IVADo

INDICATION (ICD10) C49
1. Rhabdomyosarcoma high and very high risk.

REGIMEN
Cycles 1 to 4
Day 1 VINCRISTINE 1.5mg/m^2 (maximum 2mg) in 50ml sodium chloride 0.9% IV infusion over 10 minutes
DACTINOMYCIN 1.5mg/m^2 (maximum 2mg) IV bolus
DOXORUBICIN 30mg/m^2 in 100ml sodium chloride 0.9% IV infusion over 4 hours (give after ifosfamide if administered via central line)
Mesna 1000mg/m^2 IV bolus one hour prior to ifosfamide
IFOSFAMIDE 3000mg/m^2 with Mesna 3000mg/m^2 in 1000ml sodium chloride 0.9% IV infusion over 3 hours
Mesna 3000mg/m^2 in 1000ml sodium chloride 0.9% IV infusion over 21 hours (16 hours if doxorubicin administered before ifosfamide)

Day 2 DOXORUBICIN 30mg/m^2 in 100ml sodium chloride 0.9% IV infusion over 4 hours (give after ifosfamide if administered via central line)
IFOSFAMIDE 3000mg/m^2 with Mesna 3000mg/m^2 in 1000ml sodium chloride 0.9% IV infusion over 3 hours
Mesna 3000mg/m^2 in 1000ml sodium chloride 0.9% IV infusion over 12 hours

Cycles 1 and 2 only
Day 8 VINCRISTINE 1.5mg/m^2 (maximum 2mg) in 50ml sodium chloride 0.9% IV infusion over 10 minutes
Day 15 VINCRISTINE 1.5mg/m^2 (maximum 2mg) in 50ml sodium chloride 0.9% IV infusion over 10 minutes

Cycles 5 to 9
Day 1 VINCRISTINE 1.5mg/m^2 (maximum 2mg) in 50ml sodium chloride 0.9% IV infusion over 10 minutes
DACTINOMYCIN 1.5mg/m^2 (maximum 2mg) IV bolus
Mesna 1000mg/m^2 IV bolus one hour prior to ifosfamide
IFOSFAMIDE 3000mg/m^2 with Mesna 3000mg/m^2 in 1000ml sodium chloride 0.9% IV infusion over 3 hours
Mesna 3000mg/m^2 in 1000ml sodium chloride 0.9% IV infusion over 21 hours

Day 2 IFOSFAMIDE 3000mg/m^2 with Mesna 3000mg/m^2 in 1000ml sodium chloride 0.9% IV infusion over 3 hours
Mesna 3000mg/m^2 in 1000ml sodium chloride 0.9% IV infusion over 12 hours

Consider capping doses at BSA 2.0m^2

CYCLE FREQUENCY AND NUMBER OF CYCLES
Every 21 days for 9 cycles

ANTI-EMETICS
High emetic risk days 1 and 2
Minimal emetic risk days 8 and 15

CONCURRENT MEDICATION REQUIRED

Ifosfamide	Ensure mesna administered. Ensure adequate oral fluid intake. Hydration Cotrimoxazole 480mg bd M/W/F for duration of chemotherapy. Laxatives should be prescribed
GCSF	Starting at least 24 hours after chemotherapy to maintain dose intensity (until WCC >5x10^9/l)

EXTRAVASATION AND TYPE OF LINE / FILTERS

Dactinomycin – vesicant
Doxorubicin - vesicant
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
Creatinine clearance >55ml/min
Serum creatinine every cycle
DTPA baseline and alternate cycles
Haematuria monitoring every specimen
ECHO baseline every 2 cycles
Vitamin D baseline
Hepatitis B status baseline
Baseline weight and every cycle

MAIN TOXICITES AND ADVERSE REACTIONS

Dactinomycin	Myelosuppression, mucositis, liver changes
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)

Non-haematological

Dactinomycin
Omit for duration of concurrent radiotherapy (omitted doses are not subsequently given).
In case of veno occlusive disease (VOD) dactinomycin should not be given until the main abnormalities have returned to normal and give 50% dose in the following course. If tolerated dactinomycin dose may be increased progressively in the following cycles. If the symptoms reappear during dactinomycin treatment, this drug should be withdrawn permanently.

Doxorubicin
Significant deterioration in cardiac function is indicated by a shortening fraction <28%, in this event temporarily withdraw doxorubicin.
A fall in shortening fraction by an absolute value of >10 percentile units but with an actual SF value >28% may also represent a significant deterioration in function, in this event omit doxorubicin in the next course.
If the decrease is not persistently proven, i.e. if repeated investigations (after a week) cannot reproduce the dysfunction, doxorubicin can be recommenced (and the omitted dose of doxorubicin should be supplied instead of dactinomycin with the first possible cycle).
If persistent deterioration of myocardial function occurs, eg persistent decrease in fractional shortening by an absolute value of 10 percentile points from previous tests or a persistent fractional shortening below 28%, consider further avoidance of doxorubicin and the patient should be referred to a cardiologist.

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	Discuss
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

$$Tp/C_{crea}\ [mmol/ml] = Phosphate_{serum} - \frac{Phosphate_{urine} \times creatinine_{serum}}{Creatinine_{urine}}$$

Vincristine
Grade 3-4 peripheral neuropathy (intolerable paraesthesia, marked motor loss, paralysis or paralytic ileus) one or two injections of vincristine should be omitted and restarted at a 50% dose.

Hepatic impairment

Dactinomycin

Consider dose reduction with hepatic dysfunction

Doxorubicin

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

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

Ifosfamide

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

REFERENCES

1. RMS 2005