VDC/IE – Vincristine, Doxorubicin & Cyclophosphamide (VDC) and Ifosfamide and Etoposide (IE)

Indication

Treatment of newly diagnosed Ewing's sarcoma family of tumours. Given with curative intent even when metastatic disease (lung or nodal) is present at diagnosis, or palliative in more extensive disease. May also be used in desmoplastic small round cell tumour (DSRCT).

ICD-10 codes

C40, C49

Regimen Overview

Induction phase	Cycle 1	Cycle 2	Cycle 3	Cycle 4	Cycle 5	Cycle 6	Cycle 7	Cycle 8	Cycle 9
	VDC	IE	VDC	IE	VDC	IE	VDC	IE	VDC
Definitive treatment (surgery or protons)									
Consolidation phase	Cycle 10	Cycle 11	Cycle 12	Cycle 13	Cycle 14				
	IE	VC	IE	VC	IE				

VDC – vincristine, doxorubicin, cyclophosphamide
IE – ifosfamide, etoposide
VC – vincristine, cyclophosphamide

Regimen details

NOTE: in patients whose surface area is > 2m^2 consider capping the dose

VDC

Day	Drug	Dose	Route
1	Vincristine	2mg/m^2 (dose capped at 2mg)	IV infusion over 10 mins
1 OR 1 + 2	Doxorubicin Doxorubicin	75mg/m^2 37.5mg/m2	IV bolus or IV infusion over 1 hour with dexrazoxane 750mg/m2 IV infusion given 30 minutes prior in patients ≤25 years old IV bolus or IV infusion over 1 hour
1	Mesna	240mg/m^2	IV bolus
1	Cyclophosphamide	1200mg/m^2	IV infusion over 1 hour
1	Mesna At 2 hours and 6 hours post end of cyclophosphamide infusion	480mg/m^2	Oral

IE

Day	Drug	Dose	Route
1-5	Etoposide	100mg/m^2	IV infusion over 1 hour
1-5	Mesna	360mg/m^2	IV bolus
1-5	Ifosfamide + Mesna	1800mg/m^2 1800mg/m^2	IV infusion over 1 hour
1-5	Mesna	400mg/m^2	IV infusion over 2 hours

VC

Day	Drug	Dose	Route
1	Vincristine	2mg/m^2 (dose capped at 2mg)	IV infusion over 10 mins
1	Mesna	240mg/m^2	IV bolus
1	Cyclophosphamide*	1200mg/m^2	IV infusion over 1 hour
1	Mesna At 2 hours and 6 hours post end of cyclophosphamide infusion	480mg/m^2	Oral

*Patients who required dose reduction of cyclophosphamide during VDC cycles should be reviewed for re-escalation for full dose during VC cycles.

Cycle frequency

14 days

Number of cycles

Induction – 9 cycles of alternating VDC/IE
Consolidation – 5 cycles of alternating IE/VC
See regimen overview above for full details.

Administration

VDC and VC cycles:

Vincristine is administered in 50mL sodium chloride 0.9% over 10 minutes, as per national guidance. Nurse to remain with patient throughout infusion.

Dexrazoxane (Cardioxane®, where commissioned) is administered as an intravenous infusion in compound sodium lactate over 15 minutes. Dexrazoxane should be administered 30 minutes prior to doxorubicin.

Doxorubicin may be administered as an IV bolus, or IV infusion in 250mL Sodium Chloride 0.9% over 1 hour. The latter is preferred as it may reduce the risk of cardiotoxicity. Doxorubicin is only administered during the induction phase.

Cyclophosphamide is administered in 500mL sodium chloride 0.9% over 1 hour.

Mesna is administered as an IV bolus immediately prior to cyclophosphamide. Oral mesna is then administered at 2 hours and 6 hours post the end of the cyclophosphamide infusion. Mesna is available as 400mg and 600mg tablets and doses should be rounded up to the nearest tablet size.

1000mL sodium chloride 0.9% with 20mmol potassium chloride over 2 hours should be administered immediately following cyclophosphamide administration and patients should maintain an oral intake of 2L of fluid on treatment days.

IE cycles:
Etoposide is administered in 1000mL sodium chloride 0.9% over 1 hour.

Ifosfamide with mesna is administered in 1000mL sodium chloride 0.9% over 1 hour.

Mesna is administered as an IV bolus immediately prior to ifosfamide. Mesna is also administered in 1000mL sodium chloride 0.9% as post-hydration over 2 hours following the ifosfamide infusion. A further 1000mL post-hydration should be administered over 6 hours following mesna administration in patients that cannot maintain adequate oral fluid intake of 2L per day.

Pre-medication
Nil

Emetogenicity
VDC – high
VC – moderate
IE - high
NB. NK-1 inhibitors can increase exposure to ifosfamide. Consider avoiding during IE cycles if prior ifosfamide toxicity

Additional supportive medication
Antiemetics as per local policy
Benzydamine mouthwash as required
Proton pump inhibitor on days where steroids given
PCP prophylaxis e.g. co-trimoxazole
Laxatives as required
PRN Mesna doses should be prescribed to be used in event of significant haematuria. Mesna 1g IV bolus or 1800mg oral stat (see below)
PRN Methylene blue 50 mg IV bolus over 5 mins for encephalopathy (see cautions below)
GCSF for 7 days, starting on day 6 in VDC and VC cycles, day 7 in IE cycles.

Extravasation
Vincristine – vesicant
Doxorubicin – vesicant
Cyclophosphamide – neutral
Ifosfamide – neutral
Etoposide - irritant

Investigations – pre first cycle

Investigation	Validity period
FBC	14 days
U&E (including creatinine)	14 days
LFTs	14 days
Echocardiogram	3 months

Consider performing baseline measured GFR if:
- Pre-existing renal dysfunction (calculated GFR < 70ml/min)
- Disease involving the kidney or previous nephrectomy

Investigations – pre subsequent cycles

Investigation	Validity period
FBC	72 hours
U&E	72 hours
LFTs	72 hours
Echocardiogram	Pre cycle 7

Consider repeating measured GFR if:

- Persisting trend of rising creatinine by > 20mmol/L at the start of two consecutive cycles of chemotherapy
- Creatinine rises outside of the normal range
- Renal dysfunction (calculated GFR < 70ml/min)

Standard limits for administration to go ahead

If blood results not within range, authorisation to administer **must** be given by prescriber/ consultant

Investigation	Limit
Neutrophils	0.75 x10^9/L
Platelets	75 x 10^9/L
Bilirubin	see dose modifications for hepatic toxicity below
Albumin	≥35 g/dL (see hepatic toxicity section if out of range)
Creatinine Clearance	see dose modifications for renal toxicity below. If creatinine rise of >20mmol/l since previous cycle then contact doctor for review.
Left ventricular ejection fraction	≥ 50% and less that 10% decline from baseline

Monitoring required during treatment

Investigation	Frequency of monitoring
Weight	Daily during chemo (see below)
Urine dip	At baseline and after each subsequent urine void during IE cycles
Mental status	Document at start of each nursing shift during IE cycles, flag any changes to doctors immediately.

Dose modifications

- ### Haematological toxicity

If neutrophils <0.75 x 10^9/L or platelets <75 x10^9/L delay treatment until count recovery. If FBC has not recovered to required levels by day 22, reduce doses for all subsequent cycles in the current phase of treatment (i.e. induction or consolidation) as per table below:

Regimen	Dose reduction recommendations
VDC	Reduce doxorubicin and cyclophosphamide doses by 20% (but consider re-escalation of cyclophosphamide for cycles 11 and 13 when doxorubicin dropped)
IE	Reduce etoposide doses by 20%. Consider a 20% dose reduction of ifosfamide if haematological toxicity with subsequent cycles.
VC	Reduce cyclophosphamide doses by 20%

If count recovery has not occurred by day 22 despite dose reduction, reduce doses by a further 20%.

If grade 3 or 4 febrile neutropenia subsequent cycles should be reduced as above.

- **Renal impairment**

Vincristine – no dose adjustment is expected.

Dexrazoxane – if CrCl < 40ml/min, reduce to 50% dose.

Doxorubicin – no dose adjustment is expected.

Cyclophosphamide

Creatinine Clearance	Cyclophosphamide dose
>20ml/min	100%
10-20ml/min	75%
<10ml/min	50%

Ifosfamide

Creatinine Clearance	Ifosfamide dose
>60ml/min	100%
<60ml/min	Omit, switch to Cyclophosphamide 2100mg/m^2 on day 1 only.

Etoposide

Creatinine Clearance	Etoposide dose
>50ml/min	100%
15-50ml/min	75%
<15ml/min	50%

- **Hepatic impairment**

VDC cycles:

Bilirubin (mmol/L)	Vincristine dose	Doxorubicin dose	Cyclophosphamide dose
21-50	100%	50%	Full dose
51-86	50%	25%	Use full dose with caution, potential reduced efficacy
>86	Omit	Omit	

Dexrazoxane – dosing ratio, should be kept the same (i.e. 10 x doxorubicin dose) so adjust in line with doxorubicin dosing.

IE cycles:

Bilirubin (mmol/L)	Ifosfamide dose	Etoposide dose*
<26	100%	100%
26-50	100%	50%
>50	75%	25% or omit (consultant decision)

*Etoposide is highly protein bound so albumin level is a better predictor of toxicity than LFTs. Reduced albumin levels means increased free drug so increased toxicity. Therefore, consider dose reduction if albumin levels significantly reduced.

- **Other toxicities**

Toxicity	Definition	Dose adjustment
Decline in left ventricular ejection fraction (LVEF)	LVEF < 50% or a decline in LVEF by 10 percentage points or more from baseline	Hold chemo and repeat echocardiogram in 7 days. patients should be started on a beta-blocker (e.g. bisoprolol 1.25mg od) and an angiotensin-converting enzyme (ACE) inhibitor (e.g. ramipril 1.25mg od), and referred to a cardiologist. If no improvement switch to actinomycin-D 1.5mg/m^2 on day 1 only. Repeat cardiac imaging prior to next VDC cycle and if normalised, re-commence doxorubicin at usual dose
Mucositis	Grade 3: severe pain interfering with oral intake *or* Grade 4: life threatening, urgent intervention needed	If persists beyond D15 VDC then reduce subsequent doxorubicin doses to 75% If persists beyond D21 IE reduce both etoposide and ifosfamide to 75% on subsequent cycles
Weight gain due to fluid overload	Gain of >2kg during inpatient chemotherapy ***and*** symptoms or signs of fluid overload	Give furosemide 20mg IV STAT

Management of Ifosfamide-specific toxicities

Urinary monitoring for haemorrhagic cystitis and fluid status monitoring:

- Urinalysis for blood should be performed at baseline and at every subsequent urine void.
- For female patients, consider menstruation status if microscopic haematuria.
- Strict fluid input / output monitoring is required throughout admission
- Mesna 1g IV bolus or 1800mg oral stat to be written on prn side of drug chart on admission

Haemorrhagic cystitis:
Mesna is given alongside both cyclophosphamide and ifosfamide to minimise the risk of haemorrhagic cystitis.

Urine dipstick for blood	Action
0	No action
1+	No action - repeat with next void If 1+ on 2 occasions, contact medical team and give Mesna bolus
≥2+	Administer bolus of Mesna 1g iv bolus (or 1800mg oral stat) then contact medical team to consider doubling the dose of infusional Mesna on patient's chemotherapy chart.
Further positive urinalysis ≥2+	Repeat bolus of Mesna Double the dose of infusional Mesna on patient's chemotherapy chart if not done already. If occurs while Mesna running at double dose, contact consultant urgently as decision on continuation of ifosfamide will need to be made
≥ Grade 2 (symptomatic; urinary catheter required, or bladder irrigation required, limiting ADL)	Discontinue ifosfamide, continue double dose Mesna and hydration for 24hrs after chemo stopped
If dose of infusional Mesna is increased, this should also be changed for all subsequent cycles	

Ifosfamide-induced encephalopathy

Ifosfamide can cause encephalopathy. This should be actively monitored for and treated as per the grade of severity.

Assess risk factors for neurotoxicity pre-ifosfamide administration:

- Previous Ifosfamide-induced encephalitis
- Albumin <30 g/L or fluid overload
- Creatinine >150µmol/L
- Large pelvic tumour
- Hyponatraemia (<130mmol/L) / hypokalaemia (<3mmol/L)

If any risk factors present consider methylene blue* 50 mg IV bolus (over 5 mins) TDS for the duration of ifosfamide infusions.
If no risk factors present, prescribe methylene blue* 50 mg IV bolus (over 5 mins) PRN on the drug chart

Nurse to alert Doctor IMMEDIATELY if patient develops confusion, drowsiness, hallucinations, incontinence, clumsiness, agitation, change in speech, vision or hearing OR any other deviation from neurological baseline.

Situation	Action
Grade 1 - mild somnolence or agitation	• Document mental state each shift in nursing notes. • Ensure ifosfamide infusion runs no faster than 1g/m^2/hour
Grade 2 – moderate somnolence or agitation	• Ensure ifosfamide infusion is running no faster than 1g/m^2/hour • Start Methylene Blue 50mg 4 hourly • Continue 4-hourly Methylene blue until encephalopathy has resolved to Grade 0, then switch to prophylactic dose (8 hourly) • If neurotoxicity deteriorates to >grade 2, **stop ifosfamide** but continue Mesna infusion • If recurs despite prophylactic methylene blue, consider switching to cyclophosphamide.
Grade 3 – severe somnolence or agitation or onset of confusion, disorientation or hallucinations	• **Stop ifosfamide infusion** • Ensure Mesna continues to run to completion of planned infusion. • Start methylene blue* 50mg 4 hourly and continue until resolution of symptoms. • Other supportive measures may be considered • Monitor neurological status • Outreach review • Do not give further ifosfamide, instead substitute for cyclophosphamide.
Grade 4 – coma, seizure or toxic psychosis	

*Contraindications for methylene blue: known G6PD deficiency. Side effects: rare but serious; hypotension, cardiac arrhythmias. Common; nausea, abdominal pain, blue discoloration of urine, stools and saliva.

Adverse effects - for full details consult product literature/ reference texts

- **Serious side effects**

Myelosuppression
Neutropenic sepsis
Encephalopathy, memory impairment
Haemorrhagic cystitis
Peripheral neuropathy
Nephrotoxicity

- **Frequently occurring side effects**

Neutropenia
Thrombocytopenia
Anaemia
Microscopic haematuria

- **Other side effects**

Alopecia
Infertility

Significant drug interactions – for full details consult product literature/ reference texts

Warfarin/coumarin anticoagulants: increased or fluctuating anticoagulant effects. Avoid if possible, consider switching patient to a low molecular weight heparin or DOAC during treatment, or if the patient continues taking an oral anticoagulant monitor the INR at least once a week and adjust dose accordingly.

Vincristine:
Itraconazole, voriconazole, posaconazole: increase severity of neuromuscular side effects. Avoid for 72 hours either side of vincristine dose if concurrent use cannot be avoided.

Doxorubicin:
Ciclosporin: reduced clearance of doxorubicin due to CYP3A4 and P-gp inhibition. Monitor closely for toxicity.

Cyclophosphamide:
Amiodarone: increased risk of pulmonary fibrosis – avoid if possible
Clozapine: increased risk of agranulocytosis – avoid concomitant use
Digoxin tablets: reduced absorption – give as liquid form
Indapamide: prolonged leucopenia is possible - avoid
Itraconazole: may increase adverse effects of cyclophosphamide
Phenytoin: reduced absorption - may need to increase dose of phenytoin
Grapefruit juice: decreased or delayed activation of cyclophosphamide. Patients should be advised to avoid grapefruit juice for 48 hours before and on day of cyclophosphamide dose.

Ifosfamide:
Amiodarone: increased risk of pulmonary toxicity – avoid if possible
Aprepitant, Fosaprepitant, Netupitant: increases exposure of ifosfamide, avoid or use with caution.
Nephrotoxic agents: increased risk of nephrotoxicity, avoid where possible.

Etoposide:
Ciclosporin: increases exposure to etoposide, monitor closely and consider dose adjustment
Phenylbutazone, sodium salicylate and salicylic acid: can affect protein binding of etoposide.
Phenytoin, phenobarbital, carbamazepine: increased etoposide clearance and potential for reduced efficacy

Additional comments

The maximum cumulative dose of doxorubicin is 450-550mg/m^2. In patient with cardiac risk factors the maximum cumulative dose is 400mg/m^2.

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