

# Acute promyelocytic leukaemia standard risk (chemotherapy free) consolidation

ID: 1943 v.3 Endorsed

Patients with leukaemia should be considered for inclusion into clinical trials. Link to [ALLG website](#) and [ANZCTR website](#).

The anticancer drug(s) in this protocol may have been included in the ADDIKD guideline. Dose recommendations in kidney dysfunction have yet to be updated to align with the ADDIKD guideline. Recommendations will be updated once the individual protocol has been evaluated by the reference committee. For further information refer to the ADDIKD guideline. To assist with calculations, use the [eviQ Estimated Glomerular Filtration Rate \(eGFR\) calculator](#).

## International Consensus Guideline for Anticancer Drug Dosing in Kidney Dysfunction (ADDIKD)

2022

[Click here](#)



### Related pages:

- [Acute promyelocytic leukaemia standard risk \(chemotherapy free\) overview](#)
- [Acute promyelocytic leukaemia standard risk \(chemotherapy free\) induction](#)

## Treatment schedule - Overview

### Cycle 1 to 3

Drug	Dose	Route	Day
Tretinoin (ATRA)	45 mg/m <sup>2</sup> divided into TWO equal doses *	PO	1 to 14 and 29 to 42 (cycle 1 to 3 only)
Arsenic trioxide (ATO)	0.15 mg/kg	IV infusion	1 to 5, 8 to 12, 15 to 19, 22 to 26

### Cycle 4

Drug	Dose	Route	Day
Tretinoin (ATRA)	45 mg/m <sup>2</sup> divided into TWO equal doses *	PO	1 to 14 (cycle 4 only)
Arsenic trioxide (ATO)	0.15 mg/kg	IV infusion	1 to 5, 8 to 12, 15 to 19, 22 to 26

\* ATRA doses should be rounded to the nearest 10mg.

Tretinoin is given in blocks of 2 weeks on followed by 2 weeks off for a total of 7 fortnightly blocks. Arsenic is given Monday to Friday, 4 weeks on followed by 4 weeks off, for a total of 4 blocks (20 doses each block). For ease eviQ has grouped this into 4 x 56 day cycles.

Note that no drug is given D43-D56 (cycles 1-3) and D27-D56 (4th and final cycle).

**Frequency:** 56 days

**Cycles:** 4

**Drug status:** Arsenic trioxide: [\(PBS authority\)](#)

**Tretinoin** is TGA registered but not PBS listed for this indication

Tretinoin is available as **10 mg** capsules

**Cost:** ~ \$4,540 (cycles 1 to 3); \$11,045 (cycle 4 only)

## Treatment schedule - Detail

*The supportive therapies (e.g. antiemetics, premedications, etc.), infusion times, diluents, volumes and routes of administration, if included, are listed as defaults. They may vary between institutions and can be substituted to reflect individual institutional policy.*

*Antiemetics if included in the treatment schedule are based upon recommendations from national and international guidelines. These are **defaults only** and may be substituted to reflect individual institutional policy. [Select here for recommended doses of alternative antiemetics.](#)*

### Cycle 1 to 3

Day 1 to 5		
Tretinoin (ATRA)	45 mg/m <sup>2</sup> (PO)	in TWO equally divided doses daily (round to the nearest 10 mg).
Arsenic trioxide (ATO)	0.15 mg/kg (IV infusion)	in 100 mL to 250 mL sodium chloride 0.9% over 2 hours ONCE a day
Day 6 and 7		
Tretinoin (ATRA)	45 mg/m <sup>2</sup> (PO)	in TWO equally divided doses daily (round to the nearest 10 mg).
Day 8 to 12		
Tretinoin (ATRA)	45 mg/m <sup>2</sup> (PO)	in TWO equally divided doses daily (round to the nearest 10 mg).
Arsenic trioxide (ATO)	0.15 mg/kg (IV infusion)	in 100 mL to 250 mL sodium chloride 0.9% over 2 hours ONCE a day
Day 13 and 14		
Tretinoin (ATRA)	45 mg/m <sup>2</sup> (PO)	in TWO equally divided doses daily (round to the nearest 10 mg).
Day 15 to 19 and 22 to 26		
Arsenic trioxide (ATO)	0.15 mg/kg (IV infusion)	in 100 mL to 250 mL sodium chloride 0.9% over 2 hours ONCE a day
Day 29 to 42		
Tretinoin (ATRA)	45 mg/m <sup>2</sup> (PO)	in TWO equally divided doses daily (round to the nearest 10 mg).

### Cycle 4

Day 1 to 5		
Tretinoin (ATRA)	45 mg/m <sup>2</sup> (PO)	in TWO equally divided doses daily (round to the nearest 10 mg).
Arsenic trioxide (ATO)	0.15 mg/kg (IV infusion)	in 100 mL to 250 mL sodium chloride 0.9% over 2 hours ONCE a day
Day 6 and 7		
Tretinoin (ATRA)	45 mg/m <sup>2</sup> (PO)	in TWO equally divided doses daily (round to the nearest 10 mg).
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Day 15 to 19 and 22 to 26		
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Tretinoin is given in blocks of 2 weeks on followed by 2 weeks off for a total of 7 fortnightly blocks. Arsenic is given Monday to Friday, 4 weeks on followed by 4 weeks off, for a total of 4 blocks (20 doses each block). For ease eviQ has grouped this into 4 x 56 day cycles.

Note that no drug is given D43-D56 (cycles 1-3) and D27-D56 (4th and final cycle).

**Frequency:** 56 days

**Cycles:** 4

## Indications and patient population

- Acute promyelocytic leukaemia (APML)

### Induction:

- low to intermediate risk ( $WCC \leq 10 \times 10^9/L$ ) APML

### Consolidation:

- low to intermediate risk ( $WCC \leq 10 \times 10^9/L$ ) APML
- It is the consensus of the reference committee that the chemotherapy free consolidation protocol may be given to high-risk APML patients after they have received induction with an anthracycline-based chemotherapy. See [evidence section](#).

## Clinical information

<b>Caution with oral anti-cancer drugs</b>	Select links for information on the safe prescribing, dispensing and administration of orally administered anti-cancer drugs. Read more about the <a href="#">COSA guidelines</a> and <a href="#">oral anti-cancer therapy</a>
<b>Venous access required</b>	IV cannula (IVC) or central venous access device (CVAD) is required to administer this treatment. Read more about <a href="#">central venous access device line selection</a>
<b>Emetogenicity minimal or low</b>	No routine prophylaxis required. If patients experience nausea and/or vomiting, consider using the low emetogenic risk regimen. Read more about <a href="#">preventing anti-cancer therapy induced nausea and vomiting</a>

<b>Teratogenic effects</b>	<p>This treatment can cause severe congenital disabilities or death to an unborn baby. All patients of reproductive potential must use at least one reliable contraceptive method for at least 4 weeks before starting treatment, during treatment (including dose interruptions), and for 4 weeks after stopping treatment.</p> <p>In female patients of reproductive potential (if sexually active), a pregnancy test should be carried out prior to initiating treatment (after 4 weeks of contraception use), weekly during the first month of treatment and monthly thereafter.</p> <p>Effective contraception methods and adequate contraception timeframes should be discussed with all patients of reproductive potential.</p>
<b>Hyperleukocytosis</b>	<p>Treatment related hyperleukocytosis (WBC greater or equal to <math>100 \times 10^9/L</math>) develops in approximately 50% of arsenic trioxide treated patients. Peak WBC count occurs at about 20 days post first arsenic trioxide dose and usually resolves at a median of 10.5 days after the peak, despite continuation of arsenic trioxide.</p> <p>It may be managed with careful observation, checking particularly for emerging APML differentiation syndrome. Hydroxycarbamide (hydroxyurea) has been used to treat marked hyperleukocytosis associated with arsenic trioxide, but its benefit is unclear.</p>
<b>ECG abnormalities</b>	<p>Arsenic trioxide can cause QTc interval prolongation and complete atrioventricular block. Prior to commencement perform baseline electrocardiogram (ECG), correct pre-existing electrolyte abnormalities, and if possible cease drugs that may prolong the QTc interval.</p> <p>During treatment it is critical to maintain potassium concentrations above 4 mmol/L and magnesium concentrations above 0.8 mmol/L; continue ECG at least twice weekly or more frequently in unstable patients.</p> <p>Arsenic trioxide should not be commenced if QTc is greater than 500 msec. If QTc of greater than 500 msec is reached during treatment, consider suspending arsenic trioxide. If syncope or rapid or irregular heartbeat develop, suspend arsenic trioxide treatment until symptoms resolve and QTc falls to below 460 msec.</p> <p>Read more about drugs that may prolong QTc interval at <a href="https://crediblemeds.org">crediblemeds.org</a> (registration required) and <a href="#">ECG abnormalities associated with arsenic trioxide</a></p>
<b>Pseudotumour cerebri</b>	<p>Headaches are common on ATRA therapy, although the possibility of intracranial haemorrhage, particularly during induction always needs to be considered. Pseudotumour cerebri is more common in young patients less than 20, and may be associated with severe headache, nausea and vomiting. It may necessitate temporary discontinuation of ATRA and recommencement at a lower dose.</p>
<b>Peripheral neuropathy</b>	<p>Assess prior to each treatment. If a patient experiences greater than grade 3, a dose reduction or delay of treatment may be required; review by medical officer before commencing treatment.</p> <p>Read more about <a href="#">peripheral neuropathy</a></p> <p>Link to <a href="#">chemotherapy-induced peripheral neuropathy screening tool</a></p>
<b>Pneumocystis jirovecii pneumonia (PJP) prophylaxis</b>	<p>Depending on dose and duration of steroid therapy, PJP prophylaxis may be appropriate (at clinician's discretion).</p> <p>Read about <a href="#">prophylaxis of pneumocystis jirovecii (carinii) in cancer patients</a></p>
<b>Antifungal and antiviral prophylaxis</b>	<p>Antifungal and antiviral prophylaxis should be determined according to individual institutional policy. Note that azole antifungals may contribute to QTc prolongation.</p> <p>Read more about <a href="#">antiviral</a> and <a href="#">antifungal</a> prophylaxis</p>
<b>Blood product support</b>	<p>To minimise the risk of cerebral haemorrhage, an aggressive haemostatic support regimen is recommended:</p> <p>Maintain platelet count of at least <math>30 \times 10^9/L</math>.</p> <p>Fresh frozen plasma and/or cryoprecipitate daily as necessary to maintain normal prothrombin time, normal activated partial thromboplastin time, and plasma fibrinogen greater than 1.5 g/L.</p>
<b>Blood tests</b>	<p>FBC, EUC, eGFR, LFTs, APTT, PT and fibrinogen level at baseline, then throughout treatment as clinically indicated.</p>

<b>Hepatitis B screening and prophylaxis</b>	<p>Routine screening for HBsAg and anti-HBc is recommended prior to initiation of treatment. Prophylaxis should be determined according to individual institutional policy.</p> <p>Read more about <a href="#">hepatitis B screening and prophylaxis in cancer patients requiring cytotoxic and/or immunosuppressive therapy</a></p>
<b>Vaccinations</b>	<p>Live vaccines are contraindicated in cancer patients receiving immunosuppressive therapy and/or who have poorly controlled malignant disease.</p> <p>Refer to the recommended schedule of vaccination for immunocompromised patients, as outlined in the <a href="#">Australian Immunisation Handbook</a>.</p> <p>Read more about <a href="#">COVID-19 vaccines and cancer</a>.</p>
<b>Fertility and lactation</b>	<p>Cancer treatment can have harmful effects on fertility and this should be discussed with all patients of reproductive potential prior to commencing treatment.</p> <p>Possibility of infant risk should be discussed with breastfeeding patients.</p> <p>Read more about the <a href="#">effect of cancer treatment on fertility</a></p>

## Dose modifications

*Evidence for dose modifications is limited, and the recommendations made on eviQ are intended as a guide only. They are generally conservative with an emphasis on safety. Any dose modification should be based on clinical judgement, and the individual patient's situation including but not limited to treatment intent (curative vs palliative), the anti-cancer regimen (single versus combination therapy versus chemotherapy versus immunotherapy), biology of the cancer (site, size, mutations, metastases), other treatment related side effects, additional co-morbidities, performance status and patient preferences. Suggested dose modifications are based on clinical trial findings, product information, published guidelines and reference committee consensus. The dose reduction applies to each individual dose and not to the total number of days or duration of treatment cycle unless stated otherwise. Non-haematological gradings are based on [Common Terminology Criteria for Adverse Events \(CTCAE\)](#) unless otherwise specified. Renal and hepatic dose modifications have been standardised where possible. For more information see dosing considerations & disclaimer.*

The dose recommendations in kidney dysfunction (i.e. renal impairment) displayed may not reflect those in the ADDIKD guideline and have been included for historical reference only. Recommendations will be updated once the individual protocol has been evaluated by the reference committee, with this version of the protocol then being archived. Clinicians are expected to refer to the ADDIKD guideline prior to prescribing in kidney dysfunction.

[International Consensus Guideline for Anticancer Drug Dosing in Kidney Dysfunction \(ADDIKD\).](#)

### Note:

- The modifications in this protocol are as per product information unless specified otherwise.

### Renal impairment

Safety and efficacy of arsenic trioxide in patients with renal impairment have not been studied. Use with caution in patients with renal failure, as renal excretion is the main route of elimination.

### Hepatic impairment

**The following dose modifications for hepatic impairment are taken from the ALLG and ANZCHOG APML4 protocol<sup>1</sup>**

Grade 1	AST, ALT, GGT greater than ULN to 2.5 x ULN Bilirubin greater than ULN to 1.5 x ULN	Continue treatment with arsenic trioxide
Grade 2	AST, ALT, GGT greater than 2.5 x ULN to 5 x ULN Bilirubin greater than 1.5 x ULN to 3 x ULN	Continue treatment with arsenic trioxide
Grade 3	AST, ALT, GGT greater than 5 x ULN to 20 x ULN Bilirubin greater than 3 x ULN to 10 x ULN	Reduce arsenic trioxide dose to 0.08 mg/kg/day
Grade 4	AST, ALT, GGT greater than 20 x ULN Bilirubin greater than 10 x ULN	Stop arsenic trioxide. Restart at 0.08 mg/kg/day when hepatic function improves to Grade 2.

Hepatic impairment		
		Consider increasing back to 0.15 mg/kg/day if no deterioration after one week.

QT interval prolongation		
<b>The following dose modifications for QT interval prolongation are taken from the APL0406 trial<sup>2</sup></b>		
<p>If significant QT interval prolongation occurs, arsenic trioxide should be discontinued, together with any other medication known to prolong the QTc interval, and electrolytes should be corrected. The time between discontinuing arsenic trioxide and normalisation of the QTc interval may be several days. Once QTc is normalised, resume arsenic trioxide at 0.075 mg/kg (50%) for the first 7 days, and then if no further prolongation occurs, resume at 0.11 mg/kg for a second week. Thereafter, if no prolongation occurs, resume arsenic trioxide at full dose.</p>		

Peripheral neuropathy		
Grade 3 to Grade 4	Consider dose reducing or delaying arsenic trioxide	

## Interactions

*Drug interactions in eviQ protocols are under review and being updated to align with current literature. Further site-wide updates and changes will occur in due course. References & Disclaimer*

*The drug interactions shown below are not an exhaustive list. For a more comprehensive list and for detailed information on specific drug interactions and clinical management, please refer to the specific drug product information and the following key resources:*

- [MIMS - interactions tab](#) (includes link to a CYP-450 table) (login required)
- [Australian Medicines Handbook \(AMH\) – interactions tab](#) (login required)
- [Micromedex Drug Interactions](#) (login required)
- [Cancer Drug Interactions](#)
- [Cytochrome P450 Drug Interactions](#)

Arsenic Trioxide (ATO)		
	Interaction	Clinical management
<b>Nephrotoxic drugs (e.g. aminoglycosides, amphotericin, contrast dye, frusemide, NSAIDs)</b>	Additive nephrotoxicity	Avoid combination or monitor kidney function closely
<b>Drugs that may prolong the QTc interval (e.g. azole antifungals, tricyclic antidepressants, antiarrhythmics etc.)</b>	Additive effect with arsenic trioxide; may lead to torsades de pointes and cardiac arrest	Avoid combination or minimise additional risk factors (e.g. correct electrolyte imbalances) and monitor ECG for signs of cardiac arrhythmia

Tretinoin (ATRA)		
	Interaction	Clinical management
<b>Cytochrome p450 inhibitors (e.g. aprepitant, azole antifungals, clarithromycin, erythromycin, grapefruit juice, ritonavir etc.)</b>	Increased toxicity of tretinoin possible due to decreased clearance	Avoid combination or monitor for tretinoin toxicity
<b>Cytochrome p450 inducers (e.g. carbamazepine, phenytoin, phenobarbitone, rifampicin, St John's wort etc.)</b>	Reduced efficacy of tretinoin possible due to increased clearance	Avoid combination or monitor for decreased clinical response to tretinoin
<b>Antifibrinolytic agents (e.g. tranexamic acid and aprotinin)</b>	Cases of fatal thrombotic complications have been reported rarely in patients concomitantly treated with tretinoin and antifibrinolytic agents.	Avoid combination or closely monitor
<b>Tetracyclines</b>	Elevation of intracranial pressure/pseudotumour cerebri may be caused by tetracyclines and retinoids. Patients treated with tretinoin and tetracyclines in combination might be at a greater risk of experiencing this condition.	Avoid combination or monitor for elevation of intracranial pressure/pseudotumour cerebri
<b>Vitamin A</b>	Combination with vitamin A may cause or exacerbate the symptoms of hypervitaminosis A.	Combination is contraindicated

General		
	Interaction	Clinical management
<b>Warfarin</b>	Anti-cancer drugs may alter the anticoagulant effect of warfarin.	Monitor INR regularly and adjust warfarin dosage as appropriate; consider alternative anticoagulant.
<b>Direct oral anticoagulants (DOACs) e.g. apixaban, rivaroxaban, dabigatran</b>	<p>Interaction with both CYP3A4 and P-gp inhibitors /inducers.</p> <p>DOAC and anti-cancer drug levels may both be altered, possibly leading to loss of efficacy or toxicity (i.e. increased bleeding).</p>	<p>Apixaban: avoid concurrent use with strong <a href="#">CYP3A4</a> and <a href="#">P-gp</a> inhibitors. If treating VTE, avoid use with strong <a href="#">CYP3A4</a> and <a href="#">P-gp</a> inducers.</p> <p>Rivaroxaban: avoid concurrent use with strong <a href="#">CYP3A4</a> and <a href="#">P-gp</a> inhibitors.</p> <p>Dabigatran: avoid combination with strong <a href="#">P-gp</a> inducers and inhibitors.</p> <p>If concurrent use is unavoidable, monitor closely for efficacy/toxicity of both drugs.</p>
<b>Digoxin</b>	Anti-cancer drugs can damage the lining of the intestine; affecting the absorption of digoxin.	Monitor digoxin serum levels; adjust digoxin dosage as appropriate.
<b>Antiepileptics</b>	Both altered antiepileptic and anti-cancer drug levels may occur, possibly leading to loss of efficacy or toxicity.	Where concurrent use of an enzyme-inducing antiepileptic cannot be avoided, monitor antiepileptic serum levels for toxicity, as well as seizure frequency for efficacy; adjust dosage as appropriate. Also monitor closely for efficacy of the anti-cancer therapy.
<b>Antiplatelet agents and NSAIDs</b>	Increased risk of bleeding due to treatment related thrombocytopenia.	Avoid or minimise combination. If combination deemed essential, (e.g. low dose aspirin for ischaemic heart disease) monitor for signs of bleeding.
<b>Serotonergic drugs, including selective serotonin reuptake inhibitors (SSRIs e.g. paroxetine) and serotonin noradrenaline reuptake inhibitors (SNRIs e.g. venlafaxine)</b>	Increased risk of serotonin syndrome with concurrent use of 5-HT <sub>3</sub> receptor antagonists (e.g. palonosetron, ondansetron, granisetron, tropisetron, dolasetron, etc.)	<p>Avoid combination.</p> <p>If combination is clinically warranted, monitor for signs and symptoms of serotonin syndrome (e.g. confusion, agitation, tachycardia, hyperreflexia). For more information link to <a href="#">TGA Medicines Safety Update</a></p>
<b>Vaccines</b>	Diminished response to vaccines and increased risk of infection with live vaccines.	<p>Live vaccines (e.g. BCG, MMR, zoster and varicella) are contraindicated in patients on immunosuppressive therapy. Use with caution in patients on non-immunosuppressive therapy.</p> <p>For more information; refer to the recommended schedule of vaccination for cancer patients, as outlined in the <a href="#">Australian Immunisation Handbook</a></p>

## Administration cycles 1 to 3

*eviQ provides safe and effective instructions on how to administer cancer treatments. However, eviQ does not provide every treatment delivery option, and is unable to provide a comprehensive list of cancer treatment agents and their required IV line giving set/filter. There may be alternative methods of treatment administration, and alternative supportive treatments that are also appropriate. Please refer to the individual*



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## Days 1 to 5

**Approximate treatment time: 2.5 hours**

[Safe handling and waste management](#)

[Safe administration](#)

[General patient assessment](#) prior to each day of treatment.

[Peripheral neuropathy assessment tool](#).

Any toxicity grade 3 or greater may require dose reduction, delay or omission of treatment and review by medical officer before recommencing treatment.

- baseline weight

Prime IV line(s).

Insert IV cannula or access [TIVAD](#) or [CVAD](#).

### Pre treatment medication

Verify antiemetics taken or administer as prescribed.

## ⌚ Chemotherapy - Time out

### Tretinoin (ATRA)

- administer orally in TWO equally divided doses
- to be swallowed whole with a glass of water; do not break, crush or chew
- can be taken with or without food
- protect skin from sunlight

**Note:** missed doses should not be replaced; if a tablet is forgotten or vomited, normal dosing should be resumed at the next scheduled dose.

Notify medical team if the patient reports weight gain, shortness of breath and/or temperature as this may be symptoms of differentiation syndrome.

Read more about [APML differentiation syndrome](#)

### Arsenic trioxide (ATO)

#### Prior to administration:

- check BSL as indicated
- baseline ECG then at least twice weekly ECG, or more frequently in unstable patients
- maintain serum potassium above 4 mmol/L and magnesium above 0.8 mmol/L.

#### Administer arsenic trioxide:

- via IV infusion over 2 hours
- flush with 50 mL sodium chloride 0.9%
- if the patient has a vasomotor reaction (lightheadedness, changes in blood pressure) the time of the arsenic infusion may be extended up to four hours.

Remove IV cannula and/or deaccess [TIVAD](#) or [CVAD](#).

Continue [safe handling](#) precautions until 7 days after completion of drug(s)

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## Days 6 and 7

**This is an oral treatment**

[Safe handling and waste management](#) (reproductive risk only)

[Safe administration](#)

[General patient assessment](#) prior to each day of treatment.

[Peripheral neuropathy assessment tool](#).

Any toxicity grade 3 or greater may require dose reduction, delay or omission of treatment and review by medical officer before recommencing treatment.

#### **Pre treatment medication**

Verify antiemetics taken or administer as prescribed.

#### **⌚ Treatment - Time out**

##### **Tretinoin (ATRA)**

- administer orally in TWO equally divided doses
- to be swallowed whole with a glass of water; do not break, crush or chew
- can be taken with or without food
- protect skin from sunlight

**Note:** missed doses should not be replaced; if a tablet is forgotten or vomited, normal dosing should be resumed at the next scheduled dose.

Notify medical team if the patient reports weight gain, shortness of breath and/or temperature as this may be symptoms of differentiation syndrome.

Read more about [APML differentiation syndrome](#)

Continue [safe handling](#) precautions (reproductive risk only) for 7 days after completion of drug(s).

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## **Days 8 to 12**

**Approximate treatment time: 2.5 hours**

[Safe handling and waste management](#)

[Safe administration](#)

[General patient assessment](#) prior to each day of treatment.

[Peripheral neuropathy assessment tool](#).

Any toxicity grade 3 or greater may require dose reduction, delay or omission of treatment and review by medical officer before recommencing treatment.

Prime IV line(s).

Insert IV cannula or access [TIVAD](#) or [CVAD](#).

#### **Pre treatment medication**

Verify antiemetics taken or administer as prescribed.

#### **⌚ Chemotherapy - Time out**

##### **Tretinoin (ATRA)**

- administer orally in TWO equally divided doses
- to be swallowed whole with a glass of water; do not break, crush or chew
- can be taken with or without food
- protect skin from sunlight

**Note:** missed doses should not be replaced; if a tablet is forgotten or vomited, normal dosing should be resumed at the next scheduled dose.

Notify medical team if the patient reports weight gain, shortness of breath and/or temperature as this may be symptoms of differentiation syndrome.

Read more about [APML differentiation syndrome](#)

## Arsenic trioxide (ATO)

### Prior to administration:

- check BSL as indicated
- baseline ECG then at least twice weekly ECG, or more frequently in unstable patients
- maintain serum potassium above 4 mmol/L and magnesium above 0.8 mmol/L.

### Administer arsenic trioxide:

- via IV infusion over 2 hours
- flush with 50 mL sodium chloride 0.9%
- if the patient has a vasomotor reaction (lightheadedness, changes in blood pressure) the time of the arsenic infusion may be extended up to four hours.

Remove IV cannula and/or deaccess [TIVAD](#) or [CVAD](#).

Continue [safe handling](#) precautions until 7 days after completion of drug(s)

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## Days 13 and 14

**This is an oral treatment**

[Safe handling and waste management](#) (reproductive risk only)

[Safe administration](#)

[General patient assessment](#) prior to each day of treatment.

[Peripheral neuropathy assessment tool](#).

Any toxicity grade 3 or greater may require dose reduction, delay or omission of treatment and review by medical officer before recommencing treatment.

### Pre treatment medication

Verify antiemetics taken or administer as prescribed.

### 🕒 Treatment - Time out

## Tretinoin (ATRA)

- administer orally in TWO equally divided doses
- to be swallowed whole with a glass of water; do not break, crush or chew
- can be taken with or without food
- protect skin from sunlight

**Note:** missed doses should not be replaced; if a tablet is forgotten or vomited, normal dosing should be resumed at the next scheduled dose.

Notify medical team if the patient reports weight gain, shortness of breath and/or temperature as this may be symptoms of differentiation syndrome.

Read more about [APML differentiation syndrome](#)

Continue [safe handling](#) precautions (reproductive risk only) for 7 days after completion of drug(s).

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## Days 15 to 19 and 22 to 26

**Approximate treatment time: 2.5 hours**

[Safe handling and waste management](#)

[Safe administration](#)

[General patient assessment](#) prior to each day of treatment.

[Peripheral neuropathy assessment tool.](#)

Any toxicity grade 3 or greater may require dose reduction, delay or omission of treatment and review by medical officer before recommencing treatment.

Prime IV line(s).

Insert IV cannula or access [TIVAD](#) or [CVAD](#).

### Pre treatment medication

Verify antiemetics taken or administer as prescribed.

### Chemotherapy - Time out

#### Arsenic trioxide (ATO)

##### Prior to administration:

- check BSL as indicated
- baseline ECG then at least twice weekly ECG, or more frequently in unstable patients
- maintain serum potassium above 4 mmol/L and magnesium above 0.8 mmol/L.

##### Administer arsenic trioxide:

- via IV infusion over 2 hours
- flush with 50 mL sodium chloride 0.9%
- if the patient has a vasomotor reaction (lightheadedness, changes in blood pressure) the time of the arsenic infusion may be extended up to four hours.

Remove IV cannula and/or deaccess [TIVAD](#) or [CVAD](#).

Continue [safe handling](#) precautions until 7 days after completion of drug(s)

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## Days 29 to 42

**This is an oral treatment**

[Safe handling and waste management](#) (reproductive risk only)

[Safe administration](#)

[General patient assessment](#) prior to each day of treatment.

[Peripheral neuropathy assessment tool.](#)

Any toxicity grade 3 or greater may require dose reduction, delay or omission of treatment and review by medical officer before recommencing treatment.

### Pre treatment medication

Verify antiemetics taken or administer as prescribed.

### Treatment - Time out

#### Tretinoin (ATRA)

- administer orally in TWO equally divided doses
- to be swallowed whole with a glass of water; do not break, crush or chew
- can be taken with or without food
- protect skin from sunlight

**Note:** missed doses should not be replaced; if a tablet is forgotten or vomited, normal dosing should be resumed at the next scheduled dose.

Notify medical team if the patient reports weight gain, shortness of breath and/or temperature as this may be symptoms of differentiation syndrome.

Read more about [APML differentiation syndrome](#)

Continue [safe handling](#) precautions (reproductive risk only) for 7 days after completion of drug(s).

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## Discharge information

### Tretinoin capsules

- Tretinoin capsules with written instructions on how to take them

### Antiemetics

- Antiemetics as prescribed.

### Antidiarrhoeals

- Antidiarrhoeals as prescribed.

### Patient information

- Ensure patient receives patient information sheet.

## Administration cycle 4

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## Days 1 to 5

**Approximate treatment time: 2.5 hours**

### Safe handling and waste management

### Safe administration

[General patient assessment](#) prior to each day of treatment.

[Peripheral neuropathy assessment tool](#).

Any toxicity grade 3 or greater may require dose reduction, delay or omission of treatment and review by medical officer before recommencing treatment.

Prime IV line(s).

Insert IV cannula or access [TIVAD](#) or [CVAD](#).

### Pre treatment medication

Verify antiemetics taken or administer as prescribed.

## ⌚ Chemotherapy - Time out

### Tretinoin (ATRA)

- administer orally in TWO equally divided doses
- to be swallowed whole with a glass of water; do not break, crush or chew
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- protect skin from sunlight

**Note:** missed doses should not be replaced; if a tablet is forgotten or vomited, normal dosing should be resumed at the next scheduled dose.

Notify medical team if the patient reports weight gain, shortness of breath and/or temperature as this may be symptoms of differentiation syndrome.

Read more about [APML differentiation syndrome](#)

## Arsenic trioxide (ATO)

### Prior to administration:

- check BSL as indicated
- baseline ECG then at least twice weekly ECG, or more frequently in unstable patients
- maintain serum potassium above 4 mmol/L and magnesium above 0.8 mmol/L.

### Administer arsenic trioxide:

- via IV infusion over 2 hours
- flush with 50 mL sodium chloride 0.9%
- if the patient has a vasomotor reaction (lightheadedness, changes in blood pressure) the time of the arsenic infusion may be extended up to four hours.

Remove IV cannula and/or deaccess [TIVAD](#) or [CVAD](#).

Continue [safe handling](#) precautions until 7 days after completion of drug(s)

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## Days 6 and 7

This is an oral treatment

[Safe handling and waste management](#) (reproductive risk only)

[Safe administration](#)

[General patient assessment](#) prior to each day of treatment.

[Peripheral neuropathy assessment tool](#).

Any toxicity grade 3 or greater may require dose reduction, delay or omission of treatment and review by medical officer before recommencing treatment.

### Pre treatment medication

Verify antiemetics taken or administer as prescribed.

### 🕒 Treatment - Time out

## Tretinoin (ATRA)

- administer orally in TWO equally divided doses
- to be swallowed whole with a glass of water; do not break, crush or chew
- can be taken with or without food
- protect skin from sunlight

**Note:** missed doses should not be replaced; if a tablet is forgotten or vomited, normal dosing should be resumed at the next scheduled dose.

Notify medical team if the patient reports weight gain, shortness of breath and/or temperature as this may be symptoms of differentiation syndrome.

Read more about [APML differentiation syndrome](#)

Continue [safe handling](#) precautions (reproductive risk only) for 7 days after completion of drug(s).

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## Days 8 to 12

Approximate treatment time: 2.5 hours

[Safe handling and waste management](#)

[Safe administration](#)

[General patient assessment](#) prior to each day of treatment.

[Peripheral neuropathy assessment tool](#).

Any toxicity grade 3 or greater may require dose reduction, delay or omission of treatment and review by medical officer before recommencing treatment.

Prime IV line(s).

Insert IV cannula or access [TIVAD](#) or [CVAD](#).

### Pre treatment medication

Verify antiemetics taken or administer as prescribed.

## 🕒 Chemotherapy - Time out

### Tretinoin (ATRA)

- administer orally in TWO equally divided doses
- to be swallowed whole with a glass of water; do not break, crush or chew
- can be taken with or without food
- protect skin from sunlight

**Note:** missed doses should not be replaced; if a tablet is forgotten or vomited, normal dosing should be resumed at the next scheduled dose.

Notify medical team if the patient reports weight gain, shortness of breath and/or temperature as this may be symptoms of differentiation syndrome.

Read more about [APML differentiation syndrome](#)

### Arsenic trioxide (ATO)

#### Prior to administration:

- check BSL as indicated
- baseline ECG then at least twice weekly ECG, or more frequently in unstable patients
- maintain serum potassium above 4 mmol/L and magnesium above 0.8 mmol/L.

#### Administer arsenic trioxide:

- via IV infusion over 2 hours
- flush with 50 mL sodium chloride 0.9%
- if the patient has a vasomotor reaction (lightheadedness, changes in blood pressure) the time of the arsenic infusion may be extended up to four hours.

Remove IV cannula and/or deaccess [TIVAD](#) or [CVAD](#).

Continue [safe handling](#) precautions until 7 days after completion of drug(s)

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## Days 13 and 14

This is an oral treatment

[Safe handling and waste management](#) (reproductive risk only)

[Safe administration](#)

[General patient assessment](#) prior to each day of treatment.

[Peripheral neuropathy assessment tool](#).

Any toxicity grade 3 or greater may require dose reduction, delay or omission of treatment and review by medical officer before recommencing treatment.

### Pre treatment medication

Verify antiemetics taken or administer as prescribed.

## 🕒 Treatment - Time out

## Tretinoin (ATRA)

- administer orally in TWO equally divided doses
- to be swallowed whole with a glass of water; do not break, crush or chew
- can be taken with or without food
- protect skin from sunlight

**Note:** missed doses should not be replaced; if a tablet is forgotten or vomited, normal dosing should be resumed at the next scheduled dose.

Notify medical team if the patient reports weight gain, shortness of breath and/or temperature as this may be symptoms of differentiation syndrome.

Read more about [APML differentiation syndrome](#)

Continue [safe handling](#) precautions (reproductive risk only) for 7 days after completion of drug(s).

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## Days 15 to 19 and 22 to 26

**Approximate treatment time: 2.5 hours**

[Safe handling and waste management](#)

[Safe administration](#)

[General patient assessment](#) prior to each day of treatment.

[Peripheral neuropathy assessment tool](#).

Any toxicity grade 3 or greater may require dose reduction, delay or omission of treatment and review by medical officer before recommencing treatment.

Prime IV line(s).

Insert IV cannula or access [TIVAD](#) or [CVAD](#).

## Pre treatment medication

Verify antiemetics taken or administer as prescribed.

## ⌚ Chemotherapy - Time out

## Arsenic trioxide (ATO)

### Prior to administration:

- check BSL as indicated
- baseline ECG then at least twice weekly ECG, or more frequently in unstable patients
- maintain serum potassium above 4 mmol/L and magnesium above 0.8 mmol/L.

### Administer arsenic trioxide:

- via IV infusion over 2 hours
- flush with 50 mL sodium chloride 0.9%
- if the patient has a vasomotor reaction (lightheadedness, changes in blood pressure) the time of the arsenic infusion may be extended up to four hours.

Remove IV cannula and/or deaccess [TIVAD](#) or [CVAD](#).

Continue [safe handling](#) precautions until 7 days after completion of drug(s)

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## Discharge information

### Tretinoin capsules

- Tretinoin capsules with written instructions on how to take them

### Antiemetics

- Antiemetics as prescribed.



Antidiarrhoeals

- Antidiarrhoeals as prescribed.

Patient information

- Ensure patient receives patient information sheet.

Side effects

*The side effects listed below are not a complete list of all possible side effects for this treatment. Side effects are categorised into the approximate onset of presentation and should only be used as a guide.*

Immediate (onset hours to days)	
Headache	
Nausea and vomiting	Read more about <a href="#">prevention of treatment induced nausea and vomiting</a>
QT prolongation associated with arsenic trioxide	<p>This treatment can cause QTc interval prolongation and complete atrioventricular block. QTc prolongation can lead to ventricular arrhythmias that may be fatal.</p> <p>Read more about <a href="#">ECG abnormalities related to arsenic trioxide</a></p>

Early (onset days to weeks)	
<b>Neutropenia</b>	Abnormally low levels of neutrophils in the blood. This increases the risk of infection. Any fever or suspicion of infection should be investigated immediately and managed aggressively. Read more about <a href="#">immediate management of neutropenic fever</a>
<b>Thrombocytopenia</b>	A reduction in the normal levels of functional platelets, increasing the risk of abnormal bleeding.  Read more about <a href="#">thrombocytopenia</a>
<b>Abdominal pain</b>	Dull ache, cramping or sharp pains are common with some anti-cancer drugs. These are caused by either increased or decreased gastrointestinal motility and can be associated with diarrhoea or constipation.
<b>Arthralgia and myalgia</b>	Generalised joint pain or and/or stiffness and muscle aches, often worse upon waking or after long periods of inactivity. Can improve with movement. May be mild or severe, intermittent or constant and accompanied by inflammation. Read more about <a href="#">arthralgia and myalgia</a>
<b>Diarrhoea</b>	Read more about <a href="#">treatment induced diarrhoea</a>
<b>Fatigue</b>	Read more about <a href="#">fatigue</a>
<b>Hepatotoxicity</b>	Anti-cancer drugs administered either alone or in combination with other drugs and/or radiation may cause direct or indirect hepatotoxicity. Hepatic dysfunction can alter the metabolism of some drugs resulting in systemic toxicity.
<b>Hypomagnesaemia, hypokalaemia, hypocalcaemia</b>	Abnormally low levels of magnesium, potassium and calcium in the blood.
<b>Oral mucositis</b>	Erythematous and ulcerative lesions of the gastrointestinal tract (GIT). It commonly develops following chemotherapy, radiation therapy to the head, neck or oesophagus, and high dose chemotherapy followed by a blood and marrow transplant (BMT). Read more about <a href="#">oral mucositis</a>
<b>Peripheral neuropathy</b>	Typically symmetrical sensory neuropathy, affecting the fingers and toes, sometimes progressing to the hands and feet. It is associated with several classes of anti-cancer drugs. These include taxanes, platinum-based compounds, vinca alkaloids and some drugs used to treat multiple myeloma. Read more about <a href="#">peripheral neuropathy</a>
<b>Photosensitivity</b>	Increased sensitivity to ultraviolet (UV) light resulting in an exaggerated sunburn-like reaction accompanied by stinging sensations and urticaria.
<b>Skin rash</b>	Anti-cancer drugs can cause a number of changes in the skin with maculo-papular rash the most common type of drug-induced skin reaction. Read more about <a href="#">skin rash</a>
Delayed (onset months to years)	
<b>Pulmonary toxicity</b>	Pulmonary toxicity may include damage to the lungs, airways, pleura and pulmonary circulation. Read more about <a href="#">pulmonary toxicity associated with anti-cancer drugs</a>

## Evidence

Acute promyelocytic leukaemia (APML) is a biologically and clinically distinct variant of acute myeloid leukaemia characterised by t(15;17) translocation resulting in a PML-RARA fusion protein. The impaired myeloid differentiation resulting from the translocation may be restored by pharmacologic doses of all-trans-retinoic acid (ATRA).

Arsenic trioxide (ATO) acts synergistically with ATRA to degrade PML-RARA. The APL0406 trial<sup>2,3</sup> was a phase 3 noninferiority study which examined removing chemotherapy altogether from an ATO/ATRA backbone in low to intermediate-risk APML patients (white cell count  $\leq 10 \times 10^9/L$ ). The rationale was that removing chemotherapy may reduce rates of haematological toxicity and

infections when compared to a “standard” chemotherapy-containing regimen. Induction in the “no chemotherapy arm” utilised ATRA and ATO in combination until achievement of haematological complete remission (hCR) or a maximum of 60 days (patients were taken off study if hCR not achieved at this time point). For responders, this was followed by consolidation with overlapping blocks of ATRA and ATO, where notably, ATO was given on weekdays (which facilitates outpatient administration). Notable inclusion criteria included an age range of 18-71 and a WHO performance status of 0-2.

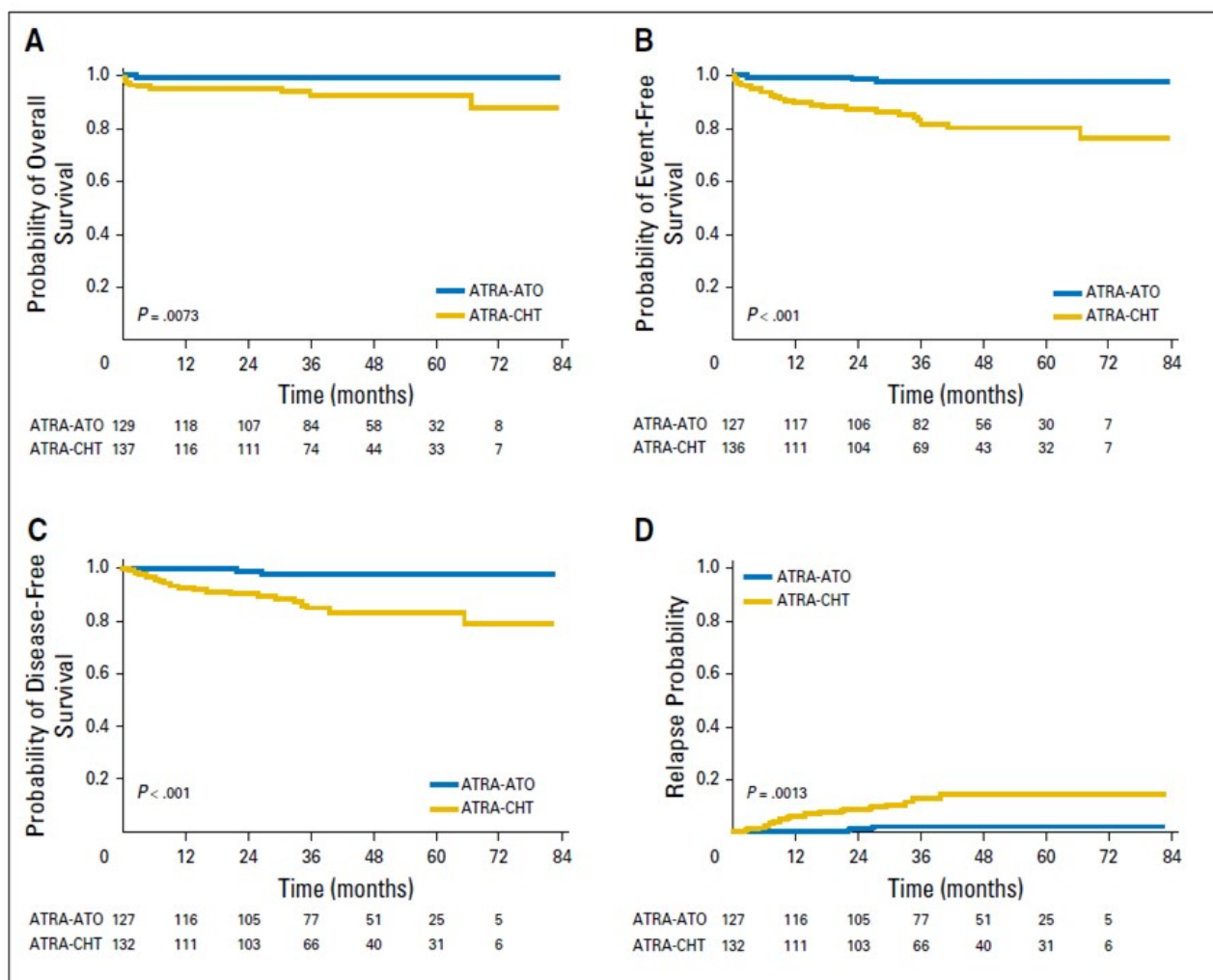
Chemotherapy-free consolidation without maintenance has been found to be beneficial in standard-risk patients, it has been utilised to a limited extent in the National Cancer Research Institute (NCRI) AML17 trial<sup>4</sup> and by the MD Anderson group<sup>5</sup> for high-risk adult patients following induction with ATO/ATRA, combined with gemtuzumab ozogamicin (GO). However, GO is currently not TGA-approved for use in APML. The Children’s Oncology Group (COG) AAML1331 study<sup>6</sup> is a nonrandomised, noninferiority trial that looked at survival outcomes in 154 paediatric patients with APML. The patients, aged between 1 and 21 years, received ATRA and arsenic throughout induction and intermittently throughout 4 cycles of consolidation. The high-risk patients (56/154) received 4 doses of idarubicin (similar to APML4). The duration of treatment was approximately 9 months without any maintenance. Shah et al.<sup>7</sup> reported a retrospective analysis of 10 high-risk APML patients, median age 44.5 years, with 7 patients receiving induction as per APML4 with idarubicin and all patients receiving consolidation with ATO/ATRA without maintenance, as per the APL0406 study<sup>1</sup>. The TUD-APOLLO-64 study (NCT02688140) is currently underway, a randomised phase 3 study of high-risk APML patients, comparing standard ATRA and anthracycline-based chemotherapy regimens with ATO/ATRA in combination with low-doses of idarubicin during induction, followed by 4 cycles of ATO/ATRA consolidation therapy. However, there are no results of this study published to date. Despite the absence of published trials for high-risk adults with APML, which involve standard of care induction combined with chemotherapy-free consolidation without maintenance, it is the consensus of the reference committee that based on the above studies, high-risk patients may receive chemotherapy-free consolidation as per [ID 1943 Acute promyelocytic leukaemia standard risk \(chemotherapy free\) consolidation](#).

## Efficacy

There were 263 evaluable patients for response to induction (127 in the ATRA/ATO arm and 136 in the ATRA-chemotherapy arm). CR was achieved in 100% (127/127) of the ATRA/ATO arm compared to 97% (132/136) for ATRA-chemotherapy (P=0.12). 4/136 ATRA-chemotherapy patients died during induction (2 differentiation syndrome, 1 stroke, 1 infection). All deaths were recorded in the initial series, and no further deaths occurred in the second cohort of 110 patients enrolled in the post-amendment period. After a median follow-up of 40.6 months (range 0.1 to 83.6 months), outcome estimates calculated at 50 months was EFS 97.3% (95% CI 94.3 to 100) in ATRA/ATO group compared with 80% (95% CI 72.9 to 88) in the ATRA-chemotherapy group (p<0.001 for non-inferiority). Overall survival (OS) was 99.2% (95% CI 97.7 to 100) for ATRA/ATO versus 92.6% (95% CI 87.9 to 97.5) for ATRA-chemotherapy group (P = 0.0073). Cumulative incidence of relapse was 1.9% (95% CI 1 to 4.5) in ATRA/ATO group versus 13.9% (95% CI 7.1 to 20.6) for ATRA-chemotherapy group (p=0.0013, gray test).<sup>3</sup>

In the Children’s Oncology Group (COG) AAML1331 study the median follow-up duration was 24.7 months for patients with standard-risk APML and 22.8 months for patients with high-risk APML. The 2-year EFS and OS for standard-risk patients was 98% and 99%, respectively, and for high-risk patients, 2-year EFS was 96.4% and OS 100%.<sup>6</sup>

## Figure 1. Outcome estimates<sup>3</sup>



**Fig 2.** Outcome estimates. (A) Overall survival. (B) Event-free survival. (C) Disease-free survival. (D) Relapse. ATO, arsenic trioxide; ATRA, all-*trans*-retinoic acid; CHT, chemotherapy.

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## Toxicity

A total of 95 serious adverse effects (43 ATRA/ATO therapy, and 52 ATRA-chemotherapy) were reported in 65 patients.<sup>3</sup>

## Tables. Haematologic and non-haematologic toxicity<sup>3</sup>

Table 2. Hematologic Toxicity								
Toxicity and Treatment Arm	Induction		First Consolidation		Second Consolidation		Third Consolidation	
	No. (%)	P	No. (%)	P	No. (%)	P	No. (%)	P
Neutropenia (grade 3-4 lasting > 15 days)		< .001		< .001		< .001		< .001
ATRA-ATO	61 (35)		8 (16)		7 (7)		5 (15)	
ATRA-CHT	109 (64)		40 (67)		90 (92)		28 (85)	
Thrombocytopenia (grade 3-4 lasting > 15 days)		< .001		< .001		< .001		< .001
ATRA-ATO	74 (38)		6 (26)		6 (7)		8 (23)	
ATRA-CHT	120 (62)		17 (74)		77 (93)		26 (76)	
Infection and FUO		< .001		.54		< .001		1.0
ATRA-ATO	30 (23)		10 (8)		4 (3)		2 (1.6)	
ATRA-CHT	75 (55)		8 (6)		46 (38)		2 (1.7)	

Abbreviations: ATO, arsenic trioxide; ATRA, all-*trans*-retinoic acid; CHT, chemotherapy; FUO, fever of unknown origin.

Toxicity and Treatment Arm	Induction		First Consolidation		Second Consolidation		Third Consolidation	
	No. (%)	P	No. (%)	P	No. (%)	P	No. (%)	P
Hepatic toxicity (grade 3-4)		< .001		.11		.49		
ATRA-ATO	51 (40)		5 (4)		1 (0.8)		0	
ATRA-CHT	4 (3)		1 (0.7)		0		0	
QTc prolongation		.0022		.11		.11		.23
ATRA-ATO	11 (8.5)		3 (2)		3 (2)		2 (1.5)	
ATRA-CHT	1 (0.7)		0		0		0	
Cardiac function (grade 3-4)		.06						
ATRA-ATO	0		0		0		0	
ATRA-CHT	5 (3.7)		0		0		0	
Neurotoxicity (all grades)		.48		.02		.01		.006
ATRA-ATO	1 (0.7)		5 (4.2)		6 (5)		7 (5.9)	
ATRA-CHT	0		0		0		0	
GI toxicity (grade 3-4)		< .001		1.0		.03		1.0
ATRA-ATO	3 (2)		0		0		0	
ATRA-CHT	25 (18.2)		1 (0.8)		6 (4.9)		0	
Hypercholesterolemia		.55		.13		.14		.27
ATRA-ATO	14 (10)		19 (16)		19 (16)		16 (14)	
ATRA-CHT	12 (8.7)		12 (9.6)		12 (9.7)		11 (9)	
Hypertriglyceridemia		0.76		.49		.12		.5
ATRA-ATO	29 (22)		22 (18.4)		17 (14.4)		16 (14)	
ATRA-CHT	29 (22)		19 (15.2)		10 (8)		13 (11)	

Abbreviations: ATO, arsenic trioxide; ATRA, all-trans-retinoic acid; CHT, chemotherapy.

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## References

- 1 Iland, H. J., K. Bradstock, S. G. Supple, et al. 2012. "All-trans-retinoic acid, idarubicin, and IV arsenic trioxide as initial therapy in acute promyelocytic leukemia (APML4)." *Blood* 120(8):1570-1580; quiz 1752.
- 2 Lo-Coco, F., G. Avvisati, M. Vignetti, et al. 2013. "Retinoic acid and arsenic trioxide for acute promyelocytic leukemia." *N Engl J Med* 369(2):111-121.
- 3 Platzbecker, U., G. Avvisati, L. Cicconi, et al. 2017. "Improved Outcomes With Retinoic Acid and Arsenic Trioxide Compared With Retinoic Acid and Chemotherapy in Non-High-Risk Acute Promyelocytic Leukemia: Final Results of the Randomized Italian-German APL0406 Trial." *J Clin Oncol* 35(6):605-612.
- 4 Burnett, A. K., N. H. Russell, R. K. Hills, et al. 2015. "Arsenic trioxide and all-trans retinoic acid treatment for acute promyelocytic leukaemia in all risk groups (AML17): results of a randomised, controlled, phase 3 trial." *Lancet Oncol* 16(13):1295-1305.
- 5 Abaza, Y., H. Kantarjian, G. Garcia-Manero, et al. 2017. "Long-term outcome of acute promyelocytic leukemia treated with all-trans-retinoic acid, arsenic trioxide, and gemtuzumab." *Blood* 129(10):1275-1283.
- 6 Kutny, M. A., T. A. Alonzo, O. Abl, et al. 2022. "Assessment of Arsenic Trioxide and All-trans Retinoic Acid for the Treatment of Pediatric Acute Promyelocytic Leukemia: A Report From the Children's Oncology Group AAML1331 Trial." *JAMA Oncol* 8(1):79-87.
- 7 Shah, G., F. M. Mikhail, K. Bachiasvili, et al. 2020. "Outcomes of high-risk acute promyelocytic leukemia patients treated with arsenic trioxide (ATO)/all trans retinoic acid (ATRA) based induction and consolidation without maintenance phase: A case Series." *Hematol Oncol Stem Cell Ther* 13(3):143-146.

## History

### Version 3

Date	Summary of changes
18/10/2023	Reviewed by the Haematology Reference Committee with the following changes made: <ul style="list-style-type: none"> <li>• update to indication and patient population</li> <li>• update of evidence to include information about chemotherapy free consolidation in high-risk patients.</li> </ul>

**Version 2**

Date	Summary of changes
20/05/2016	New protocol taken to Reference Committee meeting.
01/11/2016	Approved and published on eviQ
31/05/2017	Transferred to new eviQ website. Version number change to v.2.
21/09/2018	Protocol reviewed at Haematology Reference Committee meeting. Evidence updated. Removed ATRA 'with food' from protocol for consistency with patient information. Review in 2 years.
23/10/2020	Protocol reviewed electronically by Haematology Reference Committee. No changes. Review in 4 years.
21/12/2021	Changed antiemetic clinical information block to minimal or low, to align with new categories. See ID 7: Prevention of anti-cancer therapy induced nausea and vomiting (AINV) v5.
24/01/2022	Pulmonary toxicity added to side effects.

The information contained in this protocol is based on the highest level of available evidence and consensus of the eviQ reference committee regarding their views of currently accepted approaches to treatment. Any clinician (medical oncologist, haematologist, radiation oncologist, medical physicist, radiation therapist, pharmacist or nurse) seeking to apply or consult this protocol is expected to use independent clinical judgement in the context of individual clinical circumstances to determine any patient's care or treatment. While eviQ endeavours to link to reliable sources that provide accurate information, eviQ and the Cancer Institute NSW do not endorse or accept responsibility for the accuracy, currency, reliability or correctness of the content of linked external information sources. Use is subject to eviQ's disclaimer available at [www.eviQ.org.au](http://www.eviQ.org.au)

**First approved:** 1 November 2016

**Last reviewed:** 28 August 2023

**Review due:** 30 June 2025

***The currency of this information is guaranteed only up until the date of printing, for any updates please check:***

<https://www.eviq.org.au/p/1943>

18 Oct 2023

# Patient information - Acute promyelocytic leukaemia (APML) - Standard risk (chemotherapy free) consolidation

Patient's name:

## Your treatment

The treatment schedule below explains how the drugs for this treatment are given.


### Standard risk (chemotherapy free) consolidation

This treatment cycle is repeated every 56 days. You will have 4 cycles. It is usually started 1 to 2 weeks after you have finished induction treatment.

Day	Treatment	How it is given	How long it takes
1 to 14, 29 to 42 (cycles 1 to 3); 1 to 14 (cycle 4 only)	<b>Tretinoin (ATRA)</b> ( <i>at-ra</i> )( <i>TRET-i-NO-in</i> )	Take orally TWICE a day with or without food on day 1 to 14 and day 29 to 42 only in <b>cycles 1 to 3</b> ; and day 1 to 14 only in <b>cycle 4</b> . Swallow whole with a glass of water, do not break, crush or chew.  If you forget to take a tablet or vomit a tablet, take your normal dose the next time it is due. Do not take an extra dose.	
1 to 5, 8 to 12, 15 to 19, 22 to 26	<b>Arsenic trioxide (ATO)</b> ( <i>ar-se-nik</i> )	By a drip into a vein	About 2 hours

## When to get help

Anticancer drugs (drugs used to treat cancer) can sometimes cause serious problems. It is important to get medical help immediately if you become unwell.

 <b>IMMEDIATELY go to your nearest hospital Emergency Department, or contact your doctor or nurse if you have any of the following at any time:</b>	<b>Emergency contact details</b> Ask your doctor or nurse from your treating team who to contact if you have a problem
<ul style="list-style-type: none"><li>• a temperature of 38°C or higher</li><li>• chills, sweats, shivers or shakes</li><li>• shortness of breath</li><li>• uncontrolled vomiting or diarrhoea</li><li>• pain, tingling or discomfort in your chest or arms</li><li>• you become unwell.</li></ul>	Daytime:..... Night/weekend:..... Other instructions:..... ..... ..... .....

**During your treatment immediately** tell the doctor or nurse looking after you if you get any of the following problems:

- leaking from the area where the drugs are being given

- pain, stinging, swelling or redness in the area where the drugs are being given or at any injection sites
- a skin rash, itching, feeling short of breath, wheezing, fever, shivers, or feeling dizzy or unwell in any way (allergic reaction).

## Other information about your treatment

### Changes to your dose or treatment delays

Sometimes a treatment may be started at a lower dose or the dose needs to be changed during treatment. There may also be times when your treatment is delayed. This can happen if your doctor thinks you are likely to have severe side effects, if you get severe side effects, if your blood counts are affected and causing delays in treatment, or if you are finding it hard to cope with the treatment. This is called a dose reduction, dose change or treatment delay. Your doctor will explain if you need any changes or delays to your treatment and the reason why.

### Blood tests and monitoring

You will need to have a blood test before you start treatment and regularly throughout your treatment. Your doctor or nurse will tell you when to have these blood tests.

### Central venous access devices (CVADs)

This treatment involves having chemotherapy through a central venous access device (CVAD). Your doctor or nurse will explain this to you. For more information see the [eviQ patient information sheets](#) on CVADs.

### Other medications given during this treatment

- **Anti-sickness (anti-nausea) medication:** you may be given some anti-sickness medication. Make sure you take this medication as your doctor or nurse tells you, even if you don't feel sick. This can help to prevent the sickness starting.
- **Prophylaxis medication:** you may need to take some medications to prevent infection and to help prevent or reduce some of the side effects of the chemotherapy. Your doctor or nurse will tell you how and when to take these medications.

## Side effects

Cancer treatments can cause damage to normal cells in your body, which can cause side effects. Everyone gets different side effects, and some people will have more problems than others.

The table below shows some of the side effects you may get with this treatment. You are unlikely to get all of those listed and you may also get some side effects that have not been listed.

Tell your doctor or nurse about any side effects that worry you. Follow the instructions below and those given to you by your doctor or nurse.



Immediate (onset hours to days)	
Headache	<ul style="list-style-type: none"> <li>You can take paracetamol if you have a headache.</li> <li><b>Tell your doctor or nurse immediately, or go to the nearest hospital Emergency Department if you get a very bad headache that is not helped by pain medication.</b></li> </ul>
Nausea and vomiting	<ul style="list-style-type: none"> <li>You may feel sick (nausea) or be sick (vomit).</li> <li>Take your anti-sickness medication as directed even if you don't feel sick.</li> <li>Drink plenty of fluids (unless you are fluid restricted).</li> <li>Eat small meals more frequently.</li> <li>Try food that does not require much preparation.</li> <li>Try bland foods like dry biscuits or toast.</li> <li>Gentle exercise may help with nausea.</li> <li>Ask your doctor or nurse for eviQ patient information - <a href="#">Nausea and vomiting during cancer treatment</a>.</li> <li><b>Tell your doctor or nurse immediately, or go to the nearest hospital Emergency Department if you have uncontrolled vomiting or feel dizzy or light-headed.</b></li> </ul>
Heart changes	<ul style="list-style-type: none"> <li>You may get chest pain, shortness of breath, an abnormal heartbeat or swelling in your arms or legs.</li> <li>Before, during and after treatment, you will be asked to have tests to see how well your heart is working.</li> <li>You will also have other blood tests to check your electrolyte levels.</li> <li><b>Tell your doctor or nurse immediately, or go to the nearest hospital Emergency Department, if you get any of the symptoms listed above.</b></li> </ul>
Early (onset days to weeks)	
Infection risk (neutropenia)	<ul style="list-style-type: none"> <li>This treatment lowers the amount of white blood cells in your body. The type of white blood cells that help to fight infection are called neutrophils. Having low level of neutrophils is called neutropenia. If you have neutropenia, you are at greater risk of getting an infection. It also means that your body can't fight infections as well as usual. This is a serious side effect, and can be life threatening.</li> <li>Wash your hands often.</li> <li>Keep a thermometer at home and take your temperature regularly, and if you feel unwell.</li> <li>Do your mouth care regularly.</li> <li>Inspect your central line site (if you have one) daily for any redness, pus or swelling.</li> <li>Limit contact with people who are sick.</li> <li>Learn how to recognise the signs of infection.</li> <li>Ask your doctor or nurse for eviQ patient information - <a href="#">Infection during cancer treatment</a>.</li> <li><b>Tell your doctor or nurse immediately, or go to the nearest hospital Emergency Department if you get any of the following signs or symptoms:</b> <ul style="list-style-type: none"> <li>a temperature of 38°C or higher</li> <li>chills, shivers, sweats or shakes</li> <li>a sore throat or cough</li> <li>uncontrolled diarrhoea</li> <li>shortness of breath</li> <li>a fast heartbeat</li> <li>become unwell even without a temperature.</li> </ul> </li> </ul>

<b>Low platelets (thrombocytopenia)</b>	<ul style="list-style-type: none"> <li>• This treatment lowers the amount of platelets in your blood. Platelets help your blood to clot. When they are low, you are at an increased risk of bleeding and bruising.</li> <li>• Try not to bruise or cut yourself.</li> <li>• Avoid contact sport or vigorous exercise.</li> <li>• Clear your nose by blowing gently.</li> <li>• Avoid constipation.</li> <li>• Brush your teeth with a soft toothbrush.</li> <li>• Don't take aspirin, ibuprofen or other similar anti-inflammatory medications unless your doctor tells you to.</li> <li>• Tell your doctor or nurse if you have any bruising or bleeding.</li> <li>• <b>Tell your doctor or nurse immediately, or go to your nearest hospital Emergency Department if you have any uncontrolled bleeding.</b></li> </ul>
<b>Stomach pain</b>	<ul style="list-style-type: none"> <li>• You may get: <ul style="list-style-type: none"> <li>◦ dull aches</li> <li>◦ cramping or pain</li> <li>◦ bloating or flatulence (gas).</li> </ul> </li> <li>• <b>Tell your doctor or nurse immediately, or go to the nearest hospital Emergency Department if you have stomach pain that you are unable to control.</b></li> </ul>
<b>Joint and muscle pain and stiffness</b>	<ul style="list-style-type: none"> <li>• You may get muscle, joint or general body pain and stiffness.</li> <li>• Applying a heat pack to affected areas may help.</li> <li>• Talk to your doctor or nurse about other ways to manage these symptoms. You may need medication to help with any pain.</li> </ul>
<b>Diarrhoea</b>	<ul style="list-style-type: none"> <li>• You may get bowel motions (stools, poo) that are more frequent or more liquid.</li> <li>• You may also get bloating, cramping or pain.</li> <li>• Take your antidiarrhoeal medication as directed by your doctor.</li> <li>• Drink plenty of fluids (unless you are fluid restricted).</li> <li>• Eat and drink small amounts more often.</li> <li>• Avoid spicy foods, dairy products, high fibre foods, and coffee.</li> <li>• Ask your doctor or nurse for eviQ patient information - <a href="#">Diarrhoea during cancer treatment</a>.</li> <li>• <b>Tell your doctor or nurse immediately, or go to your nearest hospital Emergency Department if your diarrhoea is not controlled, you have 4 or more loose bowel motions per day, and if you feel dizzy or light-headed.</b></li> </ul>
<b>Tiredness and lack of energy (fatigue)</b>	<ul style="list-style-type: none"> <li>• You may feel very tired, have no energy, sleep a lot, and not be able to do normal activities or things you enjoy.</li> <li>• Do not drive or operate machinery if you are feeling tired.</li> <li>• Nap for short periods (only 1 hour at a time)</li> <li>• Prioritise your tasks to ensure the best use of your energy.</li> <li>• Eat a well balanced diet and drink plenty of fluids (unless you are fluid restricted).</li> <li>• Try some gentle exercise daily.</li> <li>• Allow your friends and family to help.</li> <li>• <b>Tell your doctor or nurse if you get any of the symptoms listed above.</b></li> </ul>
<b>Liver problems</b>	<ul style="list-style-type: none"> <li>• You may get: <ul style="list-style-type: none"> <li>◦ yellowing of your skin or eyes</li> <li>◦ itchy skin</li> <li>◦ pain or tenderness in your stomach</li> <li>◦ nausea and vomiting</li> <li>◦ loss of appetite</li> </ul> </li> <li>• You will have regular blood tests to check how well your liver is working.</li> <li>• <b>Tell your doctor or nurse as soon as possible if you notice that your urine is a dark colour, the whites of your eyes look yellow, or if you have stomach pain.</b></li> </ul>

<b>Low blood magnesium, potassium and calcium levels (hypomagnesaemia, hypokalaemia, hypocalcaemia)</b>	<ul style="list-style-type: none"> <li>• This may be found from your routine blood tests and treated by your doctor.</li> <li>• If it is severe you may get: <ul style="list-style-type: none"> <li>◦ muscle cramps or twitches</li> <li>◦ numbness or tingling in your fingers, toes or around your mouth</li> <li>◦ constipation</li> <li>◦ an irregular heartbeat</li> <li>◦ sleepy, drowsy or confused</li> </ul> </li> <li>• <b>Tell your doctor or nurse as soon as possible if you get any of the signs or symptoms listed above.</b></li> </ul>
<b>Mouth pain and soreness (mucositis)</b>	<ul style="list-style-type: none"> <li>• You may have: <ul style="list-style-type: none"> <li>◦ bleeding gums</li> <li>◦ mouth ulcers</li> <li>◦ a white coating on your tongue</li> <li>◦ pain in the mouth or throat</li> <li>◦ difficulty eating or swallowing.</li> </ul> </li> <li>• Avoid spicy, acidic or crunchy foods and very hot or cold food and drinks.</li> <li>• Try bland and soft foods.</li> <li>• Brush your teeth gently with a soft toothbrush after each meal and at bedtime. If you normally floss continue to do so.</li> <li>• Rinse your mouth after you eat and brush your teeth, using either: <ul style="list-style-type: none"> <li>◦ 1/4 teaspoon of salt in 1 cup of warm water, or</li> <li>◦ 1/4 teaspoon of bicarbonate of soda in 1 cup of warm water</li> </ul> </li> <li>• Ask your doctor or nurse for eviQ patient information - <a href="#">Mouth problems during cancer treatment</a>.</li> <li>• <b>Tell your doctor or nurse if you get any of the symptoms listed above.</b></li> </ul>
<b>Nerve damage (peripheral neuropathy)</b>	<ul style="list-style-type: none"> <li>• You may notice a change in the sensations in your hands and feet, including: <ul style="list-style-type: none"> <li>◦ tingling or pins and needles</li> <li>◦ numbness or loss of feeling</li> <li>◦ pain.</li> </ul> </li> <li>• You may find it difficult to do everyday activities, such as doing up buttons or picking up small objects.</li> <li>• Test water temperature with your elbow when bathing to avoid burns.</li> <li>• Use rubber gloves, pot holders and oven mitts in the kitchen.</li> <li>• Wear rubber shoes or boots when working in the garden or garage.</li> <li>• Keep rooms well lit and uncluttered.</li> <li>• Ask your doctor or nurse for eviQ patient information – <a href="#">Nerve problems during cancer treatment</a>.</li> <li>• Tell your doctor or nurse if you get any of the symptoms listed above.</li> </ul>
<b>Skin that is more sensitive to the sun (photosensitivity)</b>	<ul style="list-style-type: none"> <li>• After being out in the sun you may develop a rash like a bad sunburn.</li> <li>• Your skin may become red, swollen and blistered.</li> <li>• Avoid direct sunlight.</li> <li>• Protect your skin from the sun by wearing sun-protective clothing, a wide-brimmed hat, sunglasses and a sunscreen of SPF 50 or higher.</li> <li>• <b>Tell your doctor or nurse if you get any of the symptoms listed above.</b></li> </ul>
<b>Skin rash</b>	<ul style="list-style-type: none"> <li>• You may get a red, bumpy rash and dry, itchy skin.</li> <li>• Moisturise your skin with a gentle non-perfumed moisturising cream like sorbolene or aqueous cream.</li> <li>• Do not scratch your skin.</li> <li>• Protect your skin from the sun by wearing sun-protective clothing, a wide-brimmed hat, sunglasses and sunscreen of SPF 50 or higher.</li> <li>• <b>Talk to your doctor or nurse about other ways to manage your skin rash.</b></li> </ul>

## Delayed (onset months to years)

### Lung problems

- Lung problems are rare, but can be serious. They may occur throughout treatment or after the completion of treatment.
- You may get:
  - shortness of breath
  - fever
  - dry cough
  - wheezing
  - fast heartbeat
  - chest pain.
- Your doctor will monitor how well your lungs are working during your treatment.
- **Tell your doctor or nurse immediately, or go to the nearest hospital Emergency Department if you have chest pain or become short of breath.**

## General advice for people having cancer treatment

### Chemotherapy safety

- Learn how to keep you and your family safe while you are having anticancer drugs.
- See our patient information sheet - [Chemotherapy safety at home](#).

### Blood clot risk

- Cancer and anticancer drugs can increase the risk of a blood clot (thrombosis).
- Tell your doctor if you have a family history of blood clots.
- A blood clot can cause pain, redness, swelling in your arms or legs, shortness of breath or chest pain.
- If you have any of these symptoms go to your nearest hospital Emergency Department.

### Medications and vaccinations

- Before you start treatment, tell your doctor about any medications you are taking, including vitamins or herbal supplements.
- Don't stop or start any medications during treatment without talking to your doctor and pharmacist first.
- Paracetamol is safe to take if you have a headache or other mild aches and pains. It is recommended that you avoid taking aspirin, ibuprofen and other anti-inflammatory type medications for pain while you are having treatment. However, if these medications have been prescribed by your doctor, do not stop taking them without speaking with your doctor.
- Vaccinations such as flu and tetanus vaccines are safe to receive while having treatment. Do not have any live vaccines during your treatment or for 6 months after it finishes. If you are unsure, check with your doctor before you have any vaccinations.
- People you live with should be fully vaccinated, including having live vaccines according to the current vaccination schedule. Extra care needs to be taken with hand washing and careful disposal of soiled nappies for infants who have recently received the rotavirus vaccine.

### Other medical and dental treatment

- If you go to hospital or any other medical appointment (including dental appointments), always tell the person treating you that you are receiving anticancer drugs.
- Before you have any dental treatment, talk to your doctor.

### Diet and food safety

- While you are receiving this treatment, it is important that you try to maintain a healthy diet.
- Grapefruit and grapefruit juice can interact with your medication and should be avoided while you are on this treatment.
- Speak to your doctor or nurse about whether drinking alcohol is safe with your treatment.
- If you have any concerns about recent weight loss or weight gain or questions about your diet, ask to speak to a dietitian.
- There are some foods that may cause infection in high risk individuals and should be avoided. For further information on foods to avoid and food hygiene please ask for a copy of the [Listeria and food brochure](#).

### Fertility

- Some cancer treatments can reduce your fertility. This can make it difficult or impossible to get pregnant or father a child.
- Talk to your doctor or nurse before you start any treatment. Depending on your situation there may be fertility sparing options available to you and/or your partner, discuss these with your doctor or nurse.

## Pregnancy and breastfeeding

- This treatment can cause major congenital disabilities or death to unborn babies. Talk to your doctor or nurse if you think there is any chance that you could be pregnant.
- Do not try to get pregnant or father a child during this treatment. You must use contraception while having this treatment and after stopping treatment. Ask your doctor or nurse about what type of contraception you should use.
- If you are planning pregnancy/fatherhood after completing this treatment, talk to your doctor. Some doctors advise waiting between 6 months and 2 years after treatment.
- Do not breastfeed if you are on this treatment, as anti-cancer medications can also pass into breast milk.

## Sex life and sexuality

- The desire to have sex may decrease as a result of this treatment or its side effects.
- Your emotions and the way you feel about yourself may also be affected by this treatment.
- It may help to discuss your concerns with your partner and doctor or nurse.

## Risk of developing a second cancer

- Some anticancer treatments can increase your chance of developing a second cancer, this is rare. Your doctor will discuss with you the specific risks of your treatment.

## Quitting smoking

- It is never too late to quit smoking. Quitting smoking is one of the best things you can do to help your treatment work better.
- There are many effective tools to improve your chances of quitting.
- Talk to your treating team for more information and referral to a smoking cessation support service.

## Staying active

- Research shows that exercise, no matter how small, has many benefits for people during and after cancer treatment.
- Talk to your doctor before starting an exercise program. Your doctor can advise whether you need a modified exercise program.

For more information about cancer treatment, side effects and side effect management see our [Patient and carers](#) section.

## Where to get more information

### Telephone support

- Call Cancer Council on 13 11 20 for cancer information and support
- Call the Leukaemia Foundation on 1800 620 420 (Mon to Fri 9am – 5pm)
- Call the Lymphoma Nurse Support Line on 1800 953 081 (Mon to Fri 9am - 5pm)
- Call the Myeloma Australia Support Line on 1800 693 566 (Mon to Fri 9am - 5pm)

### Haematology, transplant and cellular therapy information

- Arrow bone marrow transplant foundation – [arrow.org.au](http://arrow.org.au)
- Australasian Menopause Society – [menopause.org.au](http://menopause.org.au)
- Chris O'Brien Lifehouse - Total Body Irradiation - [mylifehouse.org.au/departments/radiation-oncology/total-body-irradiation/](http://mylifehouse.org.au/departments/radiation-oncology/total-body-irradiation/)
- Healthy Male Andrology Australia – [healthymale.org.au/](http://healthymale.org.au/)
- International Myeloma Foundation – [myeloma.org](http://myeloma.org)
- Leukaemia Foundation – [leukaemia.org.au](http://leukaemia.org.au)
- Lymphoma Australia – [lymphoma.org.au](http://lymphoma.org.au)
- Myeloma Australia – [myeloma.org.au](http://myeloma.org.au)
- NSW Agency for Clinical Innovation, Blood & Marrow Transplant Network – <https://aci.health.nsw.gov.au/networks/bmtct>
- NSW Agency for Clinical Innovation - [aci.health.nsw.gov.au/projects/immune-effector-cell-service](http://aci.health.nsw.gov.au/projects/immune-effector-cell-service)
- NCCN Guidelines for Patients Immunotherapy Side Effects: CAR T-Cell Therapy - [nccn.org/patientresources/patient-resources/guidelines-for-patients](http://nccn.org/patientresources/patient-resources/guidelines-for-patients)
- Talk Blood Cancer – [cmlsupport.org.uk/organisation-type/social-media-groups](http://cmlsupport.org.uk/organisation-type/social-media-groups)

### General cancer information and support

- Australian Rare Cancer (ARC) Portal – [arcportal.org.au/](http://arcportal.org.au/)
- Beyondblue – [beyondblue.org.au](http://beyondblue.org.au)

