VAI

INDICATION (ICD10) C40, C41, C49

1. Ewing sarcoma consolidation

REGIMEN

Day 1 Mesna 1000mg/m^2 IV bolus one hour prior to ifosfamide

VINCRISTINE	1.5mg/m^2 (maximum 2mg) in 50ml sodium chloride 0.9% IV infusion over 10 minutes
DACTINOMYCIN	0.75mg/m^2 (maximum 1.5mg) IV bolus
IFOSFAMIDE	3000mg/m^2 with Mesna 3000mg/m^2 in 1000ml sodium chloride 0.9% IV infusion over 3 hours

Mesna 2000mg/m^2 in 1000ml sodium chloride 0.9% IV infusion over 20 hours

Day 2

VINCRISTINE	1.5mg/m^2 (maximum 2mg) in 50ml sodium chloride 0.9% IV infusion over 10 minutes
DACTINOMYCIN	0.75mg/m^2 (maximum 1.5mg) IV bolus
IFOSFAMIDE	3000mg/m^2 with Mesna 3000mg/m^2 in 1000ml sodium chloride 0.9% IV infusion over 3 hours

Mesna 2000mg/m^2 in 1000ml sodium chloride 0.9% IV infusion over 20 hours

CYCLE FREQUENCY AND NUMBER OF CYCLES

Every 21 days for up to 7 or 8 cycles
Consolidation post-surgery – 8 cycles of VAI or 1 cycle of VAI followed by 7 cycles of VAC

ANTI-EMETICS

High emetic risk days 1 and 2

CONCURRENT MEDICATION REQUIRED

Ifosfamide	Ensure mesna administered. Ensure adequate oral fluid intake. Cotrimoxazole 480mg bd M/W/F for duration of chemotherapy.
Vincristine	Laxatives should be prescribed
GCSF	Starting at least 24 hours after chemotherapy to maintain dose intensity (until WCC >5x10^9/l)

EXTRAVASATION AND TYPE OF LINE / FILTERS

Dactinomycin - vesicant
Ifosfamide – neutral
Vincristine – vesicant

Double lumen central line

INVESTIGATIONS

Blood results required before SACT administration
FBC, U&E and LFTs every week
Neutrophils x 10^9/L ≥1.0
Platelets x 10^9/L ≥80
DTPA baseline
Creatinine clearance >55ml/min
Serum creatinine every cycle
Haematuria monitoring every specimen
Vitamin D baseline
Hepatitis B status baseline
ECG (possible ECHO) required if patient has preexisting cardiac disease
Baseline weight and every cycle

MAIN TOXICITES AND ADVERSE REACTIONS

Dactinomycin	Myelosuppression, mucositis, liver changes
Ifosfamide	Ifosfamide encephalopathy. Nephrotoxicity: Irreversible renal failure and tubular damage can occur, and this is more frequent with cumulative doses over 25–50g/m^2 of Ifosfamide. Haematuria.
Vincristine	Neuropathy

INTERACTIONS WHICH MAY REQUIRE DOSE MODIFICATIONS

(not exhaustive list check SPC/BNF/Stockleys)

Ifosfamide	Aprepitant and fosaprepitant are predicted to increase the exposure to ifosfamide. Caution.

DOSE MODIFICATIONS

Non-haematological

Dactinomycin - omit for duration of concurrent radiotherapy (omitted doses are not subsequently given).

Reduce Ifosfamide and Dactinomycin dose if:
Delayed recovery >6 days
Neutropenic sepsis grade 3 and 4
Mucositis / GI toxicity grade 3 and 4
Give 80% dose on 1st occurrence and 60% dose on second occurrence.

Ifosfamide
Neural and nephrotoxicity grade

Toxicity Grade	GFR (ml/min/1.73m^2)	Tp/C_{crea} (Tm_p/GFR) (mmol/l)	HCO_3* (mmol/l)	Action (apply worst grade)
Grade 0/1	≥60	≥1.00	≥17.0	give 100% dose
Grade 2	40-59	0.8-0.99	14.0-16.9	Discuss
Grade 3/4	≤40	≤0.8	≤14.0	**Switch to cyclophosphamide

*Low values of HCO_3 should be re-checked when the patient is clinically stable (to rule out infection as a cause, etc) before modifying treatment.
**Discuss with consultant before and to confirm substitution of ifosfamide with cyclophosphamide 1500mg/m^2/day day 1 only.

Fractional phosphate clearance calculated

$$Tp/C_{crea}\ [mmol/ml] = Phosphate_{serum} - \frac{Phosphate_{urine} \times creatinine_{serum}}{Creatinine_{urine}}$$

Hepatic impairment
Dactinomycin
Severe hepatic impairment dactinomycin not recommended.

Ifosfamide

Bilirubin >17micromol/L or AST and ALP >2.5xULN	discuss

Vincristine

Bilirubin 25-51 or AST 60-180u/L	give 50%
Bilirubin >51micromol/L and normal AST	give 50%
Bilirubin >51micromol/L and AST >180u/L	not recommended

Renal impairment
Ifosfamide

CrCl ≥50ml/min	give 100% dose
CrCl <50ml/min	Clinical decision

REFERENCES

1. EUROEWING12 2014
2. Casali abstract no 10067 ASCO 2007
3. DE Pas T, et al Annals of Oncology 13, 161-166, 2002