SACT PROTOCOL

The Clatterbridge Cancer Centre NHS Foundation Trust

Systemic Anti Cancer Therapy Protocol

Tretinoin (ATRA) & IDARUBICIN - AIDA ACUTE PROMYELOCYTIC LEUKAEMIA (APML)

PROTOCOL REF: MPHAAIDAHA
(Version No. 2.0)

Approved for use in:

- Untreated high risk APML (high risk = white blood cell >$10x10^9$/L)
- Relapsed APML in patients previously treated with arsenic trioxide

Blueteq registration is not required

Dosage: Induction

APML is characterised by high risk of early haemorrhagic death, so current recommendations dictate that treatment with tretinoin (ATRA) is started as soon as possible upon morphologic suspicion only. If any suspicion of APML then ATRA should be initiated at the induction dose below.

Drug	Dose	Route	Frequency
Induction			
Tretinoin (All-Trans-Retinoic-Acid)	**45mg/m^2/day** (in two equally divided doses and rounded to the nearest 10mg capsule)	Oral	Twice daily for 60 days or until a complete response – whichever comes first
Idarubicin	**12mg/m^2**	IV infusion	Days 2, 4, 6 and 8.
Consolidation Cycle 1			
Tretinoin (All-Trans-Retinoic-Acid)	**45mg/m^2/day** (in two equally divided doses and rounded to the nearest 10mg capsule)	Oral	Twice daily days 1-15
Idarubicin	**5mg/m^2**	IV infusion	Days 1, 2, 3 and 4
Consolidation Cycle 2			

Tretinoin (All-Trans-Retinoic-Acid)	**45mg/m²/day** (in two equally divided doses and rounded to the nearest 10mg capsule)	Oral	Twice daily days 1-15
Mitoxantrone	**10mg/m²**	IV infusion	Days 1, 2, 3, 4 and 5
Consolidation Cycle 3			
Tretinoin (All-Trans-Retinoic-Acid)	**45mg/m²/day** (in two equally divided doses and rounded to the nearest 10mg capsule)	Oral	Twice daily days 1-15
Idarubicin	**12mg/m²**	IV infusion	Days 1 only

Cycle length 28 days or upon count recovery. Maximum of four cycles (one induction and three consolidation cycles).

Administration (+/- Counselling Points):

- All-trans retinoic acid (ATRA) should be started as soon as the diagnosis is suspected
- Leucopheresis should be avoided in high count patients
- During induction, platelet count should be maintained at >50 × 10^9/l, together with fresh frozen plasma (FFP), cryoprecipitated and Riastap to normalize the activated partial thromboplastin time (APTT) and fibrinogen levels. **Routine VTE prophylaxis with low molecular weight heparins must only be prescribed under advice of Haematology Consultant due to bleeding risk.**
- ATRA capsules should be swallowed whole with water. They should not be chewed. It is recommended to take the capsules with a meal or shortly thereafter.
- Note ATRA is teratogenic and must not be used in combination with any other vitamin A, tetracycline, retinoid products.
- Idarubicin may cause a red colouration of the urine for 1 - 2 days after administration.
- Mitoxantrone may cause a blue-green colouration to the urine for 24 hours after administration.

Emetogenic risk:

Tretinoin: low emetogenic potential

Idarubicin: severely emetogenic

Mitoxantrone: moderately emetogenic

Supportive treatments:

- Allopurinol 300mg daily for first cycle. Consider rasburicase for high risk patients
- Aciclovir 400mg twice daily
- Chlorhexidine 0.2% mouthwash 10mL four times daily when required
- Co-trimoxazole 480mg once daily
- Metoclopramide 10mg three times daily when required
- Ondansetron 8mg twice daily during parenteral chemotherapy therapy
- Norethisterone 5mg three times daily (for menstruating women only) until platelets >50x10^9/L
- Nystatin oral solution 1mL four times daily
- Posaconazole 300mg twice daily for 2 doses then once daily thereafter (review once neutrophils >1.0x10^9/L)

Extravasation risk:

Idarubicin: vesicant

Mitoxantrone: vesicant

Refer to the CCC policy for the 'Prevention and Management of Extravasation Injuries'

Dosing in renal and hepatic impairment:

Renal Dose Modifications		
	Creatinine clearance (mL/min)	**Dose Adjustment**
Idarubicin	<30	Consider 67%
ATRA	<50	25mg/m^2 daily
Mitoxantrone	No dose adjustment required	

Hepatic Dose Modifications		
	Bilirubin (micromol/L)	**Dose Adjustment**
Idarubicin	45 - 86	50%
	>86	Omit

ATRA	Consider 25mg/m^2 daily in hepatic insufficiency
Mitoxantrone	Consider 50% dose in severe dysfunction

Interactions:

Idarubicin

- The use of idarubicin in combination chemotherapy with other potentially cardiotoxic drugs, as well as the concomitant use of other cardioactive compounds (e.g., calcium channel blockers), requires monitoring of cardiac function throughout treatment.
- Ciclosporin A may increase idarubicin AUC. A dose adjustment may be necessary in some patients.

Mitoxantrone

- Inhibitors of the BCRP transporter (e.g. eltrombopag, gefitinib) could result in an increased bioavailability. Inducers of the BCRP transporter (e.g. ciclosporin) could potentially decrease mitoxantrone exposure.

Tretinoin (ATRA)

- Tretinoin is contraindicated with other retinoids (i.e. vitamin A) because of the risk of symptoms suggestive of hypervitaminosis A for daily doses greater than 10,000 IU.
- Tretinoin is also contraindicated with tetracyclines: risk of intracranial hypertension (pseudotumor cerebri).
- Tretinoin is metabolised by the hepatic P450 system, therefore pharmacokinetics may be altered if used with inducers or inhibitors of this system. CYP450 inducers include rifampicin, glucocorticoids, phenobarbital and pentobarbital. VYP450 inhibitors ketoconazole, cimetidine, erythromycin, verapamil, diltiazem and ciclosporin. There are no data to suggest that co-use with these medications increases or decreases either efficacy or toxicity of tretinoin.

Treatment schedule:

Day	Drug	Dose	Route	Diluent and rate
Induction				
1	**ATRA**	45mg/m^2/day (in two equally divided doses and rounded to the nearest 10mg capsule)	Oral	Twice daily for 60 days or until a complete response – whichever comes first.
2, 4, 6, 8	**Idarubicin**	12mg/m^2	IV	Over 20 minutes in 100mL Sodium Chloride 0.9%
Consolidation Cycle 1				
1 to 15	**ATRA**	45mg/m^2/day (in two equally divided doses and rounded to the nearest 10mg capsule)	Oral	Twice daily for 15 days
1 to 4	**Idarubicin**	5mg/m^2	IV	Over 20 minutes in 100mL Sodium Chloride 0.9%
Consolidation Cycle 2				
1 to 15	**ATRA**	45mg/m^2/day (in two equally divided doses and rounded to the nearest 10mg capsule)	Oral	Twice daily for 15 days
1 to 5	**Mitoxantrone**	10mg/m^2	IV	Over 30 minutes in 100mLs Sodium Chloride 0.9%
Consolidation Cycle 3				
1 to 15	**ATRA**	45mg/m^2/day (in two equally divided doses and rounded to the nearest 10mg capsule)	Oral	Twice daily for 15 days
1	**Idarubicin**	12mg/m^2	IV	Over 20 minutes in 100mLs Sodium Chloride 0.9%

Main toxicities:

ATRA
Differentiation sydndrome, hyperleukocytosis, raised intracranial pressure, pseudotumour cerebri, depression, anxiety, and mood alterations, headache, hearing impairment, visual impairment, arrhythmia, flushing, nausea, vomiting, diarrhea, constipation, raised triglycerides, raised cholesterol, deranged transaminases
Idarubicin / Mitoxantrone
Bone marrow suppression, anaemia, neutropenia, thrombocytopenia, secondary leukaemia, cardiotoxicity, mucositis, stomatitis, red colouration of the urine, anorexia, thrombophlebitis, nausea, vomiting, diarrhoea, rash, skin sensitivity, fever, headache, chills, fatigue

Investigations and treatment plan:

	Pre	Day 1	Day 2	Day 4	Day 6	Day 8	Prior to each cycle	Ongoing
Informed consent	X							
Clinical & SACT Assessment (including performance status and toxicity assessment)		X	X	X	X	X	X	
Hepatitis B core antibody and surface antigens & Hep C & HIV 1+2, CMV, VZV	X							
PML-RARA screen	X							Repeat as clinically indicated
Clotting screen + fibrinogen	X	X	X	X	X	X		Daily until haematological remission
FBC, U&E & LFTs & Magnesium	X	X	X	X	X	X		Repeat regularly during rest of cycle (daily until haematological remission and at least every three days thereafter)
CrCl (Cockcroft and Gault)	X							
Triglycerides and cholesterol	X							Monitor regularly throughout treatment with ATRA
ECHO and ECG	X							ECG /ECHO for all patients should be documented before starting anthracycline, unless stated by the medical team that this is not required
Bone Marrow Biopsy	X							Repeat at day+30 following induction and following each consolidation as indicated
Pregnancy Test	X							Prior to treatment and regularly throughout treatment if appropriate
Weight	X		X	X	X	X		Minimum every other day in case differentiation syndrome develops
Height	X							

Dose Modifications and Toxicity Management:

Haematological toxicity:

Induction should start regardless of cytopenias.

For subsequent cycles proceed if-

ANC ≥ 1.5 x 10^9/L	Platelets ≥ 80 x 10^9/L

These haematological guidelines assume that patients are well with good performance status, that other acute toxicities have resolved and the patient has not had a previous episode of neutropenic sepsis.

Non-Haematology Toxicity:

See previous section regarding dosing in renal and hepatic impairment.

Differentiation or ATRA syndrome

This potentially life-threatening complication of ATRA therapy is characterized by fluid retention and features of capillary leak and is most likely related to surface adhesion molecule modulation and cytokine release following induction of differentiation of APL cells. Symptoms and signs include cough, dyspnoea, fever, weight gain, oedema, pleural and pericardial effusions and pulmonary infiltrates differentiation syndrome occurs in up to a third of patients receiving ATRA as single-agent induction therapy. The syndrome typically develops approximately 10 days after initiation of ATRA, but can appear as early as 2 days and is commonly, but not invariably, associated with a rising peripheral WBC count.

Patients on ATRA should be observed very carefully for symptoms, signs or falling oxygen saturation levels indicative of impending differentiation syndrome. If there are clinical suspicions of this complication;

- ATRA should be temporarily discontinued and steroids administered promptly (dexamethasone 10 mg IV BD until disappearance of symptoms and signs, and

for a minimum of 3 days), which may prevent progression to the full blown syndrome.

- ATRA can then be cautiously re-introduced.

Differentiation syndrome during induction is not a contraindication to use of ATRA later in the patient's treatment course (including management of any relapse). Patients with a relatively high presenting WBC (>10 × 10^9/L) have in some studies been reported to be at higher risk of differentiation syndrome during induction and some trial groups advocate use of prophylactic steroids as a component of induction therapy.

Pseudotumour Cerebri

Pseudotumour cerebri is a benign intracranial hypertension with cerebral oedema and absence of a tumour, clinically characterised by headache, papilloedema, diplopia, and possibly an altered state of consciousness. The presence of severe headaches with nausea, vomiting, and visual disorders, generally developing in patients aged < 20 years. It is often necessary to discontinue ATRA temporarily and to administer opiates.

Coagulopathy

A major cause of treatment failure is induction death as a result of haemorrhage, which reflects to varying degree DIC excessive fibrinolysis and proteolysis. Patients with higher presenting WBC (i.e. >10 × 10^9/L) are at highest risk of haemorrhagic death. Patients with very high presenting leucocyte counts should not undergo leucopheresis, which commonly precipitates fatal exacerbation of the coagulopathy.

Haemorrhagic deaths may be reduced by rigorous monitoring of the coagulation profile and administration of appropriate replacement therapy until morphological CR has been attained.

APTT, prothrombin time, thrombin time, fibrinogen level and platelet count should be checked at least twice daily during the early stages of treatment. Coagulation times

should be kept within the normal range using FFP or Riaspin as replacement. Fibrinogen levels may be low due to DIC and cryoprecipitate should be given as replacement aiming for a level of approximately 2 g/L. Elevated levels of fibrinogen should be avoided because of the increased risk of thrombosis associated with APL, which may be further exacerbated by ATRA.

The platelet count should ideally be maintained above 50 × 10^9/L until morphological remission has been confirmed. Clinical studies have not established proven benefit for use of heparin or anti-fibrinolytic agents as a means of decreasing induction death rates in APL and their routine use is not recommended. Indeed, anti-fibrinolytic agents when combined with ATRA could potentially increase the inherent risk of thrombotic complications. Nevertheless, anti-fibrinolytic agents could be contemplated in situations of life-threatening haemorrhage in the presence of normal coagulation assays.

References:

1. Summary of Product Characteristics for Idarubicin. Pfizer Ltd. Updated Oct 2022. Accessed Aug 2023. https://www.medicines.org.uk/emc/product/5596/smpc#gref
2. Summary of Product Characteristics for Mitoxantrone. Baxter Healthcare Ltd. Updated Sept 2020. Accessed Aug 2023. https://www.medicines.org.uk/emc/product/1844/smpc#gref
3. Summary of Product Characteristics for Tretinoin. Neon Healthcare Ltd. Updated July 2023. Accessed Aug 2023. https://www.medicines.org.uk/emc/product/2535/smpc#gref
4. Krens S D, Lassche, Jansman G F G A, et al. Dose recommendations for anticancer drugs in patients with renal or hepatic impairment. Lancet Oncol 2019; 20: e201–08.
5. Thames Valley Strategic Clinical Network. ATRA and Arsenic Protocol v1.1. Nov 2022.

Circulation/Dissemination

Date added into Q-Pulse	For completion by DCM

Date document posted on the Intranet	For completion by DCM

Version History

Date	Version	Author name and designation	Summary of main changes
July 2020	1.0	**Aileen McCaughey (Advanced Pharmacist – Haematology)**	**New protocol**
Sept 2023	2.0	**Jennifer Gibson (Principal Pharmacist - Haematology**	**3 yearly review. Transferred to new template. Administration information added. Standard ECG/ECHO comment added.**