Acute myeloid leukaemia induction 7-3 (cytarabine and DAUNOrubicin)



ID: 2043 v.2 Endorsed Essential Medicine List

This protocol replaces a previous version of the AML Induction 7-3 protocol ID 348 (daunorubicin 50mg/m² dose) which has been discontinued.

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 <u>may</u> 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 <u>eviQ Estimated Glomerular Filtration Rate (eGFR) calculator</u>.

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

2022

Click here



Related pages:

- Acute myeloid leukaemia induction 7-3 Ida (cytarabine and iDArubicin)
- Acute myeloid leukaemia induction 7-3 high dose DAUNOrubicin (cytarabine and DAUNOrubicin) SUPERSEDED

Treatment schedule - Overview

Drug	Dose	Route	Day
DAUNOrubicin	60 mg/m ²	IV	1 to 3 *
Cytarabine (Ara-C) **	100 mg/m ²	CIV	1 to 7 *

^{*}The days of administration have been aligned with the ELN and NCCN guidelines 1, 2

Cycles: 1 or 2. Usually given once but may be repeated if remission is not achieved

Drug status: Cytarabine is on the PBS general schedule

Daunorubicin is TGA registered but not PBS listed for this indication

Cost: ~ \$4,690 per cycle

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**.

Day 1 to 3		
DAUNOrubicin	60 mg/m ² (IV)	over 5 to 15 minutes

^{**}Cytarabine at a dose of 100 - 200 mg/m² is acceptable and as per clinician discretion^{3, 4, 5, 6}

Day 1 to 3		
Cytarabine (Ara-C)	100 mg/m ² (CIV)	in sodium chloride 0.9% over 24 hours as a continuous infusion
Day 4 to 7		
Cytarabine (Ara-C)	100 mg/m ² (CIV)	in sodium chloride 0.9% over 24 hours as a continuous infusion

Note: the days of administration have been aligned with the ELN and NCCN guidelines 1, 2

Cycles: 1 or 2. Usually given once but may be repeated if remission is not achieved

Indications and patient population

• Acute myeloid leukaemia, induction

Clinical information

Venous access	Central venous access device (CVAD) is required to administer this treatment.
	Read more about central venous access device line selection
Antiemetics for multi-day protocols	Antiemetic therapy should be administered throughout the duration of the chemotherapy protocol and to cover delayed nausea. The acute and delayed emetic risk of multi-day chemotherapy protocols will overlap depending on the individual drugs and their sequence of administration. More or less antiemetic cover may be required.
	Ensure that patients also have sufficient antiemetics for breakthrough emesis:
	Metoclopramide 10 mg three times a day when necessary (maximum of 30 mg/24 hours, up to 5 days) OR
	Prochlorperazine 10 mg PO every 6 hours when necessary.
	Read more about preventing anti-cancer therapy induced nausea and vomiting
Cumulative lifetime dose of anthracyclines	Cumulative doses should take into account all previous anthracyclines received during a patient's lifetime (i.e. daunorubicin, doxorubicin, epirubicin, idarubicin and mitoxantrone). Criteria for reducing the total anthracycline cumulative lifetime dose include:
	 patient is elderly
	prior mediastinal radiation
	hypertensive cardiomegaly
	• concurrent therapy with high dose cyclophosphamide and some other cytotoxic drugs (e.g. bleomycin, dacarbazine, dactinomycin, etoposide, melphalan, mitomycin and vincristine).
	Baseline clinical assessments include echocardiogram (ECHO) or gated heart pool scan (GHPS) and electrocardiogram (ECG) evaluation.
	Patients with normal baseline cardiac function (left ventricular ejection fraction (LVEF) > 50%) and low risk patients require LVEF monitoring when greater than 70% of the anthracycline threshold is reached or if the patient displays symptoms of cardiac impairment. Post-treatment cardiac monitoring is recommended for patients who have received high levels of total cumulative doses of anthracyclines at the clinician's discretion.
	Read more about cardiac toxicity associated with anthracyclines
Cytarabine syndrome	Treatment with cytarabine may cause a "cytarabine syndrome" characterised by flu-like symptoms, skin rash and occasionally chest pain.
Tumour lysis risk	Assess patient for risk of developing tumour lysis syndrome.
	Read more about prevention and management of tumour lysis syndrome.

Pneumocystis jirovecii pneumonia (PJP) prophylaxis	Read more about prophylaxis of pneumocystis jiroveci (carinii) in cancer patients
Antiviral prophylaxis	Read more about antiviral prophylaxis drugs and doses
Antifungal prophylaxis	Read more about antifungal prophylaxis drugs and doses.
Growth factor support	G-CSF (short or long-acting) is available on the PBS for chemotherapy induced neutropenia depending on clinical indication and/or febrile neutropenia risk. Access the PBS website
Blood tests	FBC, EUC, eGFR and LFTs at baseline and prior to each treatment.
Hepatitis B screening and prophylaxis	Routine screening for HBsAg and anti-HBc is recommended prior to initiation of treatment. Prophylaxis should be determined according to individual institutional policy. Read more about hepatitis B screening and prophylaxis in cancer patients requiring cytotoxic and/or immunosuppressive therapy
Vaccinations	Live vaccines are contraindicated in cancer patients receiving immunosuppressive therapy and/or who have poorly controlled malignant disease. Refer to the recommended schedule of vaccination for immunocompromised patients, as outlined in the Australian Immunisation Handbook. Read more about COVID-19 vaccines and cancer.
Fertility, pregnancy and lactation	Cancer treatment can have harmful effects on fertility and this should be discussed with all patients of reproductive potential prior to commencing treatment. There is a risk of foetal harm in pregnant women. A pregnancy test should be considered prior to initiating treatment in females of reproductive potential if sexually active. It is important that all patients of reproductive potential use effective contraception whilst on therapy and after treatment finishes. Effective contraception methods and adequate contraception timeframe should be discussed with all patients of reproductive potential. Possibility of infant risk should be discussed with breastfeeding patients. Read more about the effect of cancer treatment on fertility

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: all dose reductions are calculated as a percentage of the starting dose.

Haematological toxicity

Dose reductions for haematological toxicity not usually recommended. Discuss with haematologist. Consider adding G-CSF

Haematological toxicity

from Day 8

Renal impairment

No specific dose modifications recommended for cytarabine in renal impairment, but please note an increased risk of neurotoxicity has been associated with high dose cytarabine with creatinine clearance less than 60 mL/min

Hepatic impairment	
Hepatic dysfunction	
Mild	Reduce daunorubicin by 25%
Moderate	Reduce daunorubicin by 50%
Severe	Omit daunorubicin. Consider alternative regimen.

Elevations in liver function tests occur with both standard and high dose cytarabine. Significant liver function abnormalities may require discontinuation or a dose reduction

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

Cytarabine		
	Interaction	Clinical management
Cytidine deaminase (CDA) inhibitors (e.g. cedazuridine)	Potential increased effect/toxicity of cytarabine due to reduced clearance	Avoid combination or monitor for increased cytarabine effect/toxicity

Daunorubicin		
	Interaction	Clinical management
Nephrotoxic drugs (e.g. aminoglycosides, amphotericin, contrast dye, frusemide, NSAIDs)	Additive nephrotoxicity	Avoid combination or monitor kidney function closely
Cardiotoxic drugs (eg. calcium channel blockers, propranolol)	Increased risk of daunorubicin-induced cardiotoxicity	Avoid combination or monitor closely for cardiotoxicity

General		
	Interaction	Clinical management
Warfarin	Anti-cancer drugs may alter the anticoagulant effect of warfarin.	Monitor INR regularly and adjust warfarin dosage as appropriate; consider alternative anticoagulant.
Direct oral anticoagulants (DOACs) e.g. apixaban, rivaroxaban, dabigatran	Interaction with both CYP3A4 and P-gp inhibitors /inducers. DOAC and anti-cancer drug levels may both be altered, possibly leading to loss of efficacy or toxicity (i.e. increased bleeding).	Apixaban: avoid concurrent use with strong CYP3A4 and P-gp inhibitors. If treating VTE, avoid use with strong CYP3A4 and P-gp inducers. Rivaroxaban: avoid concurrent use with strong CYP3A4 and P-gp inhibitors. Dabigatran: avoid combination with strong P-gp inducers and inhibitors. If concurrent use is unavoidable, monitor closely for efficacy/toxicity of both drugs.
Digoxin	Anti-cancer drugs can damage the lining of the intestine; affecting the absorption of digoxin.	Monitor digoxin serum levels; adjust digoxin dosage as appropriate.
Antiepileptics	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.
Antiplatelet agents and NSAIDs	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.
Serotonergic drugs, including selective serotonin reuptake inhibitors (SSRIs e.g. paroxetine) and serotonin noradrenaline reuptake inhibitors (SNRIs e.g. venlafaxine)	Increased risk of serotonin syndrome with concurrent use of 5-HT3 receptor antagonists (e.g. palonosetron, ondansetron, granisetron, tropisetron, dolasetron, etc.)	Avoid combination. If combination is clinically warranted, monitor for signs and symptoms of serotonin syndrome (e.g. confusion, agitation, tachycardia, hyperreflexia). For more information link to TGA Medicines Safety Update
Vaccines	Diminished response to vaccines and increased risk of infection with live vaccines.	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. For more information; refer to the recommended schedule of vaccination for cancer patients, as outlined in the Australian Immunisation Handbook

Administration

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

Days 1 to 3

Safe handling and waste management

Safe administration

General patient assessment prior to each treatment.

Any toxicity grade 2 or greater may require dose reduction, delay or omission of treatment and review by medical officer before recommencing treatment.

Prime IV line(s).

Access CVAD.

- · baseline weight
- · strict fluid balance
- dipstick urinalysis prior to treatment

Hydration if prescribed

Pre treatment medication

Verify antiemetics taken or administer as prescribed.

Ochemotherapy - Time out

Daunorubicin

Administer daunorubicin (vesicant)

- over 5 to 15 minutes
 - via a minibag OR
 - by IV bolus via a side port of a freely flowing IV infusion
- · ensure vein is patent and monitor for signs of extravasation throughout administration
- flush with ~150 mL of sodium chloride 0.9%
- potential for flare reaction during administration of daunorubicin (facial flushing and red streaking along the vein). Stop infusion
 and exclude extravasation before continuing at a slower rate of infusion.

Although rare, cardiac arrhythmias may occur during or immediately after daunorubicin administration. If sudden onset of dyspnoea, palpitations or irregular pulse occurs, stop administration immediately and obtain urgent medical officer review.

Cytarabine

- administer via continuous IV infusion over 7 days
- hang a new bag every 24 hours
- do not interrupt the infusion of cytarabine.

Observe for symptoms of cytarabine syndrome:

- fever, myalgia, bone pain, and/or occasionally rash, chest pain, or conjunctivitis which can occur 6 to 12 hours following drug administration. Symptoms usually resolve within 24 hours after cytarabine is discontinued.
- corticosteroids may be used for treatment and prophylaxis.

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

Days 4 to 7

Safe handling and waste management

Safe administration

General patient assessment prior to each treatment.

Any toxicity grade 2 or greater may require dose reduction, delay or omission of treatment and review by medical officer before recommencing treatment.

- · daily weight
- · daily dipstick urinalysis
- · strict fluid balance

Hydration if prescribed

Pre treatment medication

Verify antiemetics taken or administer as prescribed.

Ochemotherapy - Time out

Cytarabine

- · administer via continuous IV infusion over 7 days
- hang a new bag every 24 hours
- do not interrupt the infusion of cytarabine.

Observe for symptoms of cytarabine syndrome:

- fever, myalgia, bone pain, and/or occasionally rash, chest pain, or conjunctivitis which can occur 6 to 12 hours following drug administration. Symptoms usually resolve within 24 hours after cytarabine is discontinued.
- corticosteroids may be used for treatment and prophylaxis.

Deaccess CVAD.

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

Discharge information

Antiemetics

· Antiemetics as prescribed.

Growth factor support

· Arrangements for administration if prescribed.

Prophylaxis medications

· Prophylaxis medications (if prescribed) i.e. tumour lysis prophylaxis, PJP prophylaxis, antifungals, antivirals.

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)	
Extravasation, tissue or vein injury	The unintentional instillation or leakage of a drug or substance out of a blood vessel into surrounding tissue. This has the potential to cause damage to affected tissue. Read more about extravasation management
Flare reaction	Anthracycline flare reaction is caused by a localised allergic reaction. It is characterised by erythematous vein streaking, urticaria and pruritus which may occur during drug administration and is often associated with too rapid an infusion. Extravasation must be ruled out if flare occurs.
Nausea and vomiting	Read more about prevention of treatment induced nausea and vomiting
Red-orange discolouration of urine	Pink/red/orange discolouration of the urine. This can last for up to 48 hours after some anthracycline drugs.
Taste and smell alteration	Read more about taste and smell changes

Early (onset days to weeks)	
Neutropenia	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 immediate management of neutropenic fever
Thrombocytopenia	A reduction in the normal levels of functional platelets, increasing the risk of abnormal bleeding. Read more about thrombocytopenia
Anorexia	Loss of appetite accompanied by decreased food intake. Read more about anorexia
Diarrhoea	Read more about treatment induced diarrhoea
Fatigue	Read more about fatigue
Oral mucositis	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 oral mucositis
Photosensitivity	Increased sensitivity to ultraviolet (UV) light resulting in an exaggerated sunburn-like reaction accompanied by stinging sensations and urticaria.
Radiation recall	Erythematous or inflammatory skin reaction resembling severe sunburn at sites previously treated with radiation therapy can occur with certain anti-cancer drugs. Symptoms include vesiculation, desquamation and ulceration of the skin. Read more about radiation recall

Late (onset weeks to months)	
Anaemia	Abnormally low levels of red blood cells (RBCs) or haemoglobin in the blood. Read more about anaemia
Alopecia	Hair loss may occur from all parts of the body. Patients can also experience mild to moderate discomfort of the hair follicles, and rarely pain as the hair is falling out. Read more about alopecia and scalp cooling
Cognitive changes (chemo fog)	Changes in cognition characterised by memory loss, forgetfulness and feeling vague. This is also referred to as 'chemo brain' or 'chemo fog'. Read more about cognitive changes (chemo fog)

Delayed (onset months to years)

Cardiotoxicity

Anthracyclines are the most frequently implicated anti-cancer drugs associated with cardiotoxicity, which typically manifests as a reduction in left ventricular ejection fraction (LVEF), cardiomyopathy, or symptomatic CHF. Anthracycline induced cardiotoxicity has been categorised into acute, early-onset chronic progressive and late-onset chronic progressive and is usually not reversible. The risk of clinical cardiotoxicity increases with a number of risk factors including higher total cumulative doses.

Read more about cardiac toxicity associated with anthracyclines

Evidence

Modifying the anthracycline dose in acute myeloid leukaemia (AML) may improve complete remission (CR) rates and reduce relapse, hence improving overall survival (OS). Escalation of the daunorubicin dose to 90 mg/m²/day has been shown to improve OS and remission rates when compared to a daunorubicin dose of 45 mg/m²/day in some patients.^{3, 4, 5}

Only one randomised clinical trial has compared daunorubicin dose in AML induction (90 mg/m 2 vs 60 mg/m 2) with no evidence of overall benefit seen with the 90 mg/m 2 dose. A new re-analysis suggests that the higher dose may be superior for patients with FLT-3 ITD mutations.

Efficacy

Escalation of the daunorubicin to 90 mg/m²/day has been shown to improve OS and remission rates when compared to daunorubicin dose of 45 mg/m²/day, which had previously been the conventional dose for induction therapy in AML. This has been demonstrated in three randomised trials, two enrolling younger patients (<60 years) and the other patients over 60.

The first study treated 813 patients >60 years (range 60-83) with daunorubicin 90 mg/m^2 or 45 mg/m^2 for 3 days in addition to cytarabine 200 mg/m^2 continuous intravenous infusion for 7 days.³ A higher response rate was reported in the 90 mg/m^2 group when compared to the 45 mg/m^2 group with CR rates 64% vs. 54% (p= 0.002), without additional toxicity. However, there was no significant difference in OS between the two groups except in patients 60-65 years.

In the second trial, 657 enrolled patients, escalation of the daunorubicin dose to $90 \text{ mg/m}^2/\text{day}$ for 3 days in combination with cytarabine $100 \text{ mg/m}^2/\text{day}$ continuous infusion for 7 days resulted in increased complete response (CR) rates (70.6% vs 57.3%, p<0.001) and median OS compared to $45 \text{ mg/m}^2/\text{day}$ (23.7 vs 15.7 months, p=0.003). There was no major increase in toxicity- in particular, the rate of death during induction was 5.5% and 4.5% for the high-dose and standard-dose daunorubicin groups, respectively (p=0.60). Initial analysis appeared to limit the benefit of high-dose daunorubicin to younger (age <50 years) and those with favourable or intermediate risk cytogenetics. Longer follow up indicates the benefit of the higher anthracycline dose to potentially extend to patients with unfavourable cytogenetics (adjusted hazard ratio 0.66, p=0.04) and those with FLT3-ITD (HR 0.61, p=0.009). Superior outcomes in younger patients using high-dose daunorubicin has been confirmed in a contemporaneous randomised trial of 383 patients from Korea. 5

Although doses of daunorubicin higher than 45 mg/m^2 improve outcomes, particularly in younger patients with AML, it is unknown whether a dose of 90 mg/m^2 daunorubicin is required or, alternatively if 60 mg/m^2 may provide the same benefit. The UK NCRI AML17 trial was a randomised trial comparing daunorubicin 90 mg/m^2 vs 60 mg/m^2 in AML induction. 61206 patients (mostly under 60 years) were randomised to receive daunorubicin on days 1, 3, 3 and 5 at a dose of 90 mg/m^2 or 60 mg/m^2 with cytarabine 100 mg/m^2 every 12 hours on days 1 to 10 inclusive. A second course was given to patients with favourable or intermediate-risk disease, consisting of daunorubicin 50 mg/m^2 on days 1, 3 and 5 with cytarabine 100 mg/m^2 every 12 hours on days 1 to 8 inclusive. High-risk patients were randomised to receive either FLAG-Ida or clofarabine with 3 doses of daunorubicin 50 mg/m^2 .

No difference was seen in achievement of CR according to daunorubicin dose, with rates of 75% and 73% in the 60 mg/m 2 and 90 mg/m 2 groups, respectively (p=0.6). Day 30 mortality was similar in the two dose groups, but at day 60, there were increased deaths in the 90 mg/m 2 group (10% vs 5%, p=0.001). Grade 3 or 4 gastrointestinal toxicity was also higher in the 90 mg/m 2 cohort. Time to count recovery (neutrophils and platelets) and cardiac toxicity were not different between dose groups. Two-year OS was 60% in the 60 mg/m 2 group compared to 59% in the 90 mg/m 2 group (p=0.15), relapse-free survival (RFS) was also similar (48% vs 51%). Exploratory analysis did not reveal any subgroups benefiting from the higher dose of daunorubicin.

A subsequent re-analysis after extended follow up (median 28 months) now indicates that patients with FLT-3 ITD mutations experience improved RFS (45% vs 33%, p=0.02) and OS (54% vs 34%, p=0.03) if they receive 90 mg/m² daunorubicin in induction rather than 60 mg/m². This appears to be independent of NPM1 mutation status. Outcomes remain unchanged for all other subgroups.

Figure 1: Effect of daunorubicin dose on survival according to cytogenetic risk⁶

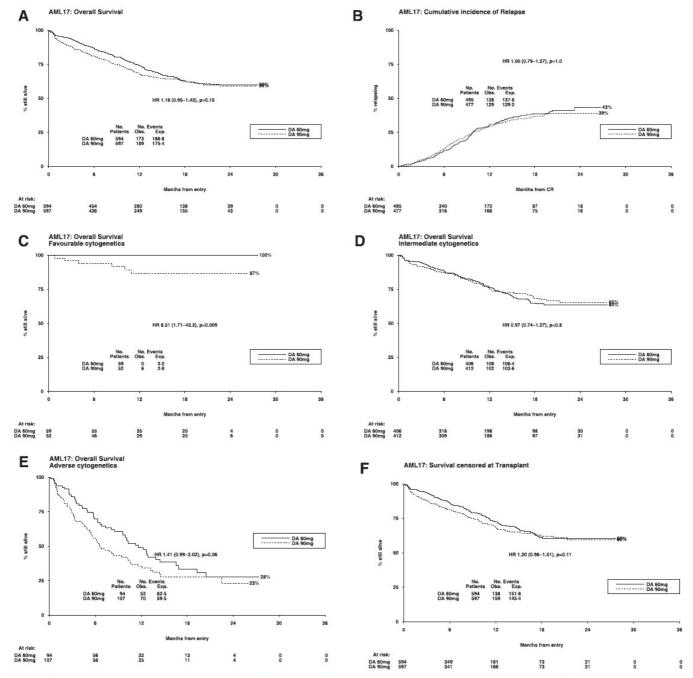
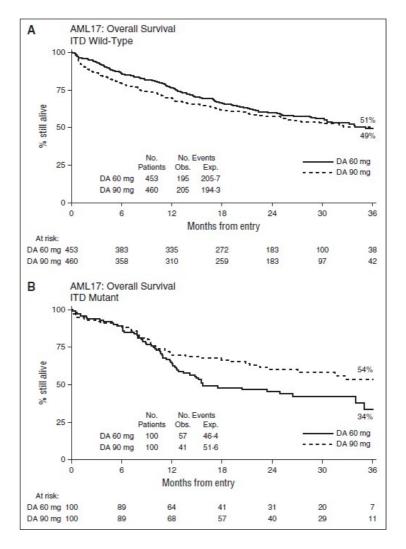


Figure 4. Outcomes after daunorubicin dose randomization. (A) Overall survival (OS); (B) cumulative incidence of relapse; (C) OS—favorable cytogenetics; (D) OS—intermediate cytogenetics; (E) OS—adverse cytogenetics; (F) survival censored at transplant.

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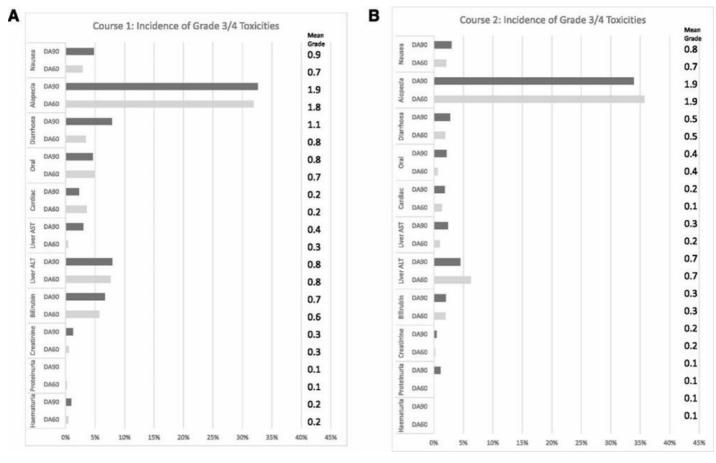
Figure 2: Effect of daunorubicin dose according to FLT-3 ITD status 8



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Toxicity

Table 1: Non-haematologic toxicity of 60 mg/m² vs 90 mg/m² daunorubicin⁶



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References

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- 3 Lowenberg, B., G. J. Ossenkoppele, W. van Putten, et al. 2009. "High-dose daunorubicin in older patients with acute myeloid leukemia." N Engl J Med 361(13):1235-1248.
- **4** Fernandez, H. F., Z. Sun, X. Yao, et al. 2009. "Anthracycline dose intensification in acute myeloid leukemia." N Engl J Med 361(13):1249-1259.
- 5 Lee, J. H., Y. D. Joo, H. Kim, et al. 2011. "A randomized trial comparing standard versus high-dose daunorubicin induction in patients with acute myeloid leukemia." Blood 118(14):3832-3841.
- **6** Burnett, A. K., Russell, N. H., Hills, R. K., et al. 2015. "A randomised comparison of daunorubicin 90mg/m2 vs 60mg/m2 in AML induction: results from the UK NCRI AML17 trial in 1206 patients." Blood 125(25):3878-3885.
- **7** Luskin, M. R., Lee, J., Fernandez, H. F., et al. 2016. "Benefit of high-dose daunorubicin in AML induction extends across cytogenetics and molecular groups." Blood 127(12):1551-1558.
- **8** Burnett A. K., N. H. Russell, R. K. Hills, et al. 2016. Higher daunorubicin exposure benefits FLT3 mutated acute myeloid leukemia. Blood 128:449-452.

History

Version 2

Date	Summary of changes
26/05/2017	Discussion held at the eviQ Haematology Reference Committee meeting (20/05/2016) regarding the updated daunorubicin dose of between 60 to 90 mg/m² for Acute Myeloid Leukaemia induction recommended in local and international (ELN and NCCN) guidelines.
	Consensus decision to increase daunorubicin dose to 60 mg/m².
	This protocol replaces a previous version ID 348 AML Induction 7-3 protocol (daunorubicin 50 mg/m² dose) which has been discontinued.
	New protocol ID 2043 Acute Myeloid Leukaemia Induction 7-3 (Cytarabine and DAUNOrubicin) with updated daunorubicin 60 mg/m² dose approved and published on eviQ.
31/05/2017	Transferred to new eviQ website. Version number change to V.2.
01/04/2019	Note added underneath the treatment schedule 'Cytarabine at a dose of $100 - 200 \text{ mg/m}^2$ is acceptable and as per clinician discretion'.
10/10/2019	Clinical information updated with PBS expanded indications for G-CSF.
11/03/2022	Reviewed by Haematology Reference Committee with no significant changes, review in 4 years.

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

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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/2043

19 Sep 2023





Patient's name:

Your treatment

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

Induction 7-3 (cytarabine and daunorubicin)						
This treatment may be given for up to two cycles. Your doctor will advise you of the number of treatments you will have.						
Day	Treatment	How it is given	How long it takes			
1 to 3	Daunorubicin (daw-noe-ROO-bi-sin)	By a drip into a vein	About 15 minutes			
1 to 7	Cytarabine (sye-TARE-a-been)	By a drip into a vein	For 7 days continuously			

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.

IMMEDIATELY go to your nearest hospital Emergency Department, or contact your doctor or nurse if you have any of the following at any time:	Emergency contact details Ask your doctor or nurse from your treating team who to contact if you have a problem
 a temperature of 38°C or higher chills, sweats, shivers or shakes shortness of breath uncontrolled vomiting or diarrhoea pain, tingling or discomfort in your chest or arms you become unwell. 	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.
- **G-CSF**: you may be given injection(s) of a drug called G-CSF (also called filgrastim, lipegfilgrastim or pegfilgrastim) under your skin. This helps to boost your white blood cell count. Your white blood cells help to fight infection. Lipegfilgrastim and pegfilgrastim are given once. Filgrastim is given for several days until your white blood cells recover. Your doctor will decide if you need this medication. Follow this link to read more information on how to give this injection.

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) • This treatment can cause serious injury if it leaks from the area where it is going into the Pain or swelling at injection site (extravasation) • This can cause pain, stinging, swelling or redness at or near the site where the drug enters the vein. • If not treated correctly, you may get blistering and ulceration. . Tell your doctor or nurse immediately if you get any of the symptoms listed above during or after treatment. • You may get redness and itching along the vein where your chemotherapy is being infused. Redness and itching along • This will usually go away within 30 minutes of stopping the injection. vein • Tell your doctor or nurse as soon as possible if you get any of the symptoms listed above. Your nurse will check to make sure the drug has not leaked out of the vein. • You may feel sick (nausea) or be sick (vomit). Nausea and vomiting • Take your anti-sickness medication as directed even if you don't feel sick. • Drink plenty of fluids (unless you are fluid restricted). • Eat small meals more frequently. • Try food that does not require much preparation. • Try bland foods like dry biscuits or toast. • Gentle exercise may help with nausea. · Ask your doctor or nurse for eviQ patient information - Nausea and vomiting during cancer 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. • Your urine will turn an orange or red colour. Urine turning orange or red • This is not harmful and should only last for up to 48 hours after treatment. • You may find that food loses its taste or tastes different. Taste and smell changes These changes are likely to go away with time. · Do your mouth care regularly. • Chew on sugar-free gum or eat sugar-free mints. • Add flavour to your food with sauces and herbs. Ask your doctor or nurse for eviQ patient information - Taste and smell changes during cancer treatment.

Early (onset days to weeks)

Infection risk (neutropenia)

- 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.
- Wash your hands often.
- Keep a thermometer at home and take your temperature regularly, and if you feel unwell.
- Do your mouth care regularly.
- Inspect your central line site (if you have one) daily for any redness, pus or swelling.
- · Limit contact with people who are sick.
- Learn how to recognise the signs of infection.
- Ask your doctor or nurse for eviQ patient information Infection during cancer treatment.
- Tell your doctor or nurse immediately, or go to the nearest hospital Emergency Department if you get any of the following signs or symptoms:
 - o a temperature of 38°C or higher
 - o chills, shivers, sweats or shakes
 - o a sore throat or cough
 - uncontrolled diarrhoea
 - shortness of breath
 - o a fast heartbeat
 - become unwell even without a temperature.

Low platelets (thrombocytopenia)

- 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.
- Try not to bruise or cut yourself.
- · Avoid contact sport or vigorous exercise.
- Clear your nose by blowing gently.
- · Avoid constipation.
- Brush your teeth with a soft toothbrush.
- Don't take aspirin, ibuprofen or other similar anti-inflammatory medications unless your doctor tells you to.
- Tell your doctor or nurse if you have any bruising or bleeding.
- Tell your doctor or nurse immediately, or go to your nearest hospital Emergency Department if you have any uncontrolled bleeding.

Appetite loss (anorexia)

- You may not feel like eating.
- Try to avoid drinking fluids at meal times.
- Try to eat small meals or snacks regularly throughout the day.
- Try to eat food that is high in protein and calories.
- If you are worried about how much food you can eat, or if you are losing weight, ask to speak to a dietitian.

Diarrhoea

- You may get bowel motions (stools, poo) that are more frequent or more liquid.
- You may also get bloating, cramping or pain.
- Take your antidiarrhoeal medication as directed by your doctor.
- Drink plenty of fluids (unless you are fluid restricted).
- · Eat and drink small amounts more often.
- Avoid spicy foods, dairy products, high fibre foods, and coffee.
- Ask your doctor or nurse for eviQ patient information Diarrhoea during cancer treatment.
- 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.

Tiredness and lack of energy (fatigue)

- You may feel very tired, have no energy, sleep a lot, and not be able to do normal activities or things you enjoy.
- Do not drive or operate machinery if you are feeling tired.
- Nap for short periods (only 1 hour at a time)
- · Prioritise your tasks to ensure the best use of your energy.
- Eat a well balanced diet and drink plenty of fluids (unless you are fluid restricted).
- Try some gentle exercise daily.
- Allow your friends and family to help.
- Tell your doctor or nurse if you get any of the symptoms listed above.

Mouth pain and soreness (mucositis)

- · You may have:
 - bleeding gums
 - o mouth ulcers
 - a white coating on your tongue
 - pain in the mouth or throat
 - o difficulty eating or swallowing.
- Avoid spicy, acidic or crunchy foods and very hot or cold food and drinks.
- Try bland and soft foods.
- Brush your teeth gently with a soft toothbrush after each meal and at bedtime. If you normally floss continue to do so.
- Rinse your mouth after you eat and brush your teeth, using either:
 - o 1/4 teaspoon of salt in 1 cup of warm water, or
 - 1/4 teaspoon of bicarbonate of soda in 1 cup of warm water
- Ask your doctor or nurse for eviQ patient information Mouth problems during cancer treatment.
- Tell your doctor or nurse if you get any of the symptoms listed above.

Skin that is more sensitive to the sun (photosensitivity)

- After being out in the sun you may develop a rash like a bad sunburn.
- · Your skin may become red, swollen and blistered.
- · Avoid direct sunlight.
- Protect your skin from the sun by wearing sun-protective clothing, a wide-brimmed hat, sunglasses and a sunscreen of SPF 50 or higher.
- Tell your doctor or nurse if you get any of the symptoms listed above.

Skin reaction in an area previously treated with radiation therapy (radiation recall)

- In the area that was treated with radiation therapy, your skin may become:
 - dry, red and itchy
 - tender and swollen
- It may also:
 - peel or blister
 - o form ulcers
- This usually happens weeks or months after chemotherapy treatment.
- · Avoid wearing tight clothing.
- Avoid direct sunlight and very hot or cold temperatures.
- Protect your skin from the sun by wearing sun-protective clothing, a wide-brimmed hat, sunglasses and a sunscreen of SPF 50 or higher.
- Tell your doctor or nurse if you get any of the symptoms listed above.

Late (onset weeks to months)	
Low red blood cells (anaemia)	 You may feel dizzy, light-headed, tired and appear more pale than usual. Tell your doctor or nurse if you have any of these signs or symptoms. You might need a blood transfusion. Tell your doctor or nurse immediately, or go to the nearest hospital Emergency Department if you have any chest pain, trouble breathing, or feel like your heart is racing.
Hair loss (alopecia)	 Your hair may start to fall out from your head and body. Hair loss usually starts 2 to 3 weeks after your first treatment. You may become completely bald and your scalp might feel tender. Use a gentle shampoo and a soft brush. Take care with hair products like hairspray, hair dye, bleaches and perms. Protect your scalp from the cold with a hat, scarf or wig. Protect your scalp from the sun with a hat or sunscreen of SPF 50 or higher. Moisturise your scalp to prevent itching. Ask your doctor or nurse about the Look Good Feel Better program
Chemo brain (chemotherapy-related cognitive impairment)	 You may notice that you are unable to concentrate, feel unusually disorganised or tired (lethargic) and have trouble with your memory. These symptoms usually improve once treatment is completed. Ask your doctor or nurse for eviQ patient information – Memory changes and chemotherapy (chemo brain). Tell your doctor or nurse if you get any of the symptoms listed above.

Delayed (onset months to years)

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- You may get:
 - o chest pain or tightness
 - · shortness of breath
 - swelling of your ankles
 - o an abnormal heartbeat.
- Heart problems can occur months to years after treatment.
- Tell your doctor if you have a history of heart problems or high blood pressure.
- Before or during treatment, you may be asked to have a test to see how well your heart is working.
- Tell your doctor or nurse immediately, or go to the nearest hospital Emergency Department if you get any of the symptoms listed above.

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.
- 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 more 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

- Some cancer treatments can be dangerous 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. Contraception should be used during 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.

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
- Australasian Menopause Society menopause.org.au
- Chris O'Brien Lifehouse Total Body Irradiation mylifehouse.org.au/departments/radiation-oncology/total-body-irradiation/
- Healthy Male Andrology Australia healthymale.org.au/
- International Myeloma Foundation myeloma.org
- Leukaemia Foundation leukaemia.org.au
- Lymphoma Australia lymphoma.org.au
- Myeloma Australia 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
- NCCN Guidelines for Patients Immunotherapy Side Effects: CAR T-Cell Therapy nccn.org/patientresources/patient-resources/guidelines-for-patients
- Talk Blood Cancer cmlsupport.org.uk/organisation-type/social-media-groups

General cancer information and support

- Australian Rare Cancer (ARC) Portal arcportal.org.au/
- Beyondblue beyondblue.org.au
- Cancer Australia canceraustralia.gov.au
- Cancer Council Australia cancer.org.au
- Cancer Voices Australia cancervoicesaustralia.org
- CanTeen canteen.org.au
- Carers Australia carersaustralia.com.au
- Carer Help carerhelp.com.au
- eviQ Cancer Treatments Online eviQ.org.au
- Food Standards Australia New Zealand: Listeria & Food Safety foodstandards.gov.au/publications/pages/listeriabrochuretext.aspx
- LGBTQI+ People and Cancer cancercouncil.com.au/cancer-information/lgbtqi
- Look Good Feel Better lgfb.org.au
- Patient Information patients.cancer.nsw.gov.au
- Radiation Oncology Targeting Cancer targetingcancer.com.au
- Redkite redkite.org.au
- Return Unwanted Medicines returnmed.com.au
- Staying active during cancer treatment patients.cancer.nsw.gov.au/coping-with-cancer/physical-wellbeing/staying-active

Quit smoking information and support

Quitting smoking is helpful even after you have been diagnosed with cancer. The following resources provide useful information and support to help you quit smoking. Talk to your treating team about any other questions you may have.

- Call Quitline on 13 QUIT (13 78 48)
- iCanQuit iCanQuit.com.au
- Patient Information patients.cancer.nsw.gov.au/coping-with-cancer/physical-wellbeing/quitting-smoking
- Quitnow quitnow.gov.au

Additional notes:	

This document is a guide only and cannot cover every possible situation. The health professionals caring for you should always consider your individual situation when making decisions about your care. Contact your cancer clinic staff or doctor if you have any questions or concerns about your treatment, or you are having problems coping with side effects. 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 of this document is subject to eviQ's disclaimer available at www.eviQ.org.au

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