Tretinoin (ATRA)/IDArubicin (PETHEMA AIDA) Induction Therapy: High Risk

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	Reimbursement Status
Treatment of patients with newly diagnosed high risk Acute Promyelocytic Leukaemia (APL)	C92	00366a	Hospital

TREATMENT:

The starting dose of the drugs detailed below may be adjusted downward by the prescribing clinician, using their independent medical judgement, to consider each patients individual clinical circumstances.

Induction therapy consists of tretinoin (ATRA) administered twice daily until complete haematological remission (CR) or up to a maximum of 60 days and IDArubicin administered on days 1, 3, 5 and 7.

Day	Drug	Dose	Route	Cycle
1 until complete remission	Tretinoin (ATRA)	45mg/m^2 in divided doses	[a]PO	Continuous until Complete Remission (CR) is achieved or up to a maximum of 60 days
1,3,5,7	IDArubicin	12mg/m^2	IV	Slow bolus in free running Sodium Chloride 0.9% drip over 5-10 min
[a] Tretinoin (ATRA) is available as 10mg capsules. Round dose to nearest 10mg. The 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.				
There is no established maximum cumulative lifetime dose for IDArubicin. **Due consideration should be given to the risk factors[i] and to the age of the patient**				

ELIGIBILITY:

- ECOG status 0-2
- Clinical diagnosis of APL and subsequently confirmed to have PML-RARA rearrangements by a validated test method
- Age ≤70 years

EXCLUSIONS:

- Hypersensitivity to IDArubicin, tretinoin (ATRA), retinoids, soya, peanut, or any of the excipients
- LVEF <50% (The treatment of patients with baseline LVEF <50% should only be initiated at the discretion of the treating consultant)
- Breast feeding

PRESCRIPTIVE AUTHORITY:

The treatment plan must be initiated by a Consultant Haematologist working in the area of haematological malignancies.

TESTS:

Baseline tests:

- FBC, renal and liver profile, Uric acid
- Coagulation profile (Activated Partial Thromboplastin time (APTT), Prothrombin time (PT), fibrinogen level)
- Triglyceride and cholesterol profile
- Pregnancy Test
- ECG
- MUGA or ECHO as clinically indicated

Regular tests:

- FBC, renal and liver profile, Uric acid, Glucose daily or as clinically indicated
- Coagulation profile: APTT, PT, fibrinogen level at least twice weekly or more frequently as clinically indicated
- Triglyceride and cholesterol profile periodically as clinically indicated

Disease monitoring:

Disease monitoring should be in line with the patient's treatment plan and any other test/s as directed by the supervising Consultant.

DOSE MODIFICATIONS:

- Any dose modification should be discussed with a Consultant
- During induction treatment, tretinoin (ATRA) may be temporarily discontinued in the presence of one of the following complications (See Table 1):
    - Differentiation syndrome
    - Pseudotumour cerebri
    - Hepatotoxicity

Table 1: Management of tretinoin (ATRA) related adverse reactions

Adverse Reaction	Action	On recovery
Differentiation (ATRA) Syndrome This is defined by the presence of: unexplained fever, weight gain, respiratory distress, interstitial pulmonary infiltrates, and pleural or pericardial effusion, with or without hyperleukocytosis. No single sign or symptom itself may be considered diagnostic of the syndrome. However, at the earliest manifestations of suspected Differentiation Syndrome (e.g. unexplained respiratory distress), and prior to development of a fulminant syndrome, the measures opposite should be immediately undertaken: In patients treated with tretinoin (ATRA), induction of hyperleucocytosis (WBC >10x10^9/L) associated with induction of blast differentiation on blood film will occur in a proportion of patients. This does not require any change in therapy, beyond careful vigilance for development of differentiation syndrome.	1. Discontinue tretinoin (ATRA) temporarily. 2. Initiate dexamethasone 10 mg i.v. 12-hourly until disappearance of symptoms and signs, and for a minimum of 3 days. 3. Furosemide when clinically required	Once symptoms/signs improve treatment with tretinoin (ATRA) is resumed at 50% of the usual dose for the first 4 days after the disappearance of differentiation syndrome, amelioration of pseudotumour cerebri or when liver tests are reduced to <4 x ULN. Thereafter, in the absence of worsening toxicity, resume 100% dose.
Pseudotumour Cerebri This is defined as presence of: severe headaches with nausea, vomiting, and visual disorders. In this case, generally developing in patients under 20 years of age.	It is often necessary to discontinue tretinoin (ATRA) treatment temporarily and to administer opiates.	
Hepatoxicity Bilirubin, AST/ALT or alkaline phosphatase >5 x upper limit of normal level (ULN).	This requires temporary discontinuation of tretinoin (ATRA).	

Renal and Hepatic Impairment:

Table 2: Dose modifications based on renal and hepatic impairment

Drug	Renal Impairment		Hepatic Impairment	
Tretinoin (ATRA)	Consideration could be given to dose reduction in renal impairment at the discretion of prescribing consultant		Consideration could be given to dose reduction in hepatic impairment at the discretion of prescribing consultant	
IDArubicin	**Creatinine (micromol/L)**	**Dose**	**Bilirubin (micromol/L)**	**Dose**
	<100	100%	<40	100%
	100-175	50%	40-85	50%
	>175	Clinical decision	>85	Omit

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL:

Tretinoin (ATRA): Minimal to low **(refer to local policy)**
IDArubicin: Moderate **(refer to local policy)**

PREMEDICATIONS: None usually required

OTHER SUPPORTIVE CARE:

- Tumour lysis syndrome prophylaxis **(Refer to local policy)**
- Anti-viral prophylaxis **(Refer to local policy)**
- Anti-fungal prophylaxis **(Refer to local policy)**

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS

The adverse effects listed are not exhaustive. Please refer to the relevant Summary of Product Characteristics for full details.

Tretinoin (ATRA):

- **Teratogenecity:** Tretinoin (ATRA) is teratogenic: Women of child bearing potential must be fully informed of the hazards of becoming pregnant before initiating treatment. They must use reliable contraception without interruption during therapy and for one month after discontinuation of treatment with tretinoin (ATRA).
- **Thrombosis (arterial and venous):** There is a risk of thrombosis during the first month of treatment and may involve any organ system. Fatal thrombotic complications have been reported rarely in patients treated concurrently with tretinoin (ATRA) and antifibrinolytic agents. Caution is advised.
- **Psychiatric disorders:** Depression, depression aggravated, anxiety, and mood alterations have been reported in patients treated with systemic retinoids, including tretinoin. Particular care should be taken in patients with a history of depression.

IDArubicin:

- **Cardiotoxicity**: Cardiac toxicity may occur, manifested by cardiac failure, arrhythmias or cardiomyopathies, either during therapy or several weeks later. The cumulative dose associated with cardiotoxicity is not known, Cardiac function monitoring must be particularly strict in patients receiving high cumulative doses and in those with risk factors. However, cardiotoxicity with IDArubicin may occur at lower cumulative doses whether or not cardiac risk factors are present.
- **Extravasation**: IDArubicin is a potent vesicant. Give through the side arm of a fast flowing infusion to avoid/minimise the risk of extravasation.

DRUG INTERACTIONS:

- Systemic treatment with retinoids may cause elevation of the intracranial pressure. As tetracyclines may also cause elevation of the intracranial pressure, patients must not be treated with tretinoin (ATRA) and tetracyclines at the same time.
- As with other retinoids, tretinoin (ATRA) must not be administered in combination with vitamin A because symptoms of hypervitaminosis A could be aggravated.
- The effect of food on the bioavailability of tretinoin (ATRA) has not been characterised. Since the bioavailability of retinoids, as a class, is known to increase in the presence of food, it is recommended that tretinoin (ATRA) be administered with a meal or shortly thereafter.
- As tretinoin (ATRA) is metabolised by the hepatic P450 system, there is the potential for alteration of pharmacokinetics parameters in patients administered concomitant medications that are also inducers or inhibitors of this system. Medications that generally induce hepatic P450 enzymes include rifampicin, glucocorticoids, phenobarbital and pentobarbital.
- Current drug interaction databases should be consulted for more information.

REFERENCES:

1. Lo-Coco et al. Retinoic acid and arsenic trioxide for acute promyelocytic leukemia. N Engl J Med 2013; 369 (2):111-21.
2. Sanz et al. on behalf of the PETHEMA and HOVON groups Risk-adapted treatment of acute promyelocytic leukemia based on all-transretinoic acid and anthracycline with addition of cytarabine in consolidation for high-risk patients: further improvements in treatment outcome. Blood 2010;115: 5137-5146
3. Cheson et al. Revised Recommendations of the International Working Group for Diagnosis, Standardization of Response Criteria, Treatment Outcomes, and Reporting Standards for Therapeutic Trials in Acute Myeloid Leukemia. J Clin Oncol, 2003;21:4642-4649.
4. Dosage Adjustment for Cytotoxics in Renal Impairment January 2009; North London Cancer Network . Available at http://londoncancer.org/media/65600/renal-impairment-dosage-adjustment-for-cytotoxics.pdf
5. Dosage Adjustment for Cytotoxics in Hepatic Impairment January 2009;North London Cancer Network. Available at http://londoncancer.org/media/65594/hepatic-impairment-dosage-adjustment-for-cytotoxics.pdf
6. Vesanoid® Summary of Product Characteristics Accessed March 2021. Available at https://www.hpra.ie/img/uploaded/swedocuments/Licence_PA1868-001-001_15022021125248.pdf

7. Zavedos® 10mg Powder for Solution for Injection. Accessed March 2021. Available at https://www.hpra.ie/img/uploaded/swedocuments/Licence_PA0822-142-004_21042020132000.pdf
8. NCCP Classification Document for Systemic Anti-Cancer Therapy (SACT) Induced Nausea and Vomiting. V2 2019. Available at: https://www.hse.ie/eng/services/list/5/cancer/profinfo/chemoprotocols/nccp-classification-document-for-systemic-anti-cancer-therapy-sact-induced-nausea-and-vomiting.pdf

Version	Date	Amendment	Approved By
1	03/07/2017		Dr Eibhlin Conneally
2	09/07/2018	Updated indication; includes high risk APL only as per updated reference. In high risk patients, as all are assumed to have WBC >10, the days of IDArubicin administration have been amended to 1,3,5,7 (previously 2,4,6,8)	Dr Ruth Clifford
3	19/03/2021	Regimen review Updated emetogenic potential Updated adverse effects/regimen specific complications for Tretinoin with regards to Psychiatric disorders as per SmPC update	Dr Eibhlin Conneally

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.

[ii]Cardiotoxicity is a risk associated with anthracycline therapy that may be manifested by early (acute) or late (delayed) effects.

Risk factors for developing anthracycline-induced cardiotoxicity include:
• high cumulative dose, previous therapy with other anthracyclines or anthracenediones
• prior or concomitant radiotherapy to the mediastinal/pericardial area
• pre-existing heart disease
• concomitant use of other potentially cardiotoxic drugs

In establishing the maximal cumulative dose of an anthracycline, consideration should be given to the risk factors above and to the age of the patient.