 x 10^9/L at start of therapy, but rapidly increases such that WBC > 6 x 10^9/L by Day 5, or > 10 x 10^9/L by Day 10, or > 15 x 10^9/L by Day 28, then chemotherapy should be immediately added.
If chemotherapy is added at any point during tretinoin therapy, the dose of tretinoin does not need to be altered.

Main Toxicities: retinoic acid syndrome (see Comments); teratogenic (see Comments); nausea; headache (may be severe – see Comments); drying and desquamation of skin and lips

Regular Investigations:		
	FBC	Day 1, Day 5, Day 10, and as indicated throughout
	U&Es	baseline, then as indicated
	LFTs	baseline, then weekly
	Pregnancy test	monthly if indicated (see Comments)

Comments: 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. 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.

Women of child bearing potential must use reliable contraception while on tretinoin and for one month after.

Retinoic acid syndrome (or ATRA syndrome) includes fever, dyspnoea, respiratory distress, hypotension, oedema, pleural or peri-cardial effusion, hepatic, renal and multi-organ failure. It is frequently associated with a raised WBC and may be fatal.

If the patient presents any signs of this syndrome (eg unexplained respiratory distress):
1. immediately discontinue tretinoin until clinical condition improves.
2. initiate dexamethasone 10mg every 12 hours for up to maximum of 3 days or until resolution of the symptoms.
3. furosemide may be clinically required

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4. within 4 days of disappearance of symptoms, re-introduce tretinoin at 50% dose. 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, within 4 days of disappearance of symptoms, re-introduce tretinoin at 50% dose. In absence of return of symptoms, full dose may then be resumed.

Dose Modifications

Haematological Toxicity:	No dose modifications required for myelosuppression.
Renal Impairment:	Limited information – SPC advises that the dose be decreased to 25mg/m^2/day as a precautionary measure. However, it does not give a cut-off for CrCl or serum creatinine.
Hepatic Impairment:	If serum bilirubin, transaminases or ALP > 5 x ULN, tretinoin should be temporarily withheld. Once serum bilirubin, transaminases or ALP < 4 x 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.
Patient Information:	Macmillan leaflet for ATRA (all-trans retinoic acid)
References:	AML15 trial, MRC 2005