

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/m² (maximum 2mg) in 50ml sodium chloride 0.9% IV infusion over 10 minutes
- DOXORUBICIN 37.5mg/m²/day* in 100ml sodium chloride 0.9% IV infusion over 24** hours
- Mesna 1000mg/m² IV bolus one hour prior to cyclophosphamide
- CYCLOPHOSPHAMIDE 1200mg/m² in 250ml sodium chloride 0.9% IV infusion over 60 minutes
- Mesna 1200mg/m² in 1000ml sodium chloride 0.9% IV infusion over 60 minutes concurrently with cyclophosphamide
- Mesna 800mg/m² in 1000ml sodium chloride 0.9% IV infusion over 23 hours
- Day 2 DOXORUBICIN 37.5mg/m²/day* in 100ml sodium chloride 0.9% IV infusion over 24** hours

*Doxorubicin may be supplied as one 75mg/m² 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/m² in 1000ml* sodium chloride 0.9% IV infusion over 2 hours
- Mesna 1000mg/m² IV bolus one hour prior to ifosfamide
- IFOSFAMIDE 1800mg/m² in 1000ml sodium chloride 0.9% IV infusion over 60 minutes
- Mesna 1800mg/m² in 1000ml sodium chloride 0.9% IV infusion over 60 minutes concurrently with ifosfamide
- ~~ETOPOSIDE 100mg/m² in 1000ml* sodium chloride 0.9% IV infusion over 2 hours~~
- Mesna 1200mg/m² 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%

CYCLE FREQUENCY AND NUMBER OF CYCLES

Every 14 days or on haematological recovery to absolute neutrophil count $\geq 0.75 \times 10^9/L$, platelets $\geq 75 \times 10^9/L$

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 $\geq 300\text{mg}/\text{m}^2$. 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 $\times 10^9/\text{L}$ ≥ 0.75

Platelets $\times 10^9/\text{L}$ ≥ 75

Haematuria monitoring every specimen IE cycles, pre treatment only VDC cycles

DTPA baseline

Creatinine clearance $> 55\text{ml}/\text{min}$

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 TOXICITIES 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/m² (in patients with cardiac dysfunction or exposed to mediastinal irradiation)
= 450-550mg/m² (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/m² 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} (T _{mp} /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 HCO₃ 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/m²/day day 1 only.

Fractional phosphate clearance calculated

$$Tp/C_{crea} [\text{mmol/ml}] = \text{Phosphate}_{\text{serum}} - \frac{\text{Phosphate}_{\text{urine}} \times \text{creatinine}_{\text{serum}}}{\text{Creatinine}_{\text{urine}}}$$

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
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Ifosfamide

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

GFR<60ml/min/1.73m² 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

Requires CAG approval