IE/VC

INDICATION (ICD10) C40, C41, C49

1. Ewing sarcoma

REGIMEN

IE cycles 1, 3 and 5

Days 1, 2, 3, 4 and 5

Mesna 1000mg/m^2 IV bolus one hour prior to ifosfamide
IFOSFAMIDE 1800mg/m^2 in 1000ml sodium chloride 0.9% IV infusion over 60 minutes
Mesna 1800mg/m^2 in 1000ml sodium chloride 0.9% IV infusion over 60 minutes concurrently with ifosfamide
ETOPOSIDE 100mg/m^2 in 1000ml* sodium chloride 0.9% IV infusion over 2 hours
Mesna 1200mg/m^2 in 1000ml sodium chloride 0.9% IV infusion over 16 hours

VC cycles 2 and 4

Day 1 VINCRISTINE 2mg/m^2 (maximum 2mg) in 50ml sodium chloride 0.9% IV infusion over 10 minutes
Mesna 1000mg/m^2 IV bolus one hour prior to cyclophosphamide
CYCLOPHOSPHAMIDE 1200mg/m^2 in 250ml sodium chloride 0.9% IV infusion over 60 minutes
Mesna 1200mg/m^2 in 1000ml sodium chloride 0.9% IV infusion over 60 minutes concurrently with ifosfamide
Mesna 800mg/m^2 in 1000ml sodium chloride 0.9% IV infusion over 23 hours

*doses 48mg to 88mg in 250ml, 96mg to 180mg in 500ml sodium chloride 0.9%

CYCLE FREQUENCY AND NUMBER OF CYCLES

Every 14 days or on haematological recovery to absolute neutrophil count ≥0.75x10^9/L, platelets ≥75x10^9/L.
Equivalent to cycles 10 to 14 following VDC/IE

ANTI-EMETICS

High emetic risk days 1, 2, 3, 4 and 5 cycles 1, 3 and 5 (consider aprepitant)
High emetic risk day 1 cycles 2 and 4 (consider aprepitant)

CONCURRENT MEDICATION REQUIRED

Cyclophosphamide	Ensure mesna administered, using separate lumen from cyclophosphamide. Ensure adequate oral fluid intake. Cotrimoxazole 480mg bd M/W/F for duration of chemotherapy. Benzydamine mouthwash
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 and stop at least 24 hours before commencing chemotherapy

EXTRAVASATION AND TYPE OF LINE / FILTERS

Cyclophosphamide - neutral
Doxorubicin – vesicant
Etoposide - irritant
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 ≥0.75
Platelets x 10^9/L ≥75
DTPA baseline
Creatinine clearance>55ml/min
Serum creatinine every cycle
Haematuria monitoring every specimen IE cycles, pre treatment only VC cycles
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

Cyclophosphamide	May irritate bladder, drink copious volumes of water. Microscopic Haemorrhagic cystitis: additional bolus dose 600mg/m^2 then continue infusion at double dose. Grade ≥2 macroscopic haemorrhagic cystitis: discontinue chemotherapy and continue double dose MESNA and hydration x 24 hours post-chemotherapy
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)

Cyclophosphamide	Cytochrome P450 enzyme inducers (e.g. rifampicin, carbamazepine, phenytoin, St Johns Wort, corticosteroids): may increase active cyclophosphamide metabolites. Allopurinol, Cimetidine and protease inhibitors: may increase active metabolites. Aprepitant, Ciprofloxacin, Fluconazole, Itraconazole: may reduce activation of cyclophosphamide and alter the effectiveness of treatment. Grapefruit juice: decreased or delayed activation of cyclophosphamide. Patients should be advised to avoid grapefruit juice.
Ifosfamide	Aprepitant and fosaprepitant are predicted to increase the exposure to ifosfamide. Caution.

DOSE MODIFICATIONS

Doxorubicin maximum lifetime dose
= 400mg/m^2 (in patients with cardiac dysfunction or exposed to mediastinal irradiation)
= 450-550mg/m^2 (with normal cardiac function).

Haematological

If platelets and ANC not recovering by day 22 give 80% VC/IE doses in subsequent cycles.

Non-haematological

Cardiac Toxicity
Fractional shortening (FS) <29% or left ventricular (LVEF) <40% or decrease by an absolute value of ≥10 percentile points from previous tests then delay chemotherapy course for 7 days and repeat cardiac tests. If FS has recovered to ≥29% then proceed to the next course. If FS remains <29% then omit doxorubicin and substitute dactinomycin 1.5mg/m^2 on day 1 only (max 1.5mg) or use liposomal doxorubicin when meet funding criteria.

Gastrointestinal toxicity
Grade 3/4 mucositis beyond day 22 after IE give 80% IE.

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	give 70% dose
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 2100mg/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

Etoposide

Bilirubin ≥50micromol/L or decreased albumin	give 50% dose

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

Cyclophosphamide

CrCl 10-29ml/min	give 75% dose

Etoposide

GFR<60ml/min/1.73m^2 then give 70% etoposide dose

Defer therapy and monitor renal function and discuss with consultant if there is a significant rise in serum creatinine, even if CrCl >60mls/min as ifosfamide may cause delayed renal impairment.

Ifosfamide

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

REFERENCES

1. EuroEwing 2012