Acute lymphoblastic leukaemia CALGB course I induction (for patients >= 60 years) SUPERSEDED

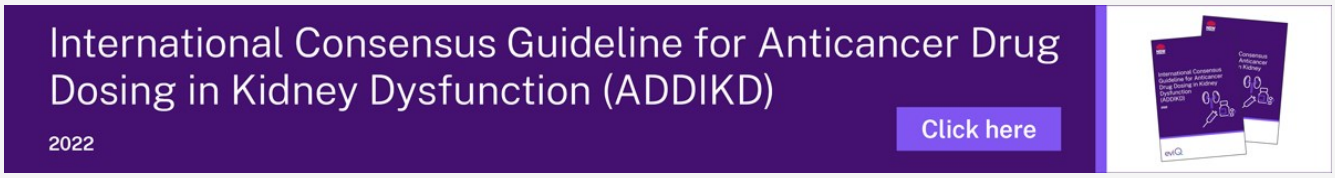
ID: 790 v.5 **Superseded** Essential Medicine List

The Haematology Reference Committee decided to supersede this protocol at the 2022 meeting as superior alternatives are available.

⚠ Asparaginase drug supply:
Native E-coli asparaginase (colaspase) ceased being manufactured in 2019. The Haematology Reference Committee recommends using protocols with evidence for the use of pegaspargase (from clinical trials) rather than substituting pegaspargase into native E-coli asparaginase containing protocols.

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- Acute lymphoblastic leukaemia CALGB overview SUPERSEDED
- Acute lymphoblastic leukaemia CALGB course I induction (less than 60 years of age) SUPERSEDED
- Management of asparaginase therapy

- Overall CALGB treatment schema

Treatment schedule - Overview

Drug	Dose	Route	Day
Prednisolone	60 mg/m^2 ONCE a day	PO	1 to 7 then taper and cease
DAUNOrubicin	30 mg/m^2	IV	1 to 3
vinCRISTine	2 mg	IV infusion	1, 8, 15, 22
CYCLOPHOSPHamide	800 mg/m^2	IV infusion	1
Filgrastim	5 micrograms/kg	Subcut	4 and continue daily until ANC > 1.0 x10^9/L
Asparaginase (colaspase) *	6,000 International Units/m^2	Subcut	5, 8, 11, 15, 18, 22

* The manufacturers of Leunase® brand of asparaginase (colaspase) have confirmed that one Kyowa Unit (KU) is equivalent to one International Unit (IU). Alternative formulations and routes of administration may be used depending on local institution policies. Link to asparaginase document for equivalent dosing.

- Administer asparaginase after prednisolone on the days that both drugs are administered to reduce toxicity from asparaginase.
- Administer asparaginase after vincristine on the days that both drugs are administered to reduce vincristine toxicity.

Duration: 28 days

Cycles: 1
Course I is administered once only.

Drug status: **Daunorubicin and asparaginase (colaspase)** is TGA registered but not PBS listed

All other drugs in this protocol are on the PBS general schedule

Filgrastim is PBS authority

Prednisolone is available as **25 mg**, **5 mg** and **1 mg** tablets

Treatment schedule - Detail

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

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

Day 1		
Prednisolone	60 mg/m^2 (PO)	ONCE a day on days 1 to 7 then taper and cease. Take in the morning with food.
DAUNOrubicin	30 mg/m^2 (IV)	over 5 to 15 minutes
vinCRISTine	2 mg (IV infusion)	in 50 mL sodium chloride 0.9% over 5 to 10 minutes via minibag
CYCLOPHOSPHamide	800 mg/m^2 (IV infusion)	in 500 mL sodium chloride 0.9% over 30 to 60 minutes

Day 2 and 3		
Prednisolone	60 mg/m^2 (PO)	ONCE a day on days 1 to 7 then taper and cease. Take in the morning with food.
DAUNOrubicin	30 mg/m^2 (IV)	over 5 to 15 minutes

Day 4		
Prednisolone	60 mg/m^2 (PO)	ONCE a day on days 1 to 7 then taper and cease. Take in the morning with food.
Filgrastim	5 micrograms/kg (Subcut)	via subcutaneous injection. Commence day 4 and continue daily until ANC >1.0 x10^9.

Day 5		
Prednisolone	60 mg/m^2 (PO)	ONCE a day on days 1 to 7 then taper and cease. Take in the morning with food.
Asparaginase (colaspase)	6,000 International Units/m^2 (Subcut)	via subcutaneous injection. Administer asparaginase after prednisolone on the days that both drugs are administered. Administer asparaginase after vincristine on the days that both drugs are administered. *

Day 6 and 7		
Prednisolone	60 mg/m^2 (PO)	ONCE a day on days 1 to 7 then taper and cease. Take in the morning with food.

Day 8		

Day 8		
vinCRISTine	2 mg (IV infusion)	in 50 mL sodium chloride 0.9% over 5 to 10 minutes via minibag
Asparaginase (colaspase)	6,000 International Units/m^2 (Subcut)	via subcutaneous injection. Administer asparaginase after prednisolone on the days that both drugs are administered. Administer asparaginase after vincristine on the days that both drugs are administered. *

Day 11		
Asparaginase (colaspase)	6,000 International Units/m^2 (Subcut)	via subcutaneous injection. Administer asparaginase after prednisolone on the days that both drugs are administered. Administer asparaginase after vincristine on the days that both drugs are administered. *

Day 15		
vinCRISTine	2 mg (IV infusion)	in 50 mL sodium chloride 0.9% over 5 to 10 minutes via minibag
Asparaginase (colaspase)	6,000 International Units/m^2 (Subcut)	via subcutaneous injection. Administer asparaginase after prednisolone on the days that both drugs are administered. Administer asparaginase after vincristine on the days that both drugs are administered. *

Day 18		
Asparaginase (colaspase)	6,000 International Units/m^2 (Subcut)	via subcutaneous injection. Administer asparaginase after prednisolone on the days that both drugs are administered. Administer asparaginase after vincristine on the days that both drugs are administered. *

Day 22		
vinCRISTine	2 mg (IV infusion)	in 50 mL sodium chloride 0.9% over 5 to 10 minutes via minibag
Asparaginase (colaspase)	6,000 International Units/m^2 (Subcut)	via subcutaneous injection. Administer asparaginase after prednisolone on the days that both drugs are administered. Administer asparaginase after vincristine on the days that both drugs are administered. *

* The manufacturers of Leunase® brand of asparaginase (colaspase) have confirmed that one Kyowa Unit (KU) is equivalent to one International Unit (IU). Alternative formulations and routes of administration may be used depending on local institution policies. Link to asparaginase document for equivalent dosing.

Duration: 28 days

Cycles: 1
Course I is administered once only.

Indications and patient population

- Acute lymphoblastic leukaemia in older adult patients
  - Induction protocol for patients 60 years of age and older

Clinical information

Safety alert vincristine administration	For safe administration of vincristine refer to the safety alert issued by the Australian Commission on Safety and Quality in Health Care
Venous access	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 asparaginase. Acute anaphylactoid reactions are the most common dose-limiting toxicity, particularly with IV administration. Patients that develop hypersensitivity to the E. coli derived formulation may be able to switch to Erwinia asparaginase. The Leunase brand of asparaginase (colaspase) is the only formulation for which the manufacturer advises an intradermal test dose prior to the initial dose or when a week or more has elapsed between doses. A negative skin reaction does not preclude the development of an allergic reaction and therefore the practice of a test dose is controversial. Read more about Management of asparaginase therapy Read more about Hypersensitivity reaction
Antiemetics for multi-day protocols	Antiemetic therapy should be administered throughout the duration of the chemotherapy protocol and to cover delayed nausea. The acute and delayed emetic risk of multi-day chemotherapy protocols will overlap depending on the individual drugs and their sequence of administration. More or less antiemetic cover may be required. Ensure that patients also have sufficient antiemetics for breakthrough emesis: Metoclopramide 10 mg three times a day when necessary (maximum of 30 mg/24 hours, up to 5 days) OR Prochlorperazine 10 mg PO every 6 hours when necessary. Read more about preventing anti-cancer therapy induced nausea and vomiting
Cumulative lifetime dose of anthracyclines	Cumulative doses should take into account all previous anthracyclines received during a patient's lifetime (i.e. daunorubicin, doxorubicin, epirubicin, idarubicin and mitoxantrone). Criteria for reducing the total anthracycline cumulative lifetime dose include: • patient is elderly • prior mediastinal radiation • hypertensive cardiomegaly • concurrent therapy with high dose cyclophosphamide and some other cytotoxic drugs (e.g. bleomycin, dacarbazine, dactinomycin, etoposide, melphalan, mitomycin and vincristine). Baseline clinical assessments include echocardiogram (ECHO) or gated heart pool scan (GHPS) and electrocardiogram (ECG) evaluation. Patients with normal baseline cardiac function (left ventricular ejection fraction (LVEF) > 50%) and low risk patients require LVEF monitoring when greater than 70% of the anthracycline threshold is reached or if the patient displays symptoms of cardiac impairment. Post-treatment cardiac monitoring is recommended for patients who have received high levels of total cumulative doses of anthracyclines at the clinician's discretion. Read more about cardiac toxicity associated with anthracyclines
Asparaginase	Asparaginase is associated with numerous toxicities including hypersensitivity, hepatotoxicity, coagulation abnormalities, pancreatitis, hyperlipidaemia, hyperglycaemia and CNS effects. Therefore routine monitoring and assessment of several parameters are required throughout treatment. There are several different formulations of asparaginase available, each with different dosing and administration recommendations. For comprehensive information on formulations, dosing, interactions, adverse reactions and specific monitoring parameters for asparaginase, see Management of asparaginase therapy document.
Pancreatitis	Pancreatitis can occur despite normal serum amylase, and can be fatal. In cases of clinical pancreatitis (unequivocal diagnosis based on lipase/amylase elevation, ultrasound and clinical findings) asparaginase treatment should be ceased and must not be resumed. Mild asymptomatic biochemical pancreatitis does not warrant discontinuing asparaginase therapy.

Peripheral neuropathy	Assess prior to each treatment. Based on clinical findings, temporary omission, dose reduction or cessation of the vinca alkaloid may be indicated; review by medical officer before commencing treatment. Read more about peripheral neuropathy Link to chemotherapy-induced peripheral neuropathy screening tool
Constipation	Prescribe prophylactic laxatives to prevent constipation related to the use of vinca alkaloids.
Corticosteroids	Diabetic patients should monitor their blood glucose levels closely. To minimise gastric irritation, advise patient to take immediately after food. Consider the use of a H2 antagonist or proton pump inhibitor if appropriate. Read more about acute short term effects from corticosteroids
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	Antifungal prophylaxis is recommended e.g. AmBisome 50 mg IV ONCE daily three times weekly (e.g. on Mondays, Wednesdays and Fridays) or fluconazole 200 mg to 400 mg PO daily. **Note**: Extended spectrum azole antifungals (e.g. posaconazole, voriconazole and itraconazole) should be avoided with vinca alkaloids. Metabolism is inhibited by azoles and neurotoxicity can be potentiated. 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
Blood product support	The use of FFP and cryoprecipitate may be required to maintain fibrinogen levels to a normal range. Read more about Management of asparaginase therapy
Blood tests	FBC, EUC, LFTs, BSL, at baseline and prior to each treatment. Monitor pancreatic lipase and serum amylase, lipids and uric acid prior to and regularly during asparaginase therapy. Monitor fibrinogen levels, INR, APTT and PT at least once or twice weekly and consider monitoring antithrombin levels.
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).

Doses are rarely modified in acute lymphoblastic leukaemia chemotherapy protocols, except in instances of severe hepatic or renal impairment or toxicity. Consult with treating team and pharmacist.

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*

Asparaginase		
	Interaction	**Clinical management**
Methotrexate	Reduced efficacy of methotrexate if asparaginase is given immediately prior to or with methotrexate. Enhanced efficacy and reduced toxicity of methotrexate if asparaginase is given shortly after methotrexate	Administer asparaginase 9 to 10 days before or, preferably, shortly after methotrexate to enhance its efficacy and reduce its toxicity (unless otherwise scheduled per protocol)
Vincristine	Increased vincristine neurotoxicity if given after or concurrently with asparaginase	Administer vincristine 12 to 24 hours before asparaginase
Prednisolone	Increased risk of asparaginase toxicity (including decreased production of clotting factors and hyperglycaemia) if given after or concurrently with asparaginase	Administer prednisolone before asparaginase to avoid increased toxicity; monitor fibrinogen, ATIII and blood glucose levels

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
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

Daunorubicin		
	Interaction	**Clinical management**
Cardiotoxic drugs (eg. calcium channel blockers, propranolol)	Increased risk of daunorubicin-induced cardiotoxicity	Avoid combination or monitor closely for cardiotoxicity

Prednisolone		
	Interaction	**Clinical management**
Antidiabetic agents (e.g. insulin, glibenclamide, glicazide, metformin, pioglitazone, etc)	The efficacy of antidiabetic agents may be decreased	Use with caution and monitor blood glucose
Azole antifungals (e.g. fluconazole, itraconazole, ketoconazole, posaconazole)	Increased toxicity of prednisolone possible due to reduced clearance	Avoid combination or monitor for prednisolone toxicity
Oestrogens (e.g. oral contraceptives)	Increased toxicity of prednisolone possible due to reduced clearance	Avoid combination or monitor for prednisolone toxicity. Dose reduction of prednisolone may be required
Ritonavir	Increased toxicity of prednisolone possible due to reduced clearance	Avoid combination or monitor for prednisolone toxicity

Vincristine		
	Interaction	**Clinical management**
CYP3A4 and P-gp inhibitors (e.g. amiodarone, aprepitant, azole-antifungals, ritonavir, lapatinib, nilotinib, sorafenib, macrolides, ciclosporin, grapefruit juice etc.)	Increased toxicity of vincristine possible due to reduced clearance	Monitor for vincristine toxicity (esp. neurotoxicity, paralytic ileus)
CYP3A4 inducers (e.g. carbamazepine, phenytoin, phenobarbitone, rifampicin, St John's wort etc.)	Reduced efficacy of vincristine possible due to increased clearance	Monitor for decreased clinical response to vincristine
Mitomycin	Acute shortness of breath and severe bronchospasm has occurred following use of vincristine in patients who had received mitomycin simultaneously or within 2 weeks	Use combination with caution
Ototoxic drugs (e.g. cisplatin, aminoglycosides, frusemide, NSAIDs)	Additive ototoxicity	Avoid combination or perform regular audiometric testing

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 1

Safe handling and waste management

Safe administration

General patient assessment prior to each day of treatment.

Peripheral neuropathy assessment tool

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).

Access CVAD.

Note: A large volume of intravenous fluid may be given with this protocol. If weight increases by more than 1 kg from baseline or fluid balance becomes positive by one litre or any other signs of fluid overload are present, review by medical officer (diuretics may be required).

- baseline weight
- baseline urinalysis
- strict fluid balance input and output

Pre treatment medication

Verify antiemetics taken or administer as prescribed.

Prednisolone

- administer orally ONCE a day **days 1 to 7**
- to be taken in the morning with or immediately after food

Note: if a dose is forgotten or vomited, contact treating team.

Chemotherapy - Time out

Daunorubicin

Administer daunorubicin (vesicant)

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

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

Vincristine

Administer vincristine (vesicant)

- via a minibag over 5 to 10 minutes
- ensure vein is patent and monitor for signs of extravasation throughout administration
- flush with ~150 mL of sodium chloride 0.9%.

Prehydration

Administer 1000 mL sodium chloride 0.9% over 2 hours.

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 hydration as prescribed.

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 treatment.

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

Note: A large volume of intravenous fluid may be given with this protocol. If weight increases by more than 1 kg from baseline or fluid balance becomes positive by one litre or any other signs of fluid overload are present, review by medical officer (diuretics may be required).

- continue daily weight
- dip stick all urine for haematuria
- strict fluid balance input and output

Hydration if prescribed.

Pre treatment medication

Verify antiemetics taken or administer as prescribed.

Prednisolone

- administer orally ONCE a day **days 1 to 7**
- to be taken in the morning with or immediately after food

Note: if a dose is forgotten or vomited, contact treating team.

Chemotherapy - Time out

Daunorubicin

Administer daunorubicin (vesicant)

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

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

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

Day 4

General patient assessment prior to each day of treatment.

- daily weight

- daily urinalysis
- strict fluid balance input and output

Hydration if prescribed.

Prednisolone

- administer orally ONCE a day **days 1 to 7**
- to be taken in the morning with or immediately after food

Note: if a dose is forgotten or vomited, contact treating team.

Filgrastim

- inject subcutaneously ONCE daily, and until neutrophil recovery

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Day 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.

- daily weight
- daily urinalysis
- strict fluid balance input and output

Hydration if prescribed.

Pre treatment medication

Verify antiemetics taken or administer as prescribed.

Prednisolone

- administer orally ONCE a day **days 1 to 7**
- to be taken in the morning with or immediately after food

Note: if a dose is forgotten or vomited, contact treating team.

Note: asparaginase (colaspase) to be administered AFTER prednisolone.

Chemotherapy - Time out

Prior to administration

Test dose

- Administer asparaginase (colaspase) 1 to 10 KU (= 1 international unit) in 0.1 mL of water for injection by intradermal injection:
- Observe the injection site for at least 60 minutes for any evidence of hypersensitivity.

Note: Leunase® product information advises an intradermal test dose to be administered prior to initial dose or when a week or more has elapsed between doses. A negative skin reaction does not preclude the development of an allergic reaction and thus the practice of an intradermal test dose is controversial.

Read more on detailed dosing information regarding asparaginase (colaspase) and the formulations available.

Asparaginase (colaspase)

Administer asparaginase (colaspase)

- via subcutaneous injection.

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

Day 6 and 7

This is an oral treatment

General patient assessment prior to each day of treatment.

- daily weight
- daily urinalysis
- strict fluid balance input and output

Hydration if prescribed.

Prednisolone

- administer orally ONCE a day **days 1 to 7**
- to be taken in the morning with or immediately after food

Note: if a dose is forgotten or vomited, contact treating team.

Day 8

Safe handling and waste management

Safe administration

General patient assessment prior to each day of treatment.

Peripheral neuropathy assessment tool

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

- daily weight
- daily urinalysis
- strict fluid balance input and output

Hydration if prescribed.

Pre treatment medication

Verify antiemetics taken or administer as prescribed.

Note: Asparaginase (colaspase) should be administered AFTER vincristine as there may be increased neuropathy if asparaginase (colaspase) is given first.

Chemotherapy - Time out

Vincristine

Administer vincristine (vesicant)

- via a minibag over 5 to 10 minutes
- ensure vein is patent and monitor for signs of extravasation throughout administration
- flush with ~150 mL of sodium chloride 0.9%.

Asparaginase (colaspase)

Administer asparaginase (colaspase)

- via subcutaneous injection.

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

Day 11

Safe handling and waste management

Safe administration

General patient assessment prior to each treatment.

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

- daily weight
- daily urinalysis
- strict fluid balance input and output

Hydration if prescribed.

Pre treatment medication

Verify antiemetics taken or administer as prescribed.

Chemotherapy - Time out

Asparaginase (colaspase)

Administer asparaginase (colaspase)

- via subcutaneous injection.

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

Day 15

Safe handling and waste management

Safe administration

General patient assessment prior to each day of treatment.

Peripheral neuropathy assessment tool.

Any toxicity grade 1 or greater may require dose reduction or delay of treatment and review by medical officer before commencing treatment.

- daily weight
- daily urinalysis
- strict fluid balance input and output

Hydration if prescribed.

Pre treatment medication

Verify antiemetics taken or administer as prescribed.

Note: Asparaginase (colaspase) should be administered AFTER vincristine as there may be increased neuropathy if asparaginase (colaspase) is given first.

Chemotherapy - Time out

Vincristine

Administer vincristine (vesicant)

- via a minibag over 5 to 10 minutes
- ensure vein is patent and monitor for signs of extravasation throughout administration
- flush with ~150 mL of sodium chloride 0.9%.

Asparaginase (colaspase)

Administer asparaginase (colaspase)

- via subcutaneous injection.

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

Day 18

Safe handling and waste management

Safe administration

General patient assessment prior to each day of treatment.

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

- daily weight
- daily urinalysis
- strict fluid balance input and output

Hydration if prescribed.

Pre treatment medication

Verify antiemetics taken or administer as prescribed.

Chemotherapy - Time out

Asparaginase (colaspase)

Administer asparaginase (colaspase)

- via subcutaneous injection.

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

Day 22

Safe handling and waste management

Safe administration

General patient assessment prior to each day of treatment.

Peripheral neuropathy assessment tool

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

- daily weight
- daily urinalysis
- strict fluid balance input and output

Hydration if prescribed.

Pre treatment medication

Verify antiemetics taken or administer as prescribed.

Note: Asparaginase (colaspase) should be administered AFTER vincristine as there may be increased neuropathy if asparaginase (colaspase) is given first.

Chemotherapy - Time out

Vincristine

Administer vincristine (vesicant)

- via a minibag over 5 to 10 minutes
- ensure vein is patent and monitor for signs of extravasation throughout administration
- flush with ~150 mL of sodium chloride 0.9%.

Asparaginase (colaspase)

Administer asparaginase (colaspase)

- via subcutaneous injection.

Deaccess CVAD.

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

Discharge information

Antiemetics

- Antiemetics as prescribed.

Laxatives

- Ensure patient has prophylactic laxatives.

Growth factor support

- Arrangements for administration if prescribed.

Prophylaxis medications

- Prophylaxis medications (if prescribed) i.e. tumour lysis prophylaxis, PJP prophylaxis, 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)	
Nausea and vomiting	Read more about prevention of treatment induced nausea and vomiting
Bone pain	Bone pain, usually in the lower back or pelvis, associated with G-CSF.
Extravasation, tissue or vein injury	The unintentional instillation or leakage of a drug or substance out of a blood vessel into surrounding tissue. This has the potential to cause damage to affected tissue. Read more about extravasation management
Flare reaction	Anthracycline flare reaction is caused by a localised allergic reaction. It is characterised by erythematous vein streaking, urticaria and pruritus which may occur during drug administration and is often associated with too rapid an infusion. Extravasation must be ruled out if flare occurs.
Hypersensitivity reaction	Anaphylaxis and infusion related reactions can occur with this treatment. Read more about hypersensitivity reaction
Injection-site reactions	Inflammation of or damage to the tissue surrounding the area where a drug was injected.
Red-orange discolouration of urine	Pink/red/orange discolouration of the urine. This can last for up to 48 hours after some anthracycline drugs.
Taste and smell alteration	Read more about taste and smell changes

Early (onset days to weeks)	
Neutropenia	Abnormally low levels of neutrophils in the blood. This increases the risk of infection. Any fever or suspicion of infection should be investigated immediately and managed aggressively. Read more about immediate management of neutropenic fever
Thrombocytopenia	A reduction in the normal levels of functional platelets, increasing the risk of abnormal bleeding. Read more about thrombocytopenia
Anorexia	Loss of appetite accompanied by decreased food intake. Read more about anorexia
Constipation	
Fatigue	Read more about fatigue
Fluid retention and oedema	An excess amount of fluid around the cells, tissues or serous cavities of the body, leading to swelling.
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
Nephrotoxicity	Renal dysfunction resulting from damage to the glomeruli, tubules or renal vasculature.
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
Side effects of corticosteroids	Insomnia, oedema, increased risk of infection e.g. oral thrush, gastric irritation, worsening of peptic ulcer disease, increased blood sugar levels, loss of diabetic control, mood and behavioural changes - including anxiety, euphoria, depression, mood swings, increased appetite and weight gain, osteoporosis and fractures (long term use), bruising and skin fragility are associated with corticosteroid use.
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
Pancreatitis	Inflammation of the pancreas with impairment of function is associated with asparaginase formulations.
Hepatotoxicity	Anti-cancer drugs administered either alone or in combination with other drugs and/or radiation may cause direct or indirect hepatotoxicity. Hepatic dysfunction can alter the metabolism of some drugs resulting in systemic toxicity.
Hyperlipidaemia and hypercholesterolaemia	Abnormally elevated levels of lipids and cholesterol in the blood.
Hyperglycaemia	High blood sugar, an excess of glucose in the blood stream.

Late (onset weeks to months)	
Anaemia	Abnormally low levels of red blood cells (RBCs) or haemoglobin in the blood. Read more about anaemia
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)
Hyperpigmentation	Darkening of an area of skin caused by the overproduction of melanin.
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

Delayed (onset months to years)	
Cardiotoxicity	Anthracyclines are the most frequently implicated anti-cancer drugs associated with cardiotoxicity, which typically manifests as a reduction in left ventricular ejection fraction (LVEF), cardiomyopathy, or symptomatic CHF. Anthracycline induced cardiotoxicity has been categorised into acute, early-onset chronic progressive and late-onset chronic progressive and is usually not reversible. The risk of clinical cardiotoxicity increases with a number of risk factors including higher total cumulative doses. Read more about cardiac toxicity associated with anthracyclines
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 Haematology Reference Committee decided to supersede this protocol at the 2022 meeting as superior alternatives are available.

The key evidence for this protocol comes from two consecutive studies, CALGB 8811 and CALGB 9111.[1, 2] CALGB 8811 studied the efficacy of a 5 drug combination regimen for the induction, of adult patients with de novo acute lymphoblastic leukaemia followed by intensive consolidation. CALGB 9111 studied the addition of G-CSF to the 8811 regimen.

In CALGB 8811, 197 patients aged 16 to 80 years, were enrolled. All received induction chemotherapy comprising of cyclophosphamide, daunorubicin, vincristine, prednisolone and L-asparaginase. 85% (167) achieved complete remission (CR), 7% (13) had persistent disease and 9% (17) died during induction. Patients who achieved CR received consolidation with a multi-agent regimen, CNS prophylaxis, late intensification and maintenance therapy for a total of 2 years. The study concluded that this intensive regimen confers a high remission rate with a high proportion of long-term remissions in adult patients with ALL. After the first 76 patient were treated it was noted that patients older than 60 years had very high rates of death during induction (6 of 10). Subsequently, patients greater than 60 received reduced doses of cyclophosphamide, daunorubicin and prednisone during induction with a resultant reduction in early death rate.[1]

In CALGB 9111, G-CSF was added to the 8811 protocol. 198 adult patients (aged 16 to 83) with de novo ALL were randomised to receive placebo or G-CSF 5 micrograms/kg/day subcutaneously from day +5 until the ANC was > 1 x 10^9/L for 2 consecutive days. The study concluded that although patients who received G-CSF had higher remission rates and lower mortality, its use did not impact on the disease free survival. All CALGB ALL protocols now include the use of G-CSF in the induction phase only.

Efficacy

In CALGB 8811, CR rates were age dependent - 94% in those patients less than 30 years old, 85% in those aged 30 to 59 and 39% for those patients equal to or greater than 60 years (p-<0.001). Patients who had a mediastinal mass (100%) or blasts of T-cell origin (97% vs 80% for those with B-cell lineage) demonstrated a higher CR rate than other patients. After a median follow-up of 43 months the median survival was 36 months. For those patients who achieved CR, median remission duration was 29 months.

In CALGB 9111, there were 41 patients over 60 years old. The CR rate was 87% for patients less than 60 years and 77% for patients 60 years and older.[2] There was no statistically significant differences in CR rates with the addition of G-CSF however the older patients who received G-CSF had more rapid platelet recovery (median 17 vs 26 days, p=0.04).

With a median follow up of 4.7 years after CALGB 9111, there was a median overall survival (OS) of 2.3 years and disease free survival (DFS) of 2.4 years in those patients who received G-CSF. In the placebo arm, median OS was 1.7 years and median DFS was 1.8 years, but these differences were not statistically significant.

Toxicity

In the CALGB 8811 study[1] myelosuppression and infection were the most frequent major toxicities. 9% (17) patients died during induction mostly from infection (gram-negative, Streptococcus pnemonia, Candida); 9 were over 60 years old. One patient died from tumour lysis syndrome-induced renal failure during induction.

During the consolidation or maintenance phases a further 11 patients died, including 3 who died of haemorrhagic events. The major toxicities for this study are summarised in the table below. It was found that the addition of G-CSF from day 5 of chemotherapy (CALGB 9111), did not significantly reduce the non-haematological toxicities and also, because of the incidence of infections, did not enable patients to complete the first 3 months of chemotherapy any more rapidly than those who received the placebo.[2]

Toxicity from Larsen et al:[1]

	Induction	Intensification	Maintenance
Leukopenia (<2,000 μL)	98%	97%	75%
Thrombocytopenia (<50,000/μL)	94	84	32
Anemia (Hgb <8 g/dL)	65	84	26
Hemorrhage	5 (1)	4 (2)	0
Infection	54 (7)	49 (4)	25
Fever without infection	4	8	2
Nausea/vomiting	8	17	8
Stomatitis	7	9	7
Diarrhea	4	3	1
Hepatic	25	28	30
Pulmonary	8	5 (1)	4
Cardiac	5 (1)	1	6
Genitourinary	8 (1)	2	1
CNS	6	13	6
Peripheral nervous system	7	12	7
Skin	4	1	2
Allergy	0	1	1

The table lists the frequencies (%) of grade 3 and 4 toxicities during each phase of treatment using the CALGB Expanded Common Toxicity Criteria. The percentage of patients with lethal toxicity is shown in parentheses.

References

1 Larson, R. A., R. K. Dodge, C. P. Burns, et al. 1995. "A five-drug remission induction regimen with intensive consolidation for adults with acute lymphoblastic leukemia: cancer and leukemia group B study 8811." Blood 85(8):2025-2037.

2 Larson, R. A., R. K. Dodge, C. A. Linker, et al. 1998. "A randomized controlled trial of filgrastim during remission induction and consolidation chemotherapy for adults with acute lymphoblastic leukemia: CALGB study 9111." Blood 92(5):1556-1564.

History

Version 5

Date	Summary of changes
11/03/2022	Reviewed by Haematology Reference Committee. Protocol to be superseded as superior alternatives are available.
22/05/2023	Protocol superseded. Review in 4 years.

Version 4

Date	Summary of changes

Date	Summary of changes
22/09/2020	Biosimilar drug added to clinical information. Version number changed to V.4
23/10/2020	Protocol reviewed electronically by Haematology Reference Committee. Asparaginase flag added to protocol. Review in 2 years.
21/01/2022	Pulmonary toxicity added to side effects.

Version 3

Date	Summary of changes
04/05/2012	New protocol taken to Haematology Reference Committee meeting
14/02/2013	Approved and published on eviQ
30/07/2014	Protocol reviewed by email survey. Added link to ALLG and ANZCTR with statement 'Patients with ALL should be considered for inclusion into clinical trials'. Added aparaginase monitoring. Next review in 2 years.
20/05/2016	Protocol reviewed at the Haematology Reference Committee meeting. The Haematology Reference Committee decided to supersede this protocol at the May 2016 meeting due to its low priority in clinical practice. It remains available for viewing on eviQ however it will no longer be maintained with ongoing literature review or other revisions.
28/03/2017	Amended prednisolone administration details in patient information table. Added prednisolone in days 6,7 and to take orally ONCE daily.
31/05/2017	Transferred to new eviQ website. Version number change to V.3. Other changes include: • diluent volume of vincristine changed from '50 to 100 mL' to '50 mL' as per Australian Injectable Handbook Sixth Edition. • L- asparaginase (colaspase) changed to asparaginase (colaspase) per TGA update, to align with names used internationally https://www.tga.gov.au/updating-medicine-ingredient-names-list-affected-ingredients#active
24/11/2017	Discussed at RCM, decision to reinstate protocol due to feedback that the protocol is still used in clinical practice.
10/10/2019	Clinical information updated with PBS expanded indications for G-CSF.

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