Systemic Anti Cancer Treatment Protocol

Ifosfamide, Vincristine, Doxorubicin, Dactinomycin (IVADo)
Sarcoma

PROTOCOL REF: MPHAIVADO
(Version No: 1.1)

Approved for use in:

Rhabdomyosarcoma

Very high risk +/- maintenance vinorelbine cyclophosphamide

High risk

Age < 40yrs

Dosage:

Schedule

IVADo x 4 -> Surgery/Radiotherapy -> **IVA x 5** -> +/- maintenance vinorelbine and cyclophosphamide

	Cycle 1			Cycle 2			Cycle 3			Cycle 4	Surgery / Radiotherapy
	IVADo	**V**	**V**	**IVADo**	**V**	**V**	**IVADo**			**IVADo**	
Week	1	2	3	4	5	6	7	8	9	10	

	Cycle 5			Cycle 6			Cycle 7			Cycle 8			Cycle 9
	IVA			IVA			IVA			IVA			IVA
Week	13	14	15	16	17	18	19	20	21	22	23	24	25

I= Ifosfamide, V= Vincristine, A= Dactinomycin, Do= Doxorubicin

Dactinomycin is omitted during radiotherapy

May be followed by Vinorelbine and cyclophosphamide maintenance after cycle 9 (see separate protocol)

IVADo (Cycles 1 to 4)

Drug	Dosage	Route	Frequency
Ifosfamide +Mesna	3000mg/m^2 + 3000mg/m^2 days 1 and 2	IV	Every 21 days
Vincristine	1.5mg/m^2 (max 2mg) days1, 8 and 15 (cycles 1 and 2 only)	IV	Every 21 days
Dactinomycin	1.5mg/m^2 (max 2mg) day 1	IV	Every 21 days
Doxorubicin	30mg/m^2 days 1 and 2	IV	Every 21 days

IVA (Cycles 5 to 9)

Drug	Dosage	Route	Frequency
Ifosfamide +Mesna	3000mg/m^2 + 3000mg/m^2 days 1 and 2	IV	Every 21 days
Vincristine	1.5mg/m^2 (max 2mg) day 1	IV	Every 21 days
Dactinomycin	1.5mg/m^2 (max 2mg) day 1	IV	Every 21 days

Consolidation – give for 5 cycles after induction

Standard risk – give for 6 cycles

Maintenance therapy – see separate protocol

Supportive treatments:

Anti-emetic risk – High

Filgrastim 30MU or 48MU daily for 7 days with FBC review

Dexamethasone tablets, 4mg twice daily for 3 days

Domperidone 10mg oral tablets, up to 3 times a day or as required

Extravasation risk:

Vincristine – vesicant – follow trust /network policy, specific antidote may apply

Dactinomycin – vesicant – follow trust /network policy, specific antidote may apply

Doxorubicin – vesicant – follow trust /network policy, specific antidote may apply

Ifosfamide – irritant

Administration:

Cycles 1 and 2 only

Day	Drug	Dosage	Route	Diluent and Rate
1	Aprepitant 30 minutes before chemotherapy	125mg	PO	
1	Dexamethasone 30 minutes before chemotherapy	8mg	PO	
1	Ondansetron 30 minutes before chemotherapy	16mg	PO	
1	**Vincristine**	1.5 mg/m^2 (max 2mg)	IV	In 50mL sodium chloride 0.9% over 5 minutes
1	**Doxorubicin**	30mg/m^2	IV	Bolus injection over 10 minutes, with concurrent fast flowing sodium chloride 0.9%
1	**Dactinomycin**	1.5mg/m^2 (max 2mg)	IV	In 100mL sodium chloride 0.9% over 30 minutes
1	**Mesna**	1200mg/m^2	IV	In 500mL sodium chloride 0.9% over 60 minutes
1	**Ifosfamide + mesna**	3000mg/m^2 + 3000mg/m^2	IV	In 1000mL sodium chloride 0.9% over 3 hours
1	**Mesna**	1200mg/m^2	IV	In 1000mL sodium chloride 0.9% over 4 hours
1	**Mesna**	1200mg/m^2	IV	In 1000mL sodium chloride 0.9% over 4 hours
2	Aprepitant	80mg	PO	24 hours after day 1 dose
2	Dexamethasone	8mg	PO	24 hours after day 1 dose
2	Ondansetron	16mg	PO	24 hours after day 1 dose
2	**Doxorubicin**	30mg/m^2	IV	Bolus injection over 10 minutes, with concurrent fast flowing sodium chloride 0.9%
2	**Mesna**	1200mg/m^2	IV	In 500mL sodium chloride 0.9% over 60 minutes
2	**Ifosfamide + mesna**	3000mg/m^2 + 3000mg/m^2	IV	In 1000mL sodium chloride 0.9% over 3 hours
2	**Mesna**	1200mg/m^2	IV	In 1000mL sodium chloride 0.9% over 4 hours
2	**Mesna**	1200mg/m^2	IV	In 1000mL sodium chloride 0.9% over 4 hours

3	Aprepitant	80mg	PO	
4	Filgrastim	30MU or 48MU	SC	By subcutaneous injection on days 4 to 7, then 9 to 11, followed by FBC review
8	**Vincristine**	1.5 mg/m^2 (max 2mg)	IV	In 50mL sodium chloride 0.9% over 5 minutes
15	**Vincristine**	1.5 mg/m^2 (max 2mg)	IV	In 50mL sodium chloride 0.9% over 5 minutes

Filgrastim dose:

For patients under 70kg: 30MU subcutaneous injection daily

For patients 70kg and above: 48MU subcutaneous injection daily

Cycles 3 and 4

Day	Drug	Dosage	Route	Diluent and Rate
1	Aprepitant 30 minutes before chemotherapy	125mg	PO	
1	Dexamethasone 30 minutes before chemotherapy	8mg	PO	
1	Ondansetron 30 minutes before chemotherapy	16mg	PO	
1	**Vincristine**	1.5 mg/m^2 (max 2mg)	IV	In 50mL sodium chloride 0.9% over 5 minutes
1	**Doxorubicin**	30mg/m^2	IV	Bolus injection over 10 minutes, with concurrent fast flowing sodium chloride 0.9%
1	**Dactinomycin**	1.5mg/m^2 (max 2mg)	IV	In 100mL sodium chloride 0.9% over 30 minutes
1	**Mesna**	1200mg/m^2	IV	In 500mL sodium chloride 0.9% over 60 minutes
1	**Ifosfamide + mesna**	3000mg/m^2 + 3000mg/m^2	IV	In 1000mL sodium chloride 0.9% over 3 hours
1	**Mesna**	1200mg/m^2	IV	In 1000mL sodium chloride 0.9% over 4 hours
1	**Mesna**	1200mg/m^2	IV	In 1000mL sodium chloride 0.9% over 4 hours
2	Aprepitant	80mg	PO	24 hours after day 1 dose
2	Dexamethasone	8mg	PO	24 hours after day 1 dose

2	Ondansetron	16mg	PO	24 hours after day 1 dose
2	**Doxorubicin**	30mg/m^2	IV	Bolus injection over 10 minutes, with concurrent fast flowing sodium chloride 0.9%
2	**Mesna**	1200mg/m^2	IV	In 500mL sodium chloride 0.9% over 60 minutes
2	**Ifosfamide + mesna**	3000mg/m^2 + 3000mg/m^2	IV	In 1000mL sodium chloride 0.9% over 3 hours
2	**Mesna**	1200mg/m^2	IV	In 1000mL sodium chloride 0.9% over 4 hours
2	**Mesna**	1200mg/m^2	IV	In 1000mL sodium chloride 0.9% over 4 hours
3	Aprepitant	80mg	PO	
4	Filgrastim	30 or 48MU	SC	By subcutaneous injection daily for 7 days, followed by FBC review

Cycles 5 to 9 IVA

Day	Drug	Dosage	Route	Diluent and Rate
1	Aprepitant 30 minutes before chemotherapy	125mg	PO	
1	Dexamethasone 30 minutes before chemotherapy	8mg	PO	
1	Ondansetron 30 minutes before chemotherapy	16mg	PO	
1	**Vincristine**	1.5 mg/m^2 (max 2mg)	IV	In 50mL sodium chloride 0.9% over 5 minutes
1	**Dactinomycin**	1.5mg/m^2 (max 2mg)	IV	In 100mL sodium chloride 0.9% over 30 minutes
1	**Mesna**	1200mg/m^2	IV	In 500mL sodium chloride 0.9% over 60 minutes
1	**Ifosfamide + mesna**	3000mg/m^2 + 3000mg/m^2	IV	In 1000mL sodium chloride 0.9% over 3 hours
1	**Mesna**	1200mg/m^2	IV	In 1000mL sodium chloride 0.9% over 4 hours
1	**Mesna**	1200mg/m^2	IV	In 1000mL sodium chloride 0.9% over 4 hours
2	Aprepitant	80mg	PO	24 hours after day 1 doses
2	Dexamethasone	8mg	PO	24 hours after day 1 doses
2	Ondansetron	16mg	PO	24 hours after day 1 doses

2	**Mesna**	1200mg/m^2	IV	In 500mL sodium chloride 0.9% over 60 minutes
2	**Ifosfamide + mesna**	3000mg/m^2 + 3000mg/m^2	IV	In 1000mL sodium chloride 0.9% over 3 hours
2	**Mesna**	1200mg/m^2	IV	In 1000mL sodium chloride 0.9% over 4 hours
2	**Mesna**	1200mg/m^2	IV	In 1000mL sodium chloride 0.9% over 4 hours
3	Aprepitant	80mg	PO	
4	Filgrastim	30MU or 48MU	SC	By subcutaneous injection daily for 7 days, followed by FBC review

Filgrastim dose:

For patients under 70kg: 30MU subcutaneous injection daily

For patients 70kg and above: 48MU subcutaneous injection daily

Notes:

Ifosfamide

Ensure adequate hydration and that fluids with mesna are prescribed and administered.

Record patients weight at the same time each day as well as a strict fluid balance chart.

If there is a positive fluid balance of 2 litres or more, weight gain of > 2kg or symptoms of fluid overload give furosemide 20mg orally.

Test urine for microscopic haematuria each cycle (see algorithm)

Observe for insidious signs of encephalopathy, initially somnolence and confusion (see algorithm)

Doxorubicin

Maximum cumulative dose of doxorubicin: 450 to 550mg/m^2

Perform baseline MUGA if patient is considered at risk of significantly impaired cardiac contractility.

Repeat MUGA during treatment if there is any suspicion of cardiac impairment

Vincristine

Administer weekly vincristine for cycles 1 and 2 only

Vincristine to be given irrespective of any pancytopenia unless unwell

Dactinomycin

May be given at the very beginning of radiotherapy (week 13) but is omitted during RT (week 16)

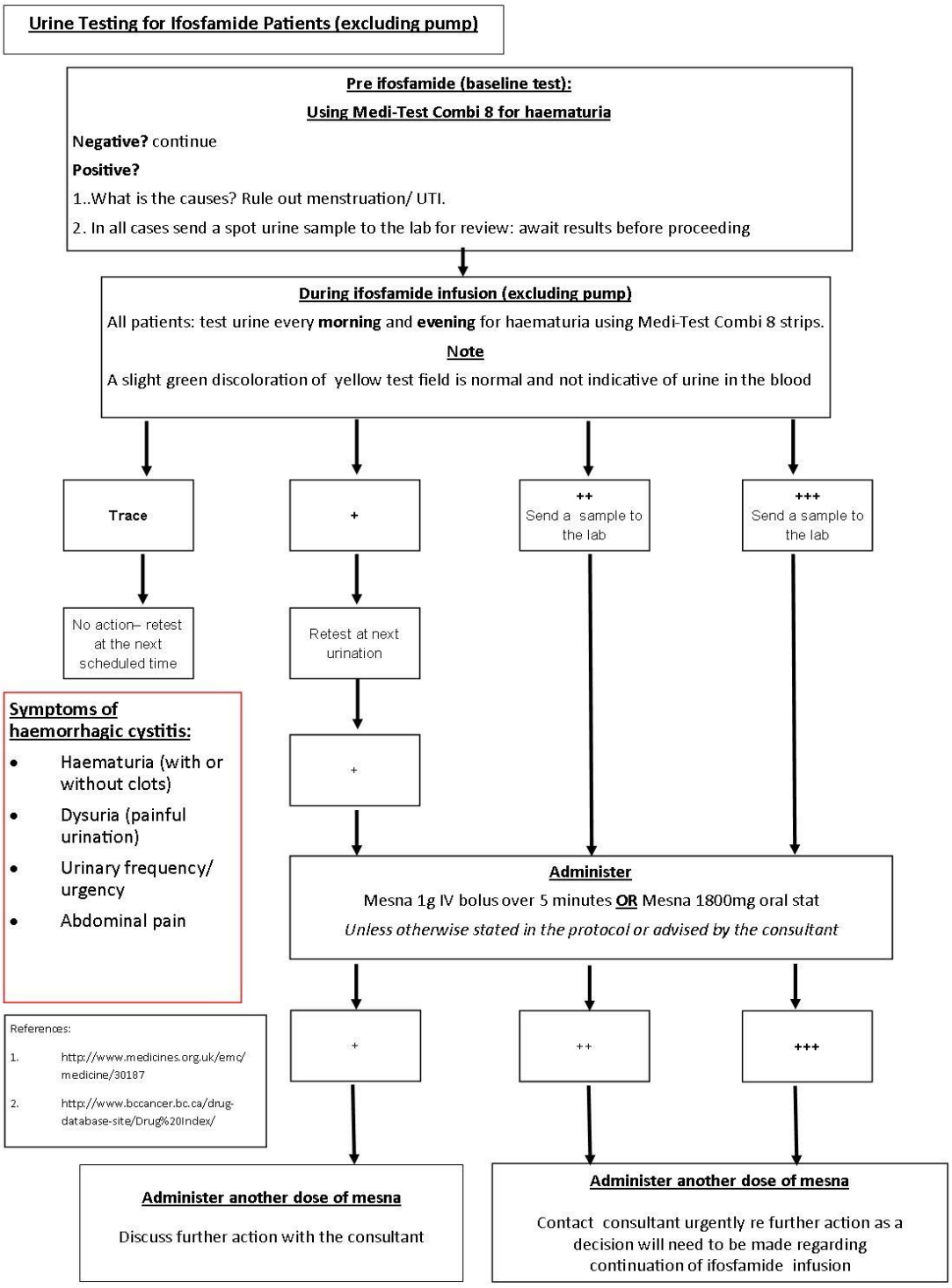
Main Toxicities:

Vincristine – neurotoxicity,

Dactinomycin - Myelosuppression, alopecia, mucositis, diarrhoea, liver changes (rare) ovarian failure / infertility

Ifosfamide – myelosuppression, mucositis, nephrotoxicity, central neurotoxicity, haemorrhagic cystitis leading to bladder fibrosis, ovarian failure

Doxorubicin - Myelosuppression, alopecia, mucositis, cardiomyopathy (see notes and treatment plan), ovarian failure / infertility


Urine Testing for Ifosfamide Patients (excluding pump)
Pre ifosfamide (baseline test):
Using Medi-Test Combi 8 for haematuria
Negative? continue
Positive?
1..What is the causes? Rule out menstruation/ UTI.
2. In all cases send a spot urine sample to the lab for review: await results before proceeding
During ifosfamide infusion (excluding pump)
All patients: test urine every morning and evening for haematuria using Medi-Test Combi 8 strips.
Note
A slight green discoloration of yellow test field is normal and not indicative of urine in the blood
Trace
+
++
Send a sample to the lab
+++
Send a sample to the lab
No action– retest at the next scheduled time
Retest at next urination
+
Symptoms of haemorrhagic cystitis:
Haematuria (with or without clots)
Dysuria (painful urination)
Urinary frequency/ urgency
Abdominal pain
Administer
Mesna 1g IV bolus over 5 minutes OR Mesna 1800mg oral stat
Unless otherwise stated in the protocol or advised by the consultant
References:
1. http://www.medicines.org.uk/emc/medicine/30187
2. http://www.bccancer.bc.ca/drug-database-site/Drug%20Index/
+
++
+++
Administer another dose of mesna
Discuss further action with the consultant
Administer another dose of mesna
Contact consultant urgently re further action as a decision will need to be made regarding continuation of ifosfamide infusion

Investigations and treatment plan

	Pre	Cycle 1	Cycle 2	Cycle 3	Cycle 4	Cycle 5 onwards	Comments
Medical Assessment	X		X	X	X	X	Every cycle
Nursing Assessment	X	X	X	X	X	X	Every cycle
ECHO	X						Repeat if clinically indicated
FBC	X	X	X	X	X	X	Every cycle
U&E & LFT	X	X	X	X	X	X	Every cycle
CrCl (Cockroft and Gault)	X	X	X	X	X	X	Every cycle
Ca^{2+}, Mg^{2+}, Cl^{-}, HCO_3	X	X	X	X	X	X	Every cycle
Urine PO_4, creatinine, osmolarity	X		X	X	X	X	Every cycle
Serum HCO_3^{-} /total CO_2, PO_4		X	X	X	X	X	Every cycle
Tp/Ccrea		X	X	X	X	X	Every Ifosfamide
CT scan	X			X			As clinically indicated
Informed Consent	X						
Blood pressure measurement	X	X	X	X	X	X	As clinically indicated
PS recorded	X	X	X	X	X	X	Every cycle
Toxicities documented	X	X	X	X	X	X	Every cycle
Weight recorded	X	X	X	X	X	X	Every cycle
Urine dipstick for protein / blood	X	X	X	X	X	X	Twice daily during ifosfamide (see algorithm)

Dose Modifications and Toxicity Management:

Haematological toxicity

Proceed on day 1 if:-

ANC ≥ 1.0 x 10^9/L	Platelets ≥ 80 x 10^9/L

Delay 1 week on day 1 if:-

ANC ≤ 0.9 x 10^9/L	Platelets ≤ 79 x 10^9/L

Day 8 and day 15 vincristine to be given irrespective of FBC

General guidelines

Dose and time intensity are essential aspect of IVADo treatment. In case of any relevant (≥CTC grade 3 toxicity) dactinomycin is the first drug to be reduced.

CTC grade 3 or 4 infection OR treatment delay ≥ 1 week due to neutropenia related toxicity – use filgrastim with subsequent cycles

Do not reduce the dose of doxorubicin unless there is cardiac dysfunction.

Non-haematological toxicity

Hepatic

Bilirubin (µmol/L)	Doxorubicin dose
20 to 50	50%
51 to 85	25%
Above 85	omit

Ifosfamide – note that ifosfamide is generally not recommended if bilirubin > ULN or ALP > 2.5 x ULN – discuss with consultant if this is the case. Note that in the reference trial patients were eligible for full dose treatment if bilirubin less than 30micromol/L.

Dactinomycin and vincristine – discuss with consultant is bilirubin > ULN and ALP > 2.5 x ULN

Renal

Monitor serum creatinine and calculate GFR using Cockroft and Gault before each cycle of Ifosfamide. Measure serum electrolytes and bicarbonate levels and calculate tubular function (Tp/Ccrea) before each cycle of Ifosfamide.

$$Tp/C_{creat} = \frac{PO_{4serum} - PO_{4urine} \times SrCr_{\mu mol/l}}{Creatinine_{Urine}}$$

Toxicity Grade*	**GFR (ml/min/1.73 m2)**	**TpCreat (mmol/L)**	**HCO_3* (mmol/L)**	**Action (apply worst grade)**
Grade 0/1	≥60	≥1.00	≥17.0	Continue Ifosfamide at 100% dose
Grade 2	40 - 59	0.80 to 0.99	14.0 to 16.9	Ifosfamide 70% dose
Grade 3/4	≤40	≤0.80	≤14.0	Use cyclophosphamide** instead dose 1500mg/m^2/d, day 1 only

*Check low values of HCO_3 when patient is clinically stable to exclude e.g. infection as a cause before modifying Ifosfamide dose / treatment

****Always discuss / check with consultant to confirm before substituting cyclophosphamide 1500mg/m^2 day 1 for ifosfamide.**

Note that there may be rises of tubular enzymes, amino acids or proteins shortly after ifosfamide. These are transient and do not require any dose modification

Gastric

Grade 3 or 4 mucositis, GI or other dactinomycin related toxicity – reduce dactinomycin **to 75%** of original dose for first occurrence
Reduce or even omit if further toxicity occurs
Doxorubicin – do not dose reduce unless there is evidence of cardiac toxicity see cardiac below

Neurotoxicity

Central
Observe closely for signs of encephalopathy. This may present insidiously in a variety of ways but usually includes somnolence and confusion initially. Report any early signs to medical staff immediately
Three risk factors may predispose to encephalopathy: renal impairment, low albumin, and large pelvic tumour mass.

Note that most mild cases of encephalopathy will resolve spontaneously in 24 to 72 hours.

If CTC grade 3 or 4 central neurotoxicity occurs (somnolence 30% of the time, disorientation / hallucination / coma or seizures on which consciousness is altered etc)
Stop Ifosfamide infusion
consider the use of methylene blue (methylonium) 50mg IV infusion as

<table>
<tr><td></td><td>follows:

50mg (5ml ampoule of 1% solution) every 4 hours, by IV slow bolus

Patients who have had an episode of ifosfamide enduced encephalopathy in a previous cycle should be treated as follows:

Give one dose of 50mg (5ml ampoule of 1% solution) IV slow bolus 24 hours prior to ifosfamide. During ifosfamide infusion, give 50mg (5ml ampoule of 1% solution) IV slow bolus every 6 hours during the infusion.

If repeated grade 3 or 4 central neurotoxicity occurs consider withholding ifosfamide and substitute cyclophosphamide 1500mg/m^2 on d1 only

Other
Vincristine may also cause neurotoxicity autonomic and/ or peripheral. Discuss with consultant if any persistant neuropathy greater than grade 1.</td></tr>
<tr><td>Cardiac</td><td>The cumulative dose of doxorubicin in this protocol is 240mg/m^2 which is below the usual reported threshold for cardiotoxicity. Nevertheless close monitoring is recommended.
- temporarily discontinue doxorubicin

<table>
<tr><td>Shortening fraction (SF) < 28% OR absolute reduction by > 10 percentile points</td><td>Temporary omit Doxorubicin from next cycle</td></tr>
<tr><td>If improved after 1 week</td><td>Reinstate doxorubicin
Missed dose of doxorubicin should replace dactinomycin at the first opportunity</td></tr>
<tr><td>Persistent cardiotoxicity as above</td><td>Consider stopping doxorubicin and refer patient to cardiologist</td></tr>
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References:

EpSSG RMS 2005, a protocol for non-metastatic rhabdomyosarcoma, v1.2

international, July 2008