Doxorubicin and Olaratumab

Indication

First-line treatment of patients with advanced soft tissue sarcoma who are not amenable to curative treatment with surgery or radiotherapy and who have not been previously treated with doxorubicin.

(NICE TA465)

ICD-10 codes

Codes prefixed with C49.

Regimen details

Combination treatment

Day	Drug	Dose	Route
1 and 8	Olaratumab	15mg/kg	IV infusion
1	Doxorubicin	75mg/m^2	IV

Olaratumab monotherapy

Day	Drug	Dose	Route
1 and 8	Olaratumab	15mg/kg	IV infusion

Cycle frequency

21 days

Number of cycles

6 cycles of combination doxorubicin and olaratumab followed by maintenance olaratumab until disease progression or unacceptable toxicity.

Administration

Olaratumab should be administered first.

Olaratumab is administered in sodium chloride 0.9% over 60 minutes. For larger doses the duration of the infusion should be increased so the rate of administration does not exceed 25mg/minute.

Patients should be observed closely for infusion related reactions, particularly during the first infusion. Resuscitation facilities must be available.

If grade 1-2 infusion related reactions occur, the infusion should be temporarily interrupted and paracetamol, chlorphenamine and dexamethasone administered. Once the reaction has resolved the infusion may be restarted at 50% infusion rate and the patient should be closely monitored. If the infusion rate has been reduced for a grade 1-2 infusion related reaction, the lower infusion rate should be used for all subsequent infusions. The infusion duration should not exceed 2 hours.

If grade 3-4 infusion related reactions olaratumab should be immediately and permanently discontinued.

Doxorubicin is administered as a slow IV bolus via a fast running drip.

Pre-medication

On days 1 and 8 of cycle 1, and thereafter on day 1 only of all combination cycles:
30-60 minutes prior to olaratumab dose:

- Chlorphenamine 10mg IV slow bolus
- Dexamethasone 8mg IV slow bolus
- Ondansetron 8mg IV/PO

If no previous infusion related reaction then for subsequent day 8 and monotherapy cycles:
30-60 minutes prior to olaratumab dose:

- Chlorphenamine 10mg IV 30-60 minutes prior to olaratumab dose

If previous infusion related reaction:
30-60 minutes prior to olaratumab dose:

- Chlorphenamine 10mg IV slow bolus
- Dexamethasone 8mg IV slow bolus
- Paracetamol 500mg-1000mg PO/IV

Emetogenicity

This regimen has moderate emetic potential.

Additional supportive medication

Antiemetics as per local guidelines
Loperamide if required.
H2 antagonist or proton pump inhibitor if required.
Mouthwashes as per local policy

Extravasation

Doxorubicin is a vesicant (Group 5)
Olaratumab is neutral (Group 1)

Investigations – pre first cycle

Investigation	Validity period
FBC	14 days
U+E (including creatinine)	14 days
LFTs	14 days
Echocardiogram / MUGA	3 months

Investigations – pre subsequent cycles

Investigation	Validity period
FBC	96 hours (and within 24 hours of day 8)
U+E (including creatinine)	7 days
LFTs	7 days
Echocardiogram / MUGA	As clinically indicated

Standard limits for administration to go ahead

If blood results not within range, authorisation to administer **must** be given by prescriber/ consultant

Investigation	**Limit**
Neutrophils	≥ 1.0 x 10^9 /L
Platelets	≥ 100 x 10^9 /L
Creatinine Clearance (CrCl)	> 30 mL/min
Bilirubin	≤ 1.5 ULN
AST/ALT	≤ 1.5 x ULN
Alkaline Phosphatase	≤ 2.5 x ULN

Dose modifications

- **Haematological toxicity**

If neutrophils < 1.0 x 10^9 /L and/or platelets < 100 x 10^9 /L delay 1 week and recheck FBC. If within standard limits for go ahead, continue with full doses.

If > 1 week delay or febrile neutropenia, and other FBC parameters are satisfactory GCSF can be considered with subsequent cycles. Otherwise doxorubicin should be reduced to 80% dose and olaratumab to 12mg/kg. If further episode of grade 4 or febrile neutropenia doxorubicin should be further reduced to 66% dose and olaratumab to 10mg/kg.

- **Renal impairment**

No olaratumab dose reductions are required in patients with mild-moderate renal impairment. There are no data to support the use of olaratumab in patients with severe renal impairment (CrCl < 30mL/min).

If CrCl < 10mL/min, consider 75% dose of doxorubicin or omit, consultant decision.

- **Hepatic impairment**

Data suggest that no dose adjustments for olaratumab are required in patients with mild hepatic impairment. There are very limited data regarding olaratumab administration in patients with moderate hepatic impairment and there are no data in patients with severe hepatic impairment.

Bilirubin (x ULN)		**AST/ALT** (x ULN)	**Doxorubicin dose**
< 1.5	and	≤ 2	100%
< 1.5	and	2-3	75%
1.5 - 3	or	> 3	50%
3 - 5			25%
> 5			Omit

- **Other toxicities**

Olaratumab:

For any grade ≥ 3 non-haematological toxicity the dose of olaratumab should be withheld until toxicity is ≤ grade 1 or has returned to pre-treatment baseline. For subsequent infusions, the dose should be reduced to 12 mg/kg for serious grade 3 toxicities and to 10 mg/kg for grade 4 toxicities. If a grade 3 toxicity recurs despite the dose reduction, the dose should be reduced further to 10 mg/kg. In case of recurrence of a grade 4 toxicity, treatment with olaratumab should be permanently discontinued.

Doxorubicin:

Toxicity	Definition	Doxorubicin dose
Stomatitis/Mucositis	Grade 1	100%
	Grade 2	Omit until ≤ grade 1
	Grade 3	Omit until ≤ grade 1 then resume at 75% dose
	Grade 4	Discontinue
Other toxicities (except alopecia or nausea and vomiting)	≤Grade 2	100%(with or without treatment delay)
	≤Grade 3	Delay until recovery then consider dose reduction (consultant decision)

If cardiotoxicity (LVEF < 50% or 20% decrease) repeat echocardiogram after 7 days. If normal, continue, if not omit all further doxorubicin doses.

Adverse effects - for full details consult product literature/ reference texts

- **Serious side effects**

Myelosuppression
Infusion-related reactions
Allergic reaction
Infertility
Cardiotoxicity
Hepatotoxicity
Peripheral neuropathy

- **Frequently occurring side effects**

Diarrhoea
Constipation
Fatigue
Nausea and vomiting
Myelosuppression
Stomatitis and mucositis
Arthralgia and myalgia
Alopecia
Headache

- **Other side effects**

Fluid retention
Deranged liver function
Phlebitis
Skin toxicity
Nail changes
Taste disturbances
Bladder irritation

Significant drug interactions – for full details consult product literature/ reference texts

Warfarin/coumarin anticoagulants: increased or fluctuating anticoagulant effects. Avoid if possible, consider switching patient to a low molecular weight heparin or NOAC during treatment or if the patient continues taking an oral anticoagulant monitor the INR at least once a week and adjust dose accordingly.

Doxorubicin is metabolised via cytochrome P450 and is a P-glycoprotein substrate. Concomitant administration of inhibitors of CYP450 and/or Pgp may lead to increased plasma concentrations of doxorubicin and thereby increased toxicity. Conversely, concomitant administration of inducers of CYP450, such as rifampicin and barbiturates, may decrease plasma concentrations of doxorubicin and reduce efficacy.

Digoxin: doxorubicin may reduce the oral bioavailability of digoxin.

Ciclosporin: can increase serum levels and toxicity of doxorubicin

Other cardiotoxic drugs: should be avoided

Antiepileptics (e.g. carbamazepine, phenytoin, valproate): absorption is decreased after concomitant use of doxorubicin.

Clozapine: increased risk of agranulocytosis – avoid concomitant use

Additional comments

Cardiotoxicity has been associated with anthracyclines, with adverse events being more common in patients with a prior history of coronary artery disease. Caution must be taken in patients with a history of significant cardiac disease, arrhythmias or angina pectoris.

Doxorubicin has a life time maximum cumulative dose of 450mg/m^2 (400mg/m^2 in patients with known cardiac dysfunction or previous mediastinal irradiation).

References

- National Institute for Clinical Excellence (TA 465) accessed 30 Nov 2017 via www.nice.org.uk
- Summary of Product Characteristics Doxorubicin (Pfizer) accessed 3 August 2017 via www.medicines.org.uk
- Summary of Product Characteristics Oaratumab (Eli Lilly) accessed 3 August 2017 via www.medicines.org.uk
- Tap W, Jones R, Van Tine B et al. Olaratumab and doxorubicin versus doxorubicin alone for treatment of soft-tissue sarcoma: an open-label phase 1b and randomised phase 2 trial. Lancet 2016; 388: 488–97

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