Chemotherapy Protocol

LYMPHOMA

CYCLOPHOSPHAMIDE-DOXORUBICIN-PREDNISOLONE-VINCRISTINE (21)

(CHOP 21)

Regimen

- Lymphoma – CHOP(21)-Cyclophosphamide-Doxorubicin-Prednisolone-Vincristine (21)

Indication

- Non Hodgkin's Lymphoma

Toxicity

Drug	Adverse Effect
Cyclophosphamide	Dysuria, haemorrhagic cystitis (rare), taste disturbances
Doxorubicin	Cardiomyopathy, alopecia, urinary discolouration (red)
Prednisolone	Weight gain, gastro-intestinal disturbances, hyperglycaemia, CNS disturbances, cushingoid changes, glucose intolerance
Vincristine	Peripheral neuropathy, constipation, jaw pain

The adverse effects listed are not exhaustive. Please refer to the relevant Summary of Product Characteristics for full details.

Monitoring

Drugs

- FBC, LFTs and U&Es prior to day one of treatment
- Ensure adequate cardiac function before starting therapy. Baseline LVEF should be measured in patients with a history of cardiac problems, cardiac risk factors or in the elderly. Discontinue doxorubicin if cardiac failure develops

Dose Modifications

The dose modifications listed are for haematological, liver and renal function and limited drug specific toxicities. Dose adjustments may be necessary for other toxicities as well.

In principle all dose reductions due to adverse drug reactions should not be re-escalated in subsequent cycles without consultant approval. It is also a general rule for chemotherapy that if a third dose reduction is necessary treatment should be stopped.

Please discuss all dose reductions / delays with the relevant consultant before prescribing, if appropriate. The approach may be different depending on the clinical circumstances.

Haematological

Dose modifications for haematological toxicity in the table below are for general guidance only. Always refer to the responsible consultant as any dose reductions or delays will be dependent on clinical circumstances and treatment intent. Low counts can be a consequence of bone marrow infiltration as well as drug toxicity.

Consider blood transfusion if patient symptomatic of anaemia or has a haemoglobin of less than 8g/dL.

Dose modifications based on haematological parameters apply to cyclophosphamide and doxorubicin only

Neutrophils ($x10^9$/L)	**Dose Modifications (cyclophosphamide and doxorubicin)**
Less than 1 on proposed day 1 of cycle	Delay therapy until neutrophils are greater than or equal to $1x10^9$/L Consider G-CSF as secondary prophylaxis. Reconsider treatment options if not recovered after 14 days.
Grade 4 neutropenia or any febrile neutropenia following any cycle	Give G-CSF with all subsequent cycles
Grade 4 neutropenia leading to infection despite G-CSF support	Reduce dose of cyclophosphamide and doxorubicin by 50% for all subsequent cycles
Grade 4 neutropenia recurs despite 50% dose reduction in cyclophosphamide and doxorubicin	Stop treatment
Platelets ($x10^9$/L)	**Dose Modifications (cyclophosphamide and doxorubicin)**
Less than 100 on proposed day 1 of cycle	Delay therapy until platelets are greater or equal to $100x10^9$/L Reconsider treatment options if not recovered after 14 days.
Grade 4 thrombocytopenia following any cycle	Reduce dose of cyclophosphamide and doxorubicin by 50% for all subsequent cycles
Grade 4 thrombocytopenia recurs despite 50% dose reduction in cyclophosphamide and doxorubicin	Stop treatment

Hepatic Impairment

Please note that the approach may be different where abnormal liver function tests are due to disease involvement.

Drug	Bilirubin (µmol/L)		AST/ALT (units/L)	Dose (% of original dose)
Cyclophosphamide	Evidence suggests dose reduction not necessary.			
Doxorubicin	less than *30	and	2-3xULN	75%
	*30-50	and/or	More than 3xULN	50%
	51-85		N/A	25%
	more than 85		N/A	omit
Vincristine	*30-51	or	60-180	50%
	more than 51	and	normal	50%
	more than 51	and	more than 180	omit

* The lower limit reflects local practice and may differ from published sources.

Renal Impairment

Drug	Creatinine Clearance (ml/min)	Dose (% of original dose)
Cyclophosphamide**	More than 20	100%
	10-20	75%
	less than 10	50%
Doxorubicin	less than 10	Consider dose reduction in severe renal failure
Vincristine	N/A	No dose adjustment needed

**Consider mesna in patients with pre-existing bladder disorders. Give an oral dose of 40% of the cyclophosphamide dose (rounded upwards to the nearest 400mg) at 0, 2 and 6 hours after the administration of the cyclophosphamide.

Other

Dose reductions or interruptions in therapy are not necessary for those toxicities that are considered unlikely to be serious or life threatening. For example, alopecia, altered taste or nail changes.

Doxorubicin

Discontinue doxorubicin if cardiac failure develops

Vincristine

Reduce the vincristine dose to 1mg if a NCI-CTC grade 2 motor or grade 3 sensory neurological toxicity occurs. For higher toxicity grades or if toxicity increases despite dose reduction stop the vincristine.

Regimen

21 day cycle for 6 cycles

Drug	Dose	Days	Administration
Cyclophosphamide	750mg/m^2	1	Intravenous bolus over 10 minutes
Doxorubicin	50mg/m^2	1	Intravenous bolus over 10 minutes
Vincristine	1.4mg/m^2 (max 2mg)	1	Intravenous bolus in 50ml sodium chloride 0.9% over 10 minutes
Prednisolone	100mg	1, 2, 3, 4, 5	Oral

Consider initial dose reduction in patients over 70 years of age. Doses may be escalated up to full dose on subsequent cycles according to tolerability.

Dose Information

- Cyclophosphamide will be dose banded according to the CSCCN agreed bands
- Doxorubicin will be dose banded according to the CSCCN agreed bands
- The maximum lifetime cumulative dose of doxorubicin is 450mg/m². However prior radiotherapy to mediastinal/pericardial area should receive a lifetime cumulative doxorubicin dose of no more than 400mg/m²
- Vincristine will be rounded to the nearest 0.1mg (up if halfway)
- The maximum dose of vincristine is 2mg

Administration Information

Extravasation

- Cyclophosphamide – neutral
- Doxorubicin – vesicant
- Vincristine - vesicant

Other

- Prednisolone should be taken in the morning with or after food

Additional Therapy

- Antiemetics

  15-30 minutes prior to chemotherapy

  - ondansetron 8mg oral or intravenous

  As take home medication

  - metoclopramide 10mg three times a day when required oral
  - ondansetron 8mg twice a day for 3 days oral

- Allopurinol 300mg once a day oral for the first cycle only

- Consider anti-infective prophylaxis in high risk patients, including:

  - aciclovir 400mg twice a day oral
  - co-trimoxazole 960mg once a day on Monday, Wednesday and Friday only oral

- Mouthwashes according to local or national policy on the treatment of mucositis

- Gastric protection with a proton pump inhibitor or a H2 antagonist may be considered in patients considered at high risk of GI ulceration or bleed.

Additional Information

- The National Patient Safety Agency report NPSA/2008/RRR04 must be followed in relation to intravenous administration of vinca alkaloids.

Coding (OPCS 4.6)

- Procurement – X70.2

- Delivery – X72.3

References
1.Pavlovsky S, Santarelli MT, Erazo A et al. Results of a randomized study of previously-untreated intermediate and high grade lymphoma using CHOP versus CNOP. Ann Oncol. 1992 Mar;3(3):205-9.
2.Linch DC, Vaughan Hudson B, Hancock BW et al. A randomised comparison of a third generation regimen (PACEBOM) with a standard regimen (CHOP) in patients with histologically aggressive non-Hodgkins lymphoma: a British National Lymphoma Investigation Report. Br J Cancer 1996; 74 (2): 318-322.
3.Tirelli U, Errante D, Van Glabbeke M et al. CHOP is the standard regimen in patients greater than or equal to seventy years of age with intermediate grade and high grade non-Hodgkins lymphoma. Results of a randomised study of the European Organisation for Research and Treatment of Cancer Lymphoma Cooperative Study Group. J Clin Oncol 1998; 16 (1): 27-34.

REGIMEN SUMMARY

CHOP(21)-Cyclophosphamide-Doxorubicin-Prednisolone-Vincristine (21)

Cycle 1

1. Ondansetron 8mg oral or intravenous injection
2. Prednisolone 100mg oral
3. Doxorubicin 50mg/m^2 intravenous bolus over 10 minutes
4. Vincristine 1.4mg/m^2 (max 2mg) intravenous bolus in 50ml sodium chloride 0.9% over 10 minutes
5. Cyclophosphamide 750mg/m^2 intravenous bolus over 10 minutes

Take Home Medicines

6. Prednisolone 100mg once a day for 4 days (starting on day 2) oral
7. Metoclopramide 10mg three times a day when required oral
8. Ondansetron 8mg twice a day for 3 days oral starting on the evening of day one of treatment
9. Allopurinol 300mg once a day oral for 21 days

Cycles 2, 3, 4, 5 and 6

1. Ondansetron 8mg oral or intravenous injection
2. Prednisolone 100mg oral
3. Doxorubicin 50mg/m^2 intravenous bolus over 10 minutes
4. Vincristine 1.4mg/m^2 (max 2mg) intravenous bolus in 50ml sodium chloride 0.9% over 10 minutes
5. Cyclophosphamide 750mg/m^2 intravenous bolus over 10 minutes

Take Home Medicines

6. Prednisolone 100mg once a day for 4 days (starting on day 2) oral
7. Metoclopramide 10mg three times a day when required oral
8. Ondansetron 8mg twice a day for 3 days oral starting on the evening of day one of treatment

DOCUMENT CONTROL

Version	Date	Amendment	Written By	Approved By
1.2	Sept 2014	Header changed Toxicities removed Hepatic & renal tables updated Metoclopramide dose changed to 10mg Mucositis recommendation changed Bolus removed from intravenous bolus throughout text Disclaimer added Document control reordered	Donna Kimber Pharmacy Technician	Rebecca Wills Pharmacist
1.1	July 2012	"In patients over 70 years of age consider using vincristine 1mg. Where appropriate dose reduction of other agents may be considered at cycle one" changed to "Consider initial dose reduction in patients over 70 years of age."	Rebecca Wills Pharmacist	Dr Debbie Wright Pharmacist
1	April 2012	None	Rebecca Wills Pharmacist Dr Debbie Wright Pharmacist	Dr A Davies Consultant Medical Oncologist Dr A Milne Consultant Haematologist

This chemotherapy protocol has been developed as part of the chemotherapy electronic prescribing project. This was and remains a collaborative project that originated from the former CSCCN. These documents have been approved on behalf of the following Trusts;

Hampshire Hospitals NHS Foundation Trust
NHS Isle of Wight
Portsmouth Hospitals NHS Trust
Salisbury Hospitals NHS Foundation Trust
University Hospital Southampton NHS Foundation Trust
Western Sussex Hospitals NHS Foundation Trust

All actions have been taken to ensure these protocols are correct. However, no responsibility can be taken for errors which occur as a result of following these guidelines.