Chemotherapy Protocol

SARCOMA

IFOSFAMIDE-LIPOSOMAL DOXORUBICIN (Caelyx)

In-Patient Regimen

Please note this protocol is based on information for the use of the Caelyx brand of liposomal doxorubicin. Brands may not be interchangeable. This is not a licensed indication for Caelyx at the time of writing.

This protocol may require funding.

Regimen

- Sarcoma – InP-Liposomal Doxorubicin (Caelyx) - Ifosfamide

Indication

- First or second line treatment of sarcoma in patients with a cardiac impairment requiring an anthracycline
- WHO performance status 0,1, 2
- Palliative intent

Toxicity

Drug	Adverse Effect
Liposomal Doxorubicin	Palmar plantar erythrodysthesia (hand and foot syndrome), rash, GI disturbances, cardiotoxicity, asthenia, paresthesia
Ifosfamide	Haemorrragic cystitis, encephalopathy, nephrotoxicity

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 (including uric acid, albumin, calcium, magnesium, bicarbonate and phosphate) prior to day one of treatment
- Urine dip test for protein every four hours the day of and the day after ifosfamide administration
- EDTA or calculated creatinine clearance prior to each cycle

- Fluid balance monitoring every four hours the day of and the day after ifosfamide administration. Urine output should be maintained above 100ml/hour

- Ensure adequate cardiac function before starting therapy. Baseline ECG and LVEF should be measured in patients with a history of cardiac problems or in the elderly. Discontinue liposomal doxorubicin if cardiac failure develops

Dose Modifications

The dose modifications listed are for haematological, liver and renal function and drug specific toxicities only. 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

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

Prior to cycle 1 the following criteria must be met;

Criteria	Eligible Level
Neutrophil	equal to or more than $1x10^9$/L
Platelets	equal to or more than $100x10^9$/L

Day 1

Neutrophils ($x10^9$/L)	Dose Modifications
1 or greater	100%
0.5 - 1	Delay until recovery to $1x10^9$/L or greater then continue at full dose
less than 0.5	Delay until recovery to $1x10^9$/L or greater then continue at 75% of the original dose
Platelets ($x10^9$/L)	**Dose Modifications**
100 or greater	100%
50 - 99	Delay until recovery to $100x10^9$/L or greater then continue at full dose
less than 50	Delay until recovery to $100x10^9$/L or greater then continue at 75% of the original dose

Hepatic Impairment

Doses recommended below are for initial dosing. If the first dose of liposomal doxorubicin is well tolerated with minimal toxicity and no increase in bilirubin or liver enzymes the dose may be increased from 75% to 100% and from 50% to 75% at the next cycle (and from 75% to 100% on subsequent cycles where appropriate.)

Drug	**Bilirubin (µmol/L)**			**Dose (% of original dose)**
Ifosfamide	more than 20	or	more than 2.5xULN	Not recommended
	or ALP more than 2.5xULN			
Liposomal Doxorubicin	less than 20			100%
	21-51			75%
	51 or greater			50%

Renal Impairment

Drug	**Creatinine Clearance (ml/min)**	**Dose (% of original dose)**
Ifosfamide	more than 60	100%
	40-59	70% or consider using cyclophosphamide at a dose of 1500mg/m^2
	Less than 40	Clinical decision, consider using cyclophosphamide at a dose of 1500mg/m^2
Liposomal Doxorubicin	30 or greater	No dose modification needed
	less than 30	Clinical decision

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.

For all other non-haematological NCI-CTC grade 3 and above toxicities delay treatment until the adverse effect has resolved to NCI-CTC grade 1 or below. The dose should then be reduced to 75% of the original dose or discontinued as appropriate.

Palmer-Plantar Erythrodesia / Stomatitis			
NCI-CTC Toxicity Grade	**Number of Weeks after the Dose of Liposomal Doxorubicin**		
	4	**5**	**6**
1	Re-dose unless patient has experienced a previous grade 3 or 4 skin toxicity, in which case wait an additional week	Re-dose unless patient has experienced a previous grade 3 or 4 skin toxicity, in which case wait an additional week	Decrease dose by 25 % and return to 4 week interval or stop treatment
2	Wait an additional week	Wait an additional week	Decrease dose by 25 % and return to 4 week interval or stop treatment
3	Wait an additional week	Wait an additional week	Stop treatment
4	Wait an additional week	Wait an additional week	Stop treatment

Ifosfamide

In the case of a NCI-CTC grade 1 neurological toxicity to ifosfamide, consider reducing the dose of ifosfamide for the next cycle. If a NCI-CTC grade 2 neurologic toxicity appears or neurologic toxicity worsens despite dose reduction consider stopping the ifosfamide.

In the case of NCI-CTC grade 3 or 4 mucositis/GI toxicity reduce dose to 80% on first occurrence and to 60% on second occurrence. In the case of NCI-CTC grade 3 or 4 neutropenic sepsis reduce dose to 80% on first occurrence and to 60% on second occurrence. In the case of delayed recovery of greater than 6 days, reduce dose to 80% on first occurrence and to 60% on second occurrence.

Risk factors for CNS toxicity include a low albumin, renal impairment, prior administration of cisplatin, poor performance status, CNS tumour, bulky pelvic disease, concomitant psychotropic drugs and younger age. Methylene blue 50mg four times a day intravenous infusion in 100ml sodium chloride 0.9% over 30 minutes can be used to prevent or treat ifosfamide induced encephalopathy.

Regimen

21 day cycle for 6 cycles

Drug	Dose	Days	Administration
Mesna	600mg/m^2	1, 2, 3	Intravenous bolus in 100ml sodium chloride 0.9% over 15 minutes
Ifosfamide	3000mg/m^2	1, 2, 3	Intravenous infusion in 1000ml sodium chloride 0.9% over 240 minutes (the ifosfamide and mesna are in the same bag)
Mesna	3000mg/m^2	1, 2, 3	
Mesna	1800mg/m^2	1, 2, 3	Intravenous infusion in 1000ml sodium chloride 0.9% over 12 hours

Liposomal Doxorubicin	40mg/m^2	1	Intravenous infusion in 250ml glucose 5%. The first infusion to be given at a maximum rate of 1mg/minute. If well tolerated subsequent infusions may be given over 60 minutes. The default time on Aria is 120 minutes.

Dose Information

- Ifosfamide will be dose banded according to the agreed bands
- Mesna will be dose banded according to the agreed bands.
- Liposomal Doxorubicin will be dose banded according to the 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. Also consider previous anthracycline exposure.

Administration Information

Extravasation

- Liposomal Doxorubicin – exfoliant
- Ifosfamide – neutral

Other

- The first infusion of liposomal doxorubicin is to be given at a maximum rate of 1mg/minute. If this is well tolerated subsequent infusions may be given over 60 minutes. The default time on Aria is 120 minutes.
- If the patient experiences early symptoms or signs of infusion reaction immediately discontinue the infusion and administer appropriate treatment with chlorpheniramine and hydrocortisone. Once the patient has fully re-covered the infusion may be restarted slowly by infusing 5% of the total dose over the first 15 minutes. If tolerated without reaction, the infusion rate may then be doubled for the next 15 minutes. If tolerated, the infusion may then be completed over the next hour for a total infusion time of 90 minutes.
- Liposomal doxorubicin is incompatible with sodium chloride 0.9%. Always use a glucose 5% flush.
- Do not use in-line filters during the administration of liposomal doxorubicin.
- Doses of liposomal doxorubicin less than 90mg may be diluted in 250ml of glucose 5%. Doses of 90mg and above should be diluted in 500ml of glucose 5%.

Additional Therapy

This is an inpatient regimen please ensure all supportive and take home medicines are prescribed on the inpatient chart or general electronic prescribing system.

Antiemetics

Starting 15-30 minutes prior to chemotherapy

- dexamethasone 4mg twice a day for 5 days oral or intravenous
- metoclopramide 10mg three times a day for 5 days then when required oral or intravenous
- ondansetron 8mg twice a day for 5 days oral or intravenous

- Growth factors according to local formulary choice. For example:

  - filgrastim or bioequivalent 30 million units once a day from day 6 subcutaneous
  - lenograstim or bioequivalent 33.6 million units once a day from day 6 subcutaneous
  - pegfilgrastim or bioequivalent 6mg once only on day 4 subcutaneous

- Ciprofloxacin 500mg twice a day for 7 days starting on day 8 of the cycle

- The final dose of mesna on day 3 may be replaced with oral mesna at a dose of 1200mg/m^2 (rounded upwards to the nearest 400mg capsule) at 0, 2 and 6 hours after the end of the ifosfamide infusion.

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

Gastric protection with a proton pump inhibitor or a H_2 antagonist may be considered in patients considered at high risk of GI ulceration or bleed.

Coding

- Procurement – X71.5

- Delivery – not relevant

References
De Sanctis, Bertuzzi A, Basso U et al. Non-pegylated liposomal doxorubicin plus ifosfamide in metastatic soft tissue sarcoma: results from a phase II trial. Anticancer Res 2015; 35 (1): 543-547.

REGIMEN SUMMARY

InP-Ifosfamide - Liposomal Doxorubicin (Caelyx)

Other than those listed below, supportive medication for this regimen will not appear in Aria as prescribed agents. The administration instructions for each warning describes the agents which must be prescribed on the in-patient chart or general electronic prescribing system

Day 1

1. Warning – Check supportive medication prescribed
   Administration Instructions
   1. Dexamethasone 4mg twice a day day for 5 days oral or intravenous bolus
   2. Metoclopramide 10mg three times a day for 5 days oral or intravenous bolus
   3. Ondansetron 8mg twice a day for 5 days oral or intravenous bolus
   4. Ciprofloxacin 500mg twice a day days 8-15 oral
   5. Growth factor according to local formulary choice. For example;
      - filgrastim or bioequivalent 30 million units once a day for 7 days from day 6 subcutaneous
      - lenograstim or bioequivalent 33.6 million units once a day for 7 days from day 6 subcutaneous
      - pegfilgrastim or bioequivalent 6mg once only on day 4 subcutaneous
   6. Consider gastric protection
   7. Consider mouthwashes

2. Liposomal doxorubicin 40mg/m^2 intravenous infusion in 250ml glucose 5% over 120 minutes
   Administration Instructions
   The first infusion of liposomal doxorubicin is to be given at a maximum rate of 1mg/minute. If this is well tolerated subsequent infusions may be given over 60 minutes. The default time on Aria is 120 minutes.

3. Mesna 600mg/m^2 intravenous bolus in 100ml sodium chloride 0.9% over 15 minutes

4. Ifosfamide 3000mg/m^2 and mesna 3000mg/m^2 intravenous infusion in 1000ml sodium chloride 0.9% over 240 minutes

5. Mesna 1800mg/m^2 intravenous infusion in 1000ml sodium chloride 0.9% over 720 minutes
   Administration Instructions
   On day 3 of the cycle (after the last of the ifosfamide infusions) this may be substituted by oral mesna at a dose of 1200mg/m^2 rounded upwards to the nearest 400mg capsule given 0, 2 and 6 hours after the end of the ifosfamide infusion.

Day 2, 3

6. Warning – Check supportive medication prescribed
   Administration Instructions
   1. Dexamethasone 4mg twice a day day for 5 days oral or intravenous bolus
   2. Metoclopramide 10mg three times a day for 5 days oral or intravenous bolus
   3. Ondansetron 8mg twice a day for 5 days oral or intravenous bolus
   4. Ciprofloxacin 500mg twice a day days 8-15 oral
   5. Growth factor according to local formulary choice. For example;
      - filgrastim or bioequivalent 30 million units once a day for 7 days from day 6 subcutaneous
      - lenograstim or bioequivalent 33.6 million units once a day for 7 days from day 6 subcutaneous
      - pegfilgrastim or bioequivalent 6mg once only on day 4 subcutaneous
   6. Consider gastric protection
   7. Consider mouthwashes

7. Mesna 600mg/m^2 intravenous bolus in 100ml sodium chloride 0.9% over 15 minutes

8. Ifosfamide 3000mg/m^2 and mesna 3000mg/m^2 intravenous infusion in 1000ml sodium chloride 0.9% over 240 minutes

9. Mesna 1800mg/m^2 intravenous infusion in 1000ml sodium chloride 0.9% over 720 minutes

   Administration Instructions
   On day 3 of the cycle (after the last of the ifosfamide infusions) this may be substituted by oral mesna at a dose of 1200mg/m^2 rounded upwards to the nearest 400mg capsule given 0, 2 and 6 hours after the end of the ifosfamide infusion.

DOCUMENT CONTROL

Version	Date	Amendment	Written By	Approved By
1	September 2015	None	Dr Deborah Wright Pharmacist	Dr Nicola Keay Consultant Medical Oncologist

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 Hospital 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.