Chronic lymphocytic leukaemia FCR (fludarabine CYCLOPHOSPHamide rituximab)

ID: 496 v.8 **Endorsed** Essential Medicine List

Patients with leukaemia should be considered for inclusion into clinical trials. Link to ALLG website and ANZCTR website.

Treatment schedule - Overview

Cycle 1

Drug	Dose	Route	Day
Rituximab *	375 mg/m^2	IV infusion	0
Fludarabine	25 mg/m^2	IV infusion **	1 to 3
CYCLOPHOSPHamide	250 mg/m^2	IV infusion **	1 to 3

Cycle 2 to 6

Drug	Dose	Route	Day
Rituximab	500 mg/m^2	IV infusion	1
Fludarabine	25 mg/m^2	IV infusion **	1 to 3
CYCLOPHOSPHamide	250 mg/m^2	IV infusion **	1 to 3

* The dose of rituximab can be split over 2 days or be administered later in the cycle.

** For oral dosing of fludarabine and cyclophosphamide refer to the evidence section.

Frequency: 28 days

Cycles: 6. Depending on response and toxicity less cycles may be given.

Notes:
This is a very immunosuppressive therapy; caution required in pre-treated patients, those with pre-existing cytopenias, those with a history of opportunistic infections and the elderly.

Concomitant treatment with steroids (excluding those used as antiemetics and rituximab premedication) should be avoided where possible due to the heightened risk of opportunistic infections.

It is the consensus of the Haematology Reference Committee that a $5HT_3$ antagonist should be given on each day of treatment, all patients should receive antiviral and PJP prophylaxis for the duration of treatment and a minimum of 3 to 6 months subsequently and antifungal prophylaxis is not routine.

Drug status: All drugs in this protocol are on the PBS general schedule

Cost: ~ $920 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.*

Cycle 1

Day 0		
Paracetamol	1,000 mg (PO)	60 minutes before treatment
Loratadine	10 mg (PO)	60 minutes before treatment
Hydrocortisone	100 mg (IV)	30 minutes before treatment
Rituximab	375 mg/m^2 (IV infusion)	in 500 mL sodium chloride 0.9% as per graded administration rate *

Day 1		
Dexamethasone	8 mg (PO)	60 minutes before chemotherapy
Palonosetron	0.25 mg (IV bolus)	30 minutes before chemotherapy
Fludarabine	25 mg/m^2 (IV infusion)	in 100 mL sodium chloride 0.9% over 30 minutes **
CYCLOPHOSPHamide	250 mg/m^2 (IV infusion)	in 500 mL sodium chloride 0.9% over 30 to 60 minutes **

Day 2 and 3		
Dexamethasone	8 mg (PO)	60 minutes before chemotherapy
Fludarabine	25 mg/m^2 (IV infusion)	in 100 mL sodium chloride 0.9% over 30 minutes **
CYCLOPHOSPHamide	250 mg/m^2 (IV infusion)	in 500 mL sodium chloride 0.9% over 30 to 60 minutes **

Day 4 and 5		
Dexamethasone	8 mg (PO)	ONCE a day (or in divided doses) with or after food. Note: dexamethasone doses on day 4 to 5 may not be required and may be reduced or omitted at the clinician's discretion. ***

Cycle 2 to 6

Day 1		
Paracetamol	1,000 mg (PO)	60 minutes before treatment
Loratadine	10 mg (PO)	60 minutes before treatment
Hydrocortisone	100 mg (IV)	30 minutes before treatment
Rituximab	500 mg/m^2 (IV infusion)	in 500 mL sodium chloride 0.9% as per graded administration rate
Palonosetron	0.25 mg (IV bolus)	30 minutes before chemotherapy
Fludarabine	25 mg/m^2 (IV infusion)	in 100 mL sodium chloride 0.9% over 30 minutes **
CYCLOPHOSPHamide	250 mg/m^2 (IV infusion)	in 500 mL sodium chloride 0.9% over 30 to 60 minutes **

Day 2 and 3		
Dexamethasone	8 mg (PO)	60 minutes before chemotherapy
Fludarabine	25 mg/m^2 (IV infusion)	in 100 mL sodium chloride 0.9% over 30 minutes **
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Dexamethasone	8 mg (PO)	ONCE a day (or in divided doses) with or after food. Note: dexamethasone doses on day 4 to 5 may not be

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		required and may be reduced or omitted at the clinician's discretion. ***

* The dose of rituximab can be split over 2 days or be administered later in the cycle.

** For oral dosing of fludarabine and cyclophosphamide refer to the evidence section.

*** Link to ID 7 Prevention of chemotherapy induced nausea and vomiting

Frequency: 28 days

Cycles: 6. Depending on response and toxicity less cycles may be given.

Indications and patient population

Indication:

- CD20 positive, B-cell chronic lymphocytic leukaemia (CLL)
  - Alternative therapy should be considered for patients with 17p deletion

Contraindication:

- Fludarabine is contraindicated if creatinine clearance is < 30mL/min.

Clinical information

Venous access required	IV cannula (IVC) or central venous access device (CVAD) is required to administer this treatment. Read more about central venous access device line selection
Hypersensitivity/infusion related reaction	High risk with rituximab. Read more about Hypersensitivity reaction
Premedication	The product information states that premedication is required for this treatment. Please refer to the treatment schedule for suggested premedication regimen. This may be substituted to reflect institutional policy.
Emetogenicity MODERATE	Suggested default antiemetics have been added to the treatment schedule, and may be substituted to reflect institutional policy. 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
Rituximab rapid infusion	This regimen is not in line with the product monograph, however published literature indicates that it can be completed safely. Read more about the rapid infusion of rituximab
Progressive multifocal leukoencephalopathy	Use of monoclonal antibodies may be associated with an increased risk of progressive multifocal leukoencephalopathy (PML), a rare but potentially fatal opportunistic viral infection of the brain. Patients must be monitored for any new or worsening neurological symptoms. Read more about progressive multifocal leukoencephalopathy and the Therapeutic Goods Administration Medicines Safety update on progressive multifocal leukoencephalopathy from the Australian Government, Department of Health.

Infection risk	It is the consensus of the haematology reference committee that, if patients are hypogammaglobulinemic with recurrent infections consider intravenous immunoglobulin replacement therapy as per the Australian Red Cross Blood services guidelines (ARCBS). Read more about the Australian Red Cross Blood services guidelines
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	PJP prophylaxis is recommended e.g. trimethoprim/sulfamethoxazole 160/800 mg PO one tablet twice daily, twice weekly (e.g. on Mondays and Thursdays) OR one tablet three times weekly (e.g. on Mondays, Wednesdays and Fridays). Read more about prophylaxis of pneumocystis jiroveci (carinii) in cancer patients
Antiviral prophylaxis	Antiviral prophylaxis is recommended. Read more about antiviral prophylaxis drugs and doses
Antifungal prophylaxis	The use of prophylaxis should be at the discretion of the treating clinician and based on patient risk factors and local guidelines. 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
Autoimmune haemolytic anaemia	The use of fludarabine in patients with CLL may increase the risk of autoimmune haemolytic anaemia (AIHA).
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
Biosimilar drug	Read more about biosimilar drugs on the Biosimilar Awareness Initiative page
Blood tests	FBC, EUC, eGFR, LFTs and LDH at baseline, and prior to each cycle and as clinically indicated.
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	
ANC x 10^9/L (pre-treatment blood test)	
Less than 1.0 or previous episode of febrile neutropenia	Delay treatment until recovery and consider adding G-CSF for subsequent cycles. Consider reducing fludarabine by 25% for repeat grade 3 or 4 neutropenia (on Day 1 of cycle).
Platelets x 10^9/L (pre-treatment blood test)	
Less than 75	Delay treatment until recovery. No dose reduction if decreased platelet count is due to disease. Consider reducing fludarabine by 25% for repeat grade 3 or 4 thrombocytopenia (on Day 1 of cycle).

Renal impairment	
Creatinine clearance (mL/min)	
30 - 60	Reduce fludarabine to 20 mg/m^2
less than 30	Use alternative treatment

Note: Landmark trials excluded patients with CrCl <70 mL/min. Other clinical trials have used FCR without dose reduction with CrCl as low as 40 mL/min, however increased toxicity may be expected. There are few data on efficacy/toxicity with dose reduction due to CrCl for this regimen.

Hepatic impairment
Hepatic dysfunction
No dose modifications recommended

Peripheral neuropathy
Consider delaying or discontinuing fludarabine if neurotoxicity occurs

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*

Cyclophosphamide		
	Interaction	**Clinical management**
CYP3A4 inducers (e.g. carbamazepine, phenytoin, phenobarbitone, rifampicin, St John's wort etc.)	Increased toxicity of cyclophosphamide possible due to increased conversion to active (and inactive) metabolites	Avoid combination or monitor for cyclophosphamide toxicity
CYP3A4 inhibitors (e.g. aprepitant, azole antifungals, clarithromycin, erythromycin, grapefruit juice, ritonavir etc.)	Reduced efficacy of cyclophosphamide possible due to decreased conversion to active (and inactive) metabolites	Avoid combination or monitor for decreased clinical response to cyclophosphamide
Nephrotoxic drugs (e.g. aminoglycosides, amphotericin, contrast dye, frusemide, NSAIDs)	Additive nephrotoxicity	Avoid combination or monitor kidney function closely
Amiodarone	Possible additive pulmonary toxicity with high-dose cyclophosphamide (i.e. doses used prior to stem cell transplant; 60 mg/kg daily or 120 to 270 mg/kg over a few days)	Avoid combination or monitor closely for pulmonary toxicity
Allopurinol, hydrochlorothiazide, indapamide	Delayed effect. Increased risk of bone marrow depression; probably due to reduced clearance of active metabolites of cyclophosphamide	Avoid combination, consider alternative antihypertensive therapy or monitor for myelosuppression
Ciclosporin	Reduced efficacy of ciclosporin due to reduced serum concentration	Monitor ciclosporin levels; adjust dosage as appropriate; monitor response to ciclosporin
Suxamethonium	Prolonged apnoea due to marked and persistent inhibition of cholinesterase by cyclophosphamide	Alert the anaesthetist if a patient has been treated with cyclophosphamide within ten days of planned general anaesthesia

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

Rituximab		
	Interaction	**Clinical management**
Antihypertensives	Additive hypotensive effect	Consider withholding antihypertensive medications 12 hours prior to the rituximab infusion

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 cycle 1

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

Handling of monoclonal antibodies and waste management

Safe administration

General patient assessment prior to each day of treatment.

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

Prime IV line(s).

Insert IV cannula or access TIVAD or CVAD.

- baseline weight
- baseline urinalysis

Note: Rituximab is given on day 0 of cycle 1 and then on day 1 of cycles 2 to 6.

Treatment - Time out

Rituximab

Prior to administration:

- check baseline observations
- check for previous adverse events during previous infusions
- verify premedication has been taken. If not, administer 30 to 60 minutes prior to rituximab administration:
  - paracetamol 1000 mg orally AND
  - loratadine 10 mg orally (or similar antihistamine)
  - a steroid may also be included as a premed according to local guidelines

Initial infusion:

- **commence rituximab** infusion at 50 mg/hr for 30 minutes
- repeat observations prior to each rate increase
- **increase rate** by 50 mg/hr every 30 minutes, up to a maximum of 400 mg/hr if observations are stable
- flush with ~ 50 mL of sodium chloride 0.9%

If an infusion reaction occurs, temporarily discontinue the infusion and notify medical officer

- when symptoms have completely resolved, recommence the infusion at half the rate prior to the reaction
- for severe reactions **stop** infusion and manage as per emergency

Transient hypotension may occur. Consider withholding antihypertensive medication for 12 hours before and during infusion.

Subsequent infusions:

If an adverse event was experienced with initial infusion recommence infusion at the same rate as initial infusion

- **commence** rituximab infusion at 100 mg/hr
- repeat observations prior to each rate increase
- increase rate by 100 mg/hr increments every 30 minutes to a maximum of 400 mg/hr if observations are stable
- flush with ~ 50 mL of sodium chloride 0.9%

If an infusion reaction occurs, temporarily discontinue the infusion and notify medical officer

- when symptoms have resolved, recommence the infusion at **half the rate** prior to the reaction
- for severe reactions **stop** infusion and manage as per emergency

Read more about rapid infusion rituximab

Days 1 to 3

Safe handling and waste management

Safe administration

General patient assessment prior to each day of treatment.

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

Prime IV line(s).

Pre treatment medication

Verify antiemetics taken or administer as prescribed.

Chemotherapy - Time out

Fludarabine

Administer fludarabine:

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

Cyclophosphamide

Administer cyclophosphamide:

- via IV infusion over 30 to 60 minutes
- flush with ~ 50 mL of sodium chloride 0.9%
- rapid infusion can cause dizziness, rhinitis, nausea and perioral numbness. If symptoms develop, slow infusion rate.

Remove IV cannula and/or deaccess TIVAD or 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.

Administration cycles 2 to 6

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 1

Approximate treatment time: 4 to 6 hours (initial); 3 to 4 hours (subsequent)

Safe handling and waste management

Safe administration

General patient assessment prior to each day of treatment.

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

Prime IV line(s).

Insert IV cannula or access TIVAD or CVAD.

- baseline weight
- baseline urinalysis

Pre treatment medication

Treatment - Time out

Rituximab

Prior to administration:

- check baseline observations
- check for previous adverse events during previous infusions
- verify premedication has been taken. If not, administer 30 to 60 minutes prior to rituximab administration:
  - paracetamol 1000 mg orally AND
  - loratadine 10 mg orally (or similar antihistamine)
  - a steroid may also be included as a premed according to local guidelines

Initial infusion:

- **commence rituximab** infusion at 50 mg/hr for 30 minutes
- repeat observations prior to each rate increase
- **increase rate** by 50 mg/hr every 30 minutes, up to a maximum of 400 mg/hr if observations are stable
- flush with ~ 50 mL of sodium chloride 0.9%

If an infusion reaction occurs, temporarily discontinue the infusion and notify medical officer

- when symptoms have completely resolved, recommence the infusion at half the rate prior to the reaction
- for severe reactions **stop** infusion and manage as per emergency

Transient hypotension may occur. Consider withholding antihypertensive medication for 12 hours before and during infusion.

Subsequent infusions:

If an adverse event was experienced with initial infusion recommence infusion at the same rate as initial infusion

- **commence** rituximab infusion at 100 mg/hr
- repeat observations prior to each rate increase
- increase rate by 100 mg/hr increments every 30 minutes to a maximum of 400 mg/hr if observations are stable
- flush with ~ 50 mL of sodium chloride 0.9%

If an infusion reaction occurs, temporarily discontinue the infusion and notify medical officer

- when symptoms have resolved, recommence the infusion at **half the rate** prior to the reaction
- for severe reactions **stop** infusion and manage as per emergency

Read more about rapid infusion rituximab

Verify antiemetics taken or administer as prescribed.

Chemotherapy - Time out

Fludarabine

Administer fludarabine:

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

Cyclophosphamide

Administer cyclophosphamide:

- via IV infusion over 30 to 60 minutes
- flush with ~ 50 mL of sodium chloride 0.9%
- rapid infusion can cause dizziness, rhinitis, nausea and perioral numbness. If symptoms develop, slow infusion rate.

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

Days 2 and 3

Safe handling and waste management

Safe administration

General patient assessment prior to each day of treatment.

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

Prime IV line(s).

Pre treatment medication

Verify antiemetics taken or administer as prescribed.

Chemotherapy - Time out

Fludarabine

Administer fludarabine:

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

Cyclophosphamide

Administer cyclophosphamide:

- via IV infusion over 30 to 60 minutes
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- rapid infusion can cause dizziness, rhinitis, nausea and perioral numbness. If symptoms develop, slow infusion rate.

Remove IV cannula and/or deaccess TIVAD or 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)	
Flu-like symptoms	
Hypersensitivity reaction	Anaphylaxis and infusion related reactions can occur with this treatment. Read more about hypersensitivity reaction
Nausea and vomiting	Read more about prevention of treatment induced nausea and vomiting

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
Constipation	
Diarrhoea	Read more about treatment induced diarrhoea
Fatigue	Read more about fatigue
Haemorrhagic cystitis	An inflammatory process, characterised by diffuse bladder mucosal inflammation resulting in haemorrhage. Patients are at risk following blood and marrow transplant (BMT) or treatment with cyclophosphamide, ifosfamide and/or radiation therapy. Read more about haemorrhagic cystitis
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
Peripheral neuropathy	Typically symmetrical sensory neuropathy, affecting the fingers and toes, sometimes progressing to the hands and feet. It is associated with several classes of anti-cancer drugs. These include taxanes, platinum-based compounds, vinca alkaloids and some drugs used to treat multiple myeloma. Read more about peripheral neuropathy

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
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.
Progressive multifocal leukoencephalopathy (PML)	A rare opportunistic viral infection of the brain, usually leading to death or severe disability, can occur with monoclonal antibodies (e.g. rituximab, obinutuzumab, ofatumumab, brentuximab vedotin) and other targeted therapies (e.g. ibrutinib, ruxolitinib, idelalisib). Onset may occur up to months after the final dose. Read more about progressive multifocal leukoencephalopathy (PML)

Delayed (onset months to years)	
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

The chemoimmunotherapy combination of fludarabine, cyclophosphamide and rituximab (FCR) is recommended for young, or fit elderly patients with previously untreated chronic lymphocytic leukaemia (CLL).

The German CLL study group (GCLLSG) CLL8 study, a phase III randomised controlled trial compared the combination of rituximab, fludarabine and cyclophosphamide (FCR, n=408 patients) to fludarabine and cyclophosphamide (FC) alone (n=409), and demonstrated superior response rates (Table 1), progression-free survival (PFS) and overall survival (OS) for patients who received FCR.[1] The overall response rate (ORR) was 90% (FCR) compared to 80% (FC, p<0.0001) including a complete response rate (CR) of 44% (FCR) vs. 22% (FC, p<0.0001). The hazard ratios for PFS and OS were 0.56 [95%CI: 0.46 – 0.69] and 0·67 [0·48–0·92], respectively.

The MD Anderson group updated their outcomes with the FCR regimen.[2] The 6-year median OS of 77% and failure-free survival of 51% suggest that a significant proportion of patients may achieve long-lasting remissions with this chemoimmunotherapy regimen. Both studies demonstrated that patients with 17p deletions were less likely to achieve long-lasting responses following either FC or FCR.

Table 1: Response rates - FC alone vs. FCR [1]

	FC		FCR	
	CR	ORR	CR	ORR
All Patients	22	80	44	90
Less than 65 years	20	79	45	89
Greater than or equal to 65 years	24	83	43	93
FISH Result				
13q deletion	23	80	48	96
11q deletion	15	87	51	93
Trisomy 12	19	84	71	100
17p deletion	0	34	5	68
No abnormality	28	91	35	89

The GCLLSG CLL10 study confirmed the superiority of FCR over bendamustine-rituximab as first-line therapy in fit patients, with a higher CR rate (40% vs. 31%) and improved median PFS (55 vs. 42 months), but no difference in OS.[3] However, in the subgroup analysis of age > 65, the difference in PFS was not evident.

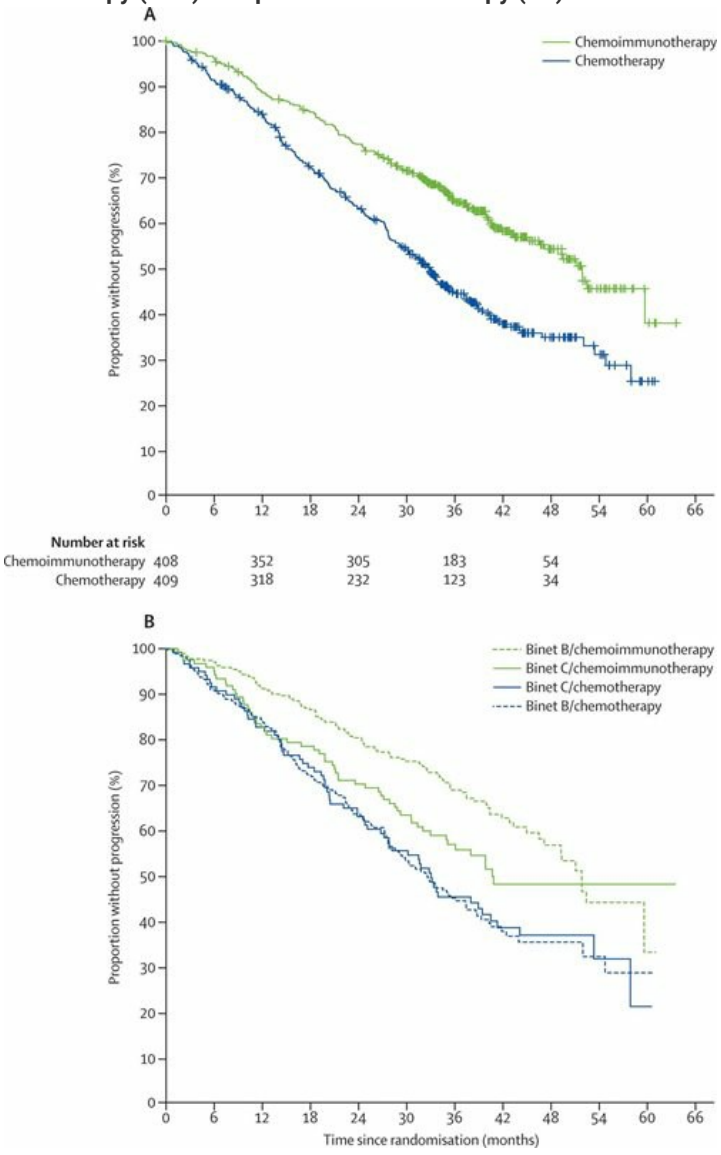
The ECOG-ACRIN E1912 study compared 6 cycles of ibrutinib and rituximab followed by ongoing ibrutinib until progression or toxicity with FCR. In this study, FCR demonstrated statistically inferior 3-year PFS (73% vs. 89%) and OS (92% vs. 99%), most marked in patients with unmutated IgHV.[4]

FCR may also be used in the relapsed CLL setting. The REACH study[5] demonstrated superior responses and PFS of FCR over FC in patients with CLL in first relapse who had received prior fludarabine or alkylator-based therapy. Patients who had received prior FC or rituximab were excluded. There was no statistical difference in OS between the two groups at a median follow-up time of 25 months.[5]

The MD Anderson group updated their experience with FCR in a phase II single-arm study of FCR for patients with relapsed CLL. This study demonstrated good responses (ORR 74% and CR 30% for all patients) and PFS (21 months) following administration of FCR in this population. CLL patients who had received more than 3 prior treatments were fludarabine-refractory, or patients with chromosome 17 abnormalities experienced suboptimal responses and short PFS.[6]

Efficacy

GCLLSG CLL8 study: Progression-free survival (A) and overall survival (B) in all patients with previously untreated chronic leukaemia receiving chemoimmunotherapy (FCR) compared to chemotherapy (FC)[1]



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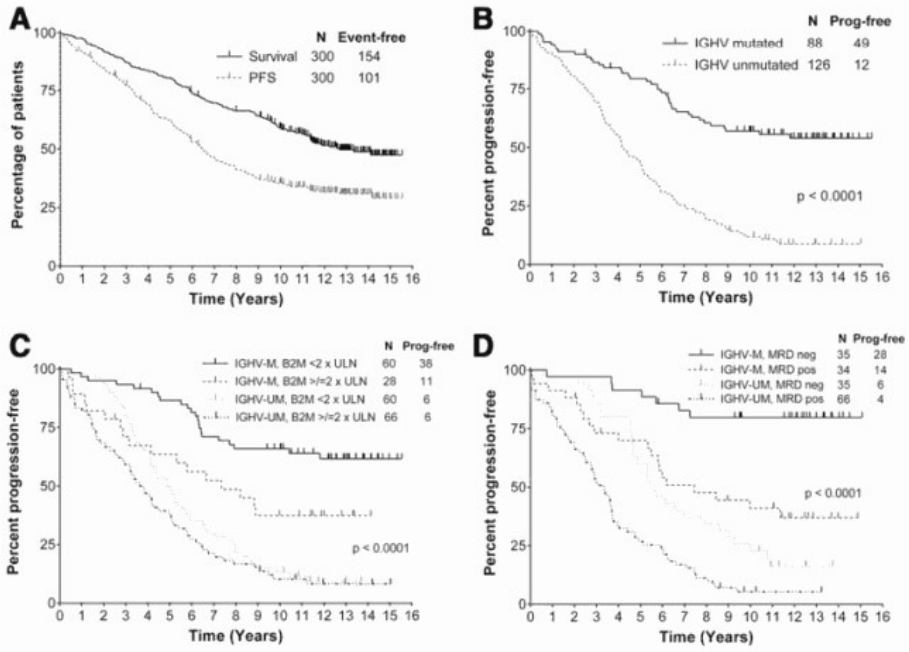
In a meta-analysis conducted by Nunes et al. comparing FC and FCR in patients with CLL, the PFS was 32.8 months in the FC group and 51.8 months in the FCR group. The difference between the two groups was statistically significant ($p<0.05$).[7]

The subgroup analysis conducted by Thompson et al. found long-term disease-free survival after FCR therapy in patients with the mutated immunoglobulin heavy chain variable (IGHV) gene (IGHV-M). The original patient cohort (n=300) who received FCR in the phase II study was reviewed to identify long-term disease-free survivors.[8]

Estimates of PFS and OS in the total cohort and PFS according to mutation status[8]

Figure 1. Estimates of PFS and overall survival in the total cohort and PFS according to mutation status, B2M, and posttreatment MRD. (A) PFS and survival in the total cohort. (B) PFS according to mutation status. (C) PFS according to mutation status and baseline B2M. (D) Six-month landmark PFS according to mutation status and achievement of post-treatment MRD-negativity.

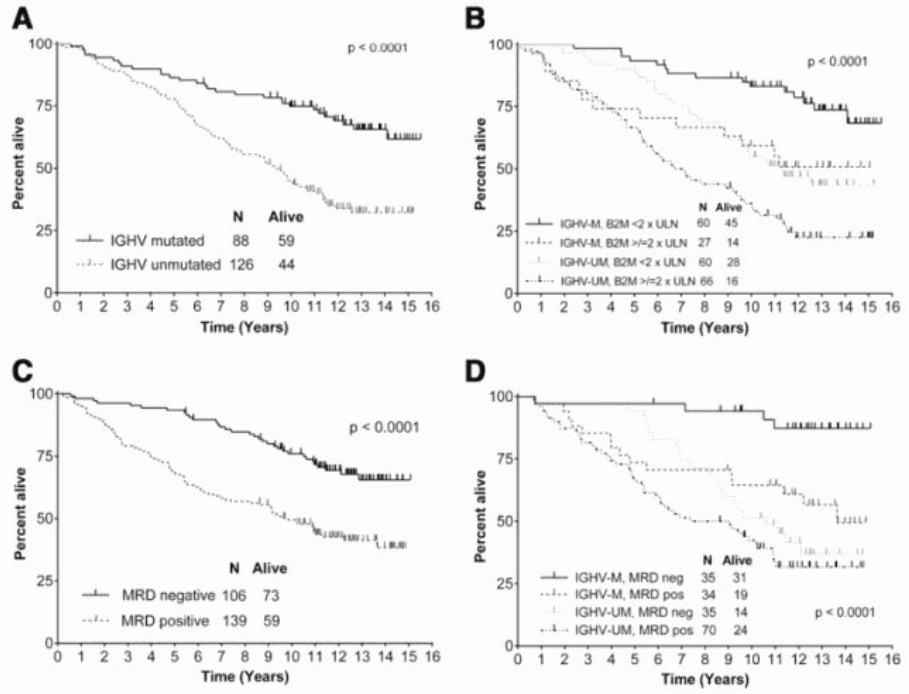


Median PFS was not reached (NR) for patients with IGHV-M and was 4.2 years for patients with IGHV-UM (p<0.001). PFS at 12.8 years was 53.9% for patients with IGHV-M vs. 8.7% for patients with unmutated IGHV (IGHV-UM). Furthermore, 50.7% of patients with IGHV-M who achieved MRD-negativity post-treatment had a PFS of 79.8% at 12.8 years. No relapses occurred beyond 10.4 years in 42 patients (total follow-up 105.4 patient-years) with IGHV-M, which resulted in a plateau on the PFS curve.[8]

Although IGHV-UM patients had inferior PFS compared to the IGHV-M patients, 9 of 126 patients with IGHV-UM remained in clinical remission beyond 10 years. The difference in PFS translated into a significant survival advantage for patients with IGHV-M. Patients who achieved MRD-negativity by PCR at completion of treatment had prolonged PFS of a median of 13.7 years compared to patients who remained MRD-positive with a median PFS of 4.0 years. Furthermore, patients with IGHV-M who were PCR negative at end-of-treatment had a 12.8-year PFS of 79.8% compared to a PFS of 36.9% if patients were MRD-positive.[8]

Estimates of OS according to pre-treatment mutation status and post-treatment MRD[8]

Figure 3. Estimates of overall survival according to pretreatment mutation status, B2M, and posttreatment MRD. (A) OS according to mutation status. (B) OS according to mutation status and baseline B2M. (C) Six-month landmark OS according to the achievement of posttreatment MRD-negativity. (D) Six-month landmark OS from end-of-therapy according to mutation status and the achievement of posttreatment MRD-negativity.



The median OS for the total cohort was 12.7 years. Survival was significantly inferior for patients with IGHV-UM compared with IGHV-M (median, 9.4 years vs NR and 12.8-years, 32.2% vs 65.5%; p<0.001). Additionally, B2-microglobulin (B2M) ≥4.0 was

predictive of inferior survival regardless of whether patients had IGHV mutation or not (IGHV-UM p=0.002 and IGHV-M p=0.011).[8]

MRD-negativity was associated with superior long-term survival in patients with IGHV-M only. A survival of 87.2% for MRD-negative patients and 56.5% for MRD-positive patients was observed at 12.8 years. MRD status did not affect IGHV-UM patients according to MRD status (p=0.146).[8]

Toxicity

In the German CLL8 study, 76% of patients experienced at least one grade 3 or 4 adverse event following chemoimmunotherapy with FCR (table 2). The majority of these events were haematological toxicity (56%), with neutropenia (34%) being most common. Chemoimmunotherapy with FCR was associated with a higher rate of grade 3 or 4 neutropenia compared to FC (34% vs. 21%, respectively, p<0.0001); however, the rates of severe infections were similar (25% vs. 21%, p=0.18).

In the GCLLSG CLL10 study, FCR was more toxic than bendamustine-rituximab with increased neutropenia (84% vs. 59%) and severe infections (39% vs. 25%).[3] In the ECOG-ACRIN E1912 study, grade >3 infections were higher in the FCR arm (20%) than in the ibrutinib-rituximab arm.[4]

Similar rates of grade 3 or 4 complications were noted in the REACH study (Table 3).[5] Almost all patients experienced grade 3 or 4 neutropenia during the study, with a slightly higher incidence in the FCR arm (FCR 89% vs. FC 84%). Despite this, the overall incidence of infections (FC 51% and FCR 49%) and grade 3 or 4 infections (FC 19% and FCR 18%) did not differ between arms. Fatal adverse events occurred in 10% (FC) and 14% (FCR) of patients, mostly related to serious infections. In the phase II MD Anderson study for relapsed CLL, patients older than 70 years with relapsed CLL were less likely to complete therapy and had a higher incidence of serious infections and myelosuppression.[6]

This regimen should be used with caution in elderly patients and patients with co-morbidities, including reduced creatinine clearance. Landmark clinical trials demonstrating efficacy and survival for the FCR regimen excluded patients with CrCl <70 mL/min.[1, 3] Other clinical trials have included patients with creatinine clearance as low as 40 mL/min without dose modification.[4] There is no clear data on efficacy and toxicity when modifying dose due to renal dysfunction.

Grade 3 or 4 toxicity of FCR as initial therapy for chronic lymphocytic leukaemia[1]

	Chemotherapy (n=396)	Chemoimmunotherapy (n=404)	p value	<65 years (n=560)	≥65 years (n=240)	p value
Total number of patients with at least one grade 3 or 4 event	249 (63%)	309 (76%)	<0·0001	375 (67%)	183 (76%)	0·009
Haematological toxicity	157 (40%)	225 (56%)	<0·0001	254 (45%)	128 (53%)	0·04
Neutropenia	83 (21%)	136 (34%)	<0·0001	146 (26%)	73 (30%)	0·21
Leucocytopenia	48 (12%)	97 (24%)	<0·0001	106 (19%)	39 (16%)	0·37
Thrombocytopenia	44 (11%)	30 (7%)	0·07	50 (9%)	24 (10%)	0·63
Anaemia	27 (7%)	22 (5%)	0·42	35 (6%)	14 (6%)	0·82
Autoimmune haemolytic anaemia	4 (1%)	3 (<1%)	0·69	4 (<1%)	3 (1%)	0·46
Tumour lysis syndrome	2 (<1%)	1 (<1%)	0·55	3 (<1%)	0	0·26
Cytokine release syndrome	0	1 (<1%)	0·32	1 (<1%)	0	0·51
Infections, total	85 (21%)	103 (25%)	0·18	127 (23%)	61 (25%)	0·4
Infections, not specified	68 (17%)	83 (21%)	0·19	104 (19%)	46 (19%)	0·84
Bacterial infection	5 (1%)	11 (3%)	0·14	6 (1%)	10 (4%)	0·004
Viral infection	17 (4%)	17 (4%)	0·95	26 (5%)	8 (3%)	0·4
Fungal infection	1 (<1%)	3 (<1%)	0·33	3 (<1%)	1 (<1%)	0·83
Parasitic infection	0	1 (<1%)	0·32	0	1 (<1%)	0·13

Data are number (%), unless otherwise indicated. Chemotherapy=fludarabine and cyclophosphamide. Chemoimmunotherapy=fludarabine, cyclophosphamide, and rituximab.

Toxicity of FCR as first salvage therapy of relapsed chronic lymphocytic leukaemia[5]

Table 2. Overview of AEs

AE	FC (n = 272) No. of Patients	%	R-FC (n = 274) No. of Patients	%
Any AE	260	96	270	99
Grade 3 or 4 AEs	200	74	219	80
Serious AEs	130	48	137	50
Fatal AEs	26	10	36	14
AE leading to discontinuation	69	25	72	26
AE leading to dose modification/interruption	105	39	141	51
Treatment-related deaths	14	5	19	7
All deaths	68	25	62	23
Grade 3 or 4 hematologic toxicity during treatment (laboratory data)				
Hemoglobin	52	19	53	19
Platelets	71	26	74	27
Neutrophils	229	84	245	89
Most common nonhematologic AEs (≥ 10% of patients, all grades)				
Nausea	96	35	110	40
Vomiting	51	19	58	21
Pyrexia	42	15	69	25
Fatigue	45	17	45	16
Asthenia	30	11	28	10
Chills	6	2	45	15
Constipation	30	11	40	15
Diarrhea	32	12	33	12
Cough	24	9	34	12
Headache	30	11	25	9
Most common grade 3 or 4 AEs (≥ 5% of patients)				
Neutropenia	108	40	116	42
Febrile neutropenia	32	12	33	12
Anemia	35	13	33	12
Thrombocytopenia	24	9	29	11
Granulocytopenia	12	4	18	7
Pancytopenia	13	5	9	3
Pneumonia	17	6	15	5
Other grade 3/4 AEs with a ≥ 2% difference in incidence between arms				
Hepatitis B	—	—	5	1.8
Possible infusion-related AEs				
AEs on day 1 or 2 of any treatment cycle	131	48	176	64
Grade 3 or 4 AEs on day 1 or 2 of cycle 1	11	4	17	6
Grade 3 or 4 AEs during rituximab infusion	—	—	18 (7)	

Abbreviations: AE, adverse event; FC, fludarabine and cyclophosphamide; R-FC, rituximab plus fludarabine and cyclophosphamide.

In a more recent study conducted by Benjamini et al., the risk of second cancers was found to be 2.38 times higher than the expected risk in the general population (40% had other cancers before and 28% after FCR). Second cancer risk after frontline FCR is mainly due to high rates of acute myeloid leukaemia / myelodysplastic syndrome (t-AML/MDS) (5.1%) and Richter transformation (RT) (9%), whilst solid tumours were not increased. The survival of affected patients is shorter.[9]

Oral FCR

Early studies incorporating single agent fludarabine confirmed similar pharmacokinetic data for IV fludarabine 25mg and oral fludarabine 40mg. Retrospective reviews of studies in fludarabine and cyclophosphamide demonstrate comparable efficacy, but increased gastrointestinal toxicity when substituting with oral fludarabine.[10] With this data, oral FCR has been incorporated into clinical trials, although there are no head-to-head trials of IV and oral FCR. The ARCTIC and ADMIRE studies used the regimen of fludarabine 24 mg/m^2 daily and cyclophosphamide 150 mg/m^2 daily for 5 days with similar outcomes to historical IV FCR.[11, 12] The CLL2007 SA study[13] used oral fludarabine 40 mg/m^2 and cyclophosphamide 250 mg/m^2 for 3 days and the ICORG 07-01 study[14] allowed IV or oral formulations, however cycle numbers were limited to 4, and direct comparisons cannot be made. Oral fludarabine and cyclophosphamide utilising modified dosing may be considered.

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History

Version 8

Date	Summary of changes
05/06/2023	Subcutaneous rituximab information removed from the following sections – treatment schedule, clinical information, administration, patient information. Increased to version 8.
25/07/2023	Neurotoxicity added to "Late" category of Side effects section.

Version 7

Date	Summary of changes
27/03/2020	Protocol reviewed at Haematology Reference Committee meeting with the following changes: • Note regarding fludarabine and cyclophosphamide oral dosing added. • Dose modifications updated.

Date	Summary of changes
	• Evidence updated. • Review in 2 years.
01/10/2021	Drug status updated: rituximab SC is TGA registered but no longer PBS listed.
24/01/2022	Pulmonary toxicity added to side effects.
11/03/2022	Reviewed at Haematology Reference Committee meeting; no significant changes, Review in 4 years.

Version 6

Date	Summary of changes
09/03/2020	Biosimilar rituximab added to clinical information. Version number changed to v.6

Version 5

Date	Summary of changes
30/11/2009	Reviewed and transferred to eviQ.
13/07/2010	Amendment of rituximab dosing to reflect current evidence and TGA licensing for use in CLL ie 375 mg/m^2 day 1 cycle 1, then 500 mg/m^2 day 1 cycle 2 to 6.
08/04/2012	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.
13/04/2012	Addition of information on PML associated with rituximab (preclinical information and side effect). Update of rituximab PBS authority status.
10/05/2013	Reviewed at Haematology Reference Committee Meeting - changes made and republished.
11/09/2015	Reviewed at Haematology Reference Committee Meeting: • Treatment schedule updated - rituximab cycle one changed administration day to day 0 as per Hallek and Robak et al. papers. Number of cycles updated to 'Cycles: 6. Depending on response and toxicity less cycles may be given.' • Drug status section updated. • Clinical information- emetogenicity block updated • Evidence section updated to include two new references: Nunes et al. 2015 and Benjamini et al. 2015.
04/07/2016	Removed rapid infusion link for rituximab as there is limited evidence for 500 mg/m^2.
31/05/2017	Transferred to new eviQ website. Version number change to v.4.
13/03/2018	**Added:** • Link to subcutaneous rituximab document underneath the treatment schedule. • Clinical information block on subcutaneous rituximab. • Link to the subcutaneous rituximab document into administration section. • Injection-site reaction side effect. • Note about subcutaneous rituximab added to the patient information. • Version number changed to v.5.
25/07/2018	Reviewed by Haematology Reference Committee with updates to: • Antiemetic: dexamethasone updated to be in line with international guidelines. • Evidence updated. • Review in 5 years.
10/10/2019	Clinical information updated with PBS expanded indications for G-CSF.

First approved: 22 March 2006
Last reviewed: 11 March 2022
Review due: 30 June 2026

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/496
31 Aug 2023

Patient information - Chronic lymphocytic leukaemia (CLL) - FCR (fludarabine, cyclophosphamide, rituximab)

Patient's name:

Your treatment

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

FCR (fludarabine, cyclophosphamide, rituximab)

This treatment cycle is repeated every 28 days. You will have up to 6 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	**Rituximab** (*ri-TUX-i-mab*) - (For Cycle 1 only, this is given a day before chemotherapy)	By a drip into a vein	**1st cycle:** About 4 to 6 hours **Cycles thereafter:** About 3 to 4 hours
	Fludarabine (*Flu-dara-been*)	By a drip into a vein	About 30 minutes
	Cyclophosphamide (*SYE-kloe-FOS-fa-mide*)	By a drip into a vein	About 1 hour
2 and 3	**Fludarabine**	By a drip into a vein	About 30 minutes
	Cyclophosphamide	By a drip into a vein	About 1 hour

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

Anti-cancer drugs can reduce the number of blood cells in your body. You will need to have regular blood tests to check that your blood cell count has returned to normal. If your blood count is low, your treatment may be delayed until it has returned to normal. Your doctor or nurse will tell you when to have these blood tests.

Central venous access devices (CVADs)

This treatment may involve 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.

Medications for blood pressure

Rituximab may lower your blood pressure. Tell your doctor if you are taking any blood pressure medications. Your doctor may advise you to temporarily stop your blood pressure medications before your rituximab infusions.

Treatment with cyclophosphamide

You should drink at least 8 to 10 glasses of fluid (unless you are fluid restricted) for 2 days after treatment with cyclophosphamide. You should also empty your bladder often.

Other medications given during this treatment

- **Rituximab premedication:** before your treatment with rituximab you will need to take some tablets called a premedication to help prevent you from having a reaction to the rituximab.
- **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)	
Flu-like symptoms	• You may get: ◦ a fever ◦ chills or sweats ◦ muscle and joint pain ◦ a cough ◦ headaches. • Tell your doctor or nurse if you get any of the symptoms listed above. • **Tell your doctor or nurse immediately, or go to the nearest hospital Emergency Department if you have a temperature of 38°C or higher.**
Allergic reaction	• Allergic reactions are uncommon but can be life threatening. • **If you feel unwell during the infusion or shortly after it, or:** ◦ **get a fever, shivers or shakes** ◦ **feel dizzy, faint, confused or anxious** ◦ **start wheezing or have difficulty breathing** ◦ **have a rash, itch or redness of the face** **<u>While you are in hospital:</u> Tell your doctor or nurse immediately.** **<u>After you leave:</u> Contact your doctor or nurse immediately, or go to the nearest hospital Emergency Department.**
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.**

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.**
Constipation	• You may have bowel motions (stools, poo) that are less frequent, harder, smaller, painful or difficult to pass. • You may also get: ◦ bloating, cramping or pain ◦ a loss of appetite ◦ nausea or vomiting. • Drink plenty of fluids (unless you are fluid restricted). • Eat plenty of fibre-containing foods such as fruit, vegetables and bran. • Take laxatives as directed by your doctor. • Try some gentle exercise daily. • **Tell your doctor or nurse if you have not opened your bowels for more than 3 days.**
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.**
Bladder irritation (haemorrhagic cystitis)	• You may get: ◦ blood in your urine, sometimes with blood clots ◦ pain or burning when you urinate ◦ the urge to urinate more than normal ◦ stomach or pelvic pain or discomfort. • When you go home, make sure you drink plenty of fluids (unless you are fluid restricted). • Empty your bladder often. • **Tell your doctor or nurse as soon as possible if you notice any blood in your urine.**

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.**
Nerve damage (peripheral neuropathy)	• You may notice a change in the sensations in your hands and feet, including: ◦ tingling or pins and needles ◦ numbness or loss of feeling ◦ pain. • You may find it difficult to do everyday activities, such as doing up buttons or picking up small objects. • Test water temperature with your elbow when bathing to avoid burns. • Use rubber gloves, pot holders and oven mitts in the kitchen. • Wear rubber shoes or boots when working in the garden or garage. • Keep rooms well lit and uncluttered. • Ask your doctor or nurse for eviQ patient information – Nerve problems during cancer treatment. • 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
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.**
Changes in the way your brain works [progressive multifocal leukoencephalopathy (PML)]	• This treatment can affect your central nervous system. This can be very serious. • **Tell your doctor or nurse immediately, or go to the nearest hospital Emergency Department if you get any of the following symptoms:** ◦ **trouble with your speech or vision** ◦ **confusion or memory loss** ◦ **changes in your personality** ◦ **weakness in your arms and legs** ◦ **poor balance or coordination** ◦ **fits (seizures).**

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

General advice for people having cancer treatment

Chemotherapy safety

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

Blood clot risk

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

Medications and vaccinations

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

Other medical and dental treatment

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

Diet and food safety

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

Fertility

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

Pregnancy and breastfeeding

- 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.

Risk of developing a second cancer

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

Quitting smoking

- It is never too late to quit smoking. Quitting smoking is one of the best things you can do to help your treatment work better.

- There are many effective tools to improve your chances of quitting.
- Talk to your treating team for more information and referral to a smoking cessation support service.

Staying active

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

For more information about cancer treatment, side effects and side effect management see our Patient and carers section.

Where to get more information

Telephone support

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

Haematology, transplant and cellular therapy information

- Arrow bone marrow transplant foundation – arrow.org.au
- 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

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