VIDE

INDICATION (ICD10) C40, C41, C49

1. Ewing sarcoma
2. Desmoplastic small round cell sarcoma

REGIMEN

Day 1 VINCRISTINE 1.5mg/m^2 (maximum 2mg) in 50ml sodium chloride 0.9% IV infusion over 10 minutes

DOXORUBICIN 20mg/m^2 in 100ml sodium chloride 0.9% IV infusion over 4** hours

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

ETOPOSIDE 150mg/m^2 in 1000ml* sodium chloride 0.9% IV infusion over 60 minutes

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 16 hours

Days 2 and 3

DOXORUBICIN 20mg/m^2 in 100ml sodium chloride 0.9% IV infusion over 4** hours

ETOPOSIDE 150mg/m^2 in 1000ml* sodium chloride 0.9% IV infusion over 60 minutes

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 16 hours

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

**Reduce doxorubicin infusion duration to 1 hour each day for those receiving dexrazoxane (administered 30 minutes before doxorubicin).

CYCLE FREQUENCY AND NUMBER OF CYCLES

Every 21 days for up to 6 cycles

PBPC mobilisation and harvesting is strongly recommended following VIDE 3 and/or 4.
This is advised in patients with localised tumours <200ml and mandatory in patients with localised tumours ≥200ml or metastases to lungs/pleura only.

ANTI-EMETICS

High emetic risk days 1, 2 and 3 (consider aprepitant)

CONCURRENT MEDICATION REQUIRED

Doxorubicin – dexrazoxane cardioprotection	Dexrazoxane (Blueteq registration required) for patients under the age of 25 years receiving a cumulative anthracycline dose equivalent to doxorubicin ≥300mg/m^2. See OUH 'Dexrazoxane (Cardioxane®) Guidelines for Preventing Cardiotoxicity with High-dose Anthracyclines in Paediatric Haematology and Oncology' guidelines for dose, number of doses and administration information.
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 for 7 days

EXTRAVASATION AND TYPE OF LINE / FILTERS

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 ≥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
ECHO baseline and every 2nd cycle
Baseline weight and every cycle

MAIN TOXICITES AND ADVERSE REACTIONS

Doxorubicin	Cardiotoxicity – Monitor cardiac function to minimise the risk of anthracycline induced cardiac failure. Doxorubicin may be stopped in future cycles if signs of cardiotoxicity e.g. cardiac arrhythmias, pericardial effusion, tachycardia with fatigue.
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

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

Dose/time intensity is regarded as an essential aspect of induction strategy. In case of significant bone marrow toxicity preference should be given to GCSF support rather than dose reduction in order to maintain dose intensity.

If neutrophils <1.0x10^9/L or platelets <80x10^9/L then defer therapy by 1 week.

If significant toxicity continues as defined by:

Haematological recovery delayed > 6 days then give 80% etoposide dose

Neutropenic sepsis grade 3 or 4 then give 80% etoposide dose

Further episodes of toxicity should result in reductions in etoposide to 60% dose. If necessary it is advised to omit etoposide completely rather than reduce the doses of the other three drugs.

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

Mucositis/gastrointestinal (GI) toxicity grade 3 or 4 then give 80% etoposide dose

Further episodes of toxicity should result in reductions in etoposide to 60% dose. If necessary it is advised to omit etoposide completely rather than reduce the doses of the other three drugs.

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 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

Doxorubicin

Bilirubin 20-50micromol/L	give 50% dose
Bilirubin 51-85micromol/L	give 25% dose
Bilirubin >85micromol/L or Child-Pugh C	not recommended

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

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