Systemic Anti Cancer Therapy Protocol

Doxorubicin, ICE, VCA +/- Intrathecal methotrexate

PROTOCOL REF: MPHADIVSA
(Version No: 1.0)

Approved for use in:

Atypical teratoid or rhabdoid tumour of the CNS

Dosage:

Schedule:

Cycle	1	2	3	4	5	6
Every 21 days	DOX (+MTX)	ICE (+MTX)	VAC (+MTX)	DOX (+MTX)	ICE (+MTX)	VAC
Cycle	**7**	**8**	**9**			
Every 21 days	DOX	ICE	VAC			

DOX- Doxorubicin

ICE- Ifosfamide, Carboplatin /Etoposide

VCA-Vincristine, Cyclophosphamide, Dactinomycin

MTX- Intrathecal Methotrexate (to be given only if clinically indicated)

DOX

Drug	Dose	Route	Frequency
Doxorubicin	**75mg/ m^2**	IV	Day 1

Maximum cumulative dose of doxorubicin: 450 to 550mg/m^2

Perform baseline ejection function assessment (ECHO or MUGA) if patient is considered at risk of significantly impaired cardiac contractility.

Use alternative regimen if cardiac ejection fraction < 50%

ICE

Drug	Dose	Route	Frequency
Ifosfamide	**2000mg/ m^2**	IV infusion	Days 1,2 and 3
Carboplatin	**AUC 4 or 5**	IV infusion	Day 1
Etoposide	**100mg/ m^2**	IV infusion	Days 1,2 and 3
Mesna	See administration		

Calvert formula for Carboplatin dosage-

Carboplatin dose in mg = AUC x (creatinine clearance + 25)

If estimated GFR is used the Wright formula must be used for creatinine clearance.

Creatinine clearance should be capped at 125mL/min for carboplatin

Avoid the use of Cockcroft and Gault formulae as it is less accurate.

VAC

Drug	Dose	Route	Frequency
Vincristine	**1.5mg/ m^2** (max 2mg)	IV infusion	Days 1 and 8
Dactinomycin	**0.75mg/m2** (max 1.5mg)	IV infusion	Days 1 and 2.
Cyclophosphamide	**1500mg/m2**	IV infusion	Day 1
Mesna	See administration		

Omit dactinomycin for the duration of radiotherapy

Resume dactinomycin after completion of radiotherapy according to symptoms

MTX

To be prescribed on an intrathecal chart only if clinically indicated.

Intrathecal methotrexate should only be used **before** radiotherapy not concurrent or after radiotherapy.

Drug	Dose	Route	Frequency
Methotrexate	**12.5mg**	intrathecal	Cycles **1 to 5.** See treatment schedule below for details of treatment days

See the intrathecal policy for further information.

Note the MTX should be administered in the designated intrathecal room.

Administration:

Emetogenic risk

Anti-emetic risk - High

Aprepitant 125mg day 1, and 80mg days 2 and 3 (of ICE)

Dexamethasone tablets, 4mg twice a day for 3 days

Domperidone 10mg oral tablets, up to 3 times a day or as required

Supportive treatments:

Filgrastim (following ICE and VAC)

For patients under 70kg: 30MU subcutaneous injection daily

For patients 70kg and above: 48MU subcutaneous injection daily

Extravasation risk (if applicable):

Doxorubicin- vesicant- follow Trust policy,

Ifosfamide- irritant

Carboplatin- irritant

Etoposide- irritant

Vincristine- vesicant- follow Trust policy, specific antidote may be required

Dactinomycin- vesicant- follow Trust policy,

Cyclophosphamide- non vesicant

Vincristine- vesicant- follow Trust/network policy, specific antidote may be required

Refer to the CCC policy for the 'Prevention and Management of Extravasation Injuries'

Treatment schedule:

	DOX (cycles 1, 4 and 7)			
Day	**Drug**	**Dose**	**Route**	**Diluent and rate**
1	Dexamethasone	8mg	PO	30 mins before chemotherapy
	Ondansetron	16mg	PO	30 mins before chemotherapy
	Doxorubicin	**75mg/m^2**	**IV**	IV bolus over 10 to 15 minutes Concurrent administration, doxorubicin at 400ml/hr and sodium chloride 0.9% at 100ml/hr
	Methotrexate	**12.5mg**	**Intrathecal**	Cycle 1 and 4 only
2	**Methotrexate**	**12.5mg**	**Intrathecal**	Cycle 1 and 4 only
3	**Methotrexate**	**12.5mg**	**Intrathecal**	Cycle 1 and 4 only
4	**Methotrexate**	**12.5mg**	**Intrathecal**	Cycle 1 and 4 only

	ICE (cycles 2, 5 and 8)			
Day	**Drug**	**Dose**	**Route**	**Diluent and rate**
1	Aprepitant	125mg	PO	30 minutes before chemotherapy
	Dexamethasone	8mg	PO	30 minutes before chemotherapy
	Ondansetron	16mg	PO	30 minutes before chemotherapy
	Etoposide	**100mg/m^2**	IV	in 1000ml of sodium chloride 0.9% over 1 hour
	Carboplatin	**AUC 4 or 5**	**IV**	in 500ml glucose 5% over 1 hour
	Mesna	400mg/m^2	IV	in 500mL sodium chloride 0.9% over 1 hour
	Ifosfamide + mesna	**2000mg/m^2 + 2000mg/m^2**	**IV**	in 1000mL sodium chloride 0.9% over 4 hours
	Mesna	1200mg/m^2	IV	in 1000mL sodium chloride over 8 hours
	Methotrexate	**12.5mg**	**Intrathecal**	Cycle 2 and 5 only
2	Aprepitant	80mg	PO	30 minutes before chemotherapy
	Dexamethasone	8mg	PO	30 minutes before chemotherapy
	Ondansetron	16mg	PO	30 minutes before chemotherapy
	Mesna	400mg/m2	IV	In 500ml sodium chloride 0.9% over 1 hour
	Etoposide	**100mg/m^2**	**IV**	in 1000ml of sodium chloride 0.9% over 1 hour
	Ifosfamide + mesna	**2000mg/m^2 + 2000mg/m^2**	**IV**	in 1000mL sodium chloride 0.9% over 4 hours
	Mesna	1200mg/m^2	IV	in 1000mL sodium chloride over 8 hours
	Methotrexate	**12.5mg**	**Intrathecal**	Cycle 2 and 5 only

	Aprepitant	80mg	PO	30 minutes before chemotherapy
	Dexamethasone	8mg	PO	30 minutes before chemotherapy
	Ondansetron	16mg	PO	30 minutes before chemotherapy
	Mesna	400mg/m2	IV	In 500ml sodium chloride 0.9% over 1 hour
	Etoposide	**100mg/m^2**	**IV**	in 1000ml of sodium chloride 0.9% over 1 hour
	Ifosfamide + mesna	**2000mg/m^2 + 2000mg/m^2**	**IV**	in 1000mL sodium chloride 0.9% over 4 hours
	Mesna	1200mg/m^2	IV	in 1000mL sodium chloride over 8 hours
3	**Methotrexate**	**12.5mg**	**Intrathecal**	Cycle 2 and 5 only
4	**Methotrexate**	**12.5mg**	**Intrathecal**	Cycle 2 and 5 only
	Filgrastim	**30MU or 48MU**	**S/C**	By subcutaneous injection daily for 7 days and then repeat FBC

Facilities to treat anaphylaxis must be present when administering carboplatin.

If a patient experiences an infusion-related reaction, give future does with pre-medication cover of IV chlorphenamine 10mg and IV hydrocortisone 100mg (see Trusts 'Management of Hypersensitivity Policy')

	VAC (cycles 3, 6 and 9)			
Day	**Drug**	**Dose**	**Route**	**Diluent and rate**
1	Dexamethasone	8mg	PO	30 minutes before chemotherapy
	Ondansetron	16mg	PO	30 minutes before chemotherapy
	Vincristine	1.5 mg/m^2 (max 2mg)	IV	in 50mL sodium chloride 0.9%
	Dactinomycin	0.75mg/m^2 (max 1.5mg)	IV	in 100mL sodium chloride 0.9% over 30 minutes
	Mesna	500mg/m^2	IV	in 500mL sodium chloride 0.9% over 1 hour
	Cyclophosphamide + mesna	1500mg/m^2 + 1500mg/m^2	IV	in 1000mL sodium chloride 0.9% over 3 hours
	Mesna	1500mg/m^2	IV	in 1000mL sodium chloride over 8 hours
	Methotrexate	**12.5mg**	**Intrathecal**	Cycle 3 only
2	Dexamethasone	8mg	PO	24 hours after day 1 dose
	Ondansetron	16mg	PO	24 hours after day 1 dose
	Dactinomycin	0.75mg/m^2 (max 1.5mg)	IV	in 100mL sodium chloride 0.9% over 30 minutes
	Methotrexate	**12.5mg**	**Intrathecal**	Cycle 3 only
3	**Methotrexate**	**12.5mg**	**Intrathecal**	Cycle 3 only
	Filgrastim	**30MU or**	**SC**	By subcutaneous injection daily

		48MU		for 7 days and then repeat FBC
8	**Vincristine**	1.5 mg/m^2 (max 2mg)	IV	in 50mL sodium chloride 0.9%

Main toxicities:

Thrombocytopenia, neutropenia, anaemia, nausea, vomiting, diarrhoea

Dox	
Doxorubicin	Ovarian failure/infertility
ICE	
Ifosfamide	Nephrotoxicity, central neurotoxicity, haemorrhagic cystitis leading to bladder fibrosis, ovarian failure
Carboplatin	Anaphylaxis, nephrotoxicity, dehydration, tumour lysis syndrome, neuropathy, ototoxicity
Etoposide	Dizziness, hypertension, hepatoxicity
VAC	
Vincristine	neurotoxicity,
Dactinomycin	alopecia, mucositis, liver changes (rare) ovarian failure / infertility
Cyclophosphamide	alopecia, mucositis, haemorrhagic cystitis

See individual SPCs for further information

Investigations and treatment plan:

	Pre	Cycle 1	Cycle 2	Cycle 3	Cycle 4	Cycle 5	Cycle 6	Cycle 7	Cycle 8	Cycle 9	Ongoing
Informed Consent	X										
Clinical Assessment	X	x	x	x	x	x	x	x	x	x**	As clinically indicated or at the end of treatment
SACT Assessment (to include PS and toxicities)	X	x	x	x	x	x	x	x	x	x	Every cycle
FBC	X	x	x	x	x	x	x	x	x	x	Every cycle
U&E & LFTs & Magnesium	X	x	x	x	x	x	x	x	x	x	Every Cycle
CrCl (Cockcroft and Gault and wright)	X	x	x	x	x	x	x	x	x	x	Every cycle
CT scan**	X										At the end of treatment and if clinically indicated
ECG											If clinically indicated by the consultant
Weight recorded	X	x	x	x	x	x	x	x	x	x	Every cycle
Urine dipstick for protein/blood	X	x	x	x	x	x	x	x	x	x	

Dose Modifications and Toxicity Management:

DOX

Haematological toxicity

Proceed on day 1 if all apply:-

ANC ≥ 1.0 x 10^9/L	Platelets ≥ 100 x 10^9/L

Delay 2 days at day 1 if any apply:-

ANC ≤ 0.9 x 10^9/L	Platelets ≤ 99 x 10^9/L

If platelets or ANC still below required levels for treatment after deferral, patient will need assessment and consideration of chemotherapy dose reduction. **Refer to the consultant**

Non-haematological toxicity

<table>
<tr><td>Renal</td><td>No dose adjustments needed</td></tr>
<tr><td>Hepatic</td><td>
<table>
<tr><th>Bilirubin (µmol/L)</th><th>Doxorubicin dose</th></tr>
<tr><td>20 to 50</td><td>50%</td></tr>
<tr><td>51 to 85</td><td>25%</td></tr>
<tr><td>Above 85</td><td>Omit</td></tr>
</table>
</td></tr>
<tr><td>Cardiomyopathy</td><td>Perform baseline MUGA in any patient with suspected cardiac impairment. If cardiac ejection fraction < 50% discuss with consultant and consider an alternative regimen.

Consider a lower maximum cumulative doxorubicin dose of 400mg/m^2 for any patient with cardiac dysfunction or that has been exposed to mediastinal radiation

Note that cardiomyopathy may be delayed – if 20% reduction if LVEF after 300mg/m^2 then stop doxorubicin</td></tr>
</table>

ICE

Haematological toxicity

Proceed on day 1 if:-

WCC ≥ 1.0 x 10^9/L	ANC ≥ 1.0 x 10^9/L	Platelets ≥ 100 x 10^9/L

If below these levels, discuss with consultant and repeat every 2 to 3 days until recovered.

Ensure that filgrastim is prescribed and given.

If there is significant bone marrow toxicity reduce etoposide as shown rather than any of the other agents:

Parameter	Action
WBC or platelets recovery > 6 days	Give 80% etoposide
Neutropenic sepsis grade 3 / 4	Give 80% etoposide

If there is further bone marrow toxicity then reduce etoposide dose by a further 20%. If necessary omit etoposide completely rather than reduce dose of any of the other drugs.

Non-haematological toxicity

<table>
<tr><td>GI / mucositis</td><td>If grade 3 / 4 give 80% dose of etoposide. If there is further GI toxicity then reduce etoposide by a further 20%. If necessary omit etoposide completely rather than reduce doses of the other drugs.</td></tr>
<tr><td>Hepatic</td><td>Ifosfamide – note that ifosfamide is generally not recommended if bilirubin > ULN or ALP > 2.5 ULN – discuss with consultant if this is the case. See comments above about ifosfamide dose reductions

Carboplatin- minimal hepatic metabolism, no specific dose adjustment guidelines available.

Etoposide – conflicting information exists for reductions with etoposide, use table below but discuss with the consultant if in doubt
<table>
<tr><th>Bilirubin (µmol/L)</th><th>AST/ALT (units/l)</th><th>Etoposide Dose</th></tr>
<tr><td>26 to 51 or</td><td>60 to 180</td><td>50%</td></tr>
<tr><td>Above 51 or</td><td>Above 180</td><td>Clinical decision</td></tr>
</table></td></tr>
<tr><td>Renal</td><td>Measure serum creatinine each cycle and calculate CrCl using Cockroft and Gault before each cycle of Ifosfamide.</td></tr>
</table>

	<table><tr><th>GFR (mL/min)</th><th>Ifosfamide dose</th><th>Etoposide dose</th></tr><tr><td>Above 60</td><td>100%</td><td>100%</td></tr><tr><td>40 to 59</td><td>70%</td><td>70%</td></tr><tr><td>Below 40</td><td>Clinical decision</td><td>70%</td></tr></table> Monitor renal function closely and if there is a significant rise in serum creatinine even if CrCl> 60 mL/min discuss with consultant as ifosfamide may cause delayed impairment. Carboplatin: Patients with creatinine clearance values of less than 60 mL/min are at greater risk to develop myelosuppression. The optimal use of Carboplatin in patients presenting with impaired renal function requires adequate dosage adjustments and frequent monitoring of both haematological nadirs and renal function. In case of a glomerular filtration rate of ≤ 20 mL/min, carboplatin should not be administered at all.
Neurotoxicity	See treatment of ifosfamide induced encephalopathy information below

VAC

Haematological toxicity

Proceed on day 1 if:-

ANC ≥ 1.0 x 10^9/L	Platelets ≥ 100 x 10^9/L

Delay 2 days on day 1 if:-

ANC ≤ 0.9 x 10^9/L	Platelets ≤ 99 x 10^9/L

Parameter	1st Occurrence	2nd Occurrence
Delayed recovery > 6 days OR neutropenic sepsis grade 3 or 4	Reduce cyclophosphamide, dactinomycin and doxorubicin to **80%** of original dose	Reduce cyclophosphamide, dactinomycin and doxorubcin to **60%** of original dose

Non-haematological toxicity

<table>
<tr><td>Renal</td><td>Monitor serum creatinine before each cycle of chemotherapy. Calculate CrCl each time. Routine adjustment of cyclophosphamide is not needed as it is altered hepatically although most sources suggest
<table>
<tr><th>CrCl</th><th>Cyclophosphamide dose</th><th>Etoposide dose</th></tr>
<tr><td>≥10mL/min</td><td>100%</td><td>-</td></tr>
<tr><td><10mL/min</td><td>75%</td><td>-</td></tr>
<tr><td>GFR < 60mL/min/1.73m^2</td><td>-</td><td>70%</td></tr>
</table></td></tr>
<tr><td>Hepatic</td><td>No specific guidance but consider dose reductions of dactinomycin in severe hepatic dysfunction</td></tr>
<tr><td>Gastric</td><td>Grade 3 or 4 mucositis or GI toxicity – reduce dactinomycin and cyclophosphamide to 80% of original dose for first occurrence and 60% or original dose for second occurrence</td></tr>
<tr><td>Haematuria or haemorrhagic cystitis</td><td>
<table>
<tr><th>Grade</th><th>Action</th></tr>
<tr><td>Microscopic during cyclophosphamide infusion</td><td>Give additional bolus doses of Mesna then a continuous infusion at double dose</td></tr>
<tr><td>Grade 2</td><td>Discontinue cyclophosphamide, continue with double dose continuous Mesna and hydration for 24 hours after cyclophosphamide stopped</td></tr>
</table></td></tr>
<tr><td>Cardiomyopathy</td><td>Perform baseline MUGA in any patient with suspected cardiac impairment. If cardiac ejection fraction < 50% discuss with consultant and consider an alternative regimen.

Omit doxorubicin and substitute dactinomycin 1.5mg/m2 if LVEF < 40%
Repeat MUGA after next cycle and if cardiac function has recovered consider restarting doxorubicin.
Consider a lower maximum cumulative doxorubicin dose of 400mg/m2 for any patient with cardiac dysfunction or that has been exposed to mediastinal radiation
Note that cardiomyopathy may be delayed – if 20% reduction if LVEF after 300mg/m2 then stop doxorubicin</td></tr>
<tr><td>Neurotoxicity</td><td>Observe closely for signs of encephalopathy. This may present insidiously in a variety of ways but usually includes somnolence and confusion initially. Report any early signs to medical staff immediately

Three risk factors may predispose to encephalopathy: renal</td></tr>
</table>

	impairment, low albumin, and large pelvic tumour mass. Note that most mild cases of encephalopathy will resolve spontaneously in 24 to 72 hours. If grade 3 or 4 central neurotoxicity occurs (somnolence 30% of the time, disorientation / hallucination / coma or seizures on which consciousness is altered etc) Stop Ifosfamide infusion **And** consider the use of methylene blue (methylonium) 50mg IV infusion as follows: **50mg (5ml ampoule of 1% solution) every 4 hours, by IV slow bolus** Patients who have had an episode of ifosfamide induced encephalopathy in a previous cycle should be treated as follows: **Give one dose of 50mg (5ml ampoule of 1% solution) IV slow bolus 24 hours prior to ifosfamide.** During ifosfamide infusion, give 50mg (5ml ampoule of 1% solution) IV slow bolus every 6 hours during the infusion. If repeated grade 3 or 4 central neurotoxicity occurs consider withholding ifosfamide and substitute cyclophosphamide 1500mg/m2 on d1 only

References:

1. A multinational registry for rhabdoid tumors of any anatomical site. European Rhabdoid Registry V2,2919 15.11.2010
   https://www.orpha.net/data/prj/DE/Reg77865GB.pdf

2. Thames Valley Strategic Clinical Network. Interim-ICE protocol
   https://tvscn.nhs.uk/networks/cancer/cancer-topics/sarcoma/