VDC/IE

INDICATION (ICD10) C40, C41, C49

1. Ewing sarcoma
2. Desmoplastic small round cell tumour
3. Relapsed rhabdomyosarcoma

REGIMEN

VDC cycles 1, 3, 5, 7 and 9

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

DOXORUBICIN 37.5mg/m^2/day* in 100ml sodium chloride 0.9% IV infusion over 24** hours

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

CYCLOPHOSPHAMIDE 1200mg/m^2 in #ml 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 cyclophosphamide

Mesna 800mg/m^2 in 1000ml sodium chloride 0.9% IV infusion over 23 hours

Day 2 DOXORUBICIN 37.5mg/m^2/day* in 100ml sodium chloride 0.9% IV infusion over 24** hours

*Doxorubicin may be supplied as one 75mg/m^2 in 250ml sodium chloride 0.9% infusion to be administered over 48 hours starting on day 1 only

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

IE cycles 2, 4, 6 and 8

Days 1, 2, 3, 4 and 5

ETOPOSIDE 100mg/m^2 in #ml sodium chloride 0.9% IV infusion over 2 hours

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

IFOSFAMIDE 1800mg/m^2 in #ml 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

Mesna 1200mg/m^2 in 1000ml sodium chloride 0.9% IV infusion over 20 hours

diluent volume for dose prescribed as per national standardised product specification

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

ANTI-EMETICS

High emetic risk day 1 cycles 1, 3, 5, 7 and 9 (consider aprepitant)
Moderate emetic risk day 2 cycles 1, 3, 5, 7 and 9
High emetic risk days 1, 2, 3, 4 and 5 cycles 2, 4, 6 and 8 (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
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 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
Haematuria monitoring every specimen IE cycles, pre treatment only VDC cycles
DTPA baseline
Creatinine clearance >55ml/min
Serum creatinine every cycle
Vitamin D baseline
Hepatitis B status baseline
ECHO baseline every 2nd doxorubicin dose ie every 4th chemotherapy cycle
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
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)

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% VDC/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 15 after doxorubicin give 80% doxorubicin
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
Doxorubicin

Bilirubin 20-50micromol/L	give 50% dose
Bilirubin 51-86micromol/L	give 25% dose
Bilirubin >86micromol/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
Cyclophosphamide

CrC10-29ml/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