Doxorubicin & Ifosfamide

Indication
First-line treatment of patients with advanced soft tissue sarcoma in whom a rapid response is required.
Neo-adjuvant or adjuvant treatment for patients with localised soft tissue sarcoma at high risk of relapse or in whom downstaging is required to facilitate surgical resection.

ICD-10 codes
Codes prefixed with C49.

Regimen details

Day	Drug	Dose	Route
1 ***or*** 1-2	Doxorubicin Doxorubicin	60mg/m^2 30mg/m^2	In patients ≤25 years old administer as an IV bolus or IV infusion over 1 hour with dexrazoxane 750mg/m^2 IV infusion 30 minutes before doxorubicin. IV infusion over 1 hour
1-3	Mesna	600mg/m^2	IV bolus
1-3	Ifosfamide + Mesna	3g/m^2 (max dose 6320mg) + 3g/m^2	IV infusion over 4 hours
1-3	Mesna	1800mg/m2	IV infusion over 8 hours

Cycle frequency
21 days

Number of cycles
Maximum of 6 cycles

Administration
Dexrazoxane (Cardioxane®, where commissioned) is administered as an intravenous infusion in compound sodium lactate over 15 minutes. Dexrazoxane should be administered 30 minutes prior to doxorubicin.

Doxorubicin may be administered as an IV bolus (via fast running drip), or IV infusion in 250mL Sodium Chloride 0.9% over 1 hour. The latter is preferred as it may reduce the risk of cardiotoxicity.

Ifosfamide (with mesna additive) is administered in 1000mL sodium chloride 0.9% over 4 hours.

Mesna is administered as an IV bolus immediately prior to ifosfamide. Mesna is also administered in 1000mL sodium chloride 0.9% as post-hydration over 8 hours following the ifosfamide infusion. A further 1000mL post-hydration should be administered over 6 hours following mesna administration in patients that cannot maintain adequate oral fluid intake of 2L per day.

Pre-medication
Nil

Emetogenicity

This regimen has moderate-high emetic potential.
NB. NK-1 inhibitors can increase exposure to ifosfamide. Consider avoiding if prior ifosfamide toxicity

Additional supportive medication

Antiemetics as per local guidelines
PCP prophylaxis e.g. co-trimoxazole
Benzydamine mouthwash as required
Loperamide if required.
Proton pump inhibitor on days where steroids given
PRN Mesna doses should be prescribed to be used in event of significant haematuria. Mesna 1g IV bolus or 1800mg oral stat (see below)
PRN Methylene blue 50 mg IV bolus over 5 mins for encephalopathy (see cautions below)
GCSF for 7 days, starting on day 5 or as per local practice

Extravasation

Doxorubicin - vesicant
Ifosfamide – neutral

Investigations – pre first cycle

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

Consider performing baseline measured GFR if:

- Pre-existing renal dysfunction (calculated GFR < 70ml/min)
- Disease involving the kidney or previous nephrectomy

Investigations – pre subsequent cycles

Investigation	Validity period
FBC	96 hours
U+E (including creatinine)	7 days
LFTs	7 days
Echocardiogram / MUGA	As clinically indicated

Consider repeating measured GFR if:

- Persisting trend of rising creatinine by > 20mmol/L at the start of two consecutive cycles of chemotherapy
- Creatinine rises outside of the normal range
- Renal dysfunction (calculated GFR < 70ml/min)

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)	see dose modifications for renal toxicity below. If creatinine rise of >20mmol/l since previous cycle then contact doctor for review.
Bilirubin	see dose modifications for hepatic toxicity below
Left ventricular ejection fraction	≥ 50% and less that 10% decline from baseline

Monitoring required during treatment

Investigation	**Frequency of monitoring**
Weight	Daily during chemo (see below)
Urine dip	At baseline and after each subsequent urine void
Mental status	Document at start of each nursing shift, flag any changes to doctors immediately.

Dose modifications

- ### Haematological toxicity

If neutrophils < 1.0 x 10^9 /L and/or platelets < 100 x 10^9 /L delay until count recovery. If within standard limits for go ahead by day 29, continue with full doses.

If > 1 week delay or febrile neutropenia, reduce doxorubicin to 80%. If further episode of grade 4 toxicity or febrile neutropenia, despite doxorubicin dose reduction, reduce ifosfamide to 80% dose.

- ### Renal impairment

Dexrazoxane – if CrCl < 40ml/min, reduce to 50% dose.

Doxorubicin – no need for dose adjustment is expected.

Ifosfamide

Creatinine Clearance	**Ifosfamide dose**
>60ml/min	100%
<60ml/min	Omit, switch to Cyclophosphamide 2100mg/m^2 on day 1 only.

- ### Hepatic impairment

Bilirubin (mmol/L)	**Doxorubicin dose**	**Ifosfamide dose**
< 21	100%	100%
21-50	50%	100%
51-86	25%	75%
> 86	Omit	Omit

- **Other toxicities**

Toxicity	Definition	Action
Stomatitis/Mucositis	Grade 3: severe pain interfering with oral intake *or* Grade 4: life threatening, urgent intervention needed	Delay until ≤ grade 1 then resume at 80% dose of doxorubicin.
Decline in left ventricular ejection fraction (LVEF)	LVEF < 50% or a decline in LVEF by 10 percentage points or more from baseline	Hold chemo and repeat echocardiogram in 7 days. patients should be started on a beta-blocker (e.g. bisoprolol 1.25mg od) and an angiotensin-converting enzyme (ACE) inhibitor (e.g. ramipril 1.25mg od), and referred to a cardiologist. Repeat cardiac imaging prior to next cycle and if normalised, re-commence doxorubicin at usual dose
Weight gain due to fluid overload	Gain of >2kg during inpatient chemotherapy ***and*** symptoms or signs of fluid overload	Give furosemide 20mg IV STAT
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)

Management of Ifosfamide-specific toxicities

Urinary monitoring for haemorrhagic cystitis and fluid status monitoring:

- Urinalysis for blood should be performed at baseline and at every subsequent urine void.
- For female patients, consider menstruation status if microscopic haematuria.
- Strict fluid input / output monitoring is required throughout admission
- Mesna 1g IV bolus or 1800mg oral stat to be written on prn side of drug chart on admission

Haemorrhagic cystitis:

Mesna is given alongside both cyclophosphamide and ifosfamide to minimise the risk of haemorrhagic cystitis.

Urine dipstick for blood	Action
0	No action
1+	No action - repeat with next void If 1+ on 2 occasions, contact medical team and give Mesna bolus
≥2+	Administer bolus of Mesna 1g iv bolus (or 1800mg oral stat) then contact medical team to consider doubling the dose of infusional Mesna on patient's chemotherapy chart.
Further positive urinalysis ≥2+	Repeat bolus of Mesna Double the dose of infusional Mesna on patient's chemotherapy chart if not done already. If occurs while Mesna running at double dose, contact consultant urgently as decision on continuation of ifosfamide will need to be made
≥ Grade 2 (symptomatic; urinary catheter required, or bladder irrigation required, limiting ADL)	Discontinue ifosfamide, continue double dose Mesna and hydration for 24hrs after chemo stopped
If dose of infusional Mesna is increased, this should also be changed for all subsequent cycles	

Ifosfamide-induced encephalopathy

Ifosfamide can cause encephalopathy. This should be actively monitored for and treated as per the grade of severity.

Assess risk factors for neurotoxicity pre-ifosfamide administration:

- Previous Ifosfamide-induced encephalitis
- Albumin <30 g/L or fluid overload
- Creatinine >150µmol/L
- Large pelvic tumour
- Hyponatraemia (<130mmol/L) / hypokalaemia (<3mmol/L)

If any risk factors present consider methylene blue* 50 mg IV bolus (over 5 mins) TDS for the duration of ifosfamide infusions.
If no risk factors present, prescribe methylene blue* 50 mg IV bolus (over 5 mins) PRN on the drug chart

Nurse to alert Doctor IMMEDIATELY if patient develops confusion, drowsiness, hallucinations, incontinence, clumsiness, agitation, change in speech, vision or hearing OR any other deviation from neurological baseline.

Situation	Action
Grade 1 - mild somnolence or agitation	• Document mental state each shift in nursing notes. • Ensure ifosfamide infusion runs no faster than 1g/m^2/hour
Grade 2 – moderate somnolence or agitation	• Ensure ifosfamide infusion is running no faster than 1g/m^2/hour • Start Methylene Blue 50mg 4 hourly • Continue 4-hourly Methylene blue until encephalopathy has resolved to Grade 0, then switch to prophylactic dose (8 hourly) • If neurotoxicity deteriorates to >grade 2, **stop ifosfamide** but continue Mesna infusion • If recurs despite prophylactic methylene blue, consider switching to cyclophosphamide.
Grade 3 – severe somnolence or agitation or onset of confusion, disorientation or hallucinations	• **Stop ifosfamide infusion** • Ensure Mesna continues to run to completion of planned infusion. • Start methylene blue* 50mg 4 hourly and continue until resolution of symptoms. • Other supportive measures may be considered • Monitor neurological status • Outreach review • Do not give further ifosfamide, instead substitute for cyclophosphamide.
Grade 4 – coma, seizure or toxic psychosis	

*Contraindications for methylene blue: known G6PD deficiency. Side effects: rare but serious; hypotension, cardiac arrhythmias. Common; nausea, abdominal pain, blue discoloration of urine, stools and saliva.

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

- **Serious side effects**

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

- **Frequently occurring side effects**

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

- **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 DOAC during treatment or if the patient continues taking an oral anticoagulant monitor the INR at least once a week and adjust dose accordingly.
Clozapine: increased risk of agranulocytosis – avoid concomitant use

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: concomitant use with doxorubicin should be avoided

Ifosfamide:
Amiodarone: increased risk of pulmonary toxicity – avoid if possible
Aprepitant, Fosaprepitant, Netupitant: increases exposure of ifosfamide, avoid or use with caution.
Nephrotoxic agents: increased risk of nephrotoxicity, avoid where possible.

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

References

- Summary of Product Characteristics – Doxorubicin (Seacross) accessed 03 April 2025 via www.medicines.org.uk
- Summary of Product Characteristics – Ifosfamide (Baxter) accessed 03 April 2025 via www.medicines.org.uk
- Judson, I. et al. Doxorubicin alone versus intensified doxorubicin plus ifosfamide for first-line treatment of advanced or metastatic soft-tissue sarcoma: a randomised, controlled phase 3 trial. Lancet Oncol. 2014;15(4):415-423

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