IFOSFAMIDE

Advanced or metastatic soft tissue sarcoma

Drug / Dosage:	Ifosfamide	3000mg/m^2	IV daily	Day 1, Day 2 and Day 3

Administration: (repeated daily for 3 days, and starting at the same time each day)

Sodium chloride 0.9% 1 litre		IV	over 2 hours **on Day 1 only**
Mannitol 20%	200ml	IV	over 30 minutes
Mesna	600mg/m^2	IV	slow bolus
Ifosfamide	3000mg/m^2 }	IV	in 1 litre 0.9% sodium chloride IV over 4 hours
Mesna	3000mg/m^2 }		

Post-hydration: (see Comments re oral option for Day 3)	Mesna	900mg/m^2 in 1 litre sodium chloride 0.9% IV over 6 hours
	Mesna	900mg/m^2 in 1 litre sodium chloride 0.9% IV over 6 hours

Frequency: 3 weekly cycle for 6 cycles, with clinical review prior to each cycle

Main Toxicities: myelosuppression; alopecia; CNS toxicity (see Comments); haemorrhagic cystitis leading to bladder fibrosis (see Comments); nephrotoxicity; ovarian failure/infertility

Anti-emetics: highly emetogenic

Extravasation: non-vesicant

Regular Investigations:

FBC	Day 1
U&Es & LFTs	Day 1
Ca^{2+} & Mg^{2+}	Day 1
Albumin	Day 1
EDTA	prior to Cycle 1
CT scan	after cycle 3

Comments: **Cockcroft & Gault formula should not be used to predict GFR.**
EDTA should be repeated if the result is borderline at the start of treatment or if there is a 30% change in serum creatinine.

Weight should be recorded at the same time each day and a strict fluid balance chart should be maintained. If there is a weight increase of 2kg, a positive fluid balance of 2 litres, or symptoms of fluid overload, furosemide 20-40mgs po should be given.

Ifosfamide encephalopathy is an insidious condition (which can be fatal) that can present with a variety of symptoms, but usually somnolence and confusion feature strongly in the early stages. Three factors are known to predispose patients to this problem; renal impairment, low albumin and large pelvic tumour mass. If a patient has two of the three risk factors, future treatment should be reviewed by a Consultant.

Urine should be tested for signs of microscopic haematuria and, if seen, reported to Medical staff. (But note that the lowest level of blood detectable with some dipstick tests may be of

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little clinical significance) Further mesna may be given as required if haemorrhagic cystitis present eg. double the post-hydration mesna dose and give in 2L of fluid instead of 1L over the same time period in order to increase diuresis as well. If haematuria is severe, dose modification or discontinuation of ifosfamide may be required. **Discuss with Consultant**.

Note that if oral mesna is used, it is only 50% bioavailable and so doses should be adjusted accordingly. (As mesna is essentially non-toxic, always round doses up rather than down)

Post-hydration on Day 3 can be given orally to allow early discharge to patients considered suitable, as follows:
Mesna 1200mg/m^2/dose po every 4 hours for a total of 3 doses, starting 1 hour prior to end of ifosfamide infusion **along with** 2 litres of Water taken orally over 12 hours[1].

Dose Modifications

Haematological Toxicity (Day 1):

WBC < 2.0 x 10^9/l or Neutrophils 0.5 - 1.5 x 10^9/l or Platelets 25 - 100 x 10^9/l	Delay treatment for 1 week Repeat FBC and, if within normal parameters, continue with full dose treatment
Neutrophils < 0.5 x 10^9/l or Platelets < 25 x 10^9/l	Delay treatment for 1 week Repeat FBC and, if within normal parameters, continue with 25% dose reduction

In the event of neutropenic sepsis requiring hospitalisation & antibiotics, subsequent treatment will be given with a 25% dose reduction.

Renal Impairment:

GFR (ml/min)	Ifosfamide Dose
≥ 60	Give 100%
40 - 59	Give 70%
< 40	Clinical decision

[1]Note that this regimen should probably be discontinued if GFR < 45ml/minute. **Treatment should only be given in this situation with the approval of Consultant.**

Hepatic Impairment: Ifosfamide is generally not recommended if bilirubin > ULN, or if serum transaminases or ALP > 2.5 x ULN.
In the study below[2], patients were eligible for full dose treatment if bilirubin < 30µmol/l.

Encephalopathy: Somnolence and confusion are early stage symptoms, which must be promptly reported to a doctor. Treatment suspension should be considered and is mandatory if Grade 3 or 4 neurotoxicity. Methylene Blue 50mg intravenously (in 50-100ml sodium chloride 0.9% over 15 – 30 minutes), every 4 hours until symptoms resolve, can be used to attempt to reverse the encephalopathy. It should not be relied upon as a prophylactic measure, as it has not been rigourously assessed. Note that mesna has no ability to ameliorate CNS toxicity.

References:

[2]Lorigan, P et al; JCO 2007; 25 (21): 3144 - 3150
Summerhayes and Daniels, Practical Chemotherapy, 2003
[1]Royal Marsden Hospital NHS Trust Sarcoma Unit Proforma and Guidelines