Notes from the editor
All chemotherapy regimens, and associated guidelines eg antiemetics and dose bands are available on the Network website [www.tvscn.nhs.uk/networks/cancer-topics/chemotherapy/](http://www.tvscn.nhs.uk/networks/cancer-topics/chemotherapy/)

Any correspondence about the regimens should be addressed to:
Sally Coutts, Cancer Pharmacist, Thames Valley
email: sally.coutts@nhs.net

Acknowledgements
These regimens have been compiled by the Network Pharmacy Group in collaboration with key contribution from

Prof Bass Hassan, Medical Oncologist, OUH
Dr Sally Trent, Clinical Oncologist, OUH
Dr James Gildersleve, Clinical Oncologist, RBFT
Dr Sarah Pratap, Medical Oncologist, OUH
Dr Shaun Wilson, TYA - Paediatric Oncologist, OUH
Catherine Chaytor, Cancer Pharmacist, OUH
Varsha Ormerod, Cancer Pharmacist, OUH
Kristen Moorhouse, Cancer Pharmacist, OUH

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# Thames Valley Chemotherapy Regimens

**Sarcoma**

Network Chemotherapy Regimens used in the management of Sarcoma  
**Date published:** January 2019  
**Date of review:** June 2022

## Chemotherapy Regimens

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<td>Rhabdomyosarcoma</td>
<td>83</td>
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<td>Topotecan Vincristine Doxorubicin</td>
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<td>Advanced sarcoma (palliative)</td>
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<td>Dacarbazine</td>
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<td>88</td>
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<tr>
<td>Dacarbazine Gemcitabine</td>
<td>Advanced sarcoma (palliative)</td>
<td>90</td>
</tr>
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<td>Carboplatin Etoposide weekly</td>
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<td>96</td>
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<tr>
<td>Pre post hydration regimens</td>
<td></td>
<td>98</td>
</tr>
</tbody>
</table>

Cisplatin and carboplatin may be substituted if the patient is unable to tolerate, in those regimens where the platinum agent is not specified in the CDF or NICE funding.
List of amendments in this version

Regimen type: Sarcoma Tumours
Date due for review: June 2022
Previous Version number: 2.4
This version number: 2.5

Table 1 Amendments

<table>
<thead>
<tr>
<th>Page</th>
<th>Action Type</th>
<th>Amendment</th>
<th>Made / asked by</th>
</tr>
</thead>
<tbody>
<tr>
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</table>

Table 2 New regimens to be approved and checked by CAG included in this version

<table>
<thead>
<tr>
<th>Name of regimen</th>
<th>Indication</th>
<th>Reason / Proposer</th>
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<tbody>
<tr>
<td>Cisplatin Imatinib – if local Trust</td>
<td>Chordoma</td>
<td>Dr Pratap</td>
</tr>
<tr>
<td>funding agreed</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Irinotecan Temozolomide Vincristine – if</td>
<td>Rhabdomyosarcoma</td>
<td>Dr Pratap</td>
</tr>
<tr>
<td>local Trust funding agreed</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

For anti-emetic guidelines: http://tvscn.nhs.uk/networks/cancer/cancer-topics/chemotherapy/
For dose banded chemotherapy standardized product specifications:
www.england.nhs.uk/commissioning/spec-services npc-crg/group-b/b02/dose-banded-
chemotherapy-standardised-product-specifications/
IMATINIB

Indications: Gastrointestinal Stromal Tumours, Pigmented villonodular synovitis, Dermatofibrosarcoma protuberans, and Chordoma

NICE TA86 Imatinib treatment at 400mg/day is recommended as first-line management of people with KIT (CD117)-positive unresectable and/or KIT (CD117)-positive metastatic gastrointestinal stromal tumours (GISTs).

NICE TA326 Imatinib is recommended as a possible treatment for up to 3 years, for people who had gastrointestinal stromal tumours that were removed by surgery, when there is a high risk that the tumour may come back.

Ensure individual funding has been obtained prior to prescribing for all non-GIST indications.

DRUG REGIMEN
IMATINIB MESYLATE 400mg orally once daily

Cycle Frequency: Every month until disease progression (12 cycles initially)
NB tablets available as 100 or 400mg strengths.

DOSE MODIFICATIONS
Use with caution in patients with a history of cardiac dysfunction.
Patients with mild / moderate / severe impairment should be given the minimum recommended dose of 400mg/day and this should be reduced if it is not tolerated.
ANC <1.0 x 10^9/l and/or platelets <50 x 10^9/l Stop until ANC ≥1.5 x 10^9/l and platelets ≥75 x 10^9/l.
Resume treatment at previous dose (i.e. before severe adverse reaction). In the event of recurrence of ANC <1.0 x 10^9/l and/or platelets <50 x 10^9/l, repeat step 1 and resume at reduced dose of 300 mg. NB. Dose adjustments must be performed by Consultant in line with NICE guidelines and mutation testing
Dose reduction of imatinib may be necessary in selected patients.
If there is insufficient response after at least 3 months consider increased dose up to 800mg per day (400mg bd) maximum (Note: doses > 400mg OD not NICE approved and therefore individual funding is required – TA209).
Dose increases may be associated with more adverse effects.
If elevations in bilirubin >3 x institutional upper limit of normal (IULN) or in liver transaminases >5 x IULN occur, Imatinib should be withheld until bilirubin levels have returned to <1.5 x IULN and transaminase levels to <2.5 x IULN. Treatment with Imatinib may then be continued at a reduced daily dose after discussion with consultant
INVESTIGATIONS
Routine Blood test
1) Blood results required before chemotherapy administration
   
   **Give**  **Discuss**
   
   Hb x g/dL  ≥10  <10
   Plt x 10⁹/L  ≥100  <75 no treatment
   >75 and < 100 delay 7 days ± give 75% dose
   Neutrophils x 10⁹/L  ≥1.5  >0.75 and < 1.5 (<0.75 no treatment)

Liver function tests and renal function (note electrolyte disturbances with Imatinib)
Hepatitis B core antibody and hepatitis BsAg (increased risk of reactivation)

2) Non urgent tests
Tests relating to disease response/progression
   - Record all clinically assessable disease
   - Investigations may include CT scan staging every 3 months
   - PET-CTI staging properties and post-operation prior to adjuvant therapy
   - Record of WHO performance status, current height, weight and surface area
   - FBC, U&E, creatinine, Liver function tests. Creatinine clearance >55mls/min,
   - Baseline ECG with normal QTc interval
   - Urine pregnancy test in women aged 12-55, unless sterilised or undergone a hysterectomy.
   - Marking mutation factor of c-kit, PDGFR mutations and screening for wild-type GIST.

DRUG INTERACTIONS
   - Concomitant use of CYP3A4 inducers should be avoided (e.g. dexamethasone, phenytoin, carbamazepine, rifampicin, phenobarbital or St John’s Wart) as they may significantly reduce exposure to imatinib, potentially increasing the risk of therapeutic failure.
   - Caution should be taken when co-administering imatinib with CYP3A4 inhibitors (ketoconazole, itraconazole, voriconazole, erythromycin, clarithromycin), as they could increase imatinib exposure
   - Imatinib can also increase the plasma concentration of other CYP3A4 metabolised drugs (statins, benzodiazepines, dihydropyridine calcium channels blockers [e.g. amlodipine, nifedipine] cyclosporin), therefore caution is recommended
   - Concomitant use of strong CYP2D6 inducers should be avoided (e.g. rifampicin).
   - Patients requiring anticoagulation should receive heparin-formulations rather than warfarin.
   - In patients treated with metoprolol clinical monitoring should be considered.
   - In thyroidectomy patients, plasma exposure to levothyroxine may be decreased when imatinib is co-administered. Caution is therefore recommended. However, the mechanism of the observed interaction is presently unknown.

ANTIMETIC POLICY
None required
ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS

Relapsed disease
Neutropenia, thrombocytopenia, anaemia,
Headache, mild nausea, vomiting, diarrhoea, dyspepsia, abdominal pain, fluid retention, dermatitis,
muscle cramps, muscle pain.
Electrolyte disturbances
Cardiac function

REFERENCES


**SUNITINIB**

*Indication:* Treatment of unresectable and/or metastatic malignant gastrointestinal stromal tumour (GIST) after failure of imatinib mesylate treatment due to resistance or intolerance. Solitary fibrous tumour (SFT) and angiosarcomas

NICE TA179 Sunitinib is recommended as a treatment option for people with unresectable and/or metastatic malignant gastrointestinal stromal tumours if: imatinib treatment has failed because of resistance or intolerance.

*Ensure individual funding has been obtained prior to prescribing for all non-GIST indications*

**DRUG REGIMEN**

Day 1 SUNITINIB 25mg orally ONCE daily
May be increased to 37.5mg ONCE daily

*Cycle Frequency: Every 28 days*

*Note: Licensed dose for GIST is 50mg OD for 4 weeks then a 2 week rest period (6 week cycle) but local practice, based on recent evidence base is for continuous daily dosing (off label)*

**DOSE MODIFICATIONS**

*Sunitinib:*

Renal impairment
No starting dose adjustment required with mild–severe or with end-stage renal disease (ESRD) on haemodialysis. Subsequent dose adjustments should be based on individual safety and tolerability.

Hepatic impairment
No starting dose adjustment is recommended with mild or moderate hepatic impairment. It has not been studied in subjects with severe.
INVESTIGATIONS

Routine Blood test
1) Blood results required before drug administration
   
<table>
<thead>
<tr>
<th>Test</th>
<th>Give</th>
<th>Discuss</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hb x g/dL</td>
<td>10</td>
<td>&lt; 10</td>
</tr>
<tr>
<td>Plt x 10⁹/L</td>
<td>100</td>
<td>&lt; 100</td>
</tr>
<tr>
<td>Neutrophils x 10⁹/L</td>
<td>1.5</td>
<td>&lt; 1.5</td>
</tr>
</tbody>
</table>

Blood tests should initially be performed 4 weekly, but later in the treatment course can be done less often in stable patients.

Creatinine
Liver function tests (LFT)
Thyroid function tests
Blood pressure
Hepatitis B core antibody and hepatitis BsAg (increased risk of reactivation)

2) Non urgent tests
Tests relating to disease response/progression
Urine pregnancy test in women aged 12-55, unless sterilised or undergone a hysterectomy.
Urine dipsticks

CONCURRENT MEDICATION

ANTIEMETIC POLICY

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS
Skin - skin discolouration and depigmentation of the hair and skin may occur.
Palmar / plantar syndrome
Neutropenia
Mouth pain / irritation / sensitivity may occur
Haemorrhage – an increased risk of bleeding may occur.
Hypertension – treatment induced hypertension. Sunitinib treatment should temporarily be suspended until hypertension is controlled.
Gastrointestinal – serious gastrointestinal complications including gastrointestinal perforation have occurred rarely.
Hypothyroidism

REFERENCES
1.  SPC July 2010
REGORAFENIB

**Indication:** Treatment of adult patients with advanced gastro-intestinal stromal tumours (GIST) after failure of at least previous imatinib and sunitinib where histologically confirmed, metastatic or unresectable GIST, PS 0-1, disease progression on or intolerance to previous imatinib or disease progression on previous sunitinib

**DRUG REGIMEN**
Days 1 to 21 REGORAFENIB 160mg orally ONCE daily

**Cycle Frequency:** Every 28 days

**DOSE MODIFICATIONS**

**Renal impairment**
No dose adjustment is required in patients with mild or moderate renal impairment. No clinical data are available in patients with severe renal impairment (eGFR <30 mL/min/1.73m²).

**Hepatic impairment**
Regorafenib is eliminated mainly via the hepatic route. No dose adjustment is required in patients with mild hepatic impairment. Since only limited data are available for patients with moderate hepatic impairment (Child Pugh B), no dose recommendation can be provided. Close monitoring of overall safety is recommended in these patients. Regorafenib is not recommended for use in patients with severe hepatic impairment (Child-Pugh C) as regorafenib has not been studied in this population.

Observed elevations of ALT and/or AST:

≤5 x ULN Continue treatment and monitor liver function weekly until transaminases return to <3 times ULN (Grade 1) or baseline.

>5 - ≤20 x ULN ULN Interrupt regorafenib treatment. Monitor transaminases weekly until return to <3 times ULN or baseline. Restart: If the potential benefit outweighs the risk of hepatotoxicity, re-start regorafenib treatment, reduce dose by 40 mg (one tablet), and monitor liver function weekly for at least 4 weeks.

>20 x ULN Discontinue treatment with regorafenib permanently.

>3 x ULN and bilirubin >2 x ULN Discontinue treatment with regorafenib permanently. Monitor liver function weekly until resolution or return to baseline.

**Exception:** patients with Gilbert’s syndrome who develop elevated transaminases should be managed as above recommendations for the respective observed elevation of ALT and/or AST.

**Dose modification levels:**

<table>
<thead>
<tr>
<th>Dose level 0 (standard dose)</th>
<th>160 mg po od</th>
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<tbody>
<tr>
<td>Dose level -1</td>
<td>120 mg po od</td>
</tr>
<tr>
<td>Dose level -2</td>
<td>80 mg po od</td>
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INVESTIGATIONS
Routine Blood test
1) Blood results required before drug administration

<table>
<thead>
<tr>
<th>Test</th>
<th>Value</th>
<th>Reference</th>
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</thead>
<tbody>
<tr>
<td>Hb x g/dL</td>
<td>10</td>
<td>&lt; 10</td>
</tr>
<tr>
<td>Plt x 10^9/L</td>
<td>100</td>
<td>&lt; 100</td>
</tr>
<tr>
<td>Neutrophils x 10^9/L</td>
<td>1.5</td>
<td>&lt; 1.5</td>
</tr>
</tbody>
</table>

Blood tests should initially be performed 4 weekly.
Liver function tests (LFT). It is recommended to perform liver function tests (ALT, AST and bilirubin) before initiation of treatment with regorafenib and monitor closely (at least every two weeks) during the first 2 months of treatment. Thereafter, periodic monitoring should be continued at least monthly and as clinically indicated.

2) Non urgent tests
Tests relating to disease response/progression
Urine pregnancy test in women aged 12-55, unless sterilised or undergone a hysterectomy.

CONCURRENT MEDICATION

ANTIEMETIC POLICY
Low emetic risk

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS
Monitor blood pressure

REFERENCES
1) Regorafenib SPC
Long-term follow-up results of the multicenter phase II trial of regorafenib in patients with metastatic and/or unresectable GI stromal tumor after failure of standard tyrosine kinase inhibitor therapy. Ben-Ami E1, Barysauskas CM2, von Mehren M3, Heinrich MC4, Corless CL5, Butrynski JE1, Morgan JA1, Wagner AJ1, Choy E6, Yap JT7, Van den Abbeele AD8, Solomon SM1, Fletcher JA9, Demetri GD10, George S11.
PACLITAXEL weekly

**Indication:** Angiosarcoma including Kaposi sarcoma

**DRUG REGIMEN**

**Days 1, 8, 15** PREMEDICATION 30 minutes prior to infusion:
- DEXAMETHASONE 20mg IV bolus
- RANITIDINE 50mg IV bolus
- CHLORPHENAMINE 10mg IV bolus
- **PACLITAXEL** 50mg/m² in 250ml sodium chloride 0.9% infusion over 3 hours (PVC free)

**Cycle Frequency:** Every 28 days up to 6 cycles depending on tolerance and response

NB Paclitaxel dose may be increased to 80mg/m² each day

**DOSE MODIFICATIONS**

If patient complains of tingling of fingers and/or toes or motor weakness discuss with Consultant or Registrar before administration.

In the absence of Gilbert's syndrome:
Bilirubin >51micromol/L stop treatment

**INVESTIGATIONS**

Routine Blood test

1) Blood results required before chemotherapy administration

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Give</th>
<th>Discuss</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hb x g/dL</td>
<td>≥10</td>
<td>&lt;10</td>
</tr>
<tr>
<td>Plt x 10⁹/L</td>
<td>≥100</td>
<td>&lt;75 no treatment</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt;75 and &lt;100 delay 7 days ± give 75% dose</td>
</tr>
<tr>
<td>Neutrophils x 10⁹/L</td>
<td>≥1.5</td>
<td>&gt;0.75 and &lt;1.5 (&lt;0.75 no treatment)</td>
</tr>
</tbody>
</table>

2) Non urgent tests

Tests relating to disease response/progression
- Record all clinically assessable disease
- Investigations will usually include CT scan of site of measurable disease
- MRI of primary tumour site
- Record of WHO performance status, current height, weight and surface area
- FBC, U&E, creatinine, LFTs. ECG, consider ECHO
- Urine pregnancy test in women aged 12-55, unless sterilised or undergone a hysterectomy.
CONCURRENT MEDICATIONS
Ensure pre-medication is given.

ANTIEMETIC POLICY
Low emetic risk

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS
(2% risk of severe hypersensitivity)
Reactions range from mild hypotension (light-headedness) to full cardiac collapse (anaphylactic shock). Discontinue infusion and resuscitate appropriate to reaction. If reaction is mild and settles promptly (i.e. within 5-10 minutes), cautiously restart at a slower rate under close supervision. If further reactions occur stop treatment.

Peripheral neuropathy with chronic dosing

REFERENCES
1. Penel et al 2007, JCO Vol25, 18S (June 20 supplement): 10002
**Indication:** Neoadjuvant and adjuvant osteosarcoma adjuvant for de-differentiated chondrosarcoma and palliative therapy for selected patients (see EURAMOS 1 for trial regimens)

**DRUG REGIMEN**

**Day 1**
- **DOXORUBICIN** 25mg/m² in 100ml sodium chloride 0.9% IV infusion over 4 hours
- **CISPLATIN** 50mg/m² in 1000ml sodium chloride 0.9% IV infusion over 8 hours

**Day 2**
- **DOXORUBICIN** 25mg/m² in 100ml sodium chloride 0.9% IV infusion over 4 hours
- **CISPLATIN** 50mg/m² in 1000ml sodium chloride 0.9% IV infusion over 8 hours

**Day 3**
- **DOXORUBICIN** 25mg/m² in 100ml sodium chloride 0.9% IV infusion over 4 hours

**Day 4**
- **Prophylactic GCSF** as per local policy *(may be considered until WCC >5.0x10⁹/l standard GCSF continue for 7 days starting 24 hours after chemotherapy)*

**Cycle Frequency:** Every 21 days for maximum 6 cycles (3 cycles before surgery and 3 cycles post surgery)

**DOSE MODIFICATIONS**

*Cisplatin*

If patient complains of tinnitus, tingling of fingers and/or discuss with Consultant or Registrar before administration. Consider carboplatin if patient over 70 years of age.

- GFR > 60ml/min give 100% dose
- GFR 45-59ml/min give 75% dose
- GFR < 45ml/min consider carboplatin

*Doxorubicin*

Dose reduce in severe renal impairment.

- Bilirubin 20-50micromol/L give 50% dose
- Bilirubin 51-85micromol/L give 25% dose
- Bilirubin >85micromol/L omit

If AST is 2-3 x ULN give 75% dose
If AST is >3 x ULN give 50% dose

*Mucositis Grade 3 or 4 - reduce Doxorubicin to 20mg/m²/day*

Maximum cumulative dose = 450 mg/m² (in normal cardiac function)
= 400 mg/m² (in patients with cardiac dysfunction or exposed to mediastinal irradiation)
INVESTIGATIONS
Routine Blood test
1) Blood results required before chemotherapy administration

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<td>Plt x 10^9/L</td>
<td>≥100</td>
<td>&lt;75 no treatment &lt;75 and &lt;100 delay 7 day ± give 75% dose</td>
</tr>
<tr>
<td>Neutrophils x 10^9/L</td>
<td>≥1.5</td>
<td>&gt;0.75 and &lt;1.5 (&lt;0.75 no treatment)</td>
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<tr>
<td>GFR</td>
<td>≥70</td>
<td>&gt;55 and &lt;70 m/min/1.73 m²</td>
</tr>
<tr>
<td>Electrolytes+Mg</td>
<td></td>
<td>If abnormal due to cisplatin</td>
</tr>
</tbody>
</table>

- Cr-EDTA clearance or serum Creatinine with a clearance to limit above (Consider formal measurement of creatinine clearance in patients with low surface area)
- Liver function tests (LFTs) to limits in dose modifications
- ECHO FS ≥28% or LVEF≥50% at last scheduled assessment

2) Non urgent tests
Tests relating to disease response/progression
- Essential pre-treatment investigations
- Record all clinically assessable disease
- Investigations will usually include CT scan of chest and isotope bone scan
- MRI of primary tumour site
- ECG, Echocardiogram (+LVEF), repeat ECHO after 2 cycles
- Audiometry - repeat before 3rd and 5th cycles
- Record of WHO performance status, current height, weight and surface area
- FBC, U&E
- Give adequate verbal and written information for patients and relatives concerning patient’s disease, treatment strategy and side effects / mortality risk.
- If appropriate, discuss potential risk of infertility / early menopause with patient and relatives
- Urine pregnancy test in women aged 12-55, unless sterilised or undergone a hysterectomy.

CONCURRENT MEDICATION
Ensure adequate pre-and post-hydration prescribed
If fluid balance >2L positive after 8 hours post hydration or urine output is <100ml/hr during IV administration post cisplatin give 200ml mannitol 10% (preferred) or 20-40mg furosemide po/IV (only if mannitol has failed).

ANTIEMETIC POLICY
High emetic risk days 1 and 2 (and day 3 if chemo continues into day 3) plus aprepitant if funded
ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS

Cardiotoxicity – monitor cardiac function with ECHO appointment after two cycles. Doxorubicin may be stopped in future cycles if signs of cardiotoxicity e.g. cardiac arrhythmias, pericardial effusion, tachycardia with fatigue.
Note risk of delayed cardiomyopathy - if 10% reduction in LVEF after 300mg/m² - omit doxorubicin.

Nephrotoxicity – ensure adequate pre and post hydration is prescribed.
Ototoxicity – assess patient for tinnitus or hearing abnormalities, stop cisplatin if hearing loss extends to 2kHz.

REFERENCES
1. ASWCS Chemotherapy handbook Jan 2005 update
CISPLATIN IMATINIB

Indications: Chordoma

Not NHSE commissioned regimen - Trust to fund locally, and not charge to NHSE

DRUG REGIMEN
Days 1 & 15 Prehydration
CISPLATIN 25mg/m^2 in 1000ml sodium chloride 0.9% IV infusion over 2 hours
Post hydration
Days 1 to 28 IMATINIB MESYLATE 400mg orally once daily

Cycle Frequency: Every 28 days for maximum 6 to 8 cycles, then continue imatinib 400mg maintenance until progression

DOSE MODIFICATIONS
CISPLATIN
GFR >60 mL/min give 100% dose
GFR 45-60ml/min give 75% dose
GFR <45ml/min consider carboplatin

IMATINIB
Use with caution in patients with a history of cardiac dysfunction.
Patients with mild / moderate / severe impairment should be given the minimum recommended dose of 400mg/day and this should be reduced if it is not tolerated.
ANC <1.0 x 10^9/l and/or platelets <50 x 10^9/l Stop until ANC ≥1.5 x 10^9/l and platelets ≥75 x 10^9/l.
Resume treatment at previous dose (i.e. before severe adverse reaction). In the event of recurrence of ANC <1.0 x 10^9/l and/or platelets <50 x 10^9/l, repeat step 1 and resume at reduced dose of 300 mg. NB. Dose adjustments must be performed by Consultant in line with NICE guidelines and mutation testing
Dose reduction of imatinib may be necessary in selected patients.
If there is insufficient response after at least 3 months consider increased dose up to 800mg per day (400mg bd) maximum (Note: doses > 400mg OD not NICE approved and therefore individual funding is required – TA209).
Dose increases may be associated with more adverse effects.
If elevations in bilirubin >3 x institutional upper limit of normal (IULN) or in liver transaminases >5 x IULN occur, Imatinib should be withheld until bilirubin levels have returned to <1.5 x IULN and transaminase levels to <2.5 x IULN. Treatment with Imatinib may then be continued at a reduced daily dose after discussion with consultant

<table>
<thead>
<tr>
<th>Cisplatin</th>
<th>Imatinib</th>
<th>Sarcoma CAG Chair Authorisation:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Date:</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
INVESTIGATIONS

Routine Blood test

3) Blood results required before chemotherapy administration

Give  

<table>
<thead>
<tr>
<th>Test</th>
<th>Requirement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hb x g/dL</td>
<td>≥10</td>
</tr>
<tr>
<td></td>
<td>&lt;10</td>
</tr>
<tr>
<td>Plt x 10^9/L</td>
<td>≥100</td>
</tr>
<tr>
<td></td>
<td>&lt;75 no treatment</td>
</tr>
<tr>
<td></td>
<td>&gt;75 and &lt;100 delay 7 days ± give 75% dose</td>
</tr>
<tr>
<td>Neutrophils x 10^9/L</td>
<td>≥1.5</td>
</tr>
<tr>
<td></td>
<td>&gt;0.75 and &lt;1.5 (&lt;0.75 no treatment)</td>
</tr>
</tbody>
</table>

Liver function tests and renal function (note electrolyte disturbances with Imatinib)

Hepatitis B core antibody and hepatitis BsAg (increased risk of reactivation)

4) Non urgent tests

Tests relating to disease response/progression

- Record all clinically assessable disease
- Investigations may include CT scan staging every 3 months
- PET-CTI staging properties and post-operation prior to adjuvant therapy
- Record of WHO performance status, current height, weight and surface area
- FBC, U&E, creatinine, Liver function tests. Creatinine clearance >55mls/min,
- Baseline ECG with normal QTc interval
- Urine pregnancy test in women aged 12-55, unless sterilised or undergone a hysterectomy.
- Marking mutation factor of c-kit, PDGFR mutations and screening for wild-type GIST.

CONCURRENT MEDICATION

Hydration must be given pre and post cisplatin

Ensure adequate pre-and post-hydration prescribed as per day case schedule at the end of the TVCN protocols.

If urine output is < 100ml/hour or if patient gains >2kg weight during IV administration post Cisplatin give 20 - 40mg Furosemide PO/IV OR 200ml Mannitol 10% IV

ANTIEMETIC POLICY

Highly emetogenic days 1 and 15

None required other days
ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS

Nephrotoxicity – ensure adequate pre and post hydration is prescribed
Ototoxicity – assess patient for tinnitus or hearing abnormalities
Relapsed disease
Neutropenia, thrombocytopenia, anaemia,
Headache, mild nausea, vomiting, diarrhoea, dyspepsia, abdominal pain, fluid retention, dermatitis, muscle cramps, muscle pain.
Electrolyte disturbances

REFERENCES
DOXORUBICIN

Indication: Palliative chemotherapy for all sarcoma

DRUG REGIMEN
Day 1  DOXORUBICIN 60mg/m² IV infusion in 100ml sodium chloride 0.9% over 4 hours

Cycle Frequency: Every 21 days for 6 cycles subject to tolerance and response

NB Doxorubicin dose may be increased to 75mg/m² in younger patients without co-morbidity

DOSE MODIFICATIONS
Dose reduce in severe renal impairment.
Bilirubin 20-50micromol/L give 50% dose
Bilirubin 51-85micromol/L give 25% dose
Bilirubin >85micromol/L omit
If AST is 2-3 x ULN give 75% dose
If AST is >3 x ULN give 50% dose

Maximum cumulative dose = 450-550mg/m² (in normal cardiac function)
= 400 mg/m² (in patients with cardiac dysfunction or exposed to mediastinal irradiation)

INVESTIGATIONS
Routine Blood test
1) Blood results required before chemotherapy administration

<table>
<thead>
<tr>
<th></th>
<th>Give</th>
<th>Discuss</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hb x g/dL</td>
<td>≥10</td>
<td>&lt; 10</td>
</tr>
<tr>
<td>Plt x 10⁹/L</td>
<td>≥100</td>
<td>&lt; 100</td>
</tr>
<tr>
<td>Neutrophils x 10⁹/L</td>
<td>≥1.5</td>
<td>&lt; 1.5</td>
</tr>
</tbody>
</table>

Liver function tests (LFTs) to limits in dose modifications

2) Non urgent tests
Tests relating to disease response/progression
Urine pregnancy test in women aged 12-55, unless sterilised or undergone a hysterectomy.

3) Pre-treatment
- Assess cardiac risk factors
- ECG and ECHO at baseline and after cycles 2, 4, 5 and 6
- Consider scalp cooling
CONCURRENT MEDICATION

ANTIEMETIC POLICY
Moderate emetic risk

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS
Cardiotoxicity – monitor cardiac function. Doxorubicin may be stopped in future cycles if signs of cardiotoxicity e.g. cardiac arrhythmias, pericardial effusion, tachycardia with fatigue.
Note risk of delayed cardiomyopathy- if 20% reduction in LVEF after 300mg/m² - omit doxorubicin.

REFERENCES
LIPOSOMAL DOXORUBICIN (Caelyx)

**Indication:** The treatment of sarcomas where all the following criteria are met:

2. **a)** Sarcoma in patients with cardiac impairment requiring an anthracycline, 1st line indication, OR

   **b)** Sarcoma in patients with cardiac impairment requiring an anthracycline, 2nd line indication

3. To be used within the treating Trust’s governance framework, as Pegylated Liposomal Doxorubicin is not licensed in these indications

**Ensure individual funding obtained prior to prescribing**

**DRUG REGIMEN**

Day 1 Pegylated liposomal DOXORUBICIN 40mg/m² in 500ml glucose 5% infusion at a rate of 1mg/min on cycle 1

If no infusion-related reactions, subsequent cycles over 1 hour.

NB if dose is less than 90mg give in 250ml glucose 5% due to stability

**Cycle Frequency: Every 28 days for a maximum 6 cycles**

**DOSE MODIFICATIONS**

Previous neutropenic sepsis, discuss with Consultant or Registrar.

Bilirubin 20-51micromol/L give 75% dose

Bilirubin > 51micromol/L give 50% dose

Maximum cumulative dose = 450-550 mg/m² (in normal cardiac function)

= 400 mg/m² (in patients with cardiac dysfunction or exposed to mediastinal irradiation)

Palmar plantar erythema or stomatitis: (See SPC for further information)

Delay for 1 week if grade 2 -4. Use steroids (e.g. prednisolone 30mg daily or Dexamethasone 8mg daily) for treatment. Anecdotally, pyridoxine 50mg tds can be used.

Reduce dose by 25% if > 2 week delay or if grade III or above.

Withdraw patient if >2 week delay grade III of above
INVESTIGATIONS
Routine Blood test
1) Blood results required before chemotherapy administration

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Give</th>
<th>Discuss</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hb x g/dL</td>
<td>≥10</td>
<td>&lt; 10</td>
</tr>
<tr>
<td>Plt x 10^9/L</td>
<td>≥100</td>
<td>&lt; 100</td>
</tr>
<tr>
<td>Neutrophils x 10^9/L</td>
<td>≥1.5</td>
<td>&lt; 1.5</td>
</tr>
</tbody>
</table>

2) Non urgent tests
Baseline ECG
Consider baseline Echocardiogram
Tests relating to disease response/progression
Urine pregnancy test in women aged 12-55, unless sterilised or undergone a hysterectomy.

CONCURRENT MEDICATION

ANTIEMETIC POLICY
Moderate emetic risk

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS
Infusion related reactions – allergic or anaphylactic like reactions consider prophylaxis
Palmar-plantar erythema treat with steroids prednisolone 30mg od or dexamethasone 8mg od.
Consider pyridoxine.

REFERENCES
GEMCITABINE (675) DOCETAXEL (70)

**Indication:** Sarcoma especially leiomyosarcoma

**DRUG REGIMEN**

**Day 1** GEMCITABINE* 675mg/m² in 250ml sodium chloride 0.9% infusion over 30 minutes

**Day 8** GEMCITABINE* 675mg/m² in 250ml sodium chloride 0.9% infusion over 30 minutes

PREMEDICATION:
DEXAMETHASONE 8mg BD starting 24 hours before chemotherapy and continued for a total of 3 days.

**DOCETAXEL**** 70mg/m² in 250ml sodium chloride 0.9% infusion over 1 hour

**Day 9** GCSF brand as per local policy

*NB Gemcitabine start with 675mg/m² and consider escalation to 900mg/m²
**NB Docetaxel start with 70mg/m² and consider escalation to 100mg/m²

**Cycle Frequency:** Every 21 days for 6 (maximum 8) cycles

**DOSE MODIFICATIONS**

**Docetaxel**

Hepatic impairment:
Patients who have both elevations of transaminase (ALT and/or AST) > 1.5 x ULN and ALP > 2.5 x ULN: recommended SPC dose is 75mg/m².
Patients with serum bilirubin > 22micromol/L and/or ALT and AST > 3.5 x ULN associated with ALP > 6 x ULN: docetaxel should not be used unless strictly indicated.

**Gemcitabine**

CrCl <30ml/min consider dose reduction (Clinical decision)

Neutrophils >1.5x10⁹/L and platelets >100x10⁹/L give 100% dose
Neutrophils 0.5-1.5x10⁹/L or platelets 50-100x10⁹/L give 75% dose or delay based on clinical assessment
Neutrophils <0.5x10⁹/L or platelets <50x10⁹/L delay treatment (Day 1) or omit treatment (Day 8)

Day 8:
ANC <0.5 and/or platelets <50: omit day 8 gemcitabine and docetaxel, reduced both agents by 20% for next cycle and all subsequent cycles
0.5<ANC<1 and/or 50 < platelets < 100

Diarrhoea and/or mucositis
Grade 2 toxicity – omit until toxicity resolved then restart at 100% dose
Grade 3 toxicity – omit until toxicity resolved then restart at 75% dose
Grade 4 toxicity – omit until toxicity resolved then restart at 50% dose
INVESTIGATIONS
Routine Blood test
1) Blood results required before chemotherapy administration
   \[\begin{array}{ll}
   \text{Give} & \text{Discuss} \\
   \text{Hb x g/dL} & \geq 10 \quad < 10 \\
   \text{Plt x } 10^9/L & \geq 100 \quad < 100 \\
   \text{Neutrophils x } 10^9/L & \geq 1.5 \quad < 1.5 \\
   \text{Liver function tests} & \\
   \end{array}\]

2) Non urgent tests
   Tests relating to disease response/progression
   Urine pregnancy test in women aged 12-55, unless sterilised or undergone a hysterectomy.

CONCURRENT MEDICATION
Day 9 GCSF brand as per local policy needs prescribing
Do not give concurrent radiotherapy with Gemcitabine
Docetaxel Ensure pre-medications is given.
This can reduce the incidence and severity of fluid retention as well as the severity of hypersensitivity reactions

ANTIEMETIC POLICY
Low emetic risk day 1
Moderately emetogenic day 8

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS
Discuss if severe cutaneous reactions,
peripheral neuropathy or fluid retention after previous course.
Diarrhoea – see dose modifications
Mucositis – see dose modifications
Hypersensitivity Grade \(\geq 3\) omit future docetaxel
Weight gain/fluid retention Grade \(\geq 3\) omit future docetaxel
Posterior reversible encephalopathy syndrome (PRES) discontinue gemcitabine
Pulmonary symptoms of cough and breathlessness, with chest x-ray evidence of infiltration have been noted with this combination. Acute admission and supportive care required. Consider lung function tests also. If seriously impaired lung function discontinue treatment, but if symptoms recover consider proceeding. Poor lung function prior to treatment relative contraindication.

REFERENCES
IFOSFAMIDE (3g) DOXORUBICIN (30mg)

**Indication:** High Grade Sarcoma

**DRUG REGIMEN**

**Day 1**
- **DOXORUBICIN** 30mg/m² in 100ml sodium chloride 0.9% infusion over 4 hours
- **MESNA** 1g/m² in 500ml sodium chloride 0.9% IV infusion over 1 hour
- **IFOSFAMIDE** 3g/m² + **MESNA** 3g/m² in 3L sodium chloride 0.9% infusion over 24 hours

**Day 2**
- **DOXORUBICIN** 30mg/m² in 100ml sodium chloride 0.9% infusion over 4 hours
- **IFOSFAMIDE** 3g/m² + **MESNA** 3g/m² in 3L sodium chloride 0.9% infusion over 24 hours

**Day 3**
- **IFOSFAMIDE** 3g/m² + **MESNA** 3g/m² in 3L sodium chloride 0.9% infusion over 24 hours
- **MESNA** 3g/m² in 1000ml sodium chloride 0.9% IV infusion over 8-12 hours post ifosfamide

GCSF for 7 days brand as per local policy starting 24 hours after completing chemotherapy

NB Dose normally capped at 2.0mg².
If indicated, an alternative to doxorubicin in pretreated patients is liposomal doxorubicin at 30mg/m² only on day 1 (see Reference 6). Individual funding needs to be obtained prior to prescribing.

**Cycle Frequency:** Every 21 days for 6 cycles depending on tolerance and response

**DOSE MODIFICATIONS**

Previous neutropenic sepsis, discuss with Consultant or Registrar.

**Doxorubicin**
- Dose reduce in severe renal impairment.
  - Bilirubin 20-50micromol/L give 50% dose
  - Bilirubin 51-85micromol/L give 25% dose
  - Bilirubin >85micromol/L omit
- If AST is 2-3 x ULN give 75% dose
- If AST is >3 x ULN give 50% dose

Maximum cumulative dose = 450-550mg/m² (in normal cardiac function)
= 400 mg/m² (in patients with cardiac dysfunction or exposed to mediastinal irradiation)

**Ifosfamide**
- GFR >60ml/min give 100% dose
- GFR 40-59ml/min give 70% dose
- GFR <40ml/min clinical decision
- If creatinine >132mmol/L ifosfamide is not recommended
- Discuss if - Bilirubin > 17 micromol/L
- - AST and Alk Phos > 2.5 x ULN

Also refer to the ifosfamide-induced encephalopathy specific neural toxicity grade and nomogram (abridged below in full at the end of this document)
INVESTIGATIONS
Routine Blood test
1) Blood results required before chemotherapy administration

<table>
<thead>
<tr>
<th>Give</th>
<th>Discuss</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hb x g/dL</td>
<td>≥10</td>
</tr>
<tr>
<td>Plt x 10^9/L</td>
<td>≥100</td>
</tr>
<tr>
<td>Neutrophils x 10^9/L</td>
<td>≥1.5</td>
</tr>
</tbody>
</table>

EDTA, Renal function and phosphate clearance

2) Non urgent tests
Tests relating to disease response/progression
- Daily haematuria test
- Neurological assessment and neurological toxicity
- Record all clinically assessable disease
- MRI of primary tumour site
- PET-CT scan at baseline and after two cycles if neoadjuvant / palliative.
- Record of WHO performance status, current height, weight and surface area
- FBC, U&E, creatinine, LFTs. Creatinine clearance >55mls/min, ECG, consider ECHO
- Consider formal measurement of creatinine clearance in patients with low surface area
- Give adequate verbal and written information for patients and relatives concerning patient’s disease, treatment strategy and side effects / mortality risk.
- Obtain written consent from patient or guardian if appropriate
If appropriate, discuss potential risk of infertility / early menopause with patient and relatives
- Urine pregnancy test in women aged 12-55, unless sterilised or undergone a hysterectomy.

CONCURRENT MEDICATION
Difflam prn

ANTIEMETIC POLICY
High emetic risk days 1 to 3 (and day 4 if chemo continues into day 4) (plus aprepitant if funded)
ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS

Cardiotoxicity – monitor cardiac function. Doxorubicin may be stopped in future cycles if signs of cardiotoxicity e.g. cardiac arrhythmias, pericardial effusion, tachycardia with fatigue. Note option of Caelyx discuss with Consultant. Note risk of delayed cardiomyopathy- if 20% reduction in LVEF after 300mg/m² - omit doxorubicin discuss with Consultant.

Fluid overload - In the case of fluid overload and decreased urine output give 200ml Mannitol 10% over 30 minutes. Try to maintain urine output of at least 30-50ml/hour. Contact consultant if continues to be overloaded despite one dose of mannitol. Do not use furosemide.

Neural Toxicity - Assess Probability of remaining free from severe CNS toxicity (ifosfamide) refer to the ifosfamide-induced encephalopathy specific neural toxicity grade and nomogram (at end of document). Give Discuss

> 0.5 <0.5
Careful consideration should be given if <0.2

Methylthioninium chloride (methylene blue) can be given as prophylaxis against, or treatment of, ifosfamide-induced encephalopathy. Dose: 50mg tds IV. NB. 50mg = 5ml of 1% solution.

IV: administer 50mg in 50 to 100ml glucose 5% over 15 to 30 minutes

Nephrotoxicity- Irreversible renal failure and tubular damage can occur, and this is more frequent with cumulative doses over 25 – 50g/m² of Ifosfamide. Dose reductions should be instituted for GFR and changes in fractional phosphate clearance (Tmₚ/GFR mmol/l). Any dose reductions need to be discussed with a Consultant.

<table>
<thead>
<tr>
<th>Toxicity Grade</th>
<th>GFR (ml/min/1.73m²)</th>
<th>Tp/Crea (Tmₚ/GFR)mmol/l</th>
<th>HCO3(mmol/l)</th>
<th>Action (apply worst grade)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 0/1</td>
<td>≥60</td>
<td>≥1.00</td>
<td>≥17.0</td>
<td>ifos 100% total</td>
</tr>
<tr>
<td>Grade 2</td>
<td>40-59</td>
<td>0.8-0.99</td>
<td>14.0-16.9</td>
<td>Ifos 70% of total (depending on cycle)</td>
</tr>
<tr>
<td>Grade 3 /4</td>
<td>≤40</td>
<td>≤0.8</td>
<td>≤14.0</td>
<td>Cyclophosphamide 1500mg/m² day 1 only</td>
</tr>
</tbody>
</table>

Fractional phosphate clearance calculated as below

\[ \text{Tp/Crea} = \frac{\text{Phosphate}_{\text{serum}} - \text{Phosphate}_{\text{urine}} \times \text{creatinine}_{\text{serum}}}{\text{Creatinine}_{\text{urine}}} \]

NB serum creatinine is normally recorded in µmol/L

REFERENCES
1. ASWCS Chemotherapy Handbook Jan 2005 Update
3. EURO-EWING 99 Protocol
Indication: Relapsed High Grade Osteosarcoma, Chondrosarcoma and High Grade Sarcoma

**DRUG REGIMEN**

**Days 1**
- **ETOPOSIDE** 100mg/m² IV in 500ml* sodium chloride 0.9% infusion over 1 hour
- **MESNA** 1g/m² in 500ml sodium chloride 0.9% IV infusion over 1 hour
- **IFOSFAMIDE** 3g/m² + **MESNA** 3g/m² in 1-2L sodium chloride 0.9% infusion over 10 hours
- **MESNA** 3g/m² in 1000ml sodium chloride 0.9% for 12 hours post Ifosfamide infusion.

**Days 2**
- **ETOPOSIDE** 100mg/m² IV in 500ml* sodium chloride 0.9% infusion over 1 hour
- **IFOSFAMIDE** 3g/m² + **MESNA** 3g/m² in 1-2L sodium chloride 0.9% infusion over 10 hours
- **MESNA** 3g/m² 1000ml sodium chloride 0.9% over 12 hours post Ifosfamide infusion.

**Days 3**
- **ETOPOSIDE** 100mg/m² IV in 500ml* sodium chloride 0.9% infusion over 1 hour
- **IFOSFAMIDE** 3g/m² + **MESNA** 3g/m² in 1-2L sodium chloride 0.9% infusion over 10 hours
- **MESNA** 3g/m² 1000ml sodium chloride 0.9% over 12 hours post Ifosfamide infusion.

**Day 15**
- Pre-hydration for methotrexate to start by 6am (see concurrent medication)
- **METHOTREXATE** 12g/m² IV in 500ml sodium chloride 0.9% infusion over 4 hours only if pH>7.0
- Continuous concurrent hydration (see concurrent medication)
- Post-hydration for methotrexate (see concurrent medication)

* *doses 48mg to 88mg in 250ml, 200mg to 360mg in 1000ml sodium chloride 0.9%

GCSF is recommended after IEM for 7 days (until WCC >5x10⁹/l) to start 24 hours after chemotherapy

**Cycle Frequency:** Every 21 days (for up to 6 cycles as salvage chemotherapy)

**DOSE MODIFICATIONS**

Previous neutropenic sepsis, discuss with Consultant or Registrar.

**Etoposide**
- CrCl > 50ml/min give 100% dose
- CrCl 15-50ml/min give 75% dose
- CrCl <15ml/min give 50% dose
- Bilirubin 26-51micromol/L or AST 60-180u/L give 50% dose
- Bilirubin >51micromol/L or AST >180u/L Clinical decision
**Ifosfamide**
GFR >60ml/min give 100% dose
GFR 40-59ml/min give 70% dose
GFR <40ml/min clinical decision
If creatinine >132mmol/L ifosfamide is not recommended
Discuss if - Bilirubin > 17 micromol/L
- AST and Alk Phos > 2.5 x ULN

Also refer to the ifosfamide-induced encephalopathy specific neural toxicity grade and nomogram (abridged below in full at the end of this document)

**Methotrexate**
GFR <70ml/min/1.73m² delay until recovery. If renal function does not improve within 1 week, omit methotrexate and proceed to next possible cycle. If renal function subsequently improves methotrexate can be resumed.
Pneumocystis carinii prophylaxis with trimethoprim is contra-indicated with methotrexate.
Note methotrexate induces LFTs, so give if ALT<10xULN as probably methotrexate induced (ie up to 3 weeks after methotrexate). It’s expected that patients receiving high dose methotrexate will develop hypertransaminases and occasionally hyperbilirubinaemia. These elevations can last up to two weeks following the methotrexate infusion and will not be considered toxicity requiring discontinuation of the drug.
Bilirubin >1.25xULN. Persistent hyperbilirubinaemia for longer than three weeks will result in discontinuation of methotrexate.

**SEVERE METHOTREXATE TOXICITY REQUIRES PROMPT INTERVENTION**
Methotrexate can cause renal failure, hepatic dysfunction and myelosuppression. Consider carboxypeptidase G2 early if persistent raised levels and/or evidence of renal impairment (see protocol).

**INVESTIGATIONS**
Routine Blood test
Blood results required before chemotherapy administration

1. Results Prior to Ifosfamide and Etoposide (see above for methotrexate)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Give</th>
<th>Discuss</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hb x g/dL</td>
<td>≥10</td>
<td>&lt; 10</td>
</tr>
<tr>
<td>Plt x 10⁹/L</td>
<td>≥75</td>
<td>&lt; 75</td>
</tr>
<tr>
<td>Neutrophils x 10⁹/L</td>
<td>≥0.75</td>
<td>&lt; 0.75</td>
</tr>
<tr>
<td>Bilirubin</td>
<td>&lt;1.25xULN</td>
<td></td>
</tr>
<tr>
<td>GFR</td>
<td>&gt;70ml/min</td>
<td>Calculated</td>
</tr>
<tr>
<td>Urine</td>
<td>No haematuria</td>
<td></td>
</tr>
<tr>
<td>Ca++, PO₄⁻²</td>
<td>and creatinine in blood and urine</td>
<td></td>
</tr>
<tr>
<td>Urine pregnancy test in women aged 12-55, unless sterilised or undergone a hysterectomy.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tp/CCrea</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
2. Results required before chemotherapy with Methotrexate

<table>
<thead>
<tr>
<th>Give</th>
<th>Discuss</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urinary pH</td>
<td>&gt;7 &lt;7 alkalinisation of urine</td>
</tr>
<tr>
<td>Hb x g/dL</td>
<td>≥10 &lt; 10</td>
</tr>
<tr>
<td>Plt x 10⁹/L</td>
<td>&gt;50 &lt; 50</td>
</tr>
<tr>
<td>Neutrophils x 10⁹/L</td>
<td>&gt;0.25 &lt; 0.25</td>
</tr>
<tr>
<td>Bilirubin</td>
<td>&lt;1.25xULN</td>
</tr>
<tr>
<td>Transaminases</td>
<td>May be any value in absence of liver disease</td>
</tr>
<tr>
<td>GFR</td>
<td>&gt;70ml/min Calculated</td>
</tr>
</tbody>
</table>

3. Non urgent tests
Tests relating to disease response/progression
a. Daily haematuria test
b. Neurological assessment and neurological toxicity
c. Record all clinically assessable disease
d. Investigations will usually include CT scan of chest and isotope bone scan
e. MRI of primary tumour site
f. For neoadjuvant treatment consider PET-CT scan
g. Record of WHO performance status, current height, weight and surface area
h. FBC, U&E, creatinine, LFTs. Creatinine clearance >55mls/min, ECG, consider ECHO (Echocardiogram after doxorubicin 300mg/m². LVEF>50% and <20% loss of LVEF to proceed.)
i. Consider formal measurement of creatinine clearance in patients with low body surface area
j. Give adequate verbal and written information for patients and relatives concerning patient’s disease, treatment strategy and side effects / mortality risk.
k. Obtain written consent from patient or guardian
l. If appropriate, discuss potential risk of infertility / early menopause with patient and relatives

CONCURRENT MEDICATION
• **Hydration fluid** – glucose 2.5% sodium chloride 0.45% potassium chloride 20mmol/L sodium bicarbonate 50mmol/L.
  Pre-hydration (start by 6am) for 4 hours prior to commencement of methotrexate (800ml/m²)
  Hydration during methotrexate infusion - the methotrexate must be infused at the appropriate rate (500ml/m²-max 1L- 4hours), in combination with the hydration fluid at a combined rate of 125ml/m²/hour.
  Post-hydration – continue with hydration infusion at 125ml/m²/hour for a minimum of 48 hours (ensuring urinary pH is always >7.0). Glucose 2.5% sodium chloride 0.45% potassium chloride 20mmol/L sodium bicarbonate 50mmol/L at 3000ml/m²/day until Methotrexate level below 0.1micromol/L. If not, continue after 48 hours to ensure a combined oral and/or intravenous intake >3L/m²/24hours until plasma methotrexate levels <0.1micromol/L.
- **Folinic acid rescue** – plasma methotrexate samples must be taken 24, 48 hours and 72 hours after the start of methotrexate administration and then every 24 hours if not completely rescued i.e. methotrexate not <0.1 micromol/L. Folinic acid rescue will start 24 hours after the start of the 3 hour infusion, give 15mg/m² IV every 3 hours for 5 doses then 15mg/m² IV or PO every 6 hours until rescued (methotrexate level <0.1 micromol/L). If 48 hour or 72 hour methotrexate level >2 micromol/L increase the dose of folinic acid.

<table>
<thead>
<tr>
<th>Time after starting MTX</th>
<th>MTX plasma concentration (micromol/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>48 hours</td>
<td>None</td>
</tr>
<tr>
<td>72 hours</td>
<td>None</td>
</tr>
<tr>
<td>96 hours</td>
<td>None</td>
</tr>
<tr>
<td>120 hours</td>
<td>None</td>
</tr>
</tbody>
</table>

- **Alkalization** – a urine pH >7.0 required before starting methotrexate and maintained until plasma level <0.2 micromol/L.
  - An alternative is acetozolamide 500mg qds starting 12 hours prior to treatment and continuing for 48 hours after treatment.
  - Sodium bicarbonate content of pre-hydration fluid can be increased to 75mmol/L.
  - Using sodium bicarbonate solution 1.26% 250ml over 30 minutes.
  - Oral sodium bicarbonate 3g qds.

**ANTIEMETIC POLICY**
Highly emetogenic days 1 to 3 (and day 4 if chemo continues into day 4 plus aprepitant if funded). Moderately emetogenic day 15

**ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS**
Neural Toxicity - refer to the ifosfamide-induced encephalopathy specific neural toxicity grade and nomogram (abridged below in full at the end of this document)
Methylthioninium chloride (methylene blue) can be given as prophylaxis against, or treatment of, ifosfamide-induced encephalopathy. Dose: 50mg tds IV.
NB. 50mg = 5ml of 1% solution.
IV: administer 50mg in 50 to 100ml glucose 5%, over 15 to 30 minutes
Nephrotoxicity - Irreversible renal failure and tubular damage can occur, and this is more frequent with cumulative doses over 25mg/m². Dose reductions should be instituted for GFR and changes in fractional phosphate clearance (TmP/GFR mmol/l).
Nephrotoxicity - Irreversible renal failure and tubular damage can occur, and this is more frequent with cumulative doses over 25 – 50g/m² of Ifosfamide.
<table>
<thead>
<tr>
<th>Toxicity Grade</th>
<th>GFR (ml/min/1.73m²)</th>
<th>Tp/Crea (Tmₚ/GFR) mmol/l</th>
<th>HCO₃ (mmol/l)</th>
<th>Action (apply worst grade)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 0/1</td>
<td>≥60</td>
<td>≥1.00</td>
<td>≥17.0</td>
<td>Ifos 100% total</td>
</tr>
<tr>
<td>Grade 2</td>
<td>40-59</td>
<td>0.8-0.99</td>
<td>14.0-16.9</td>
<td>Ifos 70% of total</td>
</tr>
<tr>
<td>Grade 3/4</td>
<td>≤40</td>
<td>≤0.8</td>
<td>≤14.0</td>
<td>Cyclophosphamide 1500mg/m² day 1 only</td>
</tr>
</tbody>
</table>

Fractional phosphate clearance calculated as below

\[
\text{Tp/Ccrea} = \frac{\text{Phosphate}_{\text{serum}} \text{ (mmol/L)} - \frac{\text{Phosphate}_{\text{urine}} \text{ (mmol/L)} \times \text{Creatinine}_{\text{serum}} \text{ (mmol/L)}}{\text{Creatinine}_{\text{urine}} \text{ (mmol/L)}}}{\text{[mmol/ml]}}
\]

NB serum creatinine is normally recorded in µmol/L

Methotrexate induced mucositis - folinic acid (calcium folinate) rescue (see concurrent medication)
Third space Fluids etc pleural effusion and pitting oedema are contraindications to high dose methotrexate.
Avoid NSAIDs, salicylates and aminoglycosides.
MAP inpatient (APMM off study Euramos1)

*Indication: Osteosarcoma including neoadjuvant, adjuvant and primary metastatic*

**APMM (MAP)**

**DRUG REGIMEN**

**Cycles 1 to 4**

**Days 1 & 2**

**DOXORUBICIN** 37.5mg/m$^2$/day (total of 75mg/m2 over 48 hours) IV in 250ml sodium chloride 0.9% infused over 48 hours as a continuous infusion

**Pre-hydration**

**CISPLATIN** 60mg/m$^2$ IV in 500ml sodium chloride 0.9% infusion over 4 hours

**Post-hydration**

**Days 22 & 29**

Pre-hydration for methotrexate to start by 6am (see concurrent medication)

**METHOTREXATE** 12g/m$^2$ IV in 500ml sodium chloride 0.9% infusion over 4 hours only if pH>7.0

Continuous concurrent hydration (see concurrent medication)

Post-hydration for methotrexate (see concurrent medication)

GCSF is recommended after day 2 doxorubicin and cisplatin brand as per local policy for 7 days

*Cycle Frequency: every 35 days cycles 1 and 2 pre surgery and cycle 3 and 4 post surgery.*
## DOSE MODIFICATIONS

*DOxorubicin and Cisplatin (AP)*

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Grade</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myelosuppression</td>
<td>On Day 1 of cycle ANC &lt; 0.75 x 10^9/L or WBC &lt; 2.0 x 10^9/L or Plts &lt; 75 x 10^9/L</td>
<td>Delay and repeat within 3-4 days until criteria are met. Retreat at full dose unless previous dose reduction. or For repeated delay (&gt; 7 days) use G-CSF. If delayed &gt; 7 days in spite of G-CSF reduce cisplatin to give 75%</td>
</tr>
<tr>
<td>Febrile Neutropenia with or without documented infection</td>
<td>All grade 4, consider. for grade 3</td>
<td>Add G-CSF Further episodes despite G-CSF: reduce cisplatin to give 75%.</td>
</tr>
<tr>
<td>-Mucositis</td>
<td>Grade 4 mucositis or typhilitis or repeated Grade 3 mucositis</td>
<td>Delay until resolved &amp; decrease subsequent doxorubicin to 60mg/m^2/cycle.</td>
</tr>
<tr>
<td>Hearing</td>
<td>≥ Grade 2</td>
<td>Discontinue cisplatin if hearing loss extends to 2kHz or lower frequencies</td>
</tr>
<tr>
<td>Cardiotoxicity</td>
<td>LVEF &lt; 50% or SF &lt; 28%</td>
<td>Repeat echo or MUGA in one week. If echo or MUGA within normal range proceed with chemotherapy. If LVEF does not normalize, omit all further doxorubicin.</td>
</tr>
<tr>
<td>Renal Toxicity</td>
<td>Serum creatinine &gt; 1.5 x baseline or GFR&lt;70mL/min/1.73m^2</td>
<td>Delay for one week. If renal function does not improve, omit cisplatin and give doxorubicin alone. Resume cisplatin at future courses if GFR ≥ 70 mL/min/1.73m^2.</td>
</tr>
<tr>
<td>Hepatic Toxicity</td>
<td>Raised Bilirubin</td>
<td>Reduce doxorubicin as follows:</td>
</tr>
<tr>
<td></td>
<td><strong>Concentration</strong></td>
<td><strong>% Dose</strong></td>
</tr>
<tr>
<td></td>
<td>0 – 21 μmol/L</td>
<td>100%</td>
</tr>
<tr>
<td></td>
<td>22 – 35 μmol/L</td>
<td>75%</td>
</tr>
<tr>
<td></td>
<td>36 – 52 μmol/L</td>
<td>50%</td>
</tr>
<tr>
<td></td>
<td>53 – 86 μmol/L</td>
<td>25%</td>
</tr>
<tr>
<td></td>
<td>&gt; 87 μmol/L</td>
<td>0%</td>
</tr>
<tr>
<td>Neuropathy</td>
<td>Grade 1</td>
<td>Reduce cisplatin to 75% dose for all future courses. Omit cisplatin for all future courses</td>
</tr>
<tr>
<td></td>
<td>&gt;= Grade 2</td>
<td></td>
</tr>
</tbody>
</table>

Maximum cumulative dose = 450-550mg/m^2 (in normal cardiac function)  
= 400 mg/m^2 (in patients with cardiac dysfunction or exposed to mediastinal irradiation)
**Methotrexate (M)**

Note that no dose reductions will apply.

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Grade</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myelosuppression</td>
<td>On Day 1 of cycle ANC &lt; 0.25 x 10^9/L Or WBC &lt; 1.0 x 10^9/L Plts &lt; 50 x 10^9/L</td>
<td>Delay until recovery according to group practice</td>
</tr>
<tr>
<td>- Mucositis</td>
<td>Grade 3-4 mucositis or diarrhea after MTX</td>
<td>Consider leucovorin rescue adjustment. Reminder: exclude drugs interfering with excretion</td>
</tr>
<tr>
<td>- Severe abdominal pain</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Diarrhea</td>
<td>If persists for &gt;1 Wk &amp; is present on Day 29 of MAP cycle</td>
<td>Omit Day 29 methotrexate (of this cycle only) &amp; proceed to next cycle (or surgery).</td>
</tr>
<tr>
<td>Renal Toxicity</td>
<td>GFR &lt;70mL/min/1.73m²</td>
<td>Delay until recovery. If renal function does not improve within 1 week, omit MTX &amp; proceed to next possible cycle. If renal function subsequently improves, MTX can be resumed.</td>
</tr>
<tr>
<td>Abnormal LFTs</td>
<td>Not MTX induced LFTs elevated</td>
<td>Delay one week. Give if ALT &lt; 10 x ULN.</td>
</tr>
<tr>
<td></td>
<td>Probably MTX induced i.e. up to 3 weeks after MTX</td>
<td>It is expected that patients receiving high dose Methotrexate will develop hypertransaminasemia and occasionally hyperbilirubinemia. These elevations can last up to two weeks following the methotrexate infusion and will not be considered toxicity requiring discontinuation of the drug. Persistent hyperbilirubinemia for longer than three weeks will result in discontinuation of MTX.</td>
</tr>
<tr>
<td></td>
<td>Bilirubin &gt; 1.25 x ULN</td>
<td></td>
</tr>
</tbody>
</table>

(Patients receiving A alone may continue with Doxorubicin).
Requirements Methotrexate:
General clinical condition permitting chemotherapy including resolving mucositis ≤ grade 1
No serous effusions or other ‘3rd space’
Neutrophils ≥ 0.25 x10^9 /L or WBC ≥1.0 x10^9 /L
Platelets ≥ 50 x10^9 /L
Bilirubin ≤ 1.25 x ULN
Transaminases may be any value in the absence of other causes of liver dysfunction
GFR ≥ 70 mL/min/1.73m^2
Urinary pH > 7.0 immediately prior to MTX
Monitoring Availability of serum MTX level monitoring

INVESTIGATIONS
Routine Investigations
1. Results required before chemotherapy administration with Cisplatin and Doxorubicin

<table>
<thead>
<tr>
<th>Give</th>
<th>Discuss</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hb x g/dL</td>
<td>≥10</td>
</tr>
<tr>
<td>Plt x 10^9/L</td>
<td>≥75</td>
</tr>
<tr>
<td>Neutrophils x 10^9/L</td>
<td>Bilirubin</td>
</tr>
<tr>
<td>GFR</td>
<td>&gt;70ml/min</td>
</tr>
<tr>
<td>Audiology</td>
<td>&lt;Gd2 at &lt;2kHz</td>
</tr>
</tbody>
</table>

2. Results required before chemotherapy with Methotrexate

<table>
<thead>
<tr>
<th>Give</th>
<th>Discuss</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urinary pH</td>
<td>&gt;7</td>
</tr>
<tr>
<td>Hb x g/dL</td>
<td>≥10</td>
</tr>
<tr>
<td>Plt x 10^9/L</td>
<td>&gt;50</td>
</tr>
<tr>
<td>Neutrophils x 10^9/L</td>
<td>&gt;0.25</td>
</tr>
<tr>
<td>Bilirubin</td>
<td>&lt;1.25xULN</td>
</tr>
<tr>
<td>Transaminases</td>
<td>May be any value in absence of liver disease</td>
</tr>
<tr>
<td>GFR</td>
<td>&gt;70ml/min</td>
</tr>
<tr>
<td>Audiology</td>
<td>&lt;Gd2 at &lt;2kHz</td>
</tr>
</tbody>
</table>

- GFR (Cr-EDTA) prior to cycle 1
- Echocardiogram after doxorubicin 300mg/m^2. LVEF>50% and <20% loss of LVEF to proceed.
- Urine pregnancy test in women aged 12-55, unless sterilised or undergone a hysterectomy.

Tests relating to disease response/progression after 2 cycles and prior to surgery
- MRI primary site and plain X-ray
- CT chest
- PET-CT if indicated (MDT decision)
CONCURRENT MEDICATION
G-CSF consider the use of GCSF if already used for previous MAP cycles.

Folinic acid rescue: Rescue starts 24 - 28 hours after start of 4 hour MTX infusion continued until serum MTX level is considered safe according to group practice (generally either <0.1 μmol/L or <0.2 μmol/L). Leucovorin 15 mg/m2 intravenously or orally every 6th hour, beginning 24 –28 hours after starting the methotrexate infusion. Normally, leucovorin is given by 11 - 12 doses until T84. It is sufficient to give leucovorin until 6 hours after the methotrexate concentration has fallen below 0.1-0.2 μmol/L.

Methotrexate - Adequate fluid with electrolytes and bicarbonate must be given to maintain urine output and alkalinization. This should be maintained until MTX serum level is considered safe according to group practice (generally either <0.1 μmol/L or <0.2 μmol/L).

A urinary pH >7 must be achieved before starting the MTX infusion and maintained until serum level is considered safe according to group practice (generally either <0.1 μmol/L or <0.2 μmol/L).

MTX serum levels: Must be taken at 24 - 28 hours from start of MTX then daily until level is considered safe according to group practice (generally either <0.1 μmol/L or <0.2 μmol/L).

Cisplatin - Ensure adequate pre-and post-hydration prescribed as. If fluid balance is > 2L positive after 8 hours post hydration OR urine output <100ml//hour during IV administration post Cisplatin give 200ml Mannitol 10% IV (preferred) OR 20 - 40 mg Furosemide PO/IV

G-CSF is recommended when a previous AP cycle has been complicated by fever and neutropenia with non-catheter related sepsis or prolonged hospitalization (>7 days). Begin at least 24 hours after the completion of chemotherapy. Continuation until WBC > 5.0 x 109/L is recommended.

Folinic acid rescue: Rescue starts 24 - 28 hours after start of 4 hour MTX infusion continued until serum MTX level is considered safe according to group practice (generally either <0.1 μmol/L or <0.2 μmol/L). Leucovorin 15 mg/m2 intravenously or orally every 6th hour, beginning 24 –28 hours after starting the methotrexate infusion. Normally, leucovorin is given by 11 - 12 doses until T84. It is sufficient to give leucovorin until 6 hours after the methotrexate concentration has fallen below 0.1-0.2 μmol/L.

Methotrexate - Adequate fluid with electrolytes and bicarbonate must be given to maintain urine output and alkalinization. This should be maintained until MTX serum level is considered safe according to group practice (generally either <0.1 μmol/L or <0.2 μmol/L).

A urinary pH >7 must be achieved before starting the MTX infusion and maintained until serum level is considered safe according to group practice (generally either <0.1 μmol/L or <0.2 μmol/L).

MTX serum levels: Must be taken at 24 - 28 hours from start of MTX then daily until level is considered safe according to group practice (generally either <0.1 μmol/L or <0.2 μmol/L).
ANTIEMETIC POLICY
Highly emetogenic days 1 and 2 (and day 3 if chemo continues into day 3) plus aprepitant if funded
Moderately emetogenic days 22 and 29

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS
Methotrexate toxicity and delayed methotrexate excretion can pose a significant and immediate threat to any patient receiving high dose methotrexate. SEVERE TOXICITY REQUIRES PROMPT INTERVENTION.
Cardiotoxicity – monitor cardiac function. Doxorubicin may be stopped in future cycles if signs of cardiotoxicity e.g. cardiac arrhythmias, pericardial effusion, tachycardia with fatigue.
Cardioprotection wherever possible use prolonged continuous infusion.
Note risk of delayed cardiomyopathy- if 20% reduction in LVEF after 300mg/m²- omit doxorubicin.
Nephrotoxicity – ensure adequate pre and post hydration is prescribed.
Ototoxicity – assess patient for tinnitus or hearing abnormalities, stop cisplatin if hearing loss extends to 2kHz.

Drug interactions:
DO NOT co-prescribe the following medicines which reduce MTX excretion: NSAIDS, ciprofloxacin, co-trimoxazole, penicillin, probenecid, omeprazole, piperacillin- tazobactam (this list is not exhaustive – please check for drug interactions). AVOID NEPHROTOXIC DRUGS

<table>
<thead>
<tr>
<th>Time</th>
<th>Methotrexate level (µmol/L)</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>24hrs</td>
<td>&lt;20</td>
<td>Continue fluids and folinic acid 15mg/m²/dose 6 hourly</td>
</tr>
<tr>
<td></td>
<td>&gt;20</td>
<td>Increase folinic acid</td>
</tr>
<tr>
<td>48hrs</td>
<td>&lt;2</td>
<td>Continue fluids and folinic acid</td>
</tr>
<tr>
<td></td>
<td>&gt;2</td>
<td>Increase folinic acid</td>
</tr>
<tr>
<td>72 hrs</td>
<td>&lt;0.1</td>
<td>Discuss with consultant</td>
</tr>
<tr>
<td>96hrs</td>
<td>0.1 - 0.2</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Hours</th>
<th>&lt;0.1 (µmol/L)</th>
<th>0.1 – 0.2 (µmol/L)</th>
<th>&lt;2 (µmol/L)</th>
<th>&lt;20 (µmol/L)</th>
<th>&gt;20 (µmol/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>24</td>
<td>None</td>
<td>Discuss</td>
<td>15mg/m² q6hr</td>
<td>15mg/m² q6hr</td>
<td>Discuss and increase</td>
</tr>
<tr>
<td>48</td>
<td>None</td>
<td>Discuss</td>
<td>15mg/m² q6hr</td>
<td>Increase</td>
<td></td>
</tr>
<tr>
<td>72</td>
<td>None</td>
<td>Discuss</td>
<td>Increase</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
**Indication:** Osteosarcoma adjuvant and primary metastatic

**Cycles 5 and 6 (after MAP chemotherapy- optional)**

**Days 1 & 2** DOXORUBICIN 37.5mg/m²/day (total of 75mg/m² over 48 hours) IV in 250ml sodium chloride 0.9% infused over 48 hours as a continuous infusion

**Day 3** Prophylactic GCSF brand as per local policy

**Days 15 & 22** Pre-hydration for methotrexate to start by 6am (see concurrent medication) METHOTREXATE 12g/m² IV in 500ml sodium chloride 0.9% infusion over 4 hours only if pH>7.0

Continuous concurrent hydration (see concurrent medication)
Post-hydration for methotrexate (see concurrent medication)

**Cycle frequency:** every 28 days for 2 cycles only

**DOSE MODIFICATIONS**

**Doxorubicin only**

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Grade</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myelosuppression</td>
<td>On Day 1 of cycle ANC &lt; 0.75 x 10⁹/L or WBC &lt; 2.0 x 10⁹/L or Plts &lt; 75 x 10⁹/L</td>
<td>Delay and repeat within 3-4 days. For repeated delay consider decreasing doxorubicin to 60mg/m²/cycle.</td>
</tr>
<tr>
<td>Febrile Neutropenia</td>
<td>All grade 4, for grade 3</td>
<td>consider Add G-CSF. Further episodes despite G-CSF: reduce doxorubicin to 60mg/m²/cycle.</td>
</tr>
<tr>
<td>-Mucositis</td>
<td>Grade 4 mucositis after AP</td>
<td>Delay until resolved &amp; decrease subsequent doxorubicin to 60 mg/m²/cycle.</td>
</tr>
<tr>
<td>-Severe abdominal pain</td>
<td>Repeated Grade 3 mucositis</td>
<td>NB: if previous doxorubicin dose reductions other than for cardiotoxicity or grade 4 mucositis, contact CI.</td>
</tr>
<tr>
<td>-Diarrhea</td>
<td></td>
<td>Repeat echo or MUGA in one week. If echo or MUGA within normal range proceed with chemotherapy. If LVEF does not normalize, omit all further doxorubicin.</td>
</tr>
<tr>
<td>-Typhlitis</td>
<td></td>
<td>Repeat echo or MUGA in one week. If echo or MUGA within normal range proceed with chemotherapy. If LVEF does not normalize, omit all further doxorubicin.</td>
</tr>
<tr>
<td>Cardiotoxicity</td>
<td>LVEF &lt;= 50% or SF &lt;= 28%</td>
<td>Repeat echo or MUGA in one week. If echo or MUGA within normal range proceed with chemotherapy. If LVEF does not normalize, omit all further doxorubicin.</td>
</tr>
</tbody>
</table>

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**AMM** Sarcoma CAG Chair Authorisation: Page 1 of 4 Published: January 2019

Date: Review: June 2022 Version 2.5

Chemotherapy Regimens– Sarcoma 41 of 98
Dose reduce in severe renal impairment.
Bilirubin 20-50micromol/L give 50% dose
Bilirubin 51-85micromol/L give 25% dose
Bilirubin >85micromol/L omit
If AST is 2-3 x ULN give 75% dose
If AST is >3 x ULN give 50% dose
Maximum cumulative dose = 450-550mg/m² (in normal cardiac function)
= 400 mg/m² (in patients with cardiac dysfunction or exposed to mediastinal irradiation)

**Methotrexate (M)**
Note that no dose reductions will apply

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Grade</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myelosuppression</td>
<td>On Day 1 of cycle</td>
<td>Delay until recovery according to group practice</td>
</tr>
<tr>
<td></td>
<td>ANC &lt; 0.25 x 10⁹/L</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Or WBC &lt; 1.0 x 10⁹/L</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Plts &lt; 50 x 10⁹/L</td>
<td></td>
</tr>
<tr>
<td>- Mucositis</td>
<td>Grade 3-4 mucositis</td>
<td>Consider leucovorin rescue adjustment. Reminder:</td>
</tr>
<tr>
<td></td>
<td>or diarrhea after MTX</td>
<td>exclude drugs interfering with excretion</td>
</tr>
<tr>
<td>- Severe abdominal pain</td>
<td>If persists for &gt;1 Wk</td>
<td></td>
</tr>
<tr>
<td>- Diarrhea</td>
<td>&amp; is present on Day 29 of MAP cycle</td>
<td>Omit Day 29 methotrexate (of this cycle only) &amp; proceed to next cycle (or surgery).</td>
</tr>
<tr>
<td>Renal Toxicity</td>
<td>GFR &lt;70mL/min/1.73m²</td>
<td>Delay until recovery.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>If renal function does not improve within 1 week, omit MTX &amp; proceed to next possible cycle. If renal function subsequently improves, MTX can be resumed.</td>
</tr>
<tr>
<td>(Patients receiving A alone may continue with doxorubicin).</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abnormal LFTs</td>
<td>Not MTX induced</td>
<td>Delay one week. Give if ALT &lt; 10 x ULN.</td>
</tr>
<tr>
<td></td>
<td>LFTs elevated</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Probably MTX</td>
<td></td>
</tr>
<tr>
<td></td>
<td>induced i.e. up to 3 weeks after MTX</td>
<td>It is expected that patients receiving high dose Methotrexate will develop hypertransaminasemia and occasionally hyperbilirubinemia. These elevations can last up to two weeks following the methotrexate infusion and will not be considered toxicity requiring discontinuation of the drug.</td>
</tr>
<tr>
<td></td>
<td>Bilirubin &gt; 1.25 x ULN</td>
<td>Persistent hyperbilirubinemia for longer than three weeks will result in discontinuation of MTX.</td>
</tr>
</tbody>
</table>
ROUTINE BLOOD TESTS

Blood results required before A (doxorubicin) administration

<table>
<thead>
<tr>
<th>Test</th>
<th>Requirement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plt x 10^9/L</td>
<td>GIVE &gt;= 75x10^9/L</td>
</tr>
<tr>
<td>Neutrophils x 10^9/L</td>
<td>GIVE &gt;= 0.75x10^9/L</td>
</tr>
<tr>
<td>or WBC</td>
<td>GIVE &gt;= 2.0x10^9/L</td>
</tr>
<tr>
<td>Bilirubin</td>
<td>GIVE =&lt;1.25xULN</td>
</tr>
<tr>
<td>Cardiac function</td>
<td>GIVE FS&gt;=28% or LVEF &gt;= 50% at last scheduled assessment</td>
</tr>
</tbody>
</table>

Blood results required before M (methotrexate) administration

<table>
<thead>
<tr>
<th>Test</th>
<th>Requirement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plt x 10^9/L</td>
<td>GIVE &gt;= 50x10^9/L</td>
</tr>
<tr>
<td>Neutrophils x 10^9/L</td>
<td>GIVE &gt;= 0.25x10^9/L</td>
</tr>
<tr>
<td>or WBC</td>
<td>GIVE &gt;= 1.0 x10^9/L</td>
</tr>
<tr>
<td>Bilirubin</td>
<td>GIVE =&lt;1.25xULN</td>
</tr>
<tr>
<td>Transaminase</td>
<td>May be any value in the absence of other causes of liver dysfunction</td>
</tr>
<tr>
<td>GFR</td>
<td>GIVE &gt;=70ml/min/1.73m^2</td>
</tr>
<tr>
<td>Urinary pH</td>
<td>GIVE &gt;7.0 immediately prior to methotrexate</td>
</tr>
<tr>
<td>Monitoring</td>
<td>Availability of serum methotrexate level monitoring</td>
</tr>
</tbody>
</table>

Height, weight and body surface area

- Clinical examination
- Full blood count and differential white count
- Blood chemistry (creatinine, urea, sodium, potassium, calcium, magnesium, phosphate, alkaline phosphatase, albumin, bicarbonate, liver transaminase, bilirubin)
- Beyond cumulative dose of doxorubicin 300 mg/m^2: Left ventricular ejection fraction or fractional shortening (echocardiogram or radionuclide scan)
- Measurement of GFR either by estimation (see Appendix A.3 for suggested formulae) or direct measurement (e.g. radio-isotopic method)
- Audiometry before 3rd and 4th AP cycle
- Urinary pH
- Urine pregnancy test in women aged 12-55, unless sterilised or undergone a hysterectomy.

ANTIEMETIC POLICY

Moderately emetogenic days 1 and 2
Low emetogenic days 15 and 22
CONCURRENT MEDICATION
G-CSF consider the use of GCSF if already used for previous MAP cycles.

Folinic acid rescue: Rescue starts 24 - 28 hours after start of 4 hour MTX infusion continued until serum MTX level is considered safe according to group practice (generally either <0.1 μmol/L or <0.2 μmol/L). Leucovorin 15 mg/m2 intravenously or orally every 6th hour, beginning 24 –28 hours after starting the methotrexate infusion. Normally, leucovorin is given by 11 - 12 doses until T84. It is sufficient to give leucovorin until 6 hours after the methotrexate concentration has fallen below 0.1-0.2 μmol/L.

Methotrexate - Adequate fluid with electrolytes and bicarbonate must be given to maintain urine output and alkalinization. This should be maintained until MTX serum level is considered safe according to group practice (generally either <0.1 μmol/L or <0.2 μmol/L).

A urinary pH >7 must be achieved before starting the MTX infusion and maintained until serum level is considered safe according to group practice (generally either <0.1 μmol/L or <0.2 μmol/L).

MTX serum levels: Must be taken at 24 - 28 hours from start of MTX then daily until level is considered safe according to group practice (generally either <0.1 μmol/L or <0.2 μmol/L).

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS
Methotrexate toxicity and delayed methotrexate excretion can pose a significant and immediate threat to any patient receiving high dose methotrexate. SEVERE TOXICITY REQUIRES PROMPT INTERVENTION.

Cardiotoxicity – monitor cardiac function. Doxorubicin may be stopped in future cycles if signs of cardiotoxicity e.g. cardiac arrhythmias, pericardial effusion, tachycardia with fatigue.
Cardioprotection Wherever possible use prolonged continuous infusion. Dexrazoxane may be used if a confirmed 10% fall within the normal range of LVEF or similar fall within the normal range of FS occurs.
Note risk of delayed cardiomyopathy- if 10% reduction in LVEF after 300mg/m$^2$- omit doxorubicin.
MIFAMURTIDE

**Indication:** *High-grade resectable non-metastatic osteosarcoma in young adults (up to 30 years old)* NICE TA235

**DRUG REGIMEN**

Weeks 1 to 12

**Days 1 and 4** Pre-med Paracetamol 1000mg IV  
MIFAMURTIDE 2mg/m² IV infusion in 100ml sodium chloride 0.9% over 1 hour

Weeks 13 to 36

**Day 1** Pre-med Paracetamol 1000mg IV  
MIFAMURTIDE 2mg/m² IV infusion in 100ml sodium chloride 0.9% over 1 hour

**Cycle Frequency:** *For a total of 36 weeks (total 48 doses)*

**DOSE MODIFICATIONS**

*Mifamurtide*

Renal impairment
No data. Caution should be used in these patients

Hepatic impairment
No data. Caution should be used in these patients

Continued monitoring of the kidney and liver function is recommended if mifamurtide is used beyond completion of chemotherapy until all therapy is completed.

**INVESTIGATIONS**

Routine Blood test

1) Blood results required before drug administration  
   *Give*  
   *Discuss*  
   Plt x 10⁹/L  
   ≥100  
   < 100

Febrile reactions are more likely if patient has low grade infection (coryza, D&V, etc) – discuss with consultant if inflammatory condition

2) Non urgent tests

Urine pregnancy test in women aged 12-55, unless sterilised or undergone a hysterectomy.
CONCURRENT MEDICATION
Patients experience tiredness and flu like symptoms initially, and can be treated with NSAIDs and paracetamol (doses in Takeda advice pack)
Reports of increased ototoxicity with concomitant cisplatin requires careful assessment if combined.
High dose NSAIDs and ciclosporin must be avoided with Mifamurtide.
Avoid steroids where possible as may dampen the immune response, but if other emetogenic chemotherapy due on the same day then risk vs benefit should be considered and lowest possible dose of steroids given.
Not to be given on day of methotrexate
It is recommended to separate the administration times of mifamurtide and doxorubicin or other lipophilic medicinal products if used in the same chemotherapy regimen. Mifamurtide can be given within 1 hour of non-lipophilic forms of doxorubin.

ANTIEMETIC POLICY
Low emetic risk

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS
Mild moderate tachycardia, hypertension, hypotension
Dyspnoea
Musculoskeletal pain
Not to be given on day of methotrexate. It is recommended to separate the administration times of mifamurtide and doxorubicin or other lipophilic medicinal products if used in the same chemotherapy regimen. Mifamurtide can be given within 1 hour of non-lipophilic forms of doxorubin.

REFERENCES
1. SPC March 2011
2. Takeda pack for Mifamurtide
ETOPOSIDE (Oral)

**Indication:** Palliative sarcoma  Ensure individual funding is in place before being prescribed.

**DRUG REGIMEN**
Days 1 to 21 ETOPOSIDE orally 50mg/m² daily for 21 days

**Cycle frequency: Every 28 days until disease progression.**

**DOSE MODIFICATIONS**
CrCl > 50ml/min give 100% dose
CrCl 15-50ml/min give 75% dose
CrCl <15ml/min give 50% dose
Hepatic impairment: - Arguments for and against dose reduction - discuss with SpR or Consultant
Bilirubin 26-51micromol/L or ALT/AST 60-180iu/L give 50% dose
Bilirubin >51micromol/L or ALT/AST >180iu/L clinical decision

<table>
<thead>
<tr>
<th>ANC and platelet counts (10⁹/L)</th>
<th>Current Etoposide cycle</th>
<th>Prescription for subsequent Etoposide cycle</th>
</tr>
</thead>
<tbody>
<tr>
<td>ANC &gt;0.5 and platelets &gt;50</td>
<td>Continue with current Etoposide cycle</td>
<td>Continue 100%</td>
</tr>
<tr>
<td>ANC &lt;0.5 and/or platelets &lt;50</td>
<td>Stop current Etoposide cycle</td>
<td>25% dose reduction in subsequent cycle on count recovery</td>
</tr>
</tbody>
</table>

**INVESTIGATIONS**
Blood results required before chemotherapy administration
Plt x 10⁹/L  Give if>=100  Discuss < 100
Neutrophils x 10⁹/L  Give if>=1.5  Discuss < 1.5
Tp/CCrea

**CONCURRENT MEDICATION**

**ANTIEMETIC POLICY**
Low emetic risk

**ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS**
Episodes of hypertension have been reported. If clinically significant hypertension occurs in patients receiving etoposide, appropriate supportive therapy should be initiated.

**REFERENCES**
1 Etoposide SPC; [http://www.medicines.org.uk/emc/medicine/7051](http://www.medicines.org.uk/emc/medicine/7051)
**IFOSFAMIDE infusional**

*Indication: High grade soft tissue sarcoma, retroperitoneal and de-differentiated sarcoma*

**DRUG REGIMEN**

Day 1  MESNA 600mg/m² po  
Days 1 to 14 IFOSFAMIDE 1000mg/m²/day IV infusion  
MESNA 1000mg/m²/day IV infusion  
Ensure adequate oral fluid intake.

*Cycle frequency: every 28 days up to 6 cycles*

**DOSE MODIFICATIONS**

Previous neutropenic sepsis, discuss with Consultant.  
Number of infusion days can be shortened depending on co-morbidity

Ifosfamide

GFR >60ml/min give 100% dose  
GFR 40-59ml/min give 70% dose  
GFR <40ml/min clinical decision.  
Creatinine >120micromol/L ifosfamide not recommended

Discuss if  
* Bilirubin >17 micromol/L  
* AST and Alk Phos > 2.5 x upper limit of normal  
Also refer to the ifosfamide-induced encephalopathy specific neural toxicity grade and nomogram

**INVESTIGATIONS**

Routine Blood test

1) Blood results required before chemotherapy administration  
Plt x 10⁹/L  Give if>=100  Discuss < 75  
Neutrophils x 10⁹/L  Give if>=1.0  Discuss < 1.5  
Tp/CCrea
2) Non-urgent blood tests
Tests relating to disease response/progression
• Daily haematuria test
• Neurological assessment and neurological toxicity
• Record all clinically assessable disease
• Investigations will usually include CT scan of chest and isotope bone scan
• MRI of primary tumour site
• For neoadjuvant treatment consider PET-CT scan
• Record of WHO performance status, current height, weight and body surface area
• FBC, U&E, creatinine, LFTs. Creatinine clearance >55mls/min, ECG, consider ECHO
• Consider formal measurement of creatinine clearance in patients with low surface area
• Give adequate verbal and written information for patients and relatives concerning patient’s disease, treatment strategy and side effects / mortality risk.
• Obtain written consent from patient or guardian if appropriate
• If appropriate, discuss potential risk of infertility / early menopause with patient and relatives

CONCURRENT MEDICATION
Ensure adequate oral fluid intake
NB. Methylthioninium chloride (methylene blue) can be given as prophylaxis against, or treatment of, ifosfamide-induced encephalopathy

ANTIEMETIC POLICY
Moderate emetic risk

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS
Neuro Toxicity - Assess Probability of remaining free from severe CNS toxicity (ifosfamide) refer to the ifosfamide-induced encephalopathy specific neural toxicity grade and nomogram
  Give Discuss
> 0.5  <0.5
Careful consideration should be given if <0.2
Haemorrhagic cystitis

REFERENCES
1. Casali abstract no 10067 ASCO 2007
TRABECTEDIN

**Indication:** High / intermediate grade soft tissue sarcoma, myxoid liposarcoma, liposarcoma, leiomyosarcoma, synovial sarcoma after first line treatment with anthracyclines

NICE: Trabectedin is recommended as a treatment option for people with advanced soft tissue sarcoma if: treatment with anthracyclines and ifosfamide has failed or they are intolerant of or have contraindications for treatment with anthracyclines and ifosfamide and the acquisition cost of trabectedin for treatment needed after the fifth cycle is met by the manufacturer. NB: PAS scheme available. Complete paperwork each cycle. Free of Charge stock after cycle 6.

**DRUG REGIMEN**

**Day 1** Dexamethasone 20mg IV 30 minutes prior to trabectedin

TRABECTEDIN 1.5mg/m² IV in sodium chloride 0.9% over 24 hours via a central line* (Supply in a 24 hour infusor pump)

GCSF may be required

*If central venous access is not available trabectedin can be given peripherally in at least 1000ml of infusion fluid

**Cycle frequency: every 21 days subject to tolerance and response.**

**DOSE MODIFICATIONS**

Hepatic impairment

No studies special caution is advised and dose adjustments may be necessary in these patients since systemic exposure is probably increased and the risk of hepatotoxicity might be increased. Bilirubin >ULN omit

 Patients with impaired renal function

CrCl < 30 ml/min trabectedin must not be used

CrCl > 30ml/min no adjustments required

Prior to retreatment, patients must fulfill the baseline criteria. If any of the following events occur at any time between cycles, the dose must be reduced one level, according to reductions below, for subsequent cycles:

- Neutropenia < 0.5x10⁹/L lasting for more than 5 days or associated with fever or infection
- Thrombocytopenia <25x10⁹/L
- Increase of bilirubin> ULN and/or alkaline phosphatase> 2.5 x ULN
- Increase of aminotransferases (AST or ALT)> 2.5 x ULN (monotherapy) or> 5 x ULN (combination therapy), which has not recovered by day 21
- Any other grade 3 or 4 adverse reactions (such as nausea, vomiting, fatigue)
- Normal creatine kinase level (check every week in cycle 1 and 2 and prior to each administration)

Starting dose 1.5mg/m²

First reduction 1.2mg/m²

Second reduction 1mg/m²

If further dose reductions are necessary, treatment discontinuation should be considered.
Once a dose has been reduced due to toxicity, dose escalation in the subsequent cycles is not recommended. If any of these toxicities reappear in subsequent cycles in a patient exhibiting clinical benefit, the dose may be further reduced (see below). Colony stimulating factors can be administered for hematologic toxicity according to local standard practice. - Urine pregnancy test - before each course of chemotherapy in women aged 12 – 55 years of age unless they have been sterilised or undergone a hysterectomy.

**INVESTIGATIONS**

Routine Blood test
1) Blood results required before chemotherapy administration
   - Hb x g/dL Give if≥9  Discuss < 9
   - Plt x 10⁹/L Give if≥100  Discuss < 100
   - Neutrophils x 10⁹/L Give if≥1.5  Discuss < 1.5

Liver function tests (LFTs) within normal limits
Monitoring of haematological parameters, bilirubin, alkaline phosphatase, aminotransferases and Creatine kinase should be checked weekly during the first two cycles of therapy, and at least once mid cycle between treatments in subsequent cycles and If patient presents/admitted with neutropenia or other symptoms. If CK raised (>2.5xULN) must be decreased prior to treatment.

2) Non urgent tests
   - Tests relating to disease response/progression
   - Mandatory checking of creatine kinase and LDH every cycle before treatment.
   - Urine pregnancy test in women aged 12-55, unless sterilised or undergone a hysterectomy.

**ANTI-EMETICS**

Low-moderate emetogenicity

**ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS**

Rhabdomyolysis

**REFERENCES**

   Ecteinascidin-743 (ET-743) for Chemotherapy-Naive Patients With Advanced Soft Tissue Sarcomas: Multicenter Phase II and Pharmacokinetic Study
   JCO VOLUME 23 NUMBER 24 AUGUST 20 2005
OLARATUMAB DOXORUBICIN

**Indication:** advanced soft tissue sarcoma in ADULT patients where the patient has histologically proven locally advanced or metastatic disease soft tissue sarcoma. PS 0-1

In combination with doxorubicin for the treatment of advanced soft tissue sarcoma in ADULT patients where the following criteria apply:

2. The patient has histologically proven soft tissue sarcoma.
3. The patient has locally advanced or metastatic disease.
4. The patient is an adult
5. Treatment intent is palliative ie disease not amenable to potentially curative treatment with surgery and/or radiotherapy.
6. The patient has had no previous treatment with doxorubicin.
7. Olaratumab will be administered in combination with doxorubicin 75mg/m2.
8. A maximum of 6 cycles of doxorubicin will be given.
9. Olaratumab will be administered until disease progression/unacceptable toxicity
10. Olaratumab when given concurrently with chemotherapy will only be used in combination with doxorubicin (ie not with a doxorubicin-containing combination or non-doxorubicin containing regimen)
11. The patient has a performance status (PS) 0 or 1.
12. The patient has either not received previous adjuvant or neoadjuvant chemotherapy or has but this was not with any doxorubicin-containing regimen.
13. No planned treatment breaks of more than 6 weeks beyond the expected cycle length are allowed (to allow any toxicity of current therapy to settle or intercurrent comorbidities to improve).*

*Requests for continuation of treatment after unplanned treatment breaks over this duration should be made via the treatment break approval process

14. Olaratumab will otherwise be used as set out in its Summary of Product Characteristics.

**DRUG REGIMEN**

Day 1 OLARATUMAB 15mg/kg in 250ml sodium chloride 0.9% IV infusion

DOXORUBICIN 75mg/m² IV bolus

Day 8 OLARATUMAB 15mg/kg IV in 250ml sodium chloride 0.9% IV infusion

Cycle frequency: every 21 days

Doxorubicin for 6 cycles, olaratumab until disease progression

**DOSE MODIFICATIONS**

**Olaratumab**

Renal impairment

There have been no formal studies with olaratumab in patients with renal impairment. PopPK data suggest that no dose adjustments are required in patients with mild or moderate renal impairment. There are no data regarding olaratumab administration in patients with severe renal impairment (calculated creatinine clearance < 30 mL/min)
Hepatic impairment
There have been no formal studies with olaratumab in patients with hepatic impairment. PopPK data suggest that no dose adjustments are required in patients with mild hepatic impairment. There are very limited data regarding olaratumab administration in patients with moderate hepatic impairment. There are no data in patients with severe hepatic impairment.

<table>
<thead>
<tr>
<th>Toxicity grade</th>
<th>Infusion related reactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1-2</td>
<td>• Stop the infusion</td>
</tr>
<tr>
<td></td>
<td>• Paracetamol, H1 antagonist and dexamethasone should be administered as needed (see premedication section)</td>
</tr>
<tr>
<td></td>
<td>• Once the reaction has resolved, resume infusion at a 50% decreased infusion rate</td>
</tr>
<tr>
<td></td>
<td>• Monitor patient for worsening of condition.</td>
</tr>
<tr>
<td></td>
<td>• For subsequent infusions, please see premedication section.</td>
</tr>
<tr>
<td>Grade 3-4</td>
<td>• Immediately and permanently discontinue treatment with olaratumab</td>
</tr>
</tbody>
</table>

Once the infusion rate has been reduced for a Grade 1 or 2 infusion-related reaction, it is recommended that the lower infusion rate be utilized for all subsequent infusions. The infusion duration should not exceed 2 hours.

Other non-haematology toxicities
For serious Grade ≥ 3 non-haematologic toxicity deemed related to olaratumab, the dose of olaratumab should be withheld until toxicity is ≤ Grade 1 or has returned to pretreatment baseline. For subsequent infusions, the dose should be reduced to 12 mg/kg for serious Grade 3 toxicities and to 10 mg/kg for Grade 4 toxicities. If a Grade 3 toxicity recurs despite the dose reduction, the dose should be reduced further to 10 mg/kg. In case of recurrence of a Grade 4 toxicity, treatment with olaratumab should be permanently discontinued.

Neutropenia
If neutropenic fever/infection or Grade 4 neutropenia lasting longer than 1 week occurs, administration of olaratumab should be temporarily discontinued until the absolute neutrophil count is 1.0 x 10^9/L or higher and then the dose of olaratumab should be resumed at the reduced dose of 12 mg/kg. If neutropenic fever/infection or Grade 4 neutropenia lasting longer than 1 week recurs despite dose reduction, the dose should be reduced further to 10 mg/kg.

*Doxorubicin*
Dose reduce in severe renal impairment.
Bilirubin 20-50 micromol/L give 50% dose
Bilirubin 51-85 micromol/L give 25% dose
Bilirubin >85 micromol/L omit
If AST is 2-3 x ULN give 75% dose
If AST is >3 x ULN give 50% dose
Max cumulative dose
= 450 - 550 mg/m² (in normal cardiac function)
= 400 mg/m² (in patients with cardiac dysfunction or exposed to mediastinal irradiation)
INVESTIGATIONS
Routine Blood test
1) Blood results required before chemotherapy administration
   Hb x g/dL  Give if>=10  Discuss < 10
   Plt x 10^9/L  Give if>=100  Discuss < 100
   Neutrophils x 10^9/L  Give if>=1.5  Discuss < 1.5
   Liver function tests (LFTs) to limits in dose modifications

2) Non urgent blood tests
   Tests relating to disease response/progression

3) Pre-treatment
   • Assess cardiac risk factors
   • Consider ECG and ECHO
   • Consider scalp cooling

ANTIEMETIC POLICY
Moderately emetogenic

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS
Cardiotoxicity – monitor cardiac function. Doxorubicin may be stopped in future cycles if signs of cardiotoxicity e.g. cardiac arrhythmias, pericardial effusion, tachycardia with fatigue.
Note risk of delayed cardiomyopathy- if 20% reduction in LVEF after 300mg/m^2 - omit doxorubicin
Infusion related reactions
Neutropenia
Haemorrhagic events
IRINOTECAN TEMOZOLOMIDE

**Indication:** High grade sarcoma and relapsed Ewings sarcoma, WHO PS 0-2

**DRUG REGIMEN**

**Days 1 to 5**

PRE-MEDICATION (at least 30 minutes prior to treatment)

- ATROPINE 250 microgram subcutaneously
- TEMOZOLOMIDE 100mg/m² po days 1 to 5 taken 1 hour before irinotecan
- IRINOTECAN 50mg/m² in 250ml sodium chloride 0.9% IV infusion over 30 minutes

*Cycle frequency: every 21 days for 6 cycles then review (restage with PET CT or CT)*

**DOSE MODIFICATIONS**

If neutrophils < 1.0 x 10⁹/L or platelets < 75 x 10⁹/L delay 1 week, only treat when neutrophils and platelets are above these limits.

Delay > 14 days give 80% temozolomide dose for next cycle.

In the event of febrile neutropenia give to 80% for all subsequent cycles.

If Bilirubin 25 - 50 micromol/L give 50% dose

Omit if bilirubin > 3xULN

Omit if GFR < 30 ml/min.

If patients suffer from severe diarrhoea, which required IV rehydration or neutropenic fever, dose may need to be reduced.

**INVESTIGATIONS**

Routine blood tests

1. Blood results required before chemotherapy administration

- Plt x 10⁹/L GIVE if > or = 75 DISCUSS < 75
- Neutrophils x 10⁹/L GIVE if > or = 1.0 DISCUSS < 1.0

2. Non urgent tests relating to disease response / progression.

**CONCURRENT MEDICATION**

Patients who experience delayed diarrhoea will require loperamide 2 mg every 2 hours to continue for 12 hours after the last loose stool. This high dose should be discontinued after 48 hours. Consider antibiotic if indicated (cefixime 400mg daily days 1 to 8)

**ANTIEMETIC POLICY**

Moderately emetogenic risk
ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS
Acute Diarrhoea – delayed diarrhea occurring more than 24 hours after administration.
Drink large volumes of fluid containing electrolytes and an appropriate antidiarrhoeal therapy
e.g. loperamide 4mg initially then 2mg every 2 hours, continuing for 12 hours after the last liquid
stool (maximum of 48 hours in total).
Fatal liver failure has been reported with Temozolomide.

REFERENCES
2. Clinical Cancer Research Vol 10, 840-848, Feb 1, 2004
VAC (off study EuroEWING 12)

**Indication:** Sarcoma including desmoid fibromatosis and Ewings sarcoma consolidation

**DRUG REGIMEN**

Ensure patient has double lumen central line. For Ewings Sarcoma refer to EuroEwing 2012 trial protocol for possible treatment schedules.

**Day 1**

MESNA 500mg/m² IV bolus one hour prior to cyclophosphamide

VINCRISTINE 1.5mg/m² (max 2mg) in 50ml sodium chloride 0.9% IV infusion over 10 minutes

DACTINOMYCIN 0.75mg/m² (max 1.5mg) IV bolus

Run cyclophosphamide and mesna together down separate lumens:

CYCLOPHOSPHAMIDE 1500mg/m² in 250ml sodium chloride 0.9% IV infusion over 3 hours

MESNA 1500mg/m² in 1000ml sodium chloride 0.9% IV infusion over 3 hours

MESNA 1000mg/m² in 1000ml sodium chloride 0.9% IV infusion over 20 hours

**Day 2**

DACTINOMYCIN 0.75mg/m² (max 1.5mg) IV bolus

_Cycle Frequency: Every 21 days for 7 cycles._

_Consolidation chemo post surgery - 1 cycle of VAI followed by 7 cycles of VAC can be given_

**DOSE MODIFICATIONS**

_Dactinomycin (Actinomycin D)_

Consider dose reduction with hepatic dysfunction

Omit dose if concurrent radiotherapy (omitted doses are not subsequently given)

_Cyclophosphamide_

Reduce Cyclophosphamide and Dactinomycin dose if:

- Delayed recovery >6 days
- Neutropenic sepsis Grade 3 and 4
- Mucositis / GI toxicity Grade 3 and 4

Reduce to 80% dose on 1st occurrence and 60% dose on second occurrence.

**INVESTIGATIONS**

Routine Blood test

1) Blood results required before chemotherapy administration

<table>
<thead>
<tr>
<th></th>
<th>Give</th>
<th>Discuss</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plt x 10⁹/L</td>
<td>≥80</td>
<td>&lt; 80</td>
</tr>
<tr>
<td>Neutrophils x 10⁹/L</td>
<td>≥1.0</td>
<td>&lt; 1.0</td>
</tr>
<tr>
<td>WBC x 10⁹/L</td>
<td>≥2.0</td>
<td>&lt; 2.0</td>
</tr>
</tbody>
</table>

2) Non urgent tests

Tests relating to disease response/progression

Urine pregnancy test in women aged 12-55, unless sterilised or undergone a hysterectomy.
CONCURRENT MEDICATION
GCSF is recommended to maintain dose intensity (until WCC >5x10⁹/l)
Cotrimoxazole 480mg bd M/W/F as per local policy for duration of chemotherapy.
Difflam

ANTIEMETIC POLICY
High emetic risk and aprepitant if funded

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS
Cyclophosphamide may irritate bladder, drink copious volumes of water.
Microscopic Haemorrhagic cystitis: additional bolus dose 600mg/m2 then continue infusion at double dose
Grade ≥2 macroscopic haemorrhagic cystitis: discontinue chemotherapy and continue double dose MESNA and hydration x 24 hrs post-chemotherapy
Vincristine may cause neurotoxicity.

REFERENCES
1. EUROEWING12 2014
VAI (off study EuroEWING 12)

**Indication:** Sarcoma and Ewings sarcoma consolidation

**DRUG REGIMEN**
For Ewings Sarcoma refer to EuroEwing 2012 trial protocol for possible treatment schedules.

**Day 1**
- MESNA 1g/m² IV bolus one hour prior to ifosfamide
- VINCRISTINE 1.5mg/m² (max 2mg) in 50ml sodium chloride 0.9% IV infusion over 10 minutes
- DACTINOMYCIN 0.75mg/m² (max 1.5mg) IV bolus
- IFOSFAMIDE 3g/m² with MESNA 3g/m2 in 1000ml sodium chloride 0.9% IV infusion over 3 hours
- MESNA 2g/m² in 1000ml sodium chloride 0.9% IV infusion over 20 hours

**Day 2**
- VINCRISTINE 1.5mg/m² (max 2mg) in 50ml sodium chloride 0.9% IV infusion over 10 minutes
- DACTINOMYCIN 0.75mg/m² (max 1.5mg) IV bolus
- IFOSFAMIDE 3g/m² with MESNA 3g/m2 in 1000ml sodium chloride 0.9% IV infusion over 3 hours
- MESNA 2g/m² in 1000ml sodium chloride 0.9% IV infusion over 20 hours

**Cycle Frequency:** Every 21 days for 7 or 8 cycles

**Consolidation chemo post surgery - Either 1 cycle of VAI followed by 7 cycles of VAC OR 8 cycles of VAI can be given.**

**DOSE MODIFICATIONS**
In case of significant bone marrow toxicity preference should be given to GCSF support rather than dose reduction in order to maintain dose intensity.

Reduce Ifosfamide and Dactinomycin dose if;
- Delayed recovery >6 days
- Neutropenic sepsis Grade 3 and 4
- Mucositis/GI toxicity Grade 3 and 4

Reduce to 80% dose on 1st occurrence and 60% dose on second occurrence.

**Nephrotoxicity**
Irreversible renal failure and tubular damage can occur, and this is more frequent with cumulative doses over 25 - 50mg/m² of Ifosfamide.

<table>
<thead>
<tr>
<th>Toxicity Grade</th>
<th>GFR (ml/min/1.73m²)</th>
<th>Tp/Crea (Tmpr/GFR)</th>
<th>HCO3 mmol/l(mmol/l)</th>
<th>Action (apply worst grade)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 0/1</td>
<td>&gt;=60</td>
<td>=1.00</td>
<td>&gt;=17.0</td>
<td>Ifosfamide 100% total</td>
</tr>
<tr>
<td>Grade 2</td>
<td>40-59</td>
<td>0.8-0.99</td>
<td>14.0-16.9</td>
<td>Discuss</td>
</tr>
<tr>
<td>Grade 3/4</td>
<td>&lt;=40</td>
<td>&lt;=0.8</td>
<td>&lt;=14.0</td>
<td>Cyclophosphamide**</td>
</tr>
</tbody>
</table>

* Re-check low HCO3 values when patient is clinically stable (to rule out infection as a cause etc) before modifying dose / treatment.

**Discuss with Consultant before and to confirm substitution of Ifosfamide with Cyclophosphamide at 1500mg/m²/day**
Fractional phosphate clearance calculation:
\[ \text{Tp/Crea} = \frac{\text{Phosphates serum (mmol/L)} - \text{Phosphate urine (mmol/L) \times creatinine serum (mmol/L)}}{\text{Creatinine urine (mmol/L)}} \]

NB serum creatinine is normally recorded in µmol/L

**INVESTIGATIONS**

Routine Blood test

1) Blood results required before chemotherapy administration

<table>
<thead>
<tr>
<th></th>
<th>Give</th>
<th>Discuss</th>
</tr>
</thead>
<tbody>
<tr>
<td>WBC x 10⁹/L</td>
<td>≥2.0</td>
<td>&lt; 2.0</td>
</tr>
<tr>
<td>Plt x 10⁹/L</td>
<td>≥80</td>
<td>&lt; 80</td>
</tr>
<tr>
<td>Neutrophils x 10⁹/L</td>
<td>≥1.0</td>
<td>&lt; 1.0</td>
</tr>
<tr>
<td>WBC x 10⁹/L</td>
<td>≥ 2.0</td>
<td>&lt; 2.0</td>
</tr>
</tbody>
</table>

2) Non urgent tests

Tests relating to disease response/progression

Urine pregnancy test in women aged 12-55, unless sterilised or undergone a hysterectomy.

GFR EDTA

**CONCURRENT MEDICATION**

If bone marrow suppression, GCSF is recommended to maintain dose intensity (until WCC >5x10⁹/l)

Cotrimoxazole 480mg bd M/W/F as per local policy for duration of chemotherapy

Difflam

**ANTIEMETIC POLICY**

High emetic risk

**ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS**

**Central Neurotoxicity:**

If CTC grade 3 or 4 central neurotoxicity occurs (somnolence >30% of the time, disorientation / hallucination / echlalia / perseveration / coma or seizures on which consciousness is altered etc) consider the use of methylene blue (methylonium) 50mg IV infusion. Prolong ifosfamide infusion 4 to 8 hours with the next application and infuse 50mg tds.

In the next course give one dose of 50mg 24 hours prior to ifosfamide. During ifosfamide infusion give tds. If repeated grade 3 or 4 central neurotoxicity occurs consider withholding ifosfamide and substitute cyclophosphamide 1500mg/m².

Dose: 50mg tds IV. NB. 50mg = 5ml of 1% solution.

IV: administer 50mg in 50 to 100ml glucose 5%, over 15 to 30 minutes

**REFERENCES**

EUROEWING 12 2014
VIDE (off study EuroEWING 12)

**Indication:** Ewings sarcoma and high grade soft tissue sarcoma

**DRUG REGIMEN**

**Day 1**
- **VINCRIStINE** 1.5mg/m$^2$ (max 2mg) in 50ml sodium chloride 0.9% IV infusion over 10 minutes
- **DOXORUBICIN** 20mg/m$^2$ in 100ml sodium chloride 0.9% IV infusion over 4 hours
- **MESNA** 1g/m$^2$ IV bolus (pre ifosfamide dose)
- **ETOPOSIDE** 150mg/m$^2$ in 1000ml* sodium chloride 0.9% IV infusion over 1 hour
- **IFOSFAMIDE** 3g/m$^2$ plus **MESNA** 3g/m$^2$ in 1000ml sodium chloride 0.9% IV infusion over 3 hours
- **MESNA** 2g/m$^2$ in 1000ml sodium chloride 0.9% IV infusion over 16 hours (post ifosfamide dose)

**Days 2 and 3**
- **DOXORUBICIN** 20mg/m$^2$ in 100ml sodium chloride 0.9% IV infusion over 4 hours
- **ETOPOSIDE** 150mg/m$^2$ in 1000ml* sodium chloride 0.9% IV infusion over 1 hour
- **IFOSFAMIDE** 3g/m$^2$ plus **MESNA** 3g/m$^2$ in 1000ml sodium chloride 0.9% IV infusion over 3 hours
- **MESNA** 2g/m$^2$ in 1000ml sodium chloride 0.9% IV infusion over 16 hours (post ifosfamide dose)

* doses 48mg to 88mg in 250ml, 96mg to 180mg in 500ml sodium chloride 0.9%

**GCSF** brand as per local protocol (continue for 7 days) starting 24 hours after chemotherapy

**Cycle Frequency:** Every 21 days for a maximum 6 cycles

PBPC mobilisation and harvesting is strongly recommended following VIDE 3 and/or 4. This is advised in patients with localised tumours <200ml and mandatory in patients with localised tumours >= 200ml or metastases to lungs/pleura only.

**DOSE MODIFICATIONS**

Maximum cumulative dose = 450-550mg/m$^2$ (in normal cardiac function)
= 400 mg/m$^2$ (in patients with cardiac dysfunction or exposed to mediastinal irradiation)

**Haematological toxicity**

Dose/time intensity is regarded as an essential aspect of induction strategy. In case of significant bone marrow toxicity preference should be given to GCSF support rather than dose reduction in order to maintain dose intensity.

If significant toxicity continues as defined by

Haematological recovery delayed > 6 days then give 80% etoposide dose
Neutropenic sepsis grade 3 or 4 then give 80% etoposide dose

Further episodes of toxicity should result in reductions in etoposide to 60% dose. If necessary it is advised to omit etoposide completely rather than reduce the doses of the other three drugs.

**Gastrointestinal toxicity**

Mucositis/gastrointestinal (GI) toxicity grade 3 or 4 then give 80% etoposide dose

Further episodes of toxicity should result in reductions in etoposide to 60% dose. If necessary it is advised to omit etoposide completely rather than reduce the doses of the other three drugs.
**Nephrotoxicity**

Ifosfamide

<table>
<thead>
<tr>
<th>Grade</th>
<th>Toxicity</th>
<th>GFRml/min</th>
<th>Tp/Crea</th>
<th>HCO3*</th>
<th>Action (apply worst grade)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-1</td>
<td></td>
<td>&gt;= 60</td>
<td>&gt;=1</td>
<td>&gt;=17</td>
<td>give 100% dose</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>40-59</td>
<td>0.8-0.99</td>
<td>14-16.9</td>
<td>give 70% dose</td>
</tr>
<tr>
<td>3-4</td>
<td></td>
<td>&lt;=40</td>
<td>&lt;=0.8</td>
<td>&lt;=14</td>
<td>Use cyclophosphamide 1500mg/m²/day d1</td>
</tr>
</tbody>
</table>

**Low values of HCO3 should be rechecked when the patient is clinically stable (to rule out infection as a cause etc) before modifying ifosfamide dose / treatment.**

\[
\text{Tp/Ccrea} = \frac{\text{Phosphateserum (mmol/L)} - \text{Phosphateurine (mmol/L)} \times \text{creatinineserum (mmol/L)}}{\text{Creatinineurine (mmol/L)}}
\]

NB serum creatinine is normally recorded in µmol/L

- **Etoposide**
  - GFR<60ml/min/1.73m² then give 70% etoposide dose

  If neutrophils <1.0x10⁹/L or platelets <80x10⁹/L then defer therapy by 1 week.
  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.

**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.

**INVESTIGATIONS**

Routine Blood test

1) Blood results required before chemotherapy administration

*Give*  
- Plt x 10⁹/L >80 < 80
- Neutrophils x 10⁹/L >1.0 < 1.0

*Discuss*  
- Urine pregnancy test in women aged 12-55, unless sterilised or undergone a hysterectomy.

**CONCURRENT MEDICATION**

Cotrimoxazole 480mg bd M/W/F as per local policy for duration of chemotherapy

Irradiated blood products starting 1 week prior to stem cell harvest

Difflam
ANTIEMETIC POLICY
High emetic risk

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS
Central neurotoxicity
Dose adaption due to central neurotoxicity: If CTC grade 3/4 central neurotoxicity occur (somnolence >30% of the time, disorientation, hallucination etc) consider the use of methylene blue 50mg IV infusion. Prolong ifosfamide infusion to 4-8 hours with the next application and infuse methylene blue 50mg tds.
In the next course apply methylene blue one dose of 50mg 24 hours prior to ifosfamide. During ifosfamide infusion give methylene blue tds.
If repeated grade 3/4 central neurotoxicity occurs consider withholding ifosfamide and substitute cyclophosphamide 1500mg/m^2 BSA day 1
Cardiotoxicity
Nephrotoxicity: Irreversible renal failure and tubular damage can occur, and this is more frequent with cumulative doses over 25 – 50g/m^2 of Ifosfamide.
Vincristine may cause neurotoxicity.

REFERENCES
1. Euroewing 12 regimen
**Indication: Ewing's sarcoma**

**DRUG REGIMEN**

**VDC cycles 1, 3, 5, 7 and 9**
- **VINCRISTINE** 2mg/m² IV infusion (2 mg/m²/cycle) (max. single dose: 2 mg) day 1
- **DOXORUBICIN** 37.5mg/m² IV infusion over 24 hours (75 mg/m²/cycle) days 1 and 2
- **CYCLOPHOSPHAMIDE** 1200mg/m² IV infusion over 1 hour (1200 mg/m²/cycle) day 1
- **MESNA** 1200mg/m² IV infusion over 1 hour concurrently with cyclophosphamide day 1
- **MESNA** 800mg/m² IV infusion (1000ml sodium chloride 0.9% over 23 hours)

Days 2 to 8 G-CSF (brand as per local policy)

**IE cycles 2, 4, 6 and 8**
- Days 1, 2, 3, 4 and 5
- **IFOSFAMIDE** 1800mg/m²/d IV infusion over 1 hour (9g/m²/cycle)
- **MESNA** 1800mg/m² IV infusion over 1 hour concurrently with ifosfamide
- **ETOPOSIDE** 100mg/m²/d IV infusion over 2 hours (500mg/m²/cycle)
- **MESNA** 800mg/m² IV infusion 1000ml sodium chloride 0.9% over 23 hours

Days 2 to 8 G-CSF (brand as per local policy)

**Cycle frequency:** Alternating cycles of VDC and IE should be given at 14 day intervals or on haematological recovery to absolute neutrophil count (ANC) =0.75x10⁹/L, platelets =75x10⁹/L

**DOSE MODIFICATIONS**

Haematological: if plts and ANC not recovering by day 22:
- give 80% VDC/IE doses in subsequent cycles

GI:
- Grade 3/4 mucositis beyond day 15 after doxorubicin: 80% doxorubicin
- Grade 3/4 mucositis beyond day 22 after IE: 80% IE

**Vincristine**

Renal: No dose reduction necessary.

Hepatic:
- Bilirubin 26-51 (µmol/L) Or AST/ALT 60-180 Give 50% dose
- Bilirubin >51 (µmol/L) & AST/ALT normal Give 50% dose
- Bilirubin >51 (µmol/L) & AST/ALT >180 Omit
**Doxorubicin**

Renal: In patients with renal insufficiency (GFR < 10 ml/min), only 75% of the planned dose should be given. Clinical decision in severe renal impairment.

**Hepatic**

<table>
<thead>
<tr>
<th>Bilirubin (µmol/L)</th>
<th>Percentage of Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>20-51</td>
<td>Give 50% dose</td>
</tr>
<tr>
<td>51-85</td>
<td>Give 25% dose</td>
</tr>
<tr>
<td>&gt;85</td>
<td>Omit</td>
</tr>
</tbody>
</table>

If AST 2-3 x normal, give 75% dose. If AST >3x ULN, give 50% dose.

Maximum cumulative dose = 450-550mg/m² (in normal cardiac function) = 400 mg/m² (in patients with cardiac dysfunction or exposed to mediastinal irradiation).

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.

**Cyclophosphamide**

Renal:

<table>
<thead>
<tr>
<th>GFR (ml/min)</th>
<th>Percentage of Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;20</td>
<td>100% dose</td>
</tr>
<tr>
<td>10-20</td>
<td>75% dose</td>
</tr>
<tr>
<td>&lt;10</td>
<td>50% dose</td>
</tr>
</tbody>
</table>

Clinical decision – consider whether patient is being treatment with high dose treatment.

Hepatic:

A dose reduction of 25% is recommended in patients with a bilirubin of 53-86µmol/L.

SPC recommendations need to be considered (not recommended in patients with a bilirubin >17µmol/L or serum transaminases or ALP more than 2-3 xULN. In all such cases doses should be reduced). However exposure to active emtabolities may not be increased, suggesting that dose reduction may not be necessary. Clinical decision needed.

**Ifosfamide**

Renal

<table>
<thead>
<tr>
<th>GFR (ml/min)</th>
<th>Percentage of Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;60</td>
<td>100% dose</td>
</tr>
<tr>
<td>40-59</td>
<td>70% dose</td>
</tr>
<tr>
<td>&lt;40</td>
<td>Clinical decision</td>
</tr>
</tbody>
</table>

Hepatic: contra-indicated in patients with a bilirubin >17µmol/L or serum transaminases or ALP more than 2.5 x upper normal limit.
**Etoposide**

Renal

GFR (ml/min) >50  100% dose  
GFR (ml/min) 15-50  75% dose  
GFR (ml/min) <15  50% dose

Subsequent doses should be based on clinical response.

Hepatic

Bilirubin (µmol/L) 26-51  Or  AST (units) 60-180  50% dose
Bilirubin (µmol/L) >51  Or  AST (units) >180  Clinical decision

**INVESTIGATIONS**

Neutrophil count (ANC) =0.75x10⁹/L  
Platelets =75x10⁹/L

Blood counts should be obtained on day 7 and 14 of the cycle and every Monday, Wednesday, and Friday after Day 14, until the criteria for beginning the next cycle are satisfied.

**ANTIEMETIC POLICY**

High emetogenic risk

**CONCURRENT MEDICATION**

Cotrimoxazole 480mg bd M/W/F as per local policy for duration of chemotherapy  
Irradiated blood products starting 1 week prior to stem cell harvest

**ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS**

Cardiotoxicity

Nephrotoxicity: Irreversible renal failure and tubular damage can occur, and this is more frequent with cumulative doses over 25 – 50g/m² of Ifosfamide.  
Vincristine may cause neurotoxicity.

**REFERENCES**

1 Hepatic dose adjustments:  
2 Renal dose adjustments  
http://www.eastmidlandscancernetwork.nhs.uk/Library/RenalDosageAdjustments.pdf  
3 Vincristine SPC  
4 Doxorubicin SPC  
5 Cyclophosphamide SPC  
6 Ifosfamide SPC  
7 Etoposide SPC  
8 EE2012 Womer AEWS0331 JCO  
9 Euroewings 2012
Indication: Treatment of Recurrent and Primary Refractory Ewing Sarcoma

DRUG REGIMEN
Days 1 to 5
TOPOTECAN 0.75mg/m² in 50ml sodium chloride 0.9% IV infusion over 30 minutes
CYCLOPHOSPHAMIDE 250mg/m² in 250ml sodium chloride 0.9% IV infusion over 60 minutes

Cycle Frequency: Every 21 days for 6 cycles

DOSE MODIFICATIONS
Haematological toxicity:
GCSF in preference to dose reduction
Day 21 despite GCSF delayed >14 days:
• topotecan 80%
• repeated 60% topotecan

Haemorrhagic cystitis:
Microscopic haematuria give 2000mL/m²/day fluid + MESNA 100mg/m² every 8 hours
Macroscopic haematuria: stop cyclophosphamide – next cycle admit for hydration (2L/m²/24 hours) + MESNA

Topotecan
Renal:
GFR (ml/min) >40 100% dose
GFR (ml/min) 20-39 50% dose
GFR (ml/min) <20 Contraindicated

Hepatic:
Bilirubin <170µmol/L – 100% dose
Bilirubin >170µmmol/L – clinical decision

Cyclophosphamide
Renal:
GFR(ml/min) >20 100% dose
GFR(ml/min) 10-20 75% dose
GFR(ml/min) <10 50% dose

Clinical decision – consider whether patient is being treatment with high dose treatment.

Hepatic;
SPC recommendations need to be considered (not recommended in patients with a bilirubin >17µmol/L or serum transaminases or ALP more than 2-3 xULN. In all such cases doses should be reduced). However exposure to active emtabolities may not be increased, suggesting that dose reduction may not be necessary. Clinical decision needed.
INVESTIGATIONS
Neutrophil count (ANC) = $1 \times 10^9$/L
Platelets = $75 \times 10^9$/L

ANTIEMETIC POLICY
Low-moderate emetogenic risk

CONCURRENT MEDICATION
Preference should be given to GCSF support rather than dose reduction

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPlications
Ifosfamide haemorrhagic cystitis, nephrotoxicity, neurotoxicity

REFERENCES
2 Cyclophosphamide SPC
3 Topotecan SPC
5 Renal dose adjustments http://www.eastmidlandscancernetwork.nhs.uk/Library/RenalDosageAdjustments.pdf
**IFOSFAMIDE (off study rEECur)**

*Indication: Treatment of Recurrent and Primary Refractory Ewing Sarcoma*

**DRUG REGIMEN**

**Day 1** MESNA 400mg/m² IV bolus 1 hour before first ifosfamide dose

**Days 1 to 5** IFOSFAMIDE 3000mg/m² in 3000ml sodium chloride 0.9% IV infusion over 24 hours)

(Total dose: 15g/m²/cycle)

MESNA 3g/m²/day in 3000ml sodium chloride 0.9% IV infusion over 24 hours)

**Day 5** MESNA 800mg/m² IV or oral following final ifosfamide dose

**Day 7** G-CSF starting 48 hours after final ifosfamide infusion

**Cycle Frequency:** Every 21 days for 4 cycles

**DOSE MODIFICATIONS**

*Ifosfamide*

**Renal**

- GFR (ml/min) >60: 100% dose
- GFR (ml/min) 40-59: 70% dose
- GFR (ml/min) <40: Clinical decision

Hepatic: contra-indicated in patients with a bilirubin >17µmol/L or serum transaminases or ALP more than 2.5 x upper normal limit.

**Nephrotoxicity** - Irreversible renal failure and tubular damage can occur, and this is more frequent with cumulative doses over 25 – 50g/m² of Ifosfamide. Dose reductions should be instituted for GFR and changes in fractional phosphate clearance (Tmₚ/GFR mmol/l). Any dose reductions need to be discussed with a Consultant.

<table>
<thead>
<tr>
<th>Toxicty Grade</th>
<th>GFR (ml/min/1.73m²)</th>
<th>Tp/Crea (Tmₚ/GFR)mmol/l*</th>
<th>HCO³ (mmol/l)</th>
<th>Action (apply worst grade)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 0/1</td>
<td>≥60</td>
<td>≥1.00</td>
<td>≥17.0</td>
<td>ifos 100% total</td>
</tr>
<tr>
<td>Grade 2</td>
<td>40-59</td>
<td>0.8-0.99</td>
<td>14.0-16.9</td>
<td>Ifos 70% of total (depending on cycle)</td>
</tr>
<tr>
<td>Grade 3/4</td>
<td>≤40</td>
<td>≤0.8</td>
<td>≤14.0</td>
<td>Cyclophosphamide 1500mg/m² day 1 only</td>
</tr>
</tbody>
</table>

Fractional phosphate clearance calculated as below

\[
T_p/Crea = \frac{\text{Phosphateserum} \times \text{Creatinineurine}}{\text{creatinineserum} \times \text{Phosphateurine}} \times \text{mmol/ml} \\
\text{NB serum creatinine is normally recorded in µmol/L}
\]

| Ifosfamide | Sarcoma CAG Chair Authorisation: | Page 1 of 2 | Published: January 2019 | Review: June 2022 | Version 2.5 |
INVESTIGATIONS
Neutrophil count (ANC) = 1x10^9/L
Platelets = 75x10^9/L

ANTIEMETIC POLICY
Highly emetogenic

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS
Ifosfamide haemorrhagic cystitis, nephrotoxicity, neurotoxicity
Neural Toxicity - refer to the ifosfamide-induced encephalopathy specific neural toxicity grade and nomogram (abridged below in full at the end of this document)
Methylthioninium chloride (methylene blue) can be given as prophylaxis against, or treatment of, ifosfamide-induced encephalopathy. Dose: 50mg tds IV. NB. 50mg = 5ml of 1% solution.
IV: administer 50mg in 50 to 100ml glucose 5%, over 15 to 30 minutes
Nephrotoxicity - Irreversible renal failure and tubular damage can occur, and this is more frequent with cumulative doses over 25mg/m^2. Dose reductions should be instituted for GFR and changes in fractional phosphate clearance (Tm_p/GFR mmol/l).

REFERENCES
DENOSUMAB

*Indication: Neoadjuvant and maintenance single agent in giant cell tumours of the bone*

Individual funding required prior to prescribing, unless local funding agreed

**DRUG REGIMEN**

*Cycle 1*

Days 1, 8 and 15  **DENOSUMAB** 120mg OD subcutaneously

*Cycle 2 onwards*

Day 1  **DENOSUMAB** 120mg OD subcutaneously

*Cycle Frequency: Every 28 days for 6 to 12 cycles*

**DOSE MODIFICATIONS**

*Denosumab:*

Patients with renal impairment - No dose adjustment is required in patients with renal impairment

Patients with hepatic impairment - The safety and efficacy of denosumab have not been studied in patients with hepatic impairment

**INVESTIGATIONS**

Dental check prior to treatment

Routine Blood test

1) Blood results required before drug administration

<table>
<thead>
<tr>
<th></th>
<th>Give</th>
<th>Discuss</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plt x 10^9/L</td>
<td>≥100</td>
<td>&lt;100</td>
</tr>
<tr>
<td>Neutrophils x 10^9/L</td>
<td>≥1.5</td>
<td>&lt;1.5</td>
</tr>
<tr>
<td>Ca++ Creatinine. Bone profile (vitamin D, PTH), PINP</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

2) Non urgent tests

Urine pregnancy test in women aged 12-55, unless sterilised or undergone a hysterectomy prior to every cycle of treatment.

Response assessment by PET-CT, CT or MRI and plain film every visit. Timing of surgical intervention carefully managed with sarcoma MDT only.

**CONCURRENT MEDICATION**

Adequate intake of calcium and vitamin D is important in all patients, ensure vitamin D is prescribed.

Women of child bearing age must be on contraception.
ANTIEMETIC POLICY
None required

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS
Osteonecrosis of jaw/auditory canal
Infections and infestations - UTI, respiratory, diverticulitis, cellulitis and ear infections
Hypocalcaemia must be corrected by adequate intake of calcium and vitamin D before initiating therapy.
Patients with severe renal impairment (creatinine clearance < 30 ml/min) or receiving dialysis are at greater risk of developing hypocalcaemia.
Clinical monitoring of calcium levels is recommended for patients predisposed to hypocalcaemia.
Sciatica
Cataracts
Constipation
Skin - rash and eczema
Pain
Osteoecrosis of the jaw. Suspend treatment if invasive dental work needed.

REFERENCES
1. SPC June 2010


VA (off study RMS)

Indication:  Rhabdomyosarcoma (Low risk)

DRUG REGIMEN
Cycles 1, 3, 5, and 7
Day 1, 8 and 15  VINCRISTINE 1.5mg/m² (max 2mg) IV infusion
Day 1  DACTINOMYCIN 1.5mg/m² (max 2mg) IV bolus day 1

Cycles 2, 4, 6 and 8
Day 1  VINCRISTINE 1.5mg/m² (max 2mg) IV infusion
Day 1  DACTINOMYCIN 1.5mg/m² (max 2mg) IV bolus day 1

Cycle frequency: Every 3 weeks for 8 cycles

DOSE MODIFICATIONS

Dactinomycin (Actinomycin D)
Consider dose reduction in severe hepatic disease.
In case of veno occlusive disease (VOD) Dactinomycin should not be given until the main abnormalities have returned to normal and half the dose should be given 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.

Renal impairment
Clinical decision – unlikely to require a reduction.

Hepatic impairment
Consider dose reduction in severe hepatic disease.

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

Renal impairment
No dose reductions necessary

Hepatic impairment

<table>
<thead>
<tr>
<th>Bilirubin (µmol/L)</th>
<th>AST/ALT (µmol/L)</th>
<th>Dose Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>26-51</td>
<td>60-180</td>
<td>Give 50% dose</td>
</tr>
<tr>
<td>&gt;51</td>
<td>normal</td>
<td>Give 50% dose</td>
</tr>
<tr>
<td>&gt;51</td>
<td>&gt;180</td>
<td>Omit</td>
</tr>
</tbody>
</table>
INVESTIGATIONS
Routine Blood test
Cycles should not be started unless blood results as below. Weekly vincristine should be administered irrespective of pancytopenia providing patient is in good condition.

Give
Plt x 10^9/L >=80
Neutrophils x 10^9/L >=1.0
WBC >=2.0
No organ dysfunction eg (heart, kidney, liver)

CONCURRENT MEDICATION
Laxatives should be prescribed.

ANTIEMETIC POLICY
Moderate emetogenic risk

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS
Vincristine may cause neuro toxicity - peripheral and central
Dactinomycin (Actinomycin-D) GI irritation, hepatotoxicity, bone marrow depression.
Dactinomycin should not be given concurrently with radiotherapy.

REFERENCE
RMS 2005 Regimen
IVA (off study RMS)

Indication: Rhabdomyosarcoma (standard risk)

Drug Regimen

Day 1 Vincristine 1.5mg/m² (max 2mg) IV bolus
  Dactinomycin 1.5mg/m² (max 2mg) IV bolus day 1
  Mesna 1g/m² IV bolus day 1 (1 hour prior to ifosfamide)
  Ifosfamide 3g/m² IV and Mesna 3g/m² IV Infusion in 1000ml sodium chloride 0.9% over 3 hours
  Mesna 3g/m² IV Infusion in 1000ml sodium chloride 0.9% over 21 hours

Day 2 Ifosfamide 3g/m² IV and Mesna 3g/m² IV Infusion in 1000ml sodium chloride 0.9% over 3 hours
  Mesna 3g/m² IV Infusion in 1000ml sodium chloride 0.9% over 12 hours

Days 8 and 15 Vincristine 1.5mg/m² (max 2mg) IV bolus (Cycles 1 and 2 only)

Cycle frequency: every 21 days for 9 cycles

Dose Modifications

Dactinomycin
In case of veno occlusive disease (VOD) Dactinomycin should not be given until the main abnormalities have returned to normal and half the dose should be given 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.

Renal impairment
Clinical decision – unlikely to require a reduction.

Hepatic impairment
Consider dose reduction in severe hepatic disease.

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

Renal impairment
No dose reductions necessary

Hepatic impairment

<table>
<thead>
<tr>
<th>Bilirubin (µmol/L)</th>
<th>AST/ALT (µmol/L)</th>
<th>Dose Adjustment</th>
</tr>
</thead>
<tbody>
<tr>
<td>26-51</td>
<td>60-180</td>
<td>Give 50% dose</td>
</tr>
<tr>
<td>&gt;51</td>
<td>normal</td>
<td>Give 50% dose</td>
</tr>
<tr>
<td>&gt;51</td>
<td>&gt;180</td>
<td>Omit</td>
</tr>
</tbody>
</table>

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Ifosfamide

Nephrotoxicity- Irreversible renal failure and tubular damage can occur, and this is more frequent with cumulative doses over 25 – 50g/m² of Ifosfamide. Dose reductions should be instituted for GFR and changes in fractional phosphate clearance (Tmₚ/GFR mmol/l). Any dose reductions need to be discussed with a Consultant.

<table>
<thead>
<tr>
<th>Toxicity Grade</th>
<th>GFR (ml/min/1.73m²)</th>
<th>Tp/Crea (Tmₚ/GFR)mmol/l</th>
<th>HCO₃ (mmol/l)</th>
<th>Action (apply worst grade)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 0/1</td>
<td>≥60</td>
<td>≥1.00</td>
<td>≥17.0</td>
<td>ifos 100% total</td>
</tr>
<tr>
<td>Grade 2</td>
<td>40-59</td>
<td>0.8-0.99</td>
<td>14.0-16.9</td>
<td>Ifos 70% of total</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(depending on cycle)</td>
</tr>
<tr>
<td>Grade ¾</td>
<td>≤40</td>
<td>≤0.8</td>
<td>≤14.0</td>
<td>Cyclophosphamide</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1500mg/m² day 1 only</td>
</tr>
</tbody>
</table>

Tp/Ccrea = Phosphateserum (mmol/L) – Phosphateurine (mmol/L) x creatinineserum (mmol/L) 
Creatinineurine (mmol/L) 

NB serum creatinine is normally recorded in µmol/L

Serious neurological toxicity is more likely to occur in patients with impaired renal excretion of the drug, either from an obstructed urinary tract at initial diagnosis or from renal impairment later in treatment. Evidence of encephalopathy may be mild initially but should be considered in any patient who demonstrates altered level of consciousness during or shortly after the drug infusion.

In case seizures occur methylene -blue may be given: 30mg/m² (max 50mg) as a 2% aqueous solution, give by slow iv injection. The reversal of encephalopathic features should occur over the next 30-60 minutes.

If grade 3 or 4 central neurotoxicity occurs (somnolence >30% of the time, disorientation / hallucination / echolalia / perservation / coma) consider to avoid further ifosfamide and substitute with cyclophosphamide 1500mg/m² per cycles.

Neural Toxicity- refer to the ifosfamide-induced encephalopathy specific neural toxicity grade and nomogram (abridged below in full at the end of this document)

Methylthioninium chloride (methylene blue) can be given as prophylaxis against, or treatment of, ifosfamide-induced encephalopathy. Dose: 50mg tds IV.NB. 50mg = 5ml of 1% solution.

IV: administer 50mg in 50 to 100ml glucose 5% 5, over 15 to 30 minutes

Nephrotoxicity-Irreversible renal failure and tubular damage can occur, and this is more frequent with cumulative doses over 25mg/m². Dose reductions should be instituted for GFR and changes in fractional phosphate clearance (Tmₚ/GFR mmol/l).

Bladder toxicity - haemorrhagic cystitis with ifosfamide is rare if hydration and mesna are utilised appropriately. Microhaematuria usually can be tolerated. In case of macrohaematuria it is important to continue (or re-implement) hydration. In case of cystic bleeding under or within 24 hours completion of ifosfamide infusion mesna protection should be continued or started again. Only recurrent macroscopic haematuria is an indication for discontinuing ifosfamide, in which case cyclophosphamide at a dose of 1500mg/m2 per course may be substituted.
Renal toxicity: More likely to occur with an increasing cumulative dose. If nephrotoxicity (tubular or glomerular toxicity > grade 2) occurs, discontinue ifosfamide and substitute cyclophosphamide at a dose of 1500mg/m² per course for the remaining courses of treatment.

INVESTIGATIONS
Routine Blood test
1) Blood results required before chemotherapy administration
    Give
    Plt x 10⁹/L ≧80
    Neutrophils x 10⁹/L ≧1.0
    WBC x 10⁹/L ≧2.0
    Phosphate clearance

CONCURRENT MEDICATION
Laxatives should be prescribed
Co-trimoxazole 480mg bd M, W, F
GCSF brand as per local policy to start 24 hours after chemotherapy

ANTIEMETIC POLICY
High emetogenic risk days 1 and 2 (and 3 if chemotherapy overruns)

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS
Vincristine may cause neuro toxicity - peripheral and central
Dactinomycin (Actinomycin-D) GI irritation, hepatotoxicity, bone marrow depression.
Ifosfamide haemorrhagic cystitis, nephrotoxicity, neurotoxicity
Dactinomycin should not be given concurrently with radiotherapy

REFERENCES
RMS 2005 Regimen
IVADo (off study RMS)

*Indication: Rhabdomyosarcoma (high and very high risk)*

**DRUG REGIMEN**

**Cycles 1 to 4**

**Day 1**

**VINCRISTINE** 1.5mg/m² (max 2mg) IV bolus  
**DACTINOMYCIN** 1.5mg/m² (max 2mg) IV bolus day 1  
**DOXORUBICIN** 30mg/m² IV infusion in 100ml sodium chloride 0.9% over 4 hours  
**MESNA** 1g/m² IV Injection Day 1  
**IFOSFAMIDE** 3g/m² IV and **MESNA** 3g/m² IV Infusion in 1000ml sodium chloride 0.9% over 3 hours (Ifosfamide should be given before doxorubicin if patient has a central line)  
**MESNA** 3g/m² IV Infusion in 1000ml sodium chloride 0.9% over 21 hours (16 hours if doxorubicin given prior to ifosfamide)

**Day 2**

**DOXORUBICIN** 30mg/m² IV infusion in 100ml sodium chloride 0.9% over 4 hours  
**IFOSFAMIDE** 3g/m² IV and **MESNA** 3g/m² IV Infusion in 1000ml sodium chloride 0.9% over 3 hours  
**MESNA** 3.0g/m² IV Infusion in 1000ml sodium chloride 0.9% over 12 hours

**Days 8 and 15**

**VINCRISTINE** 1.5mg/m² (max 2mg) IV bolus (Cycles 1 and 2 only)

**Cycles 5 to 9**

**Day 1**

**VINCRISTINE** 1.5mg/m² (max 2mg) IV bolus  
**DACTINOMYCIN** 1.5mg/m² (max 2mg) IV day 1  
**MESNA** 1g/m² IV Injection Day 1 (1 hour prior to ifosfamide)  
**IFOSFAMIDE** 3g/m² IV and **MESNA** 3g/m² IV Infusion in 1000ml sodium chloride 0.9% over 3 hours  
**MESNA** 3g/m² IV Infusion in 1000ml sodium chloride 0.9% over 21 hours

**Day 2**

**IFOSFAMIDE** 3g/m² IV and **MESNA** 3.0g/m² IV Infusion in 1000ml sodium chloride 0.9% over 3 hours  
**MESNA** 3g/m² IV Infusion in 1000ml sodium chloride 0.9% over 12 hours

Doses capped at BSA 2.0m²
DOSE MODIFICATIONS

Dactinomycin
In case of veno occlusive disease (VOD) Dactinomycin should not be given until the main abnormalities have returned to normal and half the dose should be given 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.

Dose/time intensity is regarded to be an essential aspect of the IVADo strategy. In case of relevant (>=CTC grade 3) toxicity, dactinomycin is the 1st drug to be reduced. It is suggested that in case of life threatening neutropenic CTC grade 3 or 4 infection or treatment delay >= 1 week due to neutropenia related toxicity the use of GCSF with subsequent courses is recommended.
In case of severe mucositis or hepatotoxicity or treatment delay due to dactinomycin related cause, dactinomycin shall be reduced to 75% for the subsequent course.
If further episodes of treatment delay and / or severe mucositis / neutropenic infections should occur, the dose of dactinomycin should be further reduced or even omitted.

Renal impairment
Clinical decision – unlikely to require a reduction.

Hepatic impairment
Consider dose reduction in severe hepatic disease.

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

Renal impairment
No dose reductions necessary

Hepatic impairment

<table>
<thead>
<tr>
<th>Bilirubin 26-51 (µmol/L)</th>
<th>Or</th>
<th>AST/ALT 60-180</th>
<th>Give 50% dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bilirubin &gt;51 (µmol/L)</td>
<td>&amp;</td>
<td>AST/ALT normal</td>
<td>Give 50% dose</td>
</tr>
<tr>
<td>Bilirubin &gt;51 (µmol/L)</td>
<td>&amp;</td>
<td>AST/ALT &gt;180</td>
<td>Omit</td>
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Ifosfamide

Serious neurological toxicity is more likely to occur in patients with impaired renal excretion of the drug, either from an obstructed urinary tract at initial diagnosis or from renal impairment later in treatment. Evidence of encephalopathy may be mild initially but should be considered in any patient who demonstrates altered level of consciousness during or shortly after the drug infusion.

In case seizures occur methylene-blue may be given: 30mg/m² (max 50mg) as a 2% aqueous solution, give by slow iv injection. The reversal of encephalopathic features should occur over the next 30-60 minutes.

If grade 3 or 4 central neurotoxicity occurs (somnolence >30% of the time, disorientation / hallucination / echolalia / perservation / coma) consider to avoid further ifosfamide and substitute with cyclophosphamide 1500mg/m² per cycles.

Bladder toxicity - haemorrhagic cystitis with ifosfamide is rare if hydration and mesna are utilised appropriately. Microhaematuria usually can be tolerated. In case of macrohaematuria it is important to continue (or re-implement) hydration. In case of cystic bleeding under or within 24 hours completion of ifosfamide infusion mesna protection should be continued or started again. Only recurrent macroscopic haematuria is an indication for discontinuing ifosfamide, in which case cyclophosphamide at a dose of 1500mg/m² per course may be substituted.

Renal toxicity: More likely to occur with an increasing cumulative dose. If nephrotoxicity (tubular or glomerular toxicity > grade 2) occurs, discontinue ifosfamide and substitute cyclophosphamide at a dose of 1500mg/m² per course for the remaining courses of treatment. Irreversible renal failure and tubular damage can occur, and this is more frequent with cumulative doses over 25 – 50g/m² of Ifosfamide. Dose reductions should be instituted for GFR and changes in fractional phosphate clearance (Tmₚ/GFR mmol/l). Any dose reductions need to be discussed with a Consultant.

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<tr>
<th>Toxicity Grade</th>
<th>GFR (ml/min/1.73m²)</th>
<th>Tp/Crea (Tmₚ/GFR)mmol/l*</th>
<th>HCO₃ (mmol/l)</th>
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<td>Grade 0/1</td>
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<td>14.0-16.9</td>
<td>Ifos 70% of total (depending on cycle)</td>
</tr>
<tr>
<td>Grade 3/4</td>
<td>≤40</td>
<td>≤0.8</td>
<td>≤14.0</td>
<td>Cyclophosphamide 1500mg/m² day 1 only</td>
</tr>
</tbody>
</table>

Fractional phosphate clearance calculated as below

\[ \text{Tp/Crea} = \frac{\text{Phosphateserum (mmol/L)} - \text{Phosphateurine (mmol/L) \times creatinineserum (mmol/L)}}{\text{Creatinineurine (mmol/L)}} \]

NB serum creatinine is normally recorded in µmol/L

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**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.

Maximum cumulative dose = 450-550mg/m² (in normal cardiac function) = 400 mg/m² (in patients with cardiac dysfunction or exposed to mediastinal irradiation)

**INVESTIGATION**

Routine Blood test

1) Blood results required before chemotherapy administration

   Give

   Plt x 10⁹/L >=80

   Neutrophils x 10⁹/L >=1.0

   WBC x 10⁹/L >=2.0

**CONCURRENT MEDICATION**

Laxatives should be prescribed

Co-trimoxazole 480mg bd M, W, F

GCSF brand as per local policy to start 24 hours after chemotherapy

**ANTIEMETIC POLICY**

High emetogenic risk days 1 and 2 (a day 3 if chemotherapy over runs) with aprepitant if funded

**ADVERSE EFFECTS / REGIMEN SPECIFIC COMPILATIONS**

Vincristine may cause neuro toxicity -peripheral and central

Dactinomycin (Actinomycin-D) GI irritation, hepatotoxicity, bone marrow depression.

Ifosfamide haemorrhagic cystitis, nephrotoxicity, neurotoxicity

Doxorubicin cardiotoxicity, GI irritation

Dactinomycin should not be given concurrently with radiotherapy

**REFERENCES**

RMS 2005 Regimen
Cyclophosphamide (PO) + Vinorelbine (IV) (off study RMS)

**Indication:** Rhabdomyosarcoma high risk and very high risk MAINTENANCE

**DRUG REGIMEN**

**Days 1, 8 and 15**
- **VINORELBINE** 25mg/m² IV in 50ml sodium chloride 0.9% infusion over 10 minutes
- **CYCLOPHOSPHAMIDE** 25mg/m² OD orally continuously – total dose of 175mg/m² to be taken over 7 days see below

* As cyclophosphamide is only available as 50mg tablets the dose is prescribed as 175mg/m² and rounded to the nearest 50mg. This dose should then be split over 7 days.

**Cycle frequency:** Every 4 weeks for 6 cycles

**DOSE MODIFICATIONS**

Neutropenic <1 and/or plts <80: stop cyclophosphamide until count recovery, then give 66% vinorelbine (Days 1,8,15) and 100% cyclophosphamide doses. If recurrent myelosuppression, omit day 15 vinorelbine. Discuss with consultant

**INVESTIGATIONS**

Routine Blood test

Blood results required before chemotherapy administration

- Give
- Plt x 10⁹/L $\geq 80$
- Neutrophils x 10⁹/L $\geq 1.0$
- WBC $\geq 2.0$

No organ dysfunction eg (heart, kidney, liver)

**CONCURRENT MEDICATION**

None

**ANTIEMETIC POLICY**

Moderate

**ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS**

Cyclophosphamide - bone marrow depression, haemorrhagic cystitis, GI irritation

Vinorelbine - myelosuppression, mucositis, neurotoxic

**REFERENCE**

RMS 2005 regimen
IRINOTECAN TEMOZOLOMIDE VINCRISTINE

Indication: Relapsed alveolar rhabdomyosarcoma

Not NHSE commissioned regimen – Trust to fund locally, and not charge to NHSE

DRUG REGIMEN

Day 1  VINCRISTINE 1.5mg/m^2 (max 2mg) in 50ml sodium chloride 0.9% IV infusion
Days 1 to 5  TEMOZOLOMIDE 100mg/m^2 po days 1 to 5 taken 1 hour before irinotecan
Days 1 to 5 and 8 to 12  PREMEDICATION (at least 30 minutes prior to treatment)
  ATROPINE 250 microgram subcutaneously
  IRINOTECAN 10mg/m^2 in 250ml sodium chloride 0.9% IV infusion over 30 minutes

Cycle frequency: every 21 days for 6 cycles

DOSE MODIFICATIONS

If neutrophils<1.0x10^9/L or platelets<75x10^9/L delay 1 week, only treat when neutrophils and platelets are above these limits.
Delay >14 days give 80% temozolomide dose for next cycle.
In the event of febrile neutropenia give to 80% for all subsequent cycles.

If Bilirubin 25 - 50 micromol/L give 50% dose
Omit if bilirubin > 3xULN
Omit if GFR < 30 ml/min.
If patients suffer from severe diarrhoea, which required IV rehydration or neutropenic fever, dose may need to be reduced.

Vincristine
Bilirubin 25-51 micromol/L or AST 60-180 units/L give 50% dose
Bilirubin > 51 micromol/L and normal AST give 50% dose
Bilirubin > 51 micromol/L and AST > 180 units/L omit

INVESTIGATIONS

Routine blood tests
1. Blood results required before chemotherapy administration

  Plt x 10^9/L  GIVE if > or = 75  DISCUSS < 75
  Neutrophils x 10^9/L  GIVE if > or = 1.0  DISCUSS < 1.0

2. Non urgent tests relating to disease response / progression.
3. PET/CT after 2 cycles
CONCURRENT MEDICATION
Patients who experience delayed diarrhoea will require loperamide 2 mg every 2 hours to continue for 12 hours after the last loose stool. This high dose should be discontinued after 48 hours. Consider antibiotic if indicated (cefixime 400mg daily days 1 to 8)

ANTIEMETIC POLICY
Moderately emetogenic risk

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS
Acute Diarrhoea – delayed diarrhea occurring more than 24 hours after administration. Drink large volumes of fluid containing electrolytes and an appropriate antidiarrhoeal therapy e.g. loperamide 4mg initially then 2mg every 2 hours, continuing for 12 hours after the last liquid stool (maximum of 48 hours in total).
Fatal liver failure has been reported with Temozolomide.
Take/ give prophylactic broad spectrum antibiotics.

REFERENCES
1 Mixon BA et al, J Paediatric Haematol Oncol Volume 35, number 4 May 2013
2 Raciborska A et al, Paediatric Blood Cancer 2013;60;
TOPOTECAN VINCRISTINE DOXORUBICIN

Indication: Rhabdomyosarcoma

DRUG REGIMEN

Days 1 to 5  TOPOTECAN 1.5mg/m² in 100ml* sodium chloride 0.9% IV infusion over 30 minutes
Day 5  VINCRISTINE 1mg/m²/day (max 1mg/day) IV infusion over 48 hours
DOXORUBICIN 22.5mg/m²/day IV infusion over 48 hours
Day 9  GCSF (5mcg/kg/d) to start 72 hours after vincristine and doxorubicin until ANC >2.5x10⁹/L
* doses 0.52mg to 2.4mg in 50ml sodium chloride

Cycle frequency: Every 21 to 28 days for 2 cycles (up to 6 cycles)

DOSE MODIFICATIONS

Proceed if there is no evidence of progressive disease and no non-haematological toxicity greater than Grade 1.

Topotecan

Previous neutropenic sepsis, discuss with Consultant or Registrar.
If dose reduction is chosen for patients who experience severe neutropenia (neutrophil count < 0.5 x 10⁹/l) for seven days or more, or severe neutropenia associated with fever or infection, or who have had treatment delayed due to neutropenia, the dose should be reduced by 0.25 mg/m²/day to 1.25 mg/m²/day (or subsequently down to 1.0 mg/m²/day if necessary).
Doses should be similarly reduced if the platelet count falls below 25 x 10⁹/l. In clinical trials, topotecan was discontinued if the dose had been reduced to 1.0 mg/m² and a further dose reduction was required to manage adverse effects.
Renal impairment:
GFR 20-40ml/min give 50% dose
GFR <20ml/min omit
Hepatic impairment:
Bilirubin <170micromol/L give 100% dose.
Bilirubin >170micromol/L – clinical decision.

Doxorubicin

Renal impairment
Discuss with consultant if renal impairment severe.
Hepatic impairment
Bilirubin 20-50 micromol/L give 50% dose
Bilirubin 51-85 micromol/L give 25% dose
Bilirubin > 85 micromol/L omit
AST 2-3 x ULN give 75% dose
If AST >3 x ULN, give 50% dose

Doxorubicin maximum cumulative dose: (additive to other anthracyclines)
450-550 mg/m² (in normal cardiac function)
400 mg/m² (in patients with cardiac dysfunction or exposed to mediastinal irradiation)

Topotecan
Vincristine
Doxorubicin
Sarcoma CAG Chair Authorisation:
Date:
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Published: January 2019
Review: June 2022
Version 2.5
Vincristine
Renal impairment
None
Hepatic impairment
Bilirubin 26-51 micromol/L or ALT/AST 60-180 u/L give 50% dose
Bilirubin > 51 micromol/L & normal ALT/AST give 50% dose
Bilirubin > 51 micromol/L & ALT/AST > 180 u/L omit

Vincristine In the presence of motor weakness or severe sensory symptoms, discuss reducing or withholding vincristine with a consultant.

INVESTIGATIONS
Routine Blood test
1) Blood results required before chemotherapy administration

<table>
<thead>
<tr>
<th></th>
<th>GIVE</th>
<th>DISCUSS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hb x g/dL</td>
<td>&gt;=10</td>
<td>&lt; 10</td>
</tr>
<tr>
<td>Plt x 10⁹/L</td>
<td>&gt;=100</td>
<td>&lt; 100</td>
</tr>
<tr>
<td>Neutrophils x 10⁹/L</td>
<td>&gt;=1.5</td>
<td>&lt; 1.5</td>
</tr>
</tbody>
</table>

2) Non urgent blood tests
Tests relating to disease response/progression

CONCURRENT MEDICATION
Cotrimoxazole 480mg bd M/W/F

ANTIEMETIC POLICY
Moderate emetic risk

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS
Neutropenic colitis
Interstitial lung disease - discontinue topotecan
Cardiotoxicity - monitor cardiac function. Doxorubicin may be stopped in future cycles if signs of cardiotoxicity, e.g. cardiac arrhythmias, pericardial effusion, tachycardia with fatigue.
Vincristine may cause neurotoxicity.

REFERENCE
CYCLOPHOSPHAMIDE (oral) +/- PREDNISOLONE

Indication: Metastatic soft tissue sarcoma for patients with poor prognosis and elderly with comprehensive geriatric assessment (CGA) tool.

DRUG REGIMEN
CYCLOPHOSPHAMIDE 100mg PO twice daily days 1 to 7
PREDNISOLONE 20mg PO daily continuously (optional)
Every 14 days until progression or limited by tolerance

DOSE MODIFICATIONS
Cyclophosphamide
GFR >20ml/min give 100% dose
GFR 10-20ml/min give 75% dose
GFR <10ml/min give 50% dose

INVESTIGATIONS
Routine Blood test
1) Blood results required before chemotherapy administration
   
<table>
<thead>
<tr>
<th>GIVE</th>
<th>DISCUSS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hb x g/dL</td>
<td>&gt;=10</td>
</tr>
<tr>
<td>Plt x 10^9/L</td>
<td>&gt;=100</td>
</tr>
<tr>
<td>Neutrophils x 10^9/L</td>
<td>&gt;=1.5</td>
</tr>
</tbody>
</table>

2) Non urgent blood tests
Tests relating to disease response/progression
First and subsequent cycles
FBC.
U&Es, creatinine, glucose, calcium. LFT’s
CGA assessment

CONCURRENT MEDICATION

ANTIEMETIC POLICY
Low emetic risk.

ADVERSE EFFECTS / REGIMENT SPECIFIC COMPLICATIONS
Cyclophosphamide may irritate the bladder mucosa. Patients should be encouraged to drink a minimum of three litres of fluid per 24 hours.
Steroid side effects – monitor BMs.

REFERENCE
European Journal of Cancer vol 47 issue 4 pg 515-519 March 2011
**Dacarbazine**

*Indication:* Second / third Line metastatic soft tissue sarcoma

**Drug Regimen**

Days 1 & 2  
**Dacarbazine** 600mg/m² in 1000ml sodium chloride 0.9% infusion over 1 hour

*Cycle Frequency:* Every 21 days for 6 cycles  
*Restaging after 2 or 3 cycles depending on toxicity and response*

**Dose Modifications**

*Dacarbazine*

- CrCl 46-60ml/min give 80% dose  
- CrCl 30-45ml/min give 75% dose  
- CrCl <30ml/min give 70% dose  

Can be hepatotoxic, consider dose reduction  
Increases in AST, ALT, alk phos, LDH. Levels usually return to normal within two weeks

If blood counts unsatisfactory treatment is to be delayed by one week. If grade 3 or 4 thrombocytopenia, grade 4 neutropenia or febrile neutropenia the total dose is to be reduced to 1000mg/m² (500mg/m² day1 and day 2 and then 800 mg/m² (400mg/m² day 1 and day2). GCSF to be considered if grade 3 or 4 neutropenia

**Investigations**

Routine Blood test

1) Blood results required before chemotherapy administration

<table>
<thead>
<tr>
<th>Give</th>
<th>Discuss</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plt x 10⁹/L ≥100</td>
<td>&lt;100</td>
</tr>
<tr>
<td>Neutrophils x 10⁹/L ≥1.5</td>
<td>&lt;1.5</td>
</tr>
</tbody>
</table>

Serum creatinine

2) Non urgent blood tests - Tests relating to disease response/progression

CT or PET as clinically indicated after 2 or 3 cycles and then 2-3 monthly

**Concurrent Medication**

Anaphylaxis treatment should be prescribed if the patient has had an anaphylactic episode previously.

- Dexamethasone 20mg IV bolus  
- Chlorphenamine 10mg IV bolus  
- Ranitidine 50mg IV bolus
ANTIEMETIC POLICY
Highly emetogenic

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS
Patients have experienced an influenza type syndrome of fever, myalgias and malaise usually occurring after large single doses and approximately seven days after treatment lasting 7-21 days. Anaphylaxis can occur very rarely following administration of dacarbazine. Photosensitivity reactions may occur rarely.

REFERENCES
1) Randomized Phase II Study Comparing Gemcitabine Plus Dacarbazine Versus Dacarbazine Alone in Patients With Previously Treated Soft Tissue Sarcoma: A Spanish Group for Research on Sarcomas Study
JOURNAL OF CLINICAL ONCOLOGY VOLUME 29 _ NUMBER 18 _ JUNE 20 2011
2) Dacarbazine in Solitary Fibrous Tumor: A Case Series Analysis and Preclinical Evidence vis-a-vis Temozolomide and Antiangiogenics
Clin Cancer Res; 19(18) September 15, 2013
DACARBAZINE GEMCITABINE

Indication: Second / third Line metastatic soft tissue sarcoma

DRUG REGIMEN
Day 1  GEMCITABINE 1800mg/m² in 500ml sodium chloride infusion over 3 hours
  DACARBAZINE 500mg/m² in 1000ml sodium chloride 0.9% infusion over 1 hour

Cycle Frequency: Every 14 days for 12 cycles

DOSE MODIFICATIONS

Dacarbazine
CrCl 46-60ml/min give 80% dose
CrCl 30-45ml/min give 75% dose
CrCl <30ml/min give 70% dose
Can be hepatotoxic, consider dose reduction
Increases in AST, ALT, alk phos, LDH. Levels usually return to normal within two weeks

If blood counts unsatisfactory treatment is to be delayed by one week. If grade 3 or 4 thrombocytopenia, grade 4 neutropenia or febrile neutropenia the total dose is to be reduced to give 80% dacarbazine dose. GCSF to be considered if grade 3 or 4 neutropenia

Gemcitabine
CrCl <30ml/min consider dose reduction (Clinical decision)

Neutrophils >1.5x10⁹/L and platelets >100x10⁹/L give 100% dose
Neutrophils 0.5-1.5x10⁹/L or platelets 50-100x10⁹/L give 75% dose or delay based on clinical assessment
Neutrophils <0.5x10⁹/L or platelets <50x10⁹/L delay treatment (Day 1) or omit treatment (Day 8)

Diarrhoea and/or mucositis
Grade 2 toxicity – omit until toxicity resolved then restart at 100% dose
Grade 3 toxicity – omit until toxicity resolved then restart at 75% dose
Grade 4 toxicity – omit until toxicity resolved then restart at 50% dose
**INVESTIGATIONS**

**Routine Blood test**

1) Blood results required before chemotherapy administration

<table>
<thead>
<tr>
<th>Test</th>
<th>Lower Limit</th>
<th>Upper Limit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hb x g/dL</td>
<td>≥10</td>
<td>&lt;10</td>
</tr>
<tr>
<td>Plt x 10⁹/L</td>
<td>≥100</td>
<td>&lt;100</td>
</tr>
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<td>Neutrophils x 10⁹/L</td>
<td>≥1.5</td>
<td>&lt;1.5</td>
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Serum creatinine

2) Non urgent blood tests - Tests relating to disease response/progression

CT or PET as clinically indicated after 2 or 3 cycles and then 2-3 monthly

**CONCURRENT MEDICATION**

Anaphylaxis treatment should be prescribed if the patient has had an anaphylactic episode previously.

- Dexamethasone 20mg IV bolus
- Chlorphenamine 10mg IV bolus
- Ranitidine 50mg IV bolus

**ANTIEMETIC POLICY**

Highly emetogenic

**ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS**

Patients have experienced an influenza type syndrome of fever, myalgias and malaise usually occurring after large single doses and approximately seven days after treatment lasting 7-21 days.

Anaphylaxis can occur very rarely following administration of dacarbazine.

Photosensitivity reactions may occur rarely.

**REFERENCES**

1) Randomized Phase II Study Comparing Gemcitabine Plus Dacarbazine Versus Dacarbazine Alone in Patients With Previously Treated Soft Tissue Sarcoma: A Spanish Group for Research on Sarcomas Study

   JOURNAL OF CLINICAL ONCOLOGY VOLUME 29 _ NUMBER 18 _ JUNE 20 2011

2) Dacarbazine in Solitary Fibrous Tumor: A Case Series Analysis and Preclinical Evidence vis-à-vis Temozolomide and Antiangiogenics


   Clin Cancer Res; 19(18) September 15, 2013
**CARBOPLATIN ETOPOSIDE weekly**

**Indication:** Advanced Ewing and high grade sarcoma

**DRUG REGIMEN**

**Days 1, 8 and 15 CARBOPLATIN** AUC 2 infusion in 500ml glucose 5% infusion over 30 minutes

**Days 1, 2 and 3 ETOPOSIDE** 100mg/m² infusion in 1000ml* sodium chloride 0.9% over 60 minutes

* doses 48mg to 88mg in 250ml, 96mg to 180mg in 500ml sodium chloride 0.9%

Ideally EDTA GFR should be used,

**Cycle Frequency:** Every 21 days  
**Number of cycles:** Maximum 6 to 8 cycles

**DOSE MODIFICATIONS**

**Carboplatin**
Discuss if patient has a serum creatinine > 150 micromol/L  
If GFR / calculated CrCl = or < 20ml/min contraindicated.

**Etoposide**
CrCl >50ml/min give 100% dose  
CrCl 15-50ml/min give 75% dose  
CrCl <15ml/min give 50% dose  
Bilirubin 26-51micromol/L or AST 60-180iu/L give 50% dose  
Bilirubin >51micromol/L or AST >180iu/L Clinical decision

**INVESTIGATIONS**

Routine Blood test 1) Blood results required before chemotherapy administration

<table>
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<th>Give</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Plt x 10⁹/L ≥80</td>
<td>&lt;80</td>
</tr>
<tr>
<td>Neutrophils x 10⁹/L ≥1.0</td>
<td>&lt;1.0</td>
</tr>
</tbody>
</table>

Ideally EDTA GFR should be used (Carboplatin) Creatinine clearance (GFR) calculated, at the Consultants discretion  
Liver function tests (LFT)

2) Non urgent blood tests. Tests relating to disease response/progression
CONCURRENT MEDICATION FOR PREVENTION
Anaphylaxis treatment should be prescribed if the patient has had an anaphylactic episode previously.
DEXAMETHASONE 20mg IV bolus
CHLORPHENAMINE 10mg IV bolus
RANITIDINE 50mg IV bolus
Carboplatin should be given at a slower rate e.g. 2-4 hours.

ANTIEMETIC POLICY
Moderate emetic risk day 1

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS
Ototoxicity - monitor
Neurotoxicity – monitor.

REFERENCES
VINBLASTINE METHOTREXATE

**Indication:** Fibromatosis

**DRUG REGIMEN**

Day 1 **VINBLASTINE** 5mg/m² in 50ml sodium chloride 0.9% IV infusion over 10 minutes

**METHOTREXATE** 30mg/m² in 100ml sodium chloride 0.9% IV infusion over 30 minutes

Doses capped at BSA 2.0m²

*Cycle frequency: every 7 days for 26 weeks, then every 14 days for up to a further 26 weeks (total 52 weeks)*

**DOSE MODIFICATIONS**

**Vinblastine**

Renal: no modification is recommended for patients with impaired renal function.

Hepatic:

- Bilirubin 26-51µmol/L or AST/ALT<60-180 give 50% dose
- Bilirubin >51µmol/L or AST/ALT normal give 50% dose
- Bilirubin >51µmol/L or AST/ALT>180 omit

Delayed 2 or more weeks for myelosuppression reduce dose to 75%

- Grade 2 or greater neuropathy withhold temporarily
- ANC <1.0x10⁹/L but >0.5x10⁹/L or platelets <100x10⁹/L but >50x10⁹/L give 50% dose for 1 week.
- ANC <0.5x10⁹/L or platelets <50x10⁹/L withhold for 1 week

Withhold temporarily for >=grade 2 neuropathy

**Methotrexate**

Renal:

- Serum creatinine >3xULN withhold temporarily

Hepatic:

- Bilirubin >1.5xULN withhold temporarily
- AST >5xULN withhold temporarily

Grade 1 or 2 stomatitis reduce dose to 50% or 0%, respectively,

- ANC <1.0x10⁹/L but >0.5x10⁹/L or platelets <100x10⁹/L but >50x10⁹/L give 50% dose for 1 week.
- ANC <0.5x10⁹/L or platelets <50x10⁹/L withhold for 1 week

**INVESTIGATIONS**

1) Routine Blood test 1) Blood results required before chemotherapy administration

2) Non urgent blood tests. Tests relating to disease response/progression
CONCURRENT MEDICATION
For patient requiring Folinic acid support the dose is Folinic acid 15mg PO/IV every 6 hours for 6 doses starting 24 hours after Methotrexate especially if pleural effusions / ascites or previous mucositis or serum creatine >120µmol/L or omit chemotherapy

ANTIEMETIC POLICY
Low emetic risk

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS
Methotrexate induced mucositis – folinic acid (calcium folinate) rescue (see concurrent medication).

REFERENCES
Ifosfamide-induced encephalopathy specific neural toxicity grade and nomogram

*Methylthioninium chloride (methylene blue)*

Methylthioninium chloride (methylene blue) can be given as prophylaxis against, or treatment of, ifosfamide-induced encephalopathy (See specific neural toxicity grade and nomogram below). This should be started on the day of ifosfamide administration and continued for 24 hours after administration or until neurotoxic symptoms subside.

**Other risk factors** include cisplatin, brain irradiation, hepatic failure and advancing age.

**Dose:** 50mg tds IV. (NB. 50mg = 5ml of 1% solution.)

**Administration**

IV: administer 50mg in 50 to 100ml glucose 5%, over 15 to 30 minutes

**Nephrotoxicity** - Irreversible renal failure and tubular damage can occur, and this is more frequent with cumulative doses over 25 – 50g/m$^2$ of Ifosfamide. Dose reductions should be instituted for GFR and changes in fractional phosphate clearance ($T_{p}/GFR$ mmol/l).

**Neural toxicity grade**

Classify toxicity as grade 0-1, 2 or 3-4 and adjust ifosfamide treatment as indicated if either GFR or $T_{p}/C_{crea}$ ($T_{p}/GFR$ mmol/l) or $HCO_3$ is reduced.

<table>
<thead>
<tr>
<th>Toxicity Grade</th>
<th>GFR (ml/min/1.73m$^2$)</th>
<th>$T_{p}/C_{crea}$ ($T_{p}/GFR$) (mmol/l)</th>
<th>$HCO_3$ (mmol/l)</th>
<th>Action (apply worst grade)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 0/1</td>
<td>≥60</td>
<td>≥1.00</td>
<td>≥17.0</td>
<td>Ifos dose 100%</td>
</tr>
<tr>
<td>Grade 2</td>
<td>40-59</td>
<td>0.8-0.99</td>
<td>14.0-16.9</td>
<td>Ifos dose 70% of total</td>
</tr>
<tr>
<td>Grade 3/4</td>
<td>≤40</td>
<td>≤0.8</td>
<td>≤14.0</td>
<td>Cyclophosphamid 1500mg/m$^2$ day 1 only</td>
</tr>
</tbody>
</table>

*Toxicity is scored from 0-4, analogous to the CTC system, but for the purpose of modifying treatment grades 0-1 and 3-4 are considered together.*

** 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 cyclophosphamid 1500mg/m$^2$/day***

| Ifosfamide neural toxicity | Sarcoma CAG Chair Authorisation: Date: | Page 1 of 2 | Published: January 2019  | Review: June 2022  | Version 2.5 |
Tp/Ccrea = Phosphateserum (mmol/L) – Phosphateurine (mmol/L) x creatinineserum (mmol/L) [mmol/ml] Creatinineurine (mmol/L)
NB serum creatinine is normally recorded in µmol/L

**Neural toxicity nomogram**

![Nomogram Image]

*Fig. 1. Nomogram to determine probability of not developing grade 3–4 clinical CNS toxicity with ifosfamide/mesna 36 h infusion. The probability that a patient will NOT develop severe CNS toxicity falls on the intersection of a straight line joining their serum albumin and serum creatinine concentrations on the appropriate pelvic disease scale.*

Ifosfamide neural toxicity  
Sarcoma CAG Chair Authorisation:  
Date:  
Published: January 2019  
Review: June 2022  
Version 2.5

Chemotherapy Regimens – Sarcoma 97 of 98
Pre-hydration and post-hydration regimens

Ensure adequate diuresis is obtained prior to administration and maintained during and after administration.

1. **Inpatient**
   - **Pre** 1L sodium chloride 0.9% + 20mmol KCl + 8mmol MgSO₄ infusion over 4 hours
   - **Give cisplatin in 1000ml volume over 4 hours**
   - **Post** 1L sodium chloride 0.9% + 20mmol KCl + 8mmol MgSO₄ infusion over 4 hours
     - 1L sodium chloride 0.9% + 20mmol KCl + 8mmol MgSO₄ infusion over 4 hours
     - NB 1L sodium chloride 0.9% + 20mmol KCl + 8mmol MgSO₄ infusion over 6 hours if oral intake is inadequate

2. **Day case**
   - **Pre** 1L sodium chloride 0.9% + 20 mmol KCl + 8mmol MgSO₄ infusion over 2 hours
     - 100ml mannitol 20% infusion over 30 minutes
     - **Give cisplatin in 1000ml volume over 2 hours**
   - **Post** 1L sodium chloride 0.9% + 20 mmol KCl + 8mmol MgSO₄ infusion over 2 hours
     - NB Furosemide 40mg may be added if required