Ifosfamide (Soft tissue sarcoma)

Indication
Second-line treatment of patients with advanced soft tissue sarcoma following prior anthracycline

ICD-10 codes
Codes prefixed with C49.

Regimen details

Day	Drug	Dose	Route
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/m^2	IV infusion over 8 hours

Cycle frequency
21 days

Number of cycles
Maximum of 6 cycles

Administration
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
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)

Extravasation
Ifosfamide – neutral

Investigations – pre first cycle

Investigation	Validity period
FBC	14 days
U+E (including creatinine)	14 days
LFTs	14 days

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

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	≥ 75 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

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 < 75 x 10^9 /L delay until count recovery. If within standard limits for go ahead by day 29, continue with full doses. Add GCSF to future cycles if neutropenic.

If > 1 week delay or febrile neutropenia, reduce ifosfamide to 80%. If further episode of grade 4 toxicity or febrile neutropenia, reduce to 60% dose

- **Renal impairment**

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)	**Ifosfamide dose**
21-50	100%
51-86	75%
> 86	Omit

- **Other toxicities**

Toxicity	**Definition**	**Action**
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 Grade 4 – coma, seizure or toxic psychosis	• **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.

*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
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
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.
Clozapine: increased risk of agranulocytosis – avoid concomitant use
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

Nil

References

- Summary of Product Characteristics – Ifosfamide (Baxter) accessed 03 April 2025 via www.medicines.org.uk
- Lorigan, PC. Et al. Phase III trial of two investigational schedules of ifosfamide compared with standard dose doxorubicin in advanced or metastatic soft tissue sarcoma: a European Organisation for Research and Treatment of Cancer Soft Tissue and Bone Sarcoma Group Study. J Clin Oncol. 2007; 25(21):3144--50

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