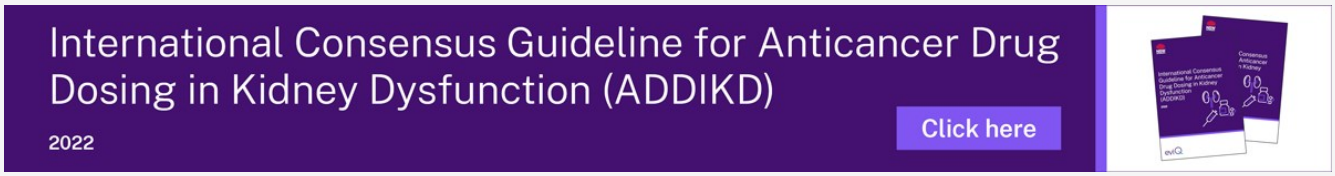
Acute myeloid leukaemia FLAG (fludarabine cytarabine and filgrastim)

ID: 346 v.6 **Endorsed** Essential Medicine List

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.



Related pages:

- Acute myeloid leukaemia FLAG-Ida (fludarabine cytarabine iDArubicin and filgrastim)

Treatment schedule - Overview

Drug	Dose	Route	Day
Filgrastim	5 micrograms/kg	Subcut	0 to 5 and continue daily until neutrophil recovery
Fludarabine	30 mg/m^2	IV infusion	1 to 5
Cytarabine (Ara-C)	2,000 mg/m^2 *	IV infusion	1 to 5

* Cytarabine dose may be reduced for older patients; consider 1000 mg/m^2 if the patient is older than 60 years of age.

Cycles: 1 or 2. Upon recovery, a second cycle may be given (generally only if the patient has responded to Cycle 1).

Notes:
The scheduling of the drugs in this protocol is important; commence cytarabine administration 4 hours after the start of the fludarabine infusion.[1]

Drug status: **Fludarabine and Cytarabine:** PBS general schedule

Filgrastim: (PBS authority)

Cost: ~ $3,080 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 0		
Filgrastim	5 micrograms/kg (Subcut)	inject subcutaneously once daily from day 0 and continue until neutrophil recovery. To be given before chemotherapy on days 1 to 5.

Day 1 to 5		
Filgrastim	5 micrograms/kg (Subcut)	inject subcutaneously once daily from day 0 and continue until neutrophil recovery. To be given before chemotherapy on days 1 to 5.
Fludarabine	30 mg/m^2 (IV infusion)	in 100 mL sodium chloride 0.9% over 30 minutes
Cytarabine (Ara-C)	2,000 mg/m^2 (IV infusion)	in 500 mL sodium chloride 0.9% over 4 hours. Administer 4 hours after commencing the fludarabine infusion.

Note: Cytarabine dose may be reduced for older patients; consider 1000 mg/m^2 if the patient is older than 60 years of age.

Cycles: 1 or 2. Upon recovery, a second cycle may be given (generally only if the patient has responded to Cycle 1).

Indications and patient population

- Relapsed or refractory acute myeloid leukaemia (predominant use)

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
Ocular toxicities	Administer corticosteroid eye drops to minimise corneal toxicity from high dose cytarabine. Commence on the day of first dose of cytarabine and continue for at least 72 hours after completion of final cytarabine dose. Read more about ocular toxicities associated with high dose cytarabine
Cytarabine syndrome	Treatment with cytarabine may cause a "cytarabine syndrome" characterised by flu-like symptoms, skin rash and occasionally chest pain.
Cytarabine-induced neurotoxicity	This may occur in patients treated with high-dose cytarabine. Assess cerebellar function prior to each cytarabine dose. Note: an increased risk of cytarabine-induced neurotoxicity has been associated with kidney dysfunction. Read more about neurotoxicity associated with high-dose cytarabine and access the cytarabine cerebellar neurotoxicity assessment chart

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.
Biosimilar drug	Read more about biosimilar drugs on the Biosimilar Awareness Initiative page
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
Irradiated blood components	The use of irradiated of blood components is recommended for patients receiving this treatment. Read more about the indications for the use of irradiated blood components
Blood tests	FBC, EUC, eGFR, LFTs, LDH 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.

Renal impairment	
Creatinine clearance (mL/min)	
30 to 50	Reduce fludarabine by 50%
less than 30	Fludarabine contraindicated
No specific dose modifications are recommended for cytarabine in renal impairment. Note: an increased risk of neurotoxicity has been associated with high-dose cytarabine and a creatinine clearance of less than 60 mL/min.	

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

Age
Cytarabine dose may be reduced for older patients. Consider reducing dose to 1000 mg/m^2 if patient is older than 60 years

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

Fludarabine		
	Interaction	**Clinical management**
Dipyridamole	Reduced efficacy of fludarabine possible due to inhibition of adenosine uptake	Avoid combination or monitor for decreased clinical response to fludarabine

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

product information monographs via the TGA website for further information.

Day 0

Subcutaneous injection

General patient assessment prior to each day of treatment.

Commence corticosteroid eye drops 24 hours before starting cytarabine. Continue for 72 hours after completion of the last dose of cytarabine.

Filgrastim

- Inject subcutaneously ONCE daily, starting on day 0 and continuing until neutrophil recovery.

Days 1 to 5

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.

- daily weight
- daily dipstick urinalysis
- strict fluid balance

Pre treatment medication

Verify antiemetics taken or administer as prescribed.

Continue corticosteroid eye drops until 72 hours after completion of the last dose of cytarabine.

Filgrastim

- Inject subcutaneously ONCE daily, starting on day 0 and continuing until neutrophil recovery.

Chemotherapy - Time out

Fludarabine

- administer via IV infusion over 30 minutes
- flush with ~ 50 mL of sodium chloride 0.9%

Administer cytarabine 4 hours AFTER commencing the fludarabine infusion

Cytarabine

Prior to administration:

Ensure corticosteroid eye drops have been administered before starting cytarabine.

Verify that cytarabine neurological assessment has been performed prior to administration of cytarabine:

- if the patient scores 0 then administer cytarabine as charted
- if the patient scores 1 or above, do not administer the cytarabine and immediately notify medical officer.

Administer cytarabine:

- via IV infusion over 4 hours
- flush with ~50 mL of sodium chloride 0.9%.

Deaccess CVAD.

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

Discharge information

Antiemetics

- Antiemetics as prescribed.

Corticosteroid eye drops

- Continue corticosteroid eye drops for at least 72 hours after completion of final cytarabine dose.

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)	
Bone pain	Bone pain, usually in the lower back or pelvis, associated with G-CSF.
Nausea and vomiting	Read more about prevention of treatment induced nausea and vomiting
Ocular toxicities	Reversible corneal toxicity (keratitis), haemorrhagic conjunctivitis, vision loss and other ocular side effects can occur with high dose cytarabine. Corticosteroid eye drops must be administered concurrently with treatment. Read more about ocular toxicities associated with cytarabine
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
Cytarabine (Ara-C) syndrome	Flu-like symptoms including fever, myalgia and malaise can occur 6 to 12 hours after cytarabine administration. Symptoms generally resolve within 24 hours of completing therapy.
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.
Skin rash	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 skin rash

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)
Neurotoxicity	Neurotoxicity related to fludarabine is a rare but potentially serious adverse event characterised by visual disturbances, altered mental state and CNS toxicity. Seizures leading to paralysis or coma have been reported in the literature. Periodic neurologic assessments are recommended.
Pulmonary toxicity	Pulmonary toxicity may include damage to the lungs, airways, pleura and pulmonary circulation. Read more about pulmonary toxicity associated with anti-cancer drugs

Evidence

Cytarabine is one of the most effective drugs used for treatment of acute myeloid leukaemia (AML) and myelodysplastic syndromes (MDS). The administration of fludarabine prior to high dose cytarabine has been shown to increase intracellular accumulation of the active metabolite, ara-CTP,[1] providing the rationale for the FLAG protocols. Estey and colleagues were the first to report the use of FLAG for treatment of newly diagnosed AML and MDS patients.[2] Most of the evidence for the FLAG protocol comes from case series with only one randomised trial testing the effect of adding fludarabine to high dose cytarabine and G-CSF. Ossenkoppele and colleagues enrolled previously untreated patients with high risk MDS or elderly AML and showed that response did not improve significantly with the addition of fludarabine, however toxicity was increased.[3]

G-CSF is included in the protocol to speed neutrophil recovery post-chemotherapy. It has also been hypothesised that giving G-CSF the day prior to chemotherapy increases the number of leukaemic cells in cycle at the time of cytotoxic administration and hence increases cell kill.[4, 5] The in vivo importance of this effect is debated, with some studies showing a benefit to concurrent vs sequential G-CSF[6] whilst others show no benefit.[2]

Efficacy

Currently, FLAG and FLAG-Ida protocols are used most commonly as salvage therapy for relapsed and refractory AML patients. There have been several studies of FLAG in this setting with reported complete response (CR) rates generally in the 50-60% range (see table below). Only the CR rates, not disease-free or overall survival, are summarised here because consolidation treatments vary significantly. In general, if induction with FLAG results in a CR, at least one further course of FLAG is recommended, followed by allogeneic transplantation if possible. Although CR rates are good, remission durations are usually short without further treatment.

Reference	N =	Age* (years)	CR (%)	TRM (%)	Comments
Visani et al 1994[7]	28	50	58	7	- relapsed/refractory AML
Clavio et al 1996[8]	51	64	59	10	- high risk AML: MDS-AML (22), relapsed/refractory (17), poor risk (12)
Huhmann et al 1996[9]	22	46	50	5	- relapsed/refractory AML
Nokes et al 1997[10]	31	-	66	13	- relapsed/refractory AML (19/4) & MDS (8)
Montillo et al 1998[11]	38	41	55	10	- relapsed/refractory AML
Carella et al 2001[12]	41	52	56	7	- relapsed/refractory AML
Jackson et al 2001[13]	21 44	48 47	81 30	18	- Group 1 = late relapse (>6 months) AML - Group 2 = early relapse or refractory AML
Thomas et al 2003[14]	177	49-56	19-35	9-19	- 3 different fludarabine and cytarabine regimens investigated sequentially in relapsed AML
Lee et al 2009[15]	61	33	48	11	- relapsed/refractory AML

** Median age in years; CR = complete remission; TRM = treatment related mortality; AML = acute myeloid leukaemia; MDS = myelodysplastic syndrome*

Toxicity

In general, FLAG is well tolerated with severe myelosuppression being the major toxicity, occurring in nearly all patients. The median time to neutrophil recovery (>0.5 x 10^9/L) ranges from 19 to 32 days and median time to platelet count >20 x 10^9/L is 20 to 41 days. [3, 9, 11, 15, 16, 13] Neutropenic fever is common and reported infection rates range from 26% to 84%.[3, 9, 11, 13, 15] Rates of fungal infection, when reported, are 7 to 10%.[11, 13, 15] Non-haematological toxicities are generally mild and include gastrointestinal toxicity, alopecia, and liver function test abnormalities. Treatment related mortality averages approximately 10% in relapsed and refractory AML patients (see table above).

References

1 Gandhi, V., E. Estey, M. J. Keating, et al. 1993. "Fludarabine potentiates metabolism of cytarabine in patients with acute myelogenous leukemia during therapy." J Clin Oncol. 11(1):116-124.

2 Estey, E., P. Thall, M. Andreeff, et al. 1994. "Use of granulocyte colony-stimulating factor before, during, and after fludarabine plus cytarabine induction therapy of newly diagnosed acute myelogenous leukemia or myelodysplastic syndromes: comparison with fludarabine plus cytarabine without granulocyte colony-stimulating factor." J Clin Oncol 12(4):671-678.

3 Ossenkoppele, G. J., W. J. Graveland, P. Sonneveld, et al. 2004. "The value of fludarabine in addition to ARA-C and G-CSF in the treatment of patients with high-risk myelodysplastic syndromes and AML in elderly patients." Blood. 103(8):2908-2913.

4 Tafuri, A. and M. Andreeff. 1990. "Kinetic rationale for cytokine-induced recruitment of myeloblastic leukemia followed by cycle-specific chemotherapy in vitro." Leukemia 4(12):826-834.

5 Tosi, P., G. Visani, E. Ottaviani, et al. 1994. "Fludarabine + Ara-C + G-CSF: cytotoxic effect and induction of apoptosis on fresh acute myeloid leukemia cells." Leukemia 8(12):2076-2082.

6 Martin, M. G., K. M. Augustin, G. L. Uy, et al. 2009. "Salvage therapy for acute myeloid leukemia with fludarabine, cytarabine, and idarubicin with or without gemtuzumab ozogamicin and with concurrent or sequential G-CSF." Am J Hematol 84(11):733-737.

7 Visani, G., P. Tosi, P. L. Zinzani, et al. 1994. "FLAG (fludarabine + high-dose cytarabine + G-CSF): an effective and tolerable protocol for the treatment of 'poor risk' acute myeloid leukemias." Leukemia 8(11):1842-1846.

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14 Thomas, M. B., C. Koller, Y. Yang, et al. 2003. "Comparison of fludarabine-containing salvage chemotherapy regimens for relapsed/refractory acute myelogenous leukemia." Leukemia 17(5):990-993.

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16 Ferrara, F., F. Leoni, A. Pinto, et al. 1999. "Fludarabine, cytarabine, and granulocyte-colony stimulating factor for the treatment of high risk myelodysplastic syndromes." Cancer 86(10):2006-2013.

History

Version 6

Date	Summary of changes
22/09/2020	Biosimilar drug added to clinical information. Version number changed to v.6
15/06/2022	Protocol reviewed electronically by Haematology Reference Committee. Evidence updated. For review in 2 years.
25/07/2023	Neurotoxicity added to "Late" category of Side effects section.

Version 5

Date	Summary of changes
12/04/2007	Minor editing
12/06/2008	Review, clarification of dose modifications and addition of extra information to increase the comprehensiveness of the protocol
24/03/2010	Review, new dose modifications and transferred to eviQ
17/09/2010	Full protocol review at Haematology Reference Committee meeting. Evidence section updated.
21/11/2011	New format to allow for export of protocol information. Protocol version number changed to v.*2.* Antiemetics and premedications added to the treatment schedule. Additional Clinical Information, Key Prescribing table and Key Administration table combined into new section titled Clinical Considerations. Drug specific information placed behind the drug name link.

Date	Summary of changes
27/06/2014	Protocol reviewed by email survey. Added link to ALLG and ANZCTR with statement 'Patients with AML should be considered for inclusion into clinical trials'. Changed the wording in the drug schema for filgrastim to read '0 and continue until neutrophil recovery' (as per the 2010 Reference Committee meeting minutes). Next review in 2 years.
02/02/2016	Standard review, no changes
31/05/2017	Transferred to new eviQ website. Version number changed to v.4.
14/12/2017	The days on which filgrastim is administered was adjusted in the overview and detail treatment schedules to mention days 1 to 5. Version number increased to v.5.
10/10/2019	Clinical information updated with PBS expanded indications for G-CSF.

First approved: 15 July 2005
Last reviewed: 15 June 2022
Review due: 30 June 2024

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/346
19 Sep 2023

Patient information - Acute myeloid leukaemia (AML) - FLAG (fludarabine, cytarabine, filgrastim)

Patient's name:

Your treatment

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

FLAG (fludarabine, cytarabine, filgrastim)			
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**
0 (and continue until white cell count increases)	**Granulocyte Colony Stimulating Factor** *(G-CSF)*	By injection under the skin	About 5 minutes
1 to 5	**Fludarabine** *(Flu-dara-been)*	By a drip into a vein	About 30 minutes
	Cytarabine *(sye-TARE-a-been)*	By a drip into a vein	About 4 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.

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

- **G-CSF:** you will 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. Follow this link to read more information on how to give this injection.
- **Eye drops:** you will be given eye drops to help prevent sore eyes. You will start using the eye drops before you have your first dose of cytarabine and continue to use the eye drops until 72 hours after your last dose of cytarabine.
- **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)	
Bone pain after G-CSF injection	• You may have discomfort or a dull ache in your pelvis, back, arms or legs. • To reduce the pain, take paracetamol before each injection. • **Tell your doctor or nurse as soon as possible if your pain is not controlled.**
Nausea and vomiting	• You may feel sick (nausea) or be sick (vomit). • 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 treatment. • **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.**
Eye problems from cytarabine	• You may get: ◦ eye pain or irritation ◦ blurred vision ◦ watery or gritty eyes ◦ sensitivity to light. • You will be given eye drops to help prevent and control these symptoms. It is important to use these eye drops as directed. • Protect your eyes from the weather (sun and wind) by wearing sunglasses, especially if you have lost your eyelashes. • Tell your doctor or nurse if you get any of the symptoms listed above.
Taste and smell changes	• You may find that food loses its taste or tastes different. • 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:** ◦ **a temperature of 38°C or higher** ◦ **chills, shivers, sweats or shakes** ◦ **a sore throat or cough** ◦ **uncontrolled diarrhoea** ◦ **shortness of breath** ◦ **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.**
Flu-like symptoms from cytarabine	• You may get a fever, skin rash, aches and pains or increased sweating. • These symptoms are caused by the drug cytarabine. • Symptoms usually happen 6 to 12 hours after your dose, and may last until 24 hours after your treatment has finished. • To reduce any pain or fever, take paracetamol, if needed. • Don't take aspirin, ibuprofen or other similar anti-inflammatory medications unless your doctor tells you to. • Tell your doctor or nurse if these symptoms do not get better after 24 hours.
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 ◦ mouth ulcers ◦ a white coating on your tongue ◦ pain in the mouth or throat ◦ 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: ◦ 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 rash	• You may get a red, bumpy rash and dry, itchy skin. • Moisturise your skin with a gentle non-perfumed moisturising cream like sorbolene or aqueous cream. • Do not scratch your skin. • Protect your skin from the sun by wearing sun-protective clothing, a wide-brimmed hat, sunglasses and sunscreen of SPF 50 or higher. • **Talk to your doctor or nurse about other ways to manage your skin rash.**

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.
Nervous system changes from fludarabine	• Doses of fludarabine can affect the nervous system. • **Tell your doctor or nurse immediately, or go to the nearest hospital Emergency Department if you get any of the following symptoms during or soon after your treatment:** ◦ **agitation or confusion** ◦ **dizziness, drowsiness or double vision** ◦ **difficulty walking in a straight line** ◦ **difficulty writing with a pen or pencil** ◦ **jerky movements or seizures** ◦ **slow, slurred speech.**
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.
- 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:

First approved: 15 July 2005
Last reviewed: 15 June 2022
Review due: 30 June 2024

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https://www.eviq.org.au/pi/346
19 Sep 2023