Authorisation of Systemic Anti-Cancer Therapy (SACT) Guidelines for bone and soft tissue sarcoma

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These SACT guidelines are being submitted by the author on behalf of the Sarcoma Oncologists group.
1.0 INTRODUCTION / PURPOSE OF POLICY

1.1 Background
Systemic anti-cancer therapy (SACT) is a key treatment in managing sarcoma. Its role is often in conjunction with local treatment (surgery and/or radiotherapy) so the decision points for proceeding with different treatment options are included. These guidelines describe the agreed management for patients with soft tissue sarcoma, bone sarcoma and fibromatosis. (GIST will be covered in the upper GI SACT policy.)

1.2 Purpose
To ensure consistent use of SACT for patients with sarcoma.

2.0 SCOPE OF THE POLICY
This document is aimed at all clinical staff involved in the management of patients receiving SACT for sarcoma.

3.0 ROLES/RESPONSIBILITIES
It is the responsibility of all clinical staff involved in the management of patients receiving SACT for sarcoma to familiarise themselves with these guidelines.

4.0 KEY POLICY PRINCIPLES

4.1 Soft tissue sarcoma

Background
There are multiple histological subtypes of soft tissue sarcoma (STS), but these are usually grouped under the heading of STS for the purpose of treatment. Some specific histological subtypes are identified where management is distinct and different.

Management of localised uterine soft tissue sarcomas and GI stromal tumours are available elsewhere and have been omitted from these guidelines.

Surgery is the chief treatment modality in the case of localised, resectable sarcoma. The aim of surgery is complete excision with negative margins. Radiotherapy is recommended in most cases (except superficial low grade tumours), to improve local control. Pre-operative radiotherapy can be considered especially where tumours are of borderline operability and radiotherapy may facilitate a complete excision. See radiotherapy guidelines.

4.1.1 Adjuvant chemotherapy for localized disease

Adjuvant chemotherapy for STS is based on the premise that recurrence following resection of primary disease can be systemic as well as local. Adjuvant chemotherapy is not associated with definite evidence of improved overall survival, but meta-analysis data has shown a significant improvement in local tumour control and relapse-free survival with the use of doxorubicin–based chemotherapy.
Adjuvant chemotherapy is therefore not given routinely, but can be considered for patients with particularly high-risk tumours, e.g. pleomorphic rhabdomyosarcoma; malignant peripheral nerve sheath (Triton) tumours; angiosarcomas (including breast); head and neck sarcomas; extra-skeletal osteosarcoma. The standard regimen is doxorubicin and ifosfamide.\(^{(1,2)}\)

**Patient selection**
Consider Adjuvant Therapy for Post-operative patients with:
- High grade, deep tumours >5cm
- Performance status ECOG 0-1
- Good renal, liver and bone marrow function
- Staging carried out pre-op with CT Scan is adequate

**Treatment Regimen**
Doxorubicin 50mg/m² day 1 and Ifosfamide 5g/m² day 1 q21 for 6 cycles

**Follow up**
There are no published data to indicate the optimal routine follow-up policy. Relapses are most likely to occur to the lungs. Follow-up therefore focuses on surveillance of the primary site and the lungs.
- Clinical examination
- Chest x-ray
- Baseline MRI of primary site can be considered 6 months after completing radiotherapy
- Other investigations as clinically indicated

Recommended intervals for follow-up:
- Every 3 months for years 1 - 2.
- Every 6 months for year 3
- Annually year 4+5

Could potentially be carried out by clinical nurse specialist

**4.1.2 Treatment of Locally Advanced Disease**

**4.1.2.1 Neoadjuvant Chemotherapy**

**Background**
Patients who have borderline resectable disease should be treated with neoadjuvant chemotherapy to downsize tumour to allow surgical resection.\(^{(3)}\) This allows chance of conservative surgery for those who otherwise are deemed unresectable or where significant surgical morbidity is anticipated. However as there is significant chemotherapy related toxicity, patients need to be appropriately selected:
- Performance status ECOG 0-2
- Good renal, hepatic and bone marrow function
- Normal LV ejection function
Staging
If patients are being considered for neoadjuvant chemotherapy they require:
• CT Scan of Chest

Treatment Regimen
Doxorubicin 50-75mg/m² day 1 and Ifosfamide up to 3000mg/m² days 1-3
21 day cycle
Reassessment at each visit
Re-imaging of primary tumour after 2-3 cycles- early referral back to MDM if evidence of progression.
Total of 6 cycles of chemotherapy

Patients with locally advanced disease who are not suitable for neoadjuvant chemotherapy require discussion of treatment options at MDM. Amputation may be appropriate for some patients whilst others may have debulking surgery and/or radiotherapy to preserve function / ameliorate symptoms or be considered for palliative chemotherapy or ongoing symptom management.

Follow up
Surgery should take place 3-4 weeks after last chemotherapy cycle and re-discussed at the MDM as to role of radiotherapy.

Recommended intervals for follow-up:
• Every 3 months for years 1 - 2.
• Every 6 months for year 3
• Annually year 4+5

• Clinical examination
• Chest x-ray
• Baseline MRI of primary site can be considered 6 months after completing radiotherapy
• Other investigations as clinically indicated

4.1.3 Advanced (Metastatic) Disease

Background
There is a modest survival benefit (2-5 months) for chemotherapy compared to active supportive care alone for patients with advanced sarcoma. The published response rates for chemotherapy in STS vary enormously; from 10–50% depending on the drugs used, patient selection and histological subtype
Single agent doxorubicin is the standard as clinical trials have not demonstrated a superior survival rate with other agents. (4) The GeDDiS trial demonstrated an increase in acute toxicity but no improvement in PFS with gemcitabine and docetaxel compared to doxorubicin for first line treatment of unresectable or metastatic disease Combination doxorubicin and ifosfamide
may be used for specific limited indications including rapidly progressive disease or when the increased response rate of combination chemotherapy is desirable. (5)

All patients will be considered for appropriate clinical trials.

**Doxorubicin and Ifosfamide**

Studies have shown an equivalent response rate and overall survival with the use of these drugs as single agents though higher toxicity rates are seen with ifosfamide. It may be used as first line if cardiac function is impaired. Dose finding studies have shown 75mg of doxorubicin and 9g/m² ifosfamide to be superior to lower doses with toxicity limiting further dose escalation. In combination there is an increased response rate but no increased survival rate. Doses in the advanced setting are lower than those in the neoadjuvant setting to limit toxicity.

Ifosfamide has limited activity in leiomyosarcoma and should be avoided.

**Other Drugs**

Further chemotherapy options include:
- Trabectedin
- Gemcitabine ± docetaxel
- Dacarbazine
- Oral cyclophosphamide and prednisolone
- Pazopanib

Pazopanib is not routinely commissioned and is subject to request through an Individual Funding Request (IFR).

**Duration of Treatment**

The optimum duration of therapy for patients with advanced sarcoma has not been identified. Most randomised phase III studies use 6 cycles of treatment and this is particularly so in those regimes containing doxorubicin due to cardiac toxicity. Trabectedin and pazopanib were given until progression.

**British Sarcoma Group Guidance**

Patients of good performance status can be offered chemotherapy to delay onset of symptoms. An alternate and equally acceptable approach is to treat symptomatic patients to improve quality of life, improve survival and control disease. The patient needs to take into account toxicities, efficacy and convenience.

**Sub-classification of Pathology**

Phase 2 trials, retrospective case series and sub-analysis of studies have identified the importance of histological subtype in selecting the optimum treatment of advanced sarcoma for patients. Specific systemic therapy options can be considered for certain histological subtypes.

Angiosarcoma:
• First-line chemotherapy: Paclitaxel
• Second-line chemotherapy options include: Doxorubicin or liposomal doxorubicin, especially for skin angiosarcomas (e.g. face and scalp), or radiation-induced usually chest wall following radiotherapy for breast cancer. (7,8)

Leiomyosarcoma
Consider use of Letrozole in low grade LMS and strongly ER positive with fairly indolent measurable or asymptomatic metastatic disease

Endometrial stromal sarcoma
Consider use of Letrozole in ER positive disease
On progression consider Exemestane or Provera

Myxoid liposarcoma:
• First-line chemotherapy: Doxorubicin.
• Trabectedin has shown particular activity in this subtype as second/third line therapy. (9)

Cardiac/pulmonary vessel sarcoma:
• Due to the risk of cardiotoxicity (as radiotherapy is administered following chemotherapy in the majority), liposomal doxorubicin can be considered instead of conventional doxorubicin.

Well/de-differentiated liposarcoma and synovial sarcoma:
• First-line chemotherapy: Doxorubicin.
• Second-line chemotherapy: Ifosfamide (standard schedule, or prolonged infusion - consider for first line in dedifferentiated liposarcoma retroperitoneal disease). (10)

Alveolar soft part sarcoma:
• Considered to be chemo-resistant, such that conventional chemotherapy is not used.
• Consider for clinical trial in Royal Marsden Hospital

extraskeletal myxoid chondrosarcoma:
• Considered to be less chemo sensitive but conventional chemotherapy remains first line.
• Consider for Sunitinib (11) or clinical trials.

Dermatofibrosarcoma protruberans:
• Consider use of imatinib (acts via blocking of PDGFRβ receptor) for locally advanced inoperable disease. (11)

Inflammatory myofibroblastic tumour:
• Consider corticosteroids.
  • If Alk rearrangement positive - consider referral for Create (Crizotinib) trial
Kaposi sarcoma
- Patients should be established on HAART
- First line for advanced disease: liposomal Doxorubicin ‘Caelyx’
- Second line: Paclitaxel

4.1.3.2 First Line Therapy

Patient selection
Patients with locally advanced and metastatic disease should be considered for systemic therapy providing they demonstrate:
- Adequate performance status (ECOG PS 0/1, but to be considered in those of ECOG PS 2)
- Adequate renal function, liver and bone marrow function

Staging
- Baseline CXR pre chemotherapy for comparison during treatment (if mets visible on CXR)
- CT Scan of chest (or site of disease)

4.1.3.2.1 Treatment Regimens

Doxorubicin 75mg/m² (consider 60mg/m² if >60yrs or frail)
21 day cycle
Continue until cycle 6 or progression or intolerable toxicity

Management
Prechemo LVEF assessment required
CT scan of disease site at baseline & after cycle 3
CXR at baseline and every cycle to look for disease progression if mets visible

Ifosfamide 9000mg/m² (if unable to use Dox)
21 day cycle
Requires double lumen PICC and inpatient bed
Given over 3 days with mesna cover
Continue until cycle 6 or progression or intolerable toxicity

In dedifferentiated liposarcoma, consider use of

Prolonged infusional Ifosfamide 1000mg/m² for 14 days via Baxter pump
28 day cycle
Requires PICC
Patient must be motivated to test urine and self treat with bicarbonate tablets and oral mesna and thiamine in case of encephalopathy

If particularly symptomatic and patient fit, consider

**Doxorubicin 50mg/m² day 1 and Ifosfamide 3000mg/m² days 1-3**
21 day cycle
Requires double lumen PICC and inpatient bed
Given over 3 days with mesna cover
Continue until cycle 6 or progression or intolerable toxicity

For Kaposi’s sarcoma

**Caelyx**
20mg/m² day 1 (cycle one slow ivi )
21 day cycle
6-10 cycles depending on response
Co-ordinate care with GUM and ensure all drug compatible with HAART
(website [www.hiv-druginteractions.org](http://www.hiv-druginteractions.org))

**Management**
Assessment for additional risk of Ifosfamide encephalopathy
Careful monitoring of renal function
CT scan of disease site at baseline & after cycle 3
CXR at baseline and every cycle to look for disease progression if mets visible

**Follow up**
Follow up initially for scan results, then as symptoms dictate (usually 1-3 months, quality of life is paramount and if patient is well 3 months is satisfactory).
CXR at every follow up or as clinically indicated.
Repeat CT scan as clinically indicated.

**4.1.3.3 Second Line Therapy**
There is no recognised “standard” therapy following failure of doxorubicin and ifosfamide. Dacarbazine has activity as do a number of newer agents—gemcitabine, taxanes and trabectedin. The evidence for gemcitabine and docetaxel is greatest for uterine leiomyosarcomas, however, subsequent studies have demonstrated activity in soft tissue leiomyosarcoma and other tumour types. Likewise trabectedin, although licensed as second-line treatment for all soft tissue sarcomas, has been licensed on the basis of a randomised trial comparing two different treatment regimens in patients with predominantly leiomyosarcoma and liposarcoma. Other tumours, such as synovial sarcoma may also be sensitive. Pegylated liposomal doxorubicin and paclitaxel have been demonstrated to have significant activity in angiosarcoma. The randomised phase 3 Palette trial demonstrated a 3 month
median PFS benefit with pazopanib over placebo but no significant overall survival advantage.⁼¹²
There is increasing evidence for the differential response to chemotherapy according to histological subtype and as knowledge increases it is expected that it will become increasingly possible to individualise treatment. For example; synovial sarcoma, leiomyosarcoma and myxoid liposarcoma are recognised as having higher response rates to chemotherapy and, conversely, alveolar soft part sarcoma and solitary fibrous tumour are generally regarded as insensitive to chemotherapy and there are only occasional reports of responses in clear cell sarcoma.
A lot of these data are based on phase II trials; the decision to offer chemotherapy and choice of agent should be based on histology and toxicity profile following full discussion with the patient.

**Funding**
Recurrent funding is available for the use of trabectedin post doxorubicin. Pazopanib, and liposomal doxorubicin require applications for funding.

**Patient selection**
- Adequate performance status (ECOG PS 0/1, but can be considered in those of ECOG PS 2)
- Ifosfamide is the standard drug of choice (bar in cases of leiomyosarcoma) though if used first line, consider trabectedin or gemcitabine/docetaxel.
- Gemcitabine/docetaxel has most evidence supporting its use in uterine leiomyosarcomas

**Treatment Regimens**

**Ifosfamide 9000mg/m² - if not used first line**
21 day cycle
Requires double lumen PICC and inpatient bed
Given over 3 days with Mesna cover
Continue until cycle 6 or progression or intolerable toxicity

or

**Gemcitabine 675mg/m² D1 & D8 and Docetaxel 75mg/ m² D8**
21 day cycle,
Treat for 6 cycles or progression or intolerable toxicity

or

**Trabectedin 1.5mg/m² iv infusion over 24hrs**
21 day cycle
Requires PICC and inpatient bed
D1 :creatinine kinase check
Dose adjustment made on
D4 cycle 1: liver function check
Cycle 1+2: weekly oncology profile, CK and FBP
Subsequent cycle: mid cycle onc profile/ CK/ FBP
Continue until progression or intolerable toxicity.

If angiosarcoma consider

Paclitaxel 80mg/m² D1
7 day cycle,
Treat for 18 cycles or progression or intolerable toxicity

or

Pegylated Liposomal Doxorubicin 50mg/m²
28 day cycle
Treat for 6 cycles or progression or intolerable toxicity

Management
CT scan of disease site at baseline & after cycle 3
CXR at baseline and every cycle to look for disease progression if mets visible

Management
• CT scan of area of disease before cycle 1, after cycle 3 and thereafter every 3 cycles
• Consider CXR prior to each cycle if disease measurable
• Careful toxicity assessment prior to each cycle
• If signs of disease progression stop treatment

4.1.3.4 Third and Subsequent Line Therapy
In carefully selected patients (PS 0 or 1) who have had a good response to first and second line SACT and who have had a progression-free interval of greater than 6 months following treatment, further lines of therapy can be considered. The choice of regimen depends on pathological subtype and prior therapy but options include:

Treatment Regimens

Trabectedin 1.5mg/m² iv infusion over 24hrs
21 day cycle
Requires PICC and inpatient bed
D1: creatinine kinase check
Dose adjustment made on
  D4 cycle 1: liver function check
  Cycle 1+2: weekly oncology profile, CK and FBP
  Subsequent cycle: mid cycle onc profile/ CK/ FBP
Continue until progression or intolerable toxicity.
or
Pazopanib 800mg po continuous
  28 day cycle
  Treat till progression or intolerable toxicity
or
Dacarbazine 850mg/m2 ivi day 1
  21 day cycle
  Continue up to 8 cycles or progression or unacceptable toxicity

4.2 Fibromatosis

4.2.1 Background
Fibromatosis is a clonal connective tissue malignancy that does not metastasize, but has a significant risk of local recurrence and is associated with morbidity and occasionally mortality. It affects 2-4 /million either sporadically or associated with a genetic disorder. It can affect the abdominal wall, mesentery or other extra-abdominal locations, including limbs. The natural history is unpredictable (with the possibility of long-lasting stable disease and even occasional spontaneous regressions).

The mainstay of therapy is surgery but recurrence rates are high at 50%. Radiotherapy can be a used in addition to surgery. When the disease recurs or is unresectable, systemic therapy can be effective in controlling disease.

Diagnosis and Staging
Pathology review
Image disease site - CT Scan if intra-abdominal disease, MRI for other sites
Appropriate evaluation of associated genetic disorder

4.2.2 First Line Therapy
Given the long and potentially unpredictable natural history of this disease, a period of observation may be the best initial option. Exceptions to this approach would be patients with potentially life-threatening extra-abdominal locations (e.g. head and neck region); and intra-abdominal fibromatosis.
For cases with demonstrated disease progression, optimal treatment needs to be individualized following multidisciplinary discussion.

Treatment options include:
Surgery (without any adjuvant therapy)
Radiation therapy
Systemic therapies:
It is reasonable to employ the less toxic therapies before the more toxic ones in a stepwise fashion.
   Options :
   
   - Hormonal therapies (tamoxifen, toremifene, GnRH analogues)\(^{(13,14)}\)
   - Non-steroidal anti-inflammatory drugs
   - Low-dose chemotherapy (e.g. methotrexate and vinblastine\(^{(15)}\); methotrexate and vinorelbine)
   - Low-dose interferon
   - Molecular therapies: imatinib\(^{(16)}\), sorafenib\(^{(17)}\)
   - Standard-dose chemotherapy (using pegylated liposomal doxorubicin\(^{(18)}\), and other regimens active in soft tissue sarcomas)

**Funding**
Imatinib, sorafenib and pegylated liposomal doxorubicin are not routinely commissioned and are subject to request through an IFR.

**Treatment Regimen**

**Hormonal therapy**

**Tamoxifen 40mg mane**
Continuous
Usually used with Sulindac 300mg po continuously

**Management**
   - Contraception advice if appropriate

**Follow up**

Every 4-6 months according to symptoms.
Repeat scans as clinically indicated – ideally \(\geq 4\) monthly

**4.2.3 Second and Subsequent Line Therapy**
Second line chemotherapy for progressive symptomatic disease.
Each patient should be discussed at the appropriate soft tissue sarcoma mdt to assess the role of local therapy.
Treatment Regimen
Chemotherapy

Methotrexate 30mg/m² and Vinblastine 6mg/m²
Weekly cycle
Treat up to 24 months or progression or intolerable toxicity

or

Pegylated Liposomal Doxorubicin 50mg/m²
28 day cycle
Treat for 6 cycles or progression or intolerable toxicity

or

Sorafenib 400mg po continuous
28 day cycle
Treat till progression or intolerable toxicity

or

Imatinib 200-600mg po continuous
(BSA ≥ 1.5m²: 300mg bd, BSA 1-1.49: 200mg bd, BSA <1m² 100mg bd)
28 day cycle
Treat till progression or intolerable toxicity

Management
- Image site at baseline
- Repeat imaging every 4 months

4.3 Rhabdomyosarcoma

Background

Rhabdomyosarcoma (RMS) is typically a cancer of childhood, and is rare in adults. It may affect the extremities, genitourinary system, head and neck region, trunk, or other less frequent sites.

Four main variants are recognised:
- Embryonal rhabdomyosarcoma (including botryoid variant)
- Alveolar rhabdomyosarcoma
- Spindle cell rhabdomyosarcoma
- Pleomorphic rhabdomyosarcoma (occurs in adults, is treated as a high grade soft tissue sarcoma)
Patients are stratified according to the risk of their disease, based on a number of prognostic factors. The principles of treatment are:

- **Low Risk →** surgery + chemotherapy.
- **Standard Risk →** surgery + chemotherapy ± radiotherapy.
- **High Risk →** chemotherapy + surgery + radiotherapy.
- **Very High Risk →** chemotherapy +/- surgery + radiotherapy.
- **Metastatic disease →** chemotherapy +/- surgery + radiotherapy.

Local therapy (surgery and/or radiotherapy) is carried out at around week 13.

Vincristine, actinomycin D, and ifosfamide are the main chemotherapy agents. For the very high risk patients doxorubicin may be added to the standard regimens. (19)

Detailed guidelines for the management of all rhabdomyosarcomas including risk classification are specified in the current European guidelines (EpSSG 2005). (20)

**Funding**

Application for funding is currently required for all 2nd line regimens.

### 4.3.1 First line therapy

**Treatment Regimens**

**Standard risk groups**

**IVA**

Ifosfamide 3000mg/m² day 1+2 with Mesna 3000mg/m² and hydration
Vincristine 1.5 mg/m² day 1, 8, 15 (day 1 only from cycle 3 onwards)
Actinomycin-D 1.5 mg/m² day 1
21 day cycle, 9 cycles

or

**For high risk and very high risk groups**

**IVADo**

Ifosfamide 3000mg/m² day 1+2 with Mesna 3000mg/m² and hydration
Vincristine 1.5 mg/m² day 1, 8, 15 (day 1 only from cycle 3 onwards)
Actinomycin-D 1.5 mg/m² day 1
Doxorubicin 30mg/ m² day 1+2
21 day cycle, 4 cycles

Followed by

Ifosfamide 3000mg/m² day 1+2 with Mesna 3000mg/m² and hydration
Vincristine 1.5 mg/m² day 1
Actinomycin-D 1.5 mg/m² day 1
21 day cycle, 5 cycles
Consider maintenance therapy for very high risk group
Vinorelbine 25mg/m² day 1,8,15
Cyclophosphamide 25mg/m² po continuous
28 day cycle for up to 2 years

Management
- CT Scan or MRI of primary site
  - at baseline
  - after 3
- Baseline echo for IVADo regimen
- Double lumen PICC and inpatient bed required
- Decision made re local therapy after cycle 3 imaging
- Omit Actinomycin-D during RT
- Consider GCSF support to maintain dose intensity

Follow up
Every 3 months in the first year.
Every 4 months in years 2 - 3.
Every 12 months in years 4 - 5.
Clinical evaluation and chest x-ray
MRI / CT scan of primary site as clinically indicated

4.3.2 Metastatic disease therapy
Patients with metastatic RMS may be treated as per the high risk arm of EpSSG 2005 study:

IVADo x 4 → IVA x 5

Local treatment remains important, and if possible should include surgical resection of the primary site, with radiotherapy to local and all metastatic sites where possible. Local treatment will be around cycles 7 – 9.

For less fit patients or those with pleomorphic subtype, consider Ifosfamide and Doxorubicin combination therapy or single agent Doxorubicin. Oral etoposide is an alternative for those with poor performance status.

Treatment Regimen
IVADo
Ifosfamide 3000mg/m² day 1+2 with Mesna 3000mg/m² and hydration
Vincristine 1.5 mg/m² day 1, 8, 15 (day 1 only from cycle 3 onwards)
Actinomycin-D 1.5 mg/m² day 1
Doxorubicin 30mg/ m² day 1+2
21 day cycle, 4 cycles
Followed by
Ifosfamide 3000mg/m² day 1+2 with Mesna 3000mg/m² and hydration
Vincristine 1.5 mg/m² day 1
Actinomycin-D 1.5 mg/m² day 1
21 day cycle, 5 cycles

or

Doxorubicin 75mg/m² (consider 60mg/m² if >60yrs or frail)
21 day cycle
Continue until cycle 6 or progression or intolerable toxicity

or

Doxorubicin 50mg/m² day 1 and Ifosfamide 3000mg/m² days 1-3
21 day cycle
Continue until cycle 6 or progression or intolerable toxicity

or

Etoposide 50mg po bd day 1-10
21 day cycle
Continue until cycle 6 or progression or intolerable toxicity

Management
- Prechemo LVEF assessment
- CT scan of disease site at baseline & after cycle 3
- CXR at baseline and every cycle to look for disease progression if mets visible
- Double lumen PICC and inpatient bed required for Ifosfamide regimens

4.3.3 Second line therapy
Treatment will be given on an individualised basis, and will depend on whether or not the primary therapy contained doxorubicin though vincristine and irinotecan is the overall first choice. If more than 3 years from standard first line therapy, a repeat course of IVA or VAC can be considered depending on initial response.

Previous doxorubicin
Recent guidelines from EpSSG have recommended Vincristine and Irinotecan as first line therapy in relapsed disease (21, 22). A CCLG phase 2 trial of irinotecan, vincristine +/- temozolamide is open to adult patients in the Royal Marsden Hospital. Vinorelbine and low dose cyclophosphamide can be given as maintenance or an alternative regime. (23)
No previous doxorubicin

Recommended chemotherapy regimens are
Vincristine and irinotecan
Vincristine, cyclophosphamide, doxorubicin and etoposide (VCDE)
Topotecan, vincristine and doxorubicin (24)
Vinorelbine and low dose cyclophosphamide

Treatment Regimen
Irinotecan 50mg/m² day 1-5
Vincristine 1.5mg/m² day 1,8
21 day cycle
Continue for 6-12 cycles unless progression or intolerable toxicity

or

Vinorelbine 25mg/m² day 1,8,15
Cyclophosphamide 25mg/m² po continuous
28 day cycle for up to 2 years

or

Vincristine 1.5mg/m² day 1
Cyclophosphamide 1.5g/m² ivi days 1-3 plus Mesna
Doxorubicin 20mg/m² ivi days 1-3
Etoposide 150mg/m² days 1-3
21 day cycle for 6 cycles

or

Topotecan 0.75mg/m² day 1-5
Vincristine 2mg/m² day 1
Doxorubicin 45mg/m² day 1
21 day cycle for 6 cycles

4.4 Osteosarcoma

Background
Curative treatment for high-grade osteosarcoma consists of surgery and chemotherapy. Compared with surgery alone, multimodal treatment of high-grade osteosarcoma increases survival probability from only 10%–20% to around 60%.
Doxorubicin, cisplatin, high-dose methotrexate, and ifosfamide have demonstrated antitumour activity in osteosarcoma and are usually
administered in protocols involving 3 or 4 drug combinations. A variety of pre- and postoperative combinations are used in common practice and in clinical trials, and the ideal combination regimen and the optimal treatment duration are yet to be defined or confirmed.

Most current protocols include a period of preoperative chemotherapy. This has not been proven to add survival benefit over postoperative chemotherapy alone, although there are clear practical advantages. Treatment is commonly given over periods of 6–9 months. The extent of histological response to pre operative chemotherapy however offers important prognostic information, but altering postoperative chemotherapy on the basis of response is not recommended outside of ongoing trials.

The immune modulator liposomal muramyl tripeptide (mifamurtide) added to postoperative chemotherapy demonstrated a statistically significant advantage in overall survival in a large randomised trial and has been approved in Europe for patients under 30 with completely resected localised osteosarcoma.

Whenever possible, patients with osteosarcoma should receive chemotherapy in the context of prospective trials, which is regarded as standard of care.

**Funding**

Mifamurtide is available for patients fulfilling the licensed indication (after complete resection in non-metastatic patients aged 2-30 years). Application for funding is currently required for all 2nd line regimens.

### 4.4.1 Neoadjuvant chemotherapy

Neo-adjuvant chemotherapy (10 weeks) → local therapy (surgery if at all possible) → post-operative adjuvant chemotherapy (18 weeks). The chemotherapy regimen is MAP (doxorubicin, cisplatin, methotrexate). This may be modified to AP alone (without methotrexate) for patients >40 years.

**Treatment Regimen**

**MAP**

- **Doxorubicin**: 37.5mg/m² ivi day 1+2
- **Cisplatin**: 60mg/m² ivi day 1+2
- **Methotrexate**: 12g/m² ivi day 22+29 with calcium folinate and sodium bicarbonate rescue
- 35 day cycle for 2 cycles

Alternatively:

- **Doxorubicin**: 25mg/m² IV day 1-3
- **Cisplatin**: 100mg/m² IV day 1
- 21 day cycle for up to 4 cycles
Management

- MRI scan primary site
  - at baseline
  - after 8 weeks
- Double lumen PICC and inpatient bed required
- Prechemo LVEF assessment
- Hydration and mannitol required
- Regular urine pH and MTx level checks required with MAP
- Care re drug interactions and other reasons to expect higher MTX levels

4.4.2 Adjuvant therapy
Patients between 2 and 30 who have had a complete surgical resection should be considered for Mifamurtide (48 doses over 36 weeks) in conjunction with their adjuvant chemotherapy.

Treatment Regimen

MAP+ Mifamurtide
Doxorubicin 37.5mg/m² ivi day 1+2
Cisplatin 60mg/m² ivi day 1+2
Mifamurtide 2mg/m² day 2+5, 9+12, 16+19, 23+26, 30+33
Methotrexate 12g/m² ivi day 22+29 with calcium folinate and sodium bicarbonate rescue
35 day cycle for 2 cycles

Followed by
Doxorubicin 37.5mg/m² ivi day 1+2
Mifamurtide 2mg/m² day 2+5, 9+12, 16, 23
Methotrexate 12g/m² ivi day 15+22 with calcium folinate and sodium bicarbonate rescue
28 day cycle for 1 cycle

Followed by
Doxorubicin 37.5mg/m² ivi day 1+2
Mifamurtide 2mg/m² day 2, 9, 16, 23
Methotrexate 12g/m² ivi day 15+22 with calcium folinate and sodium bicarbonate rescue
28 day cycle for 1 cycle

Followed by
Mifamurtide 2mg/m² day 1
7 day cycle for 18 weeks

Alternatively:

MAP
Doxorubicin 37.5mg/m² ivi day 1+2
Cisplatin 60mg/m² ivi day 1+2
Methotrexate 12g/m² ivi day 22+29 with calcium folinate and sodium bicarbonate rescue
35 day cycle for 2 cycles

Followed by
Doxorubicin 37.5mg/ m² ivi day 1+2
Methotrexate 12g/m² ivi day 15+22 with calcium folinate and sodium bicarbonate rescue
28 day cycle for 2 cycles

Alternatively:
Doxorubicin 25mg/m² IV day 1-3
Cisplatin 100mg/m² IV day 1
21 day cycle for up to total of 6 cycles (including number given neo-adj)

Management
- Double lumen PICC and inpatient bed required
- Hydration and mannitol required
- Regular urine pH and MTx level checks required with MAP
- Care re drug interactions and other reasons to expect higher MTX levels

Follow up
Every 3 months in the first year.
Every 4 months in years 2 - 3.
Every 12 months in years 4 - 5.
Clinical evaluation and chest x-ray
MRI / CT scan of primary site as clinically indicated

4.4.3 Metastatic disease

Patients presenting with metastatic osteosarcoma are a heterogeneous group and may be treated using the same regimens used for nonmetastatic osteosarcomas provided that surgical resection of all sites of disease is deemed feasible. Approximately 30% of all patients with primary metastatic osteosarcoma and >40% of those who achieve a complete surgical remission become long-term survivors.
For those with inoperable disease, treatment intent is palliative using MAP or AP depending on the patient.

Treatment Regimen
See under neo-adjuvant therapy

4.4.4 Relapsed / refractory disease
The role of second-line chemotherapy for recurrent osteosarcoma is less well defined than that of surgery, and there is no accepted standard regimen. The choice of agents may take into account the prior disease-free interval and
often includes ifosfamide ± etoposide \(^{(27)}\), or docetaxel/gemcitabine \(^{(28)}\). The use of second-line chemotherapy has been shown to correlate with limited prolongation of survival in patients with inoperable metastatic recurrences, and a positive correlation in operable disease was observed in one series.

**Treatment Regimen**

**Etoposide** 100mg/m\(^2\) IV day 1-5  
**Ifosfamide** 1800mg/m\(^2\) IV day 1-5  
21 day cycle  
Treat for 6 cycles or progression or intolerable toxicity  

or

**Gemcitabine** 675mg/m\(^2\) D1 & D8 and **Docetaxel** 75mg/ m\(^2\) D8  
21 day cycle,  
Treat for 6 cycles or progression or intolerable toxicity  

4.5 Ewings Sarcoma

**Background**  
With surgery or radiotherapy alone, 5-year survival is <10%. With treatment in current multimodality trials including chemotherapy, 5-year survival is 60%–70% in localised and 20%–40% in metastatic disease. All current trials employ three to six cycles of initial chemotherapy after biopsy, followed by local therapy and another six to ten cycles of chemotherapy usually given at 2 or 3 week intervals based on current agreed national or international protocols \(^{(29)}\). Treatment duration is thus 10–12 months. Agents considered most active include doxorubicin, cyclophosphamide, ifosfamide, vincristine, dactinomycin, and etoposide. Virtually all active protocols are based on four to six drug combinations of these agents. Chemotherapy intensity is positively associated with outcome.

Current treatment protocols used are:  
**VIDE** x 6 → **VAI** x 8 or **VAC** x 8  
**VDC/IE** x 14 cycles \(^{(30)}\)  
Enrolment and treatment in Euro-Ewing-99 study protocol in RBHSC if patient <16 years old.

Euro-Ewing 2012 is currently going through trial set up and will have 3 systemic therapy randomizations.  
Induction/consolidation chemotherapy randomisation (R1) objective is to compare VIDE with VDC/IE.  
Zoledronic acid randomisation (R2zol) objective is to determine whether the addition of zoledronic acid to consolidation chemotherapy, is associated with improved clinical outcome in patients with localised ESFT.

**Funding**  
Application for funding is currently required for all 2\(^{nd}\) line regimens.
4.5.1 Neoadjuvant chemotherapy
Neoadjuvant chemotherapy → local therapy (surgery and/or radiotherapy) → adjuvant chemotherapy. All patients will be discussed at the local MDT (MPH for extremity tumours, other sites as per appropriate MDT) with regard to local therapy and consideration for referral to the National Ewing’s Sarcoma MDT.

Treatment Regimen
VIDE

Vincristine 1.5mg/m² day 1
Ifosfamide 3000mg/m² 3 hour ivi days 1-3 plus Mesna
Doxorubicin 20mg/m² ivi days 1-3
Etoposide 150mg/m² days 1-3

21 day cycle for 6 cycles

Management
- Prechemo LVEF assessment
- MRI / CT scan of disease site at baseline & after cycle 2
- Double lumen PICC and inpatient bed
- Aim to maintain dose intensity
- Assessment for additional risk of Ifosfamide encephalopathy
- Careful monitoring of renal function

4.5.2 Adjuvant chemotherapy

Treatment Regimen
VAI
Vincristine 1.5mg/m² day 1
Actinomycin D 0.75mg/m² ivi days 1+2
Ifosfamide 3000mg/m² 3 hour ivi days 1+2

21 day cycle for 8 cycles

Treatment of primary metastatic disease

Patients with metastatic disease are still potentially curable, depending on the volume and distribution of metastases. Therefore, the same treatment approach is used as for patients with localised disease. The same chemotherapy regimens are used as for patients with localised disease. There is no evidence for using high dose chemotherapy with peripheral blood stem cell rescue outside of a clinical trial.
Treatment of recurrent disease

This will depend on sites of metastases, and timing of relapse. Patients who have relapsed more than two years from completing primary treatment, with small volume (usually lung only) metastases, may still be potentially curable, and could be considered for induction chemotherapy (ifosfamide +/- etoposide), and high dose chemotherapy (busulphan and melphelan) with peripheral blood stem cell rescue depending on disease response. This is not available in Northern Ireland and patients would have to be referred to another centre.

Patients not falling into this selected group would be considered incurable, and are treated with palliative intent.

Treatment regimens

Temozolomide 100mg/m² po once daily on days 1-5.
Irinotecan 20mg/m² infusion over 1 hour on days 1-5 and days 8-12.
28 day cycle to progression or intolerable toxicity (31)

or

Topotecan 0.75mg/m² day 1-5
Cyclophosphamide 250mg/m² day 1-5
21 day cycles to progression or intolerable toxicity (32)

4.6 Other pathology

4.6.1 Chordoma

Chordoma is acknowledged to be chemo-resistant such that there is no role for chemotherapy for metastatic disease and surgery should be considered where appropriate. Patients should be considered for appropriate clinical trial protocols. There is some limited evidence for the use of targeted therapies in advanced platelet-derived growth factor receptor β (PDGFRB) positive chordomas including imatinib, sunitinib, and mTOR inhibitors (33).

Funding

Application for funding is currently required for all these regimens

Treatment regimen

Imatinib 200-600mg po continuous
(BSA ≥ 1.5m² : 300mg bd, BSA 1-1.49: 200mg bd, BSA <1m² 100mg bd)
28 day cycle
Treat till progression or intolerable toxicity
4.6.2 PEComa
Perivascular epithelioid cell tumors (PEComas) are rare tumors driven by tuberous sclerosis complex gene mutations causing upregulation of mTOR. There is some limited evidence for the use of targeted therapies in metastatic disease, including sirolimus or temsirolimus\(^{(34)}\).

Funding
An IFR application should be made through Internal Scrutiny Committee (ISC) as this is 'off-label' use.

Treatment regimen

**Sirolimus 5 mg po daily.**
*Treat till progression/intolerable toxicity*

4.6.3 (Atypical teratoid) rhabdoid sarcoma (AT/RT)
rhabdoid sarcoma is a rare and highly aggressive tumour. It is more common in the paediatric population and in CNS or renal sites. Extracranial non renal rhabdoid sarcoma most commonly occurs in a deep axial location such as the neck or paraspinal region. There is some evidence that these tumours do respond to palliative chemotherapy \(^{(35)}\).
The choice of regimen will depend on patient’s age and site of disease and up-to-date recommendations from national experts should be sought. Regimen, drug and dose adjustments should be strongly considered depending on the patient’s age and concurrent radiotherapy treatment.

Treatment regimens

**Extracranial non renal rhabdoid sarcoma**

**V Dox C and C Carbo E**
21 day cycle.

**V Dox C:** weeks 1, 10, 13, 22 & 28 a total of 5 cycles  
**C Carbo E:** weeks 4, 7, 16, 19 & 25 a total of 5 cycles

**V Dox C**
Vincristine 1.5mg/m\(^2\) in 50ml on days 1, 8 & 15.  
Doxorubicin 37.5mg/m\(^2\) iv bolus on days 1 & 2.  
Cyclophosphamide 1200mg/m\(^2\) on day 1.

**C Carbo E**
Carboplatin dose as per GFR on day 1.  
Etoposide 100mg/m2 on days 1 to 5.  
Cyclophosphamide 440mg/m2 on days 1 to 5.
Atypical teratoid/ rhabdoid sarcoma
ICE, VAC and Doxorubicin alternating regimens

ICE
Ifosfamide 5000mg/m² on day 1
Carboplatin 400mg/m² on day 1
Etoposide 100mg/m² on day 1, 2, 3
with Mesna and hydration

VAC
As per Ewings

Dox
As per soft tissue sarcoma

4.6.4 Giant cell tumour
GCT is treated by surgery, either curettage or excision with reconstruction depending on site and extent. For inoperable metastatic disease, treatment options are limited. There is recent evidence for activity of denosumab, a RANK ligand inhibitor\(^{(36)}\).

Funding
Application for funding is currently required for this regimen.

Treatment regimen

Denosumab 120mg sc
28 day cycle
Treat till progression or intolerable toxicity

4.6.5 Desmoplastic small round cell tumour
This is an aggressive and rare tumor that primarily occurs as intra-abdominal masses. There is no clear treatment strategy and multiagent chemotherapy, surgery and radiotherapy are all used depending on the clinical scenario. Protocols as described for Ewing Sarcoma can be used.

4.7 Supportive Therapies

GCSF primary prophylaxis is required in regimens where the risk of neutropenic infection is high and/ or delays are to be avoided.

Blood transfusions should be used to maintain Hb >9.0
5.0 IMPLEMENTATION OF POLICY

5.1 Dissemination
This policy will be agreed by all consultant oncologists treating patients with SACT for sarcomas. The guideline will form the basis for development of the SACT regimen specific protocols. It will be available on the intranet for use by all doctors, nurses and pharmacists involved in all stages of SACT assessment and delivery in patients with sarcomas.

6.0 MONITORING
Use of these guidelines will be monitored using audit.

7.0 EVIDENCE BASE / REFERENCES


9. Demetri GD et al.. Efficacy and safety of trabectedin in patients with advanced or metastatic liposarcoma or leiomyosarcoma after failure of prior


35. Pedersen JV et al. A retrospective study from the Royal Marsden Hospital (RMH) of patients with malignant perivascular epithelioid cell tumors (PEComa) receiving treatment with sirolimus (SI) or temsirolimus (TSI). J Clin Oncol 30, 2012 (suppl; abstr 10038)


8.0 CONSULTATION PROCESS
Sarcoma oncologists group.

9.0 APPENDICES / ATTACHMENTS

10.0 EQUALITY STATEMENT
In line with duties under the equality legislation (Section 75 of the Northern Ireland Act 1998), Targeting Social Need Initiative, Disability discrimination and the Human Rights Act 1998, an initial screening exercise to ascertain if this policy should be subject to a full impact assessment has been carried out. The outcome of the Equality screening for this policy is:

Major impact ☐
Minor impact ☐
No impact. ☒