Chemotherapy Protocol

SARCOMA

DOXORUBICIN-OLARATUMAB

Regimen

- Sarcoma – Doxorubicin-Olaratumab

Indication

- In combination with doxorubicin for the first line treatment of advanced soft tissue sarcoma in adult patients where the following criteria apply;

  - histologically proven soft tissue sarcoma
  - locally advanced or metastatic disease
  - disease not amenable to potentially curative treatment with either surgery or radiotherapy
  - no previous treatment with systemic chemotherapy for soft tissue sarcoma

- WHO performance status of 0 or 1

Toxicity

Drug	Adverse Effect
Doxorubicin	Cardiomyopathy, alopecia, urinary discolouration (red), neutropenia, thrombocytopenia
Olaratumab	Infusion related reactions

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

Treatment should be delayed until minimum criteria detailed below are reached.

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

Consider blood transfusion if the patient is symptomatic of anaemia or has a haemoglobin of less than 8g/dL (80g/L).

If neutropenic fever or NCI-CTC grade 4 neutropenia lasting longer than seven days occurs then the olaratumab dose should be reduced to 12mg/kg and the doxorubicin dose reduced by 25% in the first instance, once neutrophils have recovered to $1x10^9$/L.

If neutropenic fever/infection or grade 4 neutropenia lasting longer than seven days recurs despite olaratumab dose reduction, the dose should be reduced further to 10mg/kg.

Hepatic Impairment

Drug	Bilirubin (µmol/L)		AST/ALT (units)	Dose (%of original dose)
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
Olaratumab	N/A		N/A	Use with caution, limited data available

Renal Impairment

Drug	Creatinine Clearance (ml/min)	Dose (% of original dose)
Doxorubicin	less than 10	Consider dose reduction in severe renal failure
Olaratumab	N/A	Use with caution, limited data in those with a creatinine clearance of less than 30ml/min

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.

Where appropriate, if dose reductions made at cycle one are well tolerated, dose increases can be considered on subsequent cycles according to tolerability.

Doxorubicin

Discontinue doxorubicin if cardiac failure develops. A baseline MUGA scan should be performed where the patient is considered at risk of having significantly impaired cardiac contractility. If ejection fraction is less than 50%, an alternative regimen should be given. MUGA scan should be repeated if there is suspicion of cardiac toxicity at any point during treatment. If the LVEF decreases by 20% or more from baseline during treatment then doxorubicin may have to be stopped.

Olaratumab

Infusion related adverse reactions have been observed in patients treated with olaratumab.

For NCI CTC grade 1 or 2 infusion related reactions in the first instance stop the infusion and administer paracetamol 1000mg oral, chlorphenamine 10mg intravenous and hydrocortisone 100mg intravenous. Once the reactions have resolved the infusion can be restarted at 50% of the original infusion rate.

Once the infusion rate has been reduced for a NCI CTC grade 1 or 2 infusion-related reaction, it is recommended that the lower infusion rate be utilized for all subsequent infusions. The infusion duration should not exceed 2 hours. Premedication with chlorphenamine 10mg intravenous, dexamethasone 8mg oral or intravenous and paracetamol 1000mg oral is recommended.

Regimen

21 day cycle for 8 cycles

Drug	Dose	Days	Administration
Doxorubicin	75mg/m^2	1	Intravenous bolus over 10 minutes
Olaratumab	15mg/kg	1, 8	Intravenous infusion in 250ml sodium chloride 0.9% over 60 minutes (maximum infusion rate of 25 mg/min, give doses of 1500mg or higher at 25mg/min)

Followed by maintenance olaratumab until disease progression or intolerance (6 cycles will be set in ARIA)

Drug	Dose	Days	Administration
Olaratumab	15mg/kg	1, 8	Intravenous infusion in 250ml sodium chloride 0.9% over 60 minutes (maximum infusion rate of 25 mg/min, give doses of 1500mg or higher at 25mg/min)

Dose Information

- Doxorubicin will be dose banded according to the national dose bands (2mg/ml)
- The maximum lifetime cumulative dose of doxorubicin is 450mg/m^2. However, prior radiotherapy to the mediastinal / pericardial area should receive a lifetime cumulative doxorubicin dose of no more than 400mg/m^2
- Olaratumab will be dose banded according to the agreed dose bands

Administration Information

Extravasation

- Doxorubicin – vesicant
- Olaratumab - neutral

Other

- The rate of administration of olaratumab should not exceed a maximum infusion rate of 25 mg/min. Doses of 1500mg or higher should be given at a rate of 25mg/min

Additional Therapy

- Olaratumab pre-medication

  30 minutes prior to olaratumab;

  - chlorphenamine 10mg intravenous bolus

- Olaratumab infusion reactions

    - Chlorphenamine 10mg intravenous bolus when required for olaratumab infusion related reactions
    - hydrocortisone 100mg intravenous bolus when required for olaratumab infusion related reactions
    - paracetamol 1000mg oral when required for olaratumab infusion related reactions

- Antiemetics

    15-30 minutes prior to doxorubicin

    - dexamethasone 8mg oral or intravenous followed by dexamethasone 4mg once a day for 2 days
    - ondansetron 8mg oral or intravenous followed by 8mg twice a day for three days oral
    - metoclopramide 10mg three time a day when required for the relief of nausea oral

- Lipegfilgrastim 6mg once only on day two of the cycle

- Mouthcare for the prophylaxis or treatment of mucositis

    - nystatin mouthwash 1ml four times a day
    - sodium chloride 0.9% mouthwash 10ml four times a day

- 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 – X

- Delivery –

References

1. Tap WD, Jones RL, van Tine BA et al. Olaratumab and doxorubicin versus doxorubicin alone in soft tissue sarcoma. Lancet 2016; 388(10043): 488–497

REGIMEN SUMMARY

Doxorubicin-Olaratumab

Cycle 1, 2, 3, 4, 5, 6, 7, 8

Day 1

1. Chlorphenamine 10mg intravenous

2. Dexamethasone 8mg oral or intravenous

3. Olaratumab 15mg/kg intravenous infusion in 250ml sodium chloride 0.9% over 60 minutes
   Administration Instructions
   The rate of administration of olaratumab should not exceed a maximum infusion rate of 25 mg/min. Doses of 1500mg or higher should be given at a rate of 25mg/min

4. Ondansetron 8mg oral or intravenous

5. Doxorubicin 75mg/m^2 intravenous bolus over 10 minutes

6. Chlorphenamine 10mg intravenous bolus when required for olaratumab infusion related reactions

7. Hydrocortisone 100mg intravenous bolus when required for olaratumab infusion related reactions

8. Paracetamol 1000mg oral when required for olaratumab infusion related reactions
   Administration Instructions
   Please check how much paracetamol the patient has taken in the last 24 hours. The maximum dose is 4000mg/24 hours

Day 8

9. Chlorphenamine 10mg intravenous

10. Olaratumab 15mg/kg intravenous infusion in 250ml sodium chloride 0.9% over 60 minutes
    Administration Instructions
    The rate of administration of olaratumab should not exceed a maximum infusion rate of 25 mg/min. Doses of 1500mg or higher should be given at a rate of 25mg/min

11. Chlorphenamine 10mg intravenous bolus when required for olaratumab infusion related reactions

12. Hydrocortisone 100mg intravenous bolus when required for olaratumab infusion related reactions

13. Paracetamol 1000mg oral when required for olaratumab infusion related reactions
    Administration Instructions
    Please check how much paracetamol the patient has taken in the last 24 hours. The maximum dose is 4000mg/24 hours

Take home medicines (day 1 only)

14. Dexamethasone 4mg once a day for 2 days stating on day 2 of the cycle

15. Metoclopramide 10mg three times a day when required for the relief of nausea oral
    Administration Instructions
    Please supply 28 days or an original pack as appropriate

16. Ondansetron 8mg twice a day for 3 days starting on the evening of day one of the cycle oral

17. Lipegfilgrastim 6mg once a day on day 2 only

Cycle 9 onwards

Day 1 and 8

18. Chlorphenamine 10mg intravenous

19. Olaratumab 15mg/kg intravenous infusion in 250ml sodium chloride 0.9% over 60 minutes
    Administration Instructions
    The rate of administration of olaratumab should not exceed a maximum infusion rate of 25 mg/min. Doses of 1500mg or higher should be given at a rate of 25mg/min

20. Chlorphenamine 10mg intravenous bolus when required for olaratumab infusion related reactions

21. Hydrocortisone 100mg intravenous bolus when required for olaratumab infusion related reactions

22. Paracetamol 1000mg oral when required for olaratumab infusion related reactions
    Administration Instructions
    Please check how much paracetamol the patient has taken in the last 24 hours. The maximum dose is 4000mg/24 hours

DOCUMENT CONTROL

Version	Date	Amendment	Written By	Approved By
1	January 2018	None	Dr Deborah Wright Pharmacist	Dr Nicola Keay Consultant Medical Oncologist