

Osteosarcoma

PI OS-1 Protocol

For The Treatment of Localized Osteosarcoma

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on behalf of the NCCN Pacific Island Working group

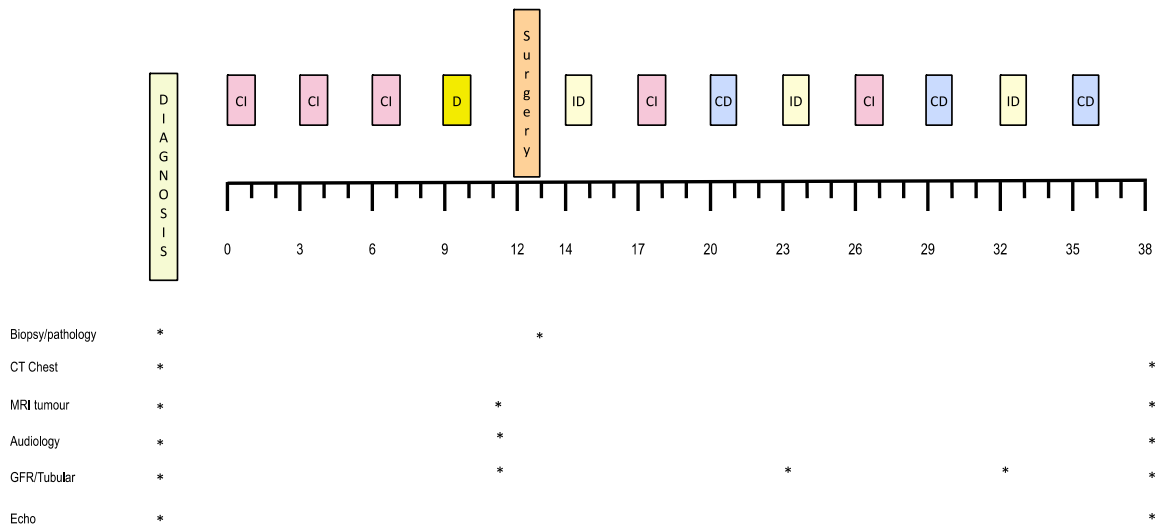
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TREATMENT SCHEMA

Pacific Osteosarcoma 1.0



1. Preoperative chemotherapy; CI on weeks 0, 3, and 6 and Dox on week 9

- **CI: Carboplatin and Ifosfamide; weeks 0, 3 and 6.**
 - Carboplatin (at 750mg/m² on Day 1) and
 - Ifosfamide (at 2.65 g/m² daily on Days 1–3) + mesna (see guideline)
- **D: Doxorubicin; week 9,**
 - Doxorubicin at 25 mg/m² daily for 3 days, Days 1-3.

2. Disease Evaluation; week 9 (see below)

3. Tumor resection; week 12 (see below)

4. Post-operative; ID: on weeks 14, 23 and 32; CI: on weeks 17, and 26, and CD: on weeks 20, 29 and 35.

- **ID: Ifosfamide and Doxorubicin, weeks 14, 23 and 32;**
 - Ifosfamide at a dose of 2.65 g/m², daily on Days 1–3), + mesna (see guideline)
 - Doxorubicin (at a dose of 25 mg/m² daily on Days 1 and 2)
- **CI: Carboplatin and Ifosfamide, weeks 17 and 26;**
 - Carboplatin (at a dose of 750mg/m² on Day 1) and
 - Ifosfamide (at a dose of 2.65 g/m² daily on Days 1–3) + mesna (see guideline)
- **CD: Carboplatin and Doxorubicin, weeks 20, 29 and 35;**
 - Carboplatin (at 750mg/m² on Day 1) and
 - Doxorubicin (at a dose of 25 mg/m² daily on Days 1 and 2)

BACKGROUND AND RATIONALE

Osteosarcoma is the most common primary bone malignancy diagnosed in children and young adolescents, even so it is still relatively rare with age-standardised incidence between 0-19 of approximately 5 per million per year. Over half of all cases occur in young people aged between 10- to-24 years old, where it accounts for >10% of all solid cancers. It is more common in males with a male: female ratio of 1.4.

The most frequent primary sites are the distal femur and proximal tibia, and while most patients have localised disease, approximately 15-20% of patients have clinically detectable metastases at the time of diagnosis.

The outcome for patients with osteosarcoma was poor before the use of effective chemotherapy, with 2-year overall survival in the range of 15-20% when treated with surgery alone. However, the administration of multi-agent chemotherapy has dramatically improved the outcome for these patients. Contemporary clinical trials for osteosarcoma now use preoperative multi-agent chemotherapy followed by aggressive surgical resection of the primary tumour and any accessible metastases, followed by post-operative continuation chemotherapy. With this approach, most current clinical trials in the “resource rich” setting report 3-year disease-free survival rates of 60-70%.

In the last decade it has been possible to assess the response of osteosarcoma to pre-operative chemotherapy via examination of the resected tumor specimen. Patients who achieve a good histological response to pre-operative chemotherapy, defined as < 10% viable tumor, have a better survival than those who have a poor response (\geq 10% viable tumor). Five-year survival for good responders is in the region of 75-80%, compared to 45-55% for poor responders.

The most active chemotherapeutic agents for osteosarcoma are cisplatin, doxorubicin and methotrexate. In recent years, ifosfamide, usually in combination with etoposide, has also shown activity in osteosarcoma. Although there is still no consensus on the optimum combination and duration of therapy, most recent clinical trials including the current EURAMOS international Osteosarcoma trial use a combination of high dose cisplatin, high dose methotrexate (HDMTX), ifosfamide and doxorubicin in pre-operative and post-operative chemotherapy.

While cisplatin and HDMTX are very effective, they cause significant toxicities and require treatment in highly specialized treatment centres. Treatment related toxicities include nephrotoxicity, ototoxicity, mucositis, hepatotoxicity, pulmonary toxicity, and neurotoxicity. In addition high dose methotrexate with leucovorin rescue requires the monitoring of methotrexate levels with specialised medical, nursing and laboratory support. This expertise is not available in many clinical settings such as the Pacific.

St Jude Osteosarcoma OS 99 Study. This PI Osteosarcoma treatment ‘protocol’ is based on the St Jude Children’s Research Hospital (OS 99) study, which was developed to overcome the complexity and toxicity of contemporary treatment strategies using a simplified approach to chemotherapy with the omission of cisplatin and high dose methotrexate.

In their OS 91 protocol St Jude evaluated the combination of carboplatin and ifosfamide given as

upfront window therapy, plus doxorubicin and HDMTX. Although single-agent carboplatin has shown very limited activity against previously untreated metastatic osteosarcoma, carboplatin combined with ifosfamide demonstrated substantial antitumor activity in the OS91 trial. This activity was not attributable to ifosfamide alone, because the rate of early disease progression was significantly lower than that noted with ifosfamide alone. For localized osteosarcoma, the OS91 trial yielded outcomes comparable to those of cisplatin-based regimens and caused less toxicity.

The OS 99 trial assessed the use of carboplatin, ifosfamide, and doxorubicin without HDMTX for the treatment of patients with localised, resectable osteosarcoma. In addition, because minimal resection of tumor-free bone may improve prosthesis fixation and help preserve growth potential in children, the OS99 trial also explored whether resection of the primary tumor with a 3-cm rather than a 5-cm (as used in the OS 91 trial) bone margin can be performed without increasing the rate of local disease recurrence.

Here we have adapted the St Jude OS 99 Osteosarcoma protocol for use in the pacific as a “Level 2” solid tumour treatment strategy. Recommended surgery and chemotherapy guidelines are given below.

CLINICAL FEATURES OF OSTEOSARCOMA

The majority of patients present with localized disease, arising in the long bones most commonly the metaphyses of the distal femur, the proximal tibia and the proximal humerus. Involvement of the axial skeleton or craniofacial bones is seen primarily in adults and is less common in children and young adults. Approximately 15-20% of patients have clinically detectable metastases at diagnosis; the majority of metastases are to the lungs but involvement of other bones can occur. Other metastatic sites such as the bone marrow are rare, but metastatic osteosarcoma has been reported in the kidney, adrenal, pleura, pericardium and brain.

Common symptoms at diagnosis are persistent and progressive bone pain localised to the knee region followed by the slow onset of localised swelling, limitation of movement and limp. Typical findings on plain X-rays reveal permeative destruction of normal bone trabeculae with new bone formation and lifting of the bone cortex forming a Codman’s triangle. As the tumour progresses from the medullary cavity and erodes through the bone cortex, a soft tissue mass will become evident in the adjacent tissues. This may be associated with ossification in the soft tissue producing the radial “sunburst” appearance on plain X-rays. However, none of the plain radiological features is pathognomonic as osteosarcoma may appear osteosclerotic, purely osteolytic, osteolytic or mixed.

Definitive diagnosis requires histological examination of tumour material, which is generally obtained by open biopsy, but trucut biopsy of an accessible soft tissue mass is appropriate.

PATHOLOGY

Conventional osteosarcoma, a high-grade malignancy, accounts for 80–90% of all osteosarcomas. Its most frequent subtypes are osteoblastic, chondroblastic, and fibroblastic. By definition, the malignant cell population must produce osteoid for a tumor to be classified as osteosarcoma. Other high-grade types are teleangiectatic, small cell osteosarcoma, and high-grade surface osteosarcoma. Low-grade central osteosarcoma and para-osteal osteosarcoma are low-grade malignancies, while periosteal osteosarcoma is an intermediate-grade chondroblastic osteosarcoma; these subtypes are all rare. Secondary osteosarcoma is a generally high-grade malignancy occurring in bone affected by pre-existing abnormalities, mainly radiation-therapy-induced changes.

The pathological diagnosis of osteosarcoma is morphological. There are no specific tumour markers and no specific genetic or molecular tests are needed for the diagnosis or are useful for prognostic stratification. Although several distinct histological subtypes of high grade osteosarcoma have been described, for the purposes of treatment, histological subtype (with a few exceptions) makes no difference and all high grade osteosarcomas are treated in the same way. However, where a tumour has had preoperative chemotherapy prior to its resection, an assessment of the extent of tumour necrosis in the resected specimen is of prognostic value.

DIAGNOSTIC STUDIES and ASSESSMENT AT DIAGNOSIS

Where a primary bone tumour is suspected, the approach to assessment is to determine the location and nature of the primary tumour, determine the presence or absence of any metastatic spread, and assess the any associated co-morbidities.

1. Primary tumour - imaging
 - Plain X-rays of the primary site; include full length of bones on both sides of any associated joint
 - MRI of primary tumour (if available) with gadolinium; include full length of bones on both sides of any associated joint
 - CT scan of primary, if MRI not available
2. Metastatic sites - imaging
 - CXR
 - CT scan of chest/thorax, with lung windows (see definition of lung metastases below)
 - Bone scan (if available but not essential)
 - Appropriate imaging must be repeated before surgery of the primary tumor or of known metastases.
3. Tumour Biopsy
 - The diagnosis of high-grade osteosarcoma must be verified histologically before initiation of chemotherapy. Open biopsy may be performed in order to obtain sufficient material for histological evaluation and ancillary studies. The biopsy specimen should be forwarded to the pathologist without prior fixation.

4. Organ Function and base line Investigations

- Full blood count
- Coagulation
- Blood Group
- Electrolytes and liver function, Ca, & PO₄
- Renal function including calculated GFR (see Appendix)
- Urine Cr
- Cardiac status – exclude previous rheumatic carditis. Cardiac Echo (if available)
- Hearing

5. General Health and Co-morbidities

- Assess general health, past medical history
- Height, weight
- Nutritional status
- Menstrual status and pregnancy test if possibly sexually active
- TB and HIV status
- Hepatitis A, B, C (if available)
- Chickenpox status

MRI: MRI is considered the most useful tool to evaluate an osteosarcoma's intramedullary and soft tissue extension and its relation to vessels and nerves. The region assessed by MRI should include the whole involved bone as well as the neighboring joints, so as to not miss skip lesions (intramedullary tumor foci without direct contact with the primary lesion).

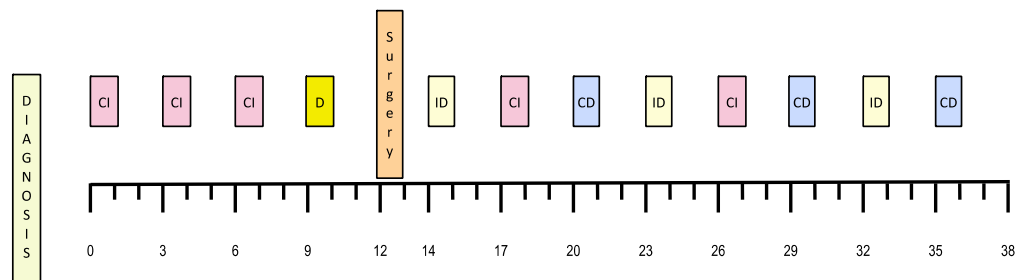
Lung Metastases – Definition: The minimum criteria determined by CT scanning are 3 or more lesions, which are ≥ 5 mm in maximum diameter or a single lesion ≥ 1 cm. These patients are classified as having “certain” pulmonary metastases. Where a scan shows a patient to have metastatic disease with fewer or smaller lesions, they are be classified as “possible” metastatic disease.

Pathology of Biopsy specimens: Biopsy sections should be review by a Pathologist with experience in bone tumours. Biopsies are classified as high-grade central or surface osteosarcomas in accordance with the WHO classification of Tumours Volume 5 (2002). Low-grade central, periosteal and para-osteal osteosarcomas are rare and should not be treated as high grade tumours. Biopsies are classified as conventional, telangiectatic, small cell or high grade surface osteosarcoma, secondary osteosarcoma or non-osteosarcoma. Conventional osteosarcomas will be divided into the following subtypes: osteoblastic, chondroblastic, fibroblastic, unusual type, or not specified. Unusual types of conventional osteosarcoma consist of one of the following: osteoblastic osteosarcoma - sclerosing type, osteosarcoma resembling osteoblastoma, chondromyxoid fibroma-like osteosarcoma, chondroblastoma-like osteosarcoma, clear-cell osteosarcoma, malignant fibrous histiocytoma-like osteosarcoma, giant cell rich osteosarcoma and epithelioid osteosarcoma.

TREATEMENT PLAN

1.0 CHEMOTHERAPY

Pacific Osteosarcoma 1.0



The protocol was comprised of 12 cycles of chemotherapy (1 cycle every 3 weeks over 35 weeks), 4 pre-operative and 8 post-operative cycles. Preoperative chemotherapy was comprised of 3 cycles of carboplatin (750mg/m² Day 1), and ifosfamide (at a dose of 2.65 g/m² daily on Days 1–3) and 1 cycle of doxorubicin (at a dose of 25 mg/ m² daily for 3 days).

Tumor resection at Week 12 was followed by 2 additional cycles of the combination of carboplatin and ifosfamide given as described above and 3 cycles each of ifosfamide (at a dose of 2.65 g/m² daily on Days 1–3) and doxorubicin (at a dose of 25 mg/m² daily on Days 1 and 2) and of carboplatin (750mg/m² Day 1), and doxorubicin (at a dose of 25 mg/m² daily on Days 1 and 2). For practical reasons, the Carboplatin dosage in this modified protocol is based on a standard surface area dosing, and not adjusted for AUC calculated by GRF.

As noted below, the timing of surgical resection is at week 12, but if needed could be brought forward or delayed so long as the pace of chemotherapy is not interrupted.

1. Preoperative chemotherapy; CI on weeks 0, 3, and 6 and Dox on week 9

CI: Carboplatin and Ifosfamide; weeks 0, 3 and 6.

Carboplatin (at 750mg/m² on Day 1) and
Ifosfamide (at 2.65 g/m² daily on Days 1–3) + mesna (see guideline)

Weeks 0, 3 and 6 CI

DAY	1	2	3	4	5
Carboplatin 750mg/m ²	↓				
Ifosfamide 2.65 g/m ²	↓	↓	↓		
Mesna 400 mg/m ²	↓↓↓	↓↓↓	↓↓↓		
Hyper hydration	*****	*****	*****		

D: Doxorubicin; week 9,

Doxorubicin at 25 mg/m² daily for 3 days, Days 1-3.

Week 9,

DAY	1	2	3	4	5
Doxorubicin at 25 mg/m ²	↓	↓	↓		

- 2. Disease Evaluation; week 9 (see below)
- 3. Tumor resection; week 12 (see below) – unless prior surgery
- 4. Post-operative; ID: on weeks 14, 23 and 32; CI: on weeks 17, and 26, and CD: on weeks 20, 29 and 35.

ID: Ifosfamide and Doxorubicin, weeks 14, 23 and 32;

Ifosfamide at a dose of 2.65 g/m², daily on Days 1–3), + mesna (see guideline) and

Doxorubicin (at a dose of 25 mg/m² daily on Days 1 and 2)

Weeks 14, 23 and 32

DAY	1	2	3	4	5
Doxorubicin 25 mg/m ²	↓	↓			
Ifosfamide 2.65 g/m ²	↓	↓	↓		
Mesna 400 mg/m ²	↓ ↓ ↓ ↓	↓ ↓ ↓ ↓	↓ ↓ ↓ ↓		
Hyper hydration	*****				

CI: Carboplatin and Ifosfamide, weeks 17 and 26;

Carboplatin (at a dose of 750mg/m² on Day 1) and

Ifosfamide (at a dose of 2.65 g/m² daily on Days 1–3) + mesna (see guideline)

Weeks 17 and 26

DAY	1	2	3	4	5
Carboplatin 750mg/m ²	↓				
Ifosfamide 2.65 g/m ²	↓	↓	↓		
Mesna 400 mg/m ²	↓ ↓ ↓ ↓	↓ ↓ ↓ ↓	↓ ↓ ↓ ↓		
Hyper hydration	*****				

CD: Carboplatin and Doxorubicin, weeks 20, 29 and 35;

Carboplatin (at $750\text{mg}/\text{m}^2$ on Day 1) and

Doxorubicin (at a dose of $25\text{ mg}/\text{m}^2$ daily on Days 1 and 2)

Weeks 20 and 29 and 35

DAY	1	2	3	4	5
Carboplatin $750\text{mg}/\text{m}^2$	↓				
Doxorubicin $25\text{ mg}/\text{m}^2$	↓	↓			

CHEMOTHERAPY ADMINISTRATION (See Appendix for details of chemotherapy drugs)

1. Carboplatin

- Dose $750\text{ mg}/\text{m}^2$ /dose: infuse in 250 ml of 5% Dextrose over 1 hour.
- Pre-administration, check Creatinine and calculate GFR prior to each cycle (see below)

2. Doxorubicin

- Dose $25\text{ mg}/\text{m}^2$ /dose: infuse in 100 ml Normal saline over 1 hour
- Check Cardiac LV function for % Fractional Shortening at diagnosis, at week 23, and end of treatment (see below)

3. Ifosfamide

- Dose $2.65\text{ g}/\text{m}^2$ /dose: infuse in Normal saline over 1 hour
- Pre-hydration; Dextrose Saline (D4S) + 30mmol/L of KCL, infuse at $125\text{ml}/\text{m}^2/\text{h}$ for 3 hours
- Post-hydration; Dextrose Saline (D4S) +30mmol/L of KCL, infuse at $125\text{ml}/\text{m}^2/\text{h}$ for 20 hrs following Day 1 of Carboplatin/Ifosfamide or Doxorubicin/Ifosfamide; and for continuous post-hydration at $125\text{ml}/\text{m}^2/\text{h}$ on Days 2 and 3 and for 23 hours after the Day 3 Ifosfamide.
- Mesna (as per WHO Expert committee guideline) to be given as chemoprotectant for Ifosfamide.
- On each day of Ifosfamide
 - -30 mins; Mesna $400\text{ mg}/\text{m}^2$ / iv over 15 minutes
 - +4 hrs: Mesna $400\text{ mg}/\text{m}^2$ / iv over 15 minutes
 - +8 hrs: Mesna $400\text{ mg}/\text{m}^2$ / iv over 15 minutes
 - +12 hrs: Mesna $400\text{ mg}/\text{m}^2$ / iv over 15 minutes

The total cumulative dose of doxorubicin is $375\text{ mg}/\text{m}^2$, and ifosfamide $63.6\text{ g}/\text{m}^2$

2.0 SURGERY

Curative treatment for high-grade osteosarcoma consists of surgery and chemotherapy. The goal of surgery is to safely remove the tumor and yet preserve as much function as possible. Most patients should be considered candidates for limb salvage. Surgical margins at least wide by Enneking's definition, implying complete removal of the tumor (including the biopsy tract) surrounded by an unviolated cuff of normal tissue, must be attempted, as narrower margins are associated with an increased risk of local recurrence. (Radiotherapy has a limited role and should be reserved for inoperable situations).

The surgical strategy in this protocol is based on current surgical approaches in the EURAMOS and OS 99 protocols, where definitive tumour resection is delayed until week 12 following completion of a 9-week course of induction chemotherapy. The histological assessment of the resected tumour can determine the degree of tumour necrosis, which may be of prognostic value, but for practical reasons there is no indication to modifying treatment based on pre-operative tumour response.

However, in Pacific countries a pragmatic approach to timing surgical intervention is appropriate. There may be clinical situations where a primary tumour resection or resection of the tumour by immediate limb amputation at the time of diagnosis may be a safe strategy, especially if there is any likelihood of delay in referral, or there issues with accessing timely surgery.

In cases where pre-operative chemotherapy is given, the timing of surgical resection of the primary tumour should be scheduled for week 12, however, the timing of surgery is not absolutely critical so bringing surgery forward or delaying if necessary maybe appropriate, so long as the pace of chemotherapy is maintained throughout the treatment.

3.0 ON TREATMENT RESPONSE EVALUATIONS:

Pre-surgical assessment, week 11

1. MRI: of primary site
2. X-ray primary tumour
3. Chest X-ray
4. CT scan Chest
5. Imaging of any symptomatic or metastatic sites.

Post-operative assessment

1. Chest X-ray 2 monthly
2. X-ray primary tumour site 4 monthly

4.0 END OF TREATMENT EVALUATION

After last cycle of chemotherapy

1. FBC and differential count
2. Blood chemistry (creatinine, urea, sodium, potassium, calcium, magnesium, phosphate,

- alkaline phosphatase, albumin, bicarbonate, liver transaminase, bilirubin)
3. Calculated glomerular filtration rate (GFR) either by estimation (see Appendix for suggested formulae)
 4. CT scan chest with lung windows
 5. MRI: of former primary site
 6. X-ray of former primary tumour
 7. Hearing assessment
 8. Cardiac Echo to determine fractional shortening
 9. Off treatment disease surveillance;
 - a. Year 1-2, Chest X-ray and X-Ray primary site 3 monthly
 - b. Year 3-5, Chest X-ray and X-Ray primary site 6 monthly

Follow-up intervals recommended in current multinational trials are every 3 months in years 1 and 2 after diagnosis, every 6 months in years 3, 4 and 5. Each visit should include a history and physical examination and a chest X-ray and X-rays of the primary tumor site. Late metastases may occur >10 years after diagnosis and there is no universally accepted stopping point for tumor surveillance. Multimodal therapy of osteosarcoma may be associated with permanent alterations of cardiac, renal, auditory and reproductive function, orthopedic problems and other late effects including secondary malignancies, and appropriate investigations should be included during regular follow-up as 60% to 70% of these patients survive with contemporary treatment regimens.

APPENDIX 1.0: CHEMOTHERAPY

CARBOPLATIN (Paraplatin®) NSC #241240 (092006)

Source and Pharmacology: The mechanism of action of carboplatin would appear to be similar to that of cisplatin. It binds to replicating DNA causing single strand breaks and interstrand cross-links with DNA. Data suggests that other factors also contribute to cytotoxicity. The α t_{1/2} is 1.1 to 2 hours and the β t_{1/2} is 2.6 to 5.9 hours. Carboplatin is not protein bound. The major route of elimination of carboplatin is renal excretion. Patients with creatinine clearances of approximately 60 mL/min or greater excrete 65% of the dose in the urine within 12 hours and 71% of the dose within 24 hours. In patients with creatinine clearances below 60 mL/min the total body and renal clearances of carboplatin decrease as the creatinine clearance decreases. Carboplatin dosages will require adjustment dependent on the glomerular filtration rate.

Toxicity:

	Common Happens to 21-100 out of every 100 children	Occasional Happens to 5-20 children out of every 100	Rare Happens to <5 children out of every 100
Immediate: Within 1-2 days of receiving drug	Nausea, vomiting	Hypersensitivity reactions ² (anaphylaxis, bronchospasm, hypotension), constipation, diarrhea	Metallic taste, rash, mucositis
Prompt: Within 2-3 weeks, prior to the next course	Myelosuppression ¹ (anemia, neutropenia, leukopenia, thrombocytopenia), Electrolyte abnormalities (↓ Na, K, Ca, Mg)	↑ LFT's (Alk Phos, AST), abdominal pain, nephrotoxicity (↓ GFR, ↑ Cr and BUN), asthenia	↑ bilirubin
Delayed: Any time later during therapy		ototoxicity (tinnitus, hearing loss)	Peripheral neuropathy with mild paresthesias, diminished sense of vibration, light touch, pinprick, and joint position, alopecia; temporary loss of vision to light and colors
Late: Any time after completion of treatment			Secondary leukemia
Unknown Frequency and Timing	Fetal toxicities and teratogenic effects of carboplatin have been noted in animals and may cause fetal harm when administered to pregnant women. It is unknown whether the drug is excreted in breast milk.		

¹ Thrombocytopenia is more severe or dose limiting.

² Hypersensitivity reactions are seen more frequently with repeated courses of therapy (after six courses in adults).

(L) Toxicity may also occur later.

Formulation and Stability: Carboplatin is available in 50mg, 150mg and 450 mg vials and 600mg vials.

Aqueous Solution: This solution is supplied as a sterile, pyrogen-free, 10 mg/mL aqueous solution of carboplatin in multidose vials.

Unopened vials of carboplatin solution are stable to the date indicated on the package when stored at 25° C (77° F); excursions permitted from 15°-30° C (59°-86° F). Protect from light. Carboplatin aqueous solution multidose vials maintain microbial, chemical, and physical stability for up to 14 days at 25° C following multiple needle entries.

Powder for Injection: Carboplatin is supplied as a sterile, white, lyophilized white powder in single dose vials containing equal parts by weight of carboplatin and mannitol. Unopened vials of carboplatin are stable to the date indicated on the package when stored at 15°-30° C (59°-86° F). Protect from light.

Guidelines for Administration: See Treatment of the protocol. I.V.: Reconstitute lyophilized powder to concentration of 10 mg/ml with sterile water for injection, 5% Dextrose, Normal Saline or use premixed 10mg/ml aqueous solution. May further dilute in dextrose or saline containing solutions

to a final concentration as low as 0.5mg/ml and infuse over 60 minutes. Carboplatin solutions, when prepared as directed are stable for 8 hours at room temperature. Aluminum can react with carboplatin, causing precipitate formation and potency loss. Do not use needles or IV administration sets containing aluminum parts that may come in contact with carboplatin for the preparation or administration of the drug.


Supplier: Commercially available from various manufacturers. See package insert for more detailed information.

DOXORUBICIN (Adriamycin®) NSC #123127 (03/25/08)

Source and Pharmacology: An anthracycline antibiotic isolated from cultures of *Streptomyces peucetius*. The cytotoxic effect of doxorubicin on malignant cells and its toxic effects on various organs are thought to be related to nucleotide base intercalation and cell membrane lipid binding activities of doxorubicin. Intercalation inhibits nucleotide replication and action of DNA and RNA polymerases. The interaction of doxorubicin with topoisomerase II to form DNA-cleavable complexes appears to be an important mechanism of doxorubicin cytotoxic activity. Doxorubicin cellular membrane binding may affect a variety of cellular functions. Enzymatic electron reduction of doxorubicin by a variety of oxidases, reductases and dehydrogenases generate highly reactive species including the hydroxyl free radical (OH•). Free radical formation has been implicated in doxorubicin cardiotoxicity by means of Cu (II) and Fe (III) reduction at the cellular level. Cells treated with doxorubicin have been shown to manifest the characteristic morphologic changes associated with apoptosis or programmed cell death. Doxorubicin-induced apoptosis may be an integral component of the cellular mechanism of action relating to therapeutic effects, toxicities, or both.

Doxorubicin serum decay pattern is multiphasic. The initial distributive t_{1/2} is approximately 5 minutes suggesting rapid tissue uptake of doxorubicin. The terminal t_{1/2} of 20 to 48 hours reflects a slow elimination from tissues. Steady-state distribution volumes exceed 20 to 30 L/kg and are indicative of extensive drug uptake into tissues. Plasma clearance is in the range of 8 to 20 mL/min/kg and is predominately by metabolism and biliary excretion. The P450 cytochromes which appear to be involved with doxorubicin metabolism are CYP2D6 and CYP3A4. Approximately 40% of the dose appears in the bile in 5 days, while only 5 to 12% of the drug and its metabolites appear in the urine during the same time period. Binding of doxorubicin and its major metabolite, doxorubicinol, to plasma proteins is about 74 to 76% and is independent of plasma concentration of doxorubicin.

Formulation and Stability: Doxorubicin is available as red-orange lyophilized powder for injection in 10 mg1, 20 mg1, 50 mg1, 150 mg2 vials and a preservative free 2 mg/mL solution in 10 mg1, 20 mg1, 50 mg1, 75 mg1, 200 mg2 vials.

1: Contains lactose monohydrate, 0.9 NS, HCl to adjust pH to 3. The Adriamycin RDF  (rapid dissolution formula) also contains methylparaben 1 mg per each 10 mg of doxorubicin to enhance dissolution.

2 Multiple dose vial contains lactose

Aqueous Solution: Store refrigerated 2° - 8°C, (36° - 46°F). Protect from light. Retain in carton until contents are used.

Powder for Injection: Store unconstituted vial at room temperature 15° - 30°C (59° - 86°F). Retain in carton until contents are used. Reconstitute with preservative-free normal saline to a final concentration of 2 mg/mL. After adding the diluent, the vial should be shaken and the contents

allowed to dissolve. The reconstituted solution is stable for 7 days at room temperature under normal room light (100 footcandles) and 15 days under refrigeration 2°- 8°C (36° -46°F). Protect from exposure to sunlight. Doxorubicin may be further diluted in 0.9%NaCl or dextrose containing solutions and administered by infusion.

Toxicity:

	Common Happens to 21-100 children out of every 100	Occasional Happens to 5-20 children out of every 100	Rare Happens to < 5 children out of every 100
Immediate: Within 1-2 days of receiving drug	Nausea, vomiting, pink or red color to urine, sweat, tears and saliva	Hyperuricemia, facial flushing, sclerosis of the vein	Diarrhea, anorexia, erythematous streaking of the vein (flare reaction), extravasation (rare) but if occurs = local ulceration, anaphylaxis, fever, chills, urticaria, acute arrhythmias
Prompt: Within 2-3 weeks, prior to the next course	Myelosuppression (leukopenia, thrombocytopenia, anemia), alopecia	Mucositis (stomatitis and esophagitis), hepatotoxicity	Radiation recall reactions, conjunctivitis and lacrimation
Delayed: Any time later during therapy		Cardiomyopathy ¹ (CHF occurs in 5-20% at cumulative doses ≥ 450 mg/m ²) (L)	Cardiomyopathy ¹ (CHF occurs in < 5% at cumulative doses ≤ 400 mg/m ²) (L), ulceration and necrosis of colon, hyper-pigmentation of nail bed and dermal crease, onycholysis
Late: Any time after completion of treatment	Subclinical cardiac dysfunction	CHF (on long term follow up in pediatric patients)	Secondary malignancy (in combination regimens)
Unknown Frequency and Timing:	Fetal and teratogenic toxicities. Carcinogenic and mutagenic effects of doxorubicin have been noted in animal models. Doxorubicin is excreted into breast milk in humans		

¹ Risk increases with cardiac irradiation, exposure at a young or advanced age.

(L) Toxicity may also occur later.

Guidelines for Administration: See Treatment sections of the protocol.

Administer IV thru

tubing of rapidly infusing solution of D5W or 0.9% NaCl preferably into a large vein .Protect the diluted solution from sunlight. To avoid extravasation, the use of a central line is suggested.

Supplier: Commercially available from various manufacturers. See package insert for further information.

IFOSFAMIDE (Isophosphamide, lphosphamide, Z4942, Ifex®) NSC #109724 (03/30/09)

Source and Pharmacology: Ifosfamide is a structural analogue of cyclophosphamide. Ifosfamide requires hepatic microsomal activation (P450 3A isoenzymes) for the production of the reactive 4-hydroxyoxazaphorine intermediate which serves as a carrier molecule for the ultimate intracellular liberation of acrolein and phosphoramidate mustard which is an active bifunctional alkylating species. Acrolein is thought to be the cause of the hemorrhagic cystitis as seen with cyclophosphamide. Ifosfamide demonstrates dose-dependent pharmacokinetics whereby the terminal half-life ranges from 7 to 16 hours at doses of 1.6-2.4 g/m² to 3.8-5 g/m², respectively. At 1.6 -

2.4 g/m²/d, 12 to 18% of the dose was excreted as unchanged drug in the urine, whereas at a 5 g/m² single- dose, 61% was excreted in the urine as the parent drug. Evidence also exists to suggest that ifosfamide metabolism is inducible, with more rapid clearance occurring in the second and later doses when a course of therapy is given as fractionated doses over 3 to 5 days. There is more chloroethyl side chain oxidation of ifosfamide (up to 50%) than of cyclophosphamide (< 10%), and the degree of such metabolism is more variable than with cyclophosphamide. Oxidation of the

chloroethyl groups produces chloroacetaldehyde, which is thought to be responsible for the neurotoxicity and renal toxicity that have been seen with ifosfamide therapy.

Toxicity

	Common Happens to 21-100 children out of every 100	Occasional Happens to 5-20 children out of every 100	Rare Happens to < 5 children out of every 100
Immediate: Within 1-2 days of receiving drug	Nausea & vomiting (acute and delayed)	CNS toxicity (somnolence, depressive psychosis and confusion)	Anorexia, diarrhea, constipation, encephalopathy which may progress to coma (L), seizure, SIADH, phlebitis, hypokalemia
Prompt: Within 2-3 weeks, prior to next course	Leukopenia, alopecia, immune suppression	Thrombocytopenia, anemia, cardiac toxicities (arrhythmia, asymptomatic ECG changes), microscopic hematuria, metabolic acidosis	↑ liver enzymes, ↑ bilirubin, hemorrhagic cystitis with macroscopic hematuria, dysuria, cystitis, and urinary frequency (<5% with mesna and vigorous hydration) (L), bladder fibrosis
Delayed: Any time later during therapy	Gonadal dysfunction : azoospermia or oligospermia (prolonged or permanent) ¹ (L)		Renal failure acute or chronic, renal tubular acidosis, Fanconi-like syndrome gonadal dysfunction, ovarian failure ¹ (L), CHF
Late: Any time after completion of treatment	Moderate nephrotoxicity (↓ in glomerular filtration rate, renal tubular threshold for phosphate, and serum bicarbonate)		Secondary malignancy, hypophosphatemic rickets
Unknown Frequency and Timing:	Fetal toxicities and teratogenic effects of ifosfamide have been noted in animals. Ifosfamide is excreted into breast milk.		

¹ Dependent on dose, age, gender and degree of pubertal development at time of treatment (L) Toxicity may also occur later.

Formulation and Stability: Available in 1 g and 3 g single dose vials of lyophilized white powder without preservatives. Reconstitute with sterile water for injection or bacteriostatic water for injection, 20ml for the 1gm vial or with 60mL for the 3gm vial to produce a final concentration of 50mg/ml ifosfamide. **Use sterile water for injection without benzyl alcohol for neonates and infants < 2 years of age or patients with hypersensitivity to benzyl alcohol.** Although the reconstituted product is stable for 7 days at room temperature and up to 6 weeks under refrigeration, the manufacturer recommends refrigeration and use within 24 hours to reduce the possibility of microbial contamination. Store unconstituted vials at room temperature 20°-25°C (68°-77° F). Protect from temperatures above 30°C (86° F). Ifosfamide may liquefy at temperatures > 35°C

Guidelines for Administration: See Treatment and Dose Modification sections of the protocol. Solutions of ifosfamide may be diluted further to concentrations of 0.6 to 20 mg/mL in dextrose or saline containing solutions. Such admixtures, when stored in large volume parenteral glass bottles, Viaflex bags or PAB bags, are physically and chemically stable for 1 week at 30°C (86°F) or 6 weeks

at 5°C (41°F). The manufacturer recommends refrigeration and use within 24 hours to reduce the possibility of microbial contamination. If available Mesna should always be administered in conjunction with ifosfamide. Adequate hydration is required. Achieve urine specific gravity ≤ 1.010 prior to start of ifosfamide.

Supplier: Commercially available from various manufacturers. See package insert for further information.

Dose/schedule

Ifosfamide give by iv infusion over 1 hr.

1. Prehydration: On Day 1 of Ifosfamide, commence Intravenous hydration Dextrose Saline (D4S) +30mmol/L of KCL, infuse at 125ml/m²/h for 4 hours (3 L/m²/24 hours).
2. Mesna: 400 mg/m²/dose commence 30 minutes before first dose of ifosfamide, then 400 mg/m²/dose at +4 hrs, + 8 hrs and + 12 hrs.
3. Posthydration; Following Ifosfamide hydration with Dextrose Saline (D4S) +30mmol/L of KCL, infuse at 125ml/m²/h for 23 hours (3 L/m²/24 hours).

Oral mesna may be substituted for part of the intravenous dose.

Ifosfamide neurotoxicity - the role of Methylene blue

Methylene Blue should be considered for all patients with Grade 2 neurocortical toxicity grading, and is indicated for patients with grade 3 and 4 toxicity.

Methylene blue is contraindicated in patients with

1. Glucose-6-phosphate dehydrogenase deficiency
 2. Pregnancy & Lactation
 3. Known sensitivity to the drug
 4. Severe renal impairment
- Mechanism of action** Whilst the exact mechanisms for Ifosfamide-induced encephalopathy are not known, various metabolic pathways have been suggested. Methylene blue may act by counteracting some of these pathways
- Drug Interactions** No significant drug
- Dose** Whilst there have been no studies to determine the best dose and scheduling for the treatment of Ifosfamide-induced encephalopathy with Methylene Blue, a review of the literature would suggest:

Treatment of Ifosfamide-induced encephalopathy:

Adults: 50 mg (5mL ampule of 1% solution) – 4 hourly

Pediatrics: 1 mg/kg/dose – 4 hourly Prophylaxis of Ifosfamide-induced encephalopathy:

Adults: 50 mg (5 mL ampoule of 1% solution) – 6 hourly **Pediatrics:** 1 mg/kg/dose – 6 hourly

Administration Either as a slow IV bolus – given over several minutes, or in 100 mL normal saline

over 15- 30 min. The methylene blue should be filtered before use using a 0.45 micron filter.

Methylene Blue Side Effects

Potentially life threatening effects: Occasionally: hypotension and cardiac arrhythmias

Symptomatic Adverse Effects

1. I.V. administration may cause abdominal pain, headache, dizziness, tremors, apprehension, confusion, chest pain, dyspnoea, tachycardia, and sweating – however, several of these symptoms are also symptoms of methaemoglobinaemia for which Methylene Blue is indicated.
2. Nausea, vomiting, diarrhea, and dysuria have been reported with oral administration
3. If MB is injected subcutaneously or extravasation occurs, necrotic abscesses may result
4. Blue discoloration of urine, stools and saliva. **Supplier** Ifosfamide is commercially available. See package insert for further information. Methylene Blue USP is available in the UK from Mayne as 5 mL ampoules or from Martindale as 10 mL ampoules containing 50 mg/mL (1% solution).

References Berardi R, Strauss S, Blake D, Whelan J

Mesna? A Case Control Study Proceedings ASCO 2000; abstract no: 2398 Watkin SM, Husband DJ, Green JA and Warenus HM (1989) Ifosfamide Encephalopathy: a Reappraisal. European Journal Cancer Clinical Oncology 25(9): 1303-1310 Cerny T, Castiglione M, Brunner K, Küpfer A, Martinelli G, and Lind M. (1990) Ifosfamide by continuous infusion to prevent encephalopathy. Lancet 335: 175 Pelgrims J, De Vos F, Van den Brande J, Schrijvers D, Prové A and Vermorken JB (2000) Methylene blue in the treatment and prevention of ifosfamide-induced encephalopathy: report of 12 cases and a review of the literature. British Journal of Cancer 82(2): 291-294

Is it safe to substi

MESNA Proposed (new/adapted) WHO Model Formulary

Information sourced from MIMS Australia Pty Ltd 2003 (<http://www.mims.com.au>)

Indications

Reduction and prevention of urinary tract toxicity (haemorrhagic cystitis) of oxazaphosphorines (see Adverse Reactions in the product information for cyclophosphamide and ifosfamide).

Contraindications

Precautions

oxazaphosphorines (i.e. ifosfamide or cyclophosphamide) not to their renal and other toxic effects. Additional prophylactic or accompanying measures recommended during treatment with oxazaphosphorines are thus not affected and should not be discontinued.

Severe allergic symptoms, such as systemic anaphylactic reactions, have occurred with mesna, especially in patients suffering from autoimmune diseases.

Due to the possibility of anaphylactoid reactions, it should be ensured that adequate emergency medication is available. Patients with autoimmune diseases who were treated with cyclophosphamide and mesna appeared to have a higher incidence of hypersensitivity reactions including skin and mucosal reactions of varying extent and severity (rash, itching, redness, vesiculation, Lyell syndrome, Stevens-Johnson syndrome), local tissue swelling (urticarial

Known hypersensitivity to the drug and

The protective effect of

oedema), conjunctivitis, rare cases of hypotension associated with circulatory reactions and increased pulse rate above 100 beats/minute (tachycardia), as well as increased respiration rate (tachypnoea) due to severe acute hypersensitivity (anaphylactoid) reactions, hypertension, ST segment elevation, myalgia and also a transient rise in certain liver function tests (e.g. transaminases). Protection of the urinary tract with mesna should therefore only be undertaken in such patients with autoimmune diseases, following careful risk/ benefit analysis and under medical supervision. Mesna does not prevent haemorrhagic cystitis in all patients. As a result, a morning specimen of urine should be examined for the presence of haematuria (microscopic evidence of red blood cells) and proteinuria, each day prior to oxazaphosphorine therapy. If haematuria develops when mesna is given with oxazaphosphorines according to the recommended dosage schedule, depending on the severity of the haematuria, dosage reduction or discontinuation of oxazaphosphorine therapy may be indicated. Urinary output should be maintained at 100 ml/hour (as required for oxazaphosphorine treatment). The urine should be monitored for haematuria and proteinuria throughout the treatment period.

Carcinogenesis, mutagenesis, impairment of fertility

No long-term animal studies have been performed to evaluate the carcinogenic potential of mesna.

Use in pregnancy

Teratology studies with oral doses of mesna given to rabbits at up to 1,000 mg/kg/day and to rats at up to 2,000 mg/kg/day have revealed no harm to the fetus. Animal studies of potential toxicity in a fertility and general reproductive screen and in a perinatal and postnatal screen have not been carried out. It is not known whether mesna can cause fetal harm when administered to a pregnant woman or affect reproductive capacity. Mesna should be given to a pregnant woman only if the benefits clearly outweigh any possible risks.

Use in lactation

It is not known whether mesna or dimesna are excreted in human milk. Because many drugs are excreted in human milk and because of the potential for adverse reactions in breastfed infants, a decision should be made whether to discontinue breastfeeding or discontinue the drug, taking into account the importance of the drug to the mother.

Adverse reactions

Infections and infestations: pharyngitis. *Blood and lymphatic system disorders:* thrombocytopenia (hypersensitivity). *Immune system disorders:* hypersensitivity reactions, anaphylactoid reactions. *Metabolism and nutrition disorders:* anorexia. *Nervous system disorders:* dizziness, somnolence, headache. *Eye disorders:* conjunctivitis. *Cardiac disorders:* ST segment elevation, tachycardia. *Vascular disorders:* flushing. Very rare: circulatory reactions, hypotension, hypertension. *Respiratory disorders:* coughing. Very rare: tachypnoea. *Gastrointestinal disorders:* nausea, vomiting, diarrhoea, constipation, colic, abdominal pain, flatulence. *Skin, mucosal and subcutaneous tissue disorders:* rash, itching, redness, vesiculation, Lyell syndrome, Stevens-Johnson syndrome, urticarial oedema, local tissue swelling. *Musculoskeletal and connective tissue disorders:* arthralgia, back pain. Very rare: myalgia, limb and joint pain.

General disorders and administration site conditions: fever, rigors, influenza-like reactions.

Injection site reactions: weakness, mucosal reactions, lack of energy, exhaustion. *Investigations:* decreased platelet count, increased respiration rate, rise in certain liver function tests, rise in transaminases.

Interactions

In vitro and in vivo animal tumour models have shown that mesna does not have any effect on the antitumour efficacy of concomitantly administered cytotoxic agents.

Laboratory tests: A false positive test for urinary ketones may arise in patients treated with mesna. In this test, a red violet colour develops which, with the addition of glacial acetic acid, will return to violet. Mesna may cause false positive or false negative reactions in the dipstick test for erythrocytes in urine. To exactly determine erythrocytes in the urine, urinary microscopy is recommended.

Dosage and administration (Intravenous)

Sufficient mesna must be given to protect the patient adequately from the urothelial toxic effects of the oxazaphosphorine. When calculating the dose of mesna, the quantity should be rounded up to the nearest whole ampoule.

15 to 30 minutes, usually at 20% of the respective oxazaphosphorine dose, at each of the times 0 (= administration of the cytostatic agent), four and eight hours. The total dose of mesna is 60% of the oxazaphosphorine dose and is repeated on each occasion that the cytotoxic agents are used.

Preparation: For intravenous administration the drug can be diluted by adding the contents of a mesna ampoule to any of the following fluids, obtaining final concentrations of mesna 1.5 to 3 mg/mL fluid: glucose injection 5%, sodium chloride injection 0.9%, sodium chloride and glucose injection (with concentrations ranging from 0 to 0.9% sodium chloride and 0 to 5% glucose), lactated Ringer's injection.

Solutions of mesna when diluted in the solutions nominated above may be prepared and, if necessary, stored for short periods under refrigeration. However, the diluted solutions do not contain an antimicrobial preservative, and in order to reduce microbial hazards it is recommended that dilution should be effected as soon as practicable prior to use, and infusion commenced as soon as practicable thereafter.

Infusion should be started within six to eight hours of preparation of the admixture and completed within 24 hours, with any residue discarded. Diluted solutions should be inspected visually before use.

Any solutions which are discoloured, hazy or contain visible particulate matter should not be used.

Compatibility and stability. In vitro, mesna is incompatible with cisplatin. The combination of an oxazaphosphorine cytostatic agent with mesna and cisplatin in the same infusion solution is not stable and is not to be used.

Ifosfamide (3 mg/mL) may be admixed with diluted mesna solutions 1.5 to 3.0 mg/mL (0.15 to 0.3%). The admixture, when diluted in sodium chloride injection 0.9%, compound sodium lactate injection, glucose injection 5% or glucose 2.5% plus sodium chloride 0.45% injection and packaged in PVC plastic bags, has been shown to be chemically and physically stable when refrigerated for 24 hours.

Admixtures are to be administered within six to eight hours of preparation due to the risk of microbial contamination.

Dosage and administration (Oral) Adults:

Intermittent oxazaphosphorine therapy. Oral mesna, 40% (w/w) of the oxazaphosphorine dose, should be given two hours prior to the oxazaphosphorine dose, and repeated at two and six hours after oxazaphosphorine administration. Alternatively, an initial intravenous dose of mesna, 20%

(w/w) of the oxazaphosphorine dose, can be given with the cytotoxic dose and additional oral mesna, 40% (w/w) of the oxazaphosphorine dose, given at two and six hours after the oxazaphosphorine. Following 24 hour infusion of ifosfamide and mesna. The first oral mesna dose of 40% (w/w) of the ifosfamide dose is given as the infusion is stopped, and the same dose is repeated after two and six hours. Higher doses of mesna can be given if urothelial toxicity occurs. *Elderly:* No specific information on the use of this product in the elderly is available. Clinical trials have included patients over 65 years and no adverse reactions specific to this age group have been reported.

Children: Due to increased micturition, children may require shorter intervals between doses and/or an increased number of individual doses.

High risk patients: Patients who have had previous irradiation of the small pelvis, occurrence of cystitis during previous cyclophosphamide or ifosfamide therapy or a history of urinary tract lesions may require shorter intervals between doses and/or an increased number of doses.

Overdosage

headache, fatigue, limb and joint pains, lack of energy (like exhaustion) and weakness, depression, irritability, rash, hypotension and tachycardia.

Overdose may lead to

APPENDIX 2.0 MEASURING RENAL FUNCTION

Measurement or calculation of Glomerular Filtration Rate (GFR): Carboplatin and Ifosfamide cause renal toxicity. Regular monitoring is essential to detect renal damage. Serum creatinine should be monitored prior to each cycle of chemotherapy. In addition, GFR should be assessed as specified within the protocol.

The optimal way to measure GFR is by measurement/EDTA clearance. However GFR can be estimated, as follows:

According to Schwartz's formula [179], creatinine clearance (C_{crea}) can be calculated from single serum samples

1. Schwartz, G.J., L.P. Brion, and A. Spitzer, *The use of plasma creatinine concentration for estimating glomerular filtration rate in infants, children, and adolescents*. *Pediatr Clin North Am*, 1987. **34(3)**: p. 571-90.
2. Cockcroft, D.W. and M.H. Gault, *Prediction of creatinine clearance from serum creatinine*. *Nephron*, 1976. **16(1)**: p. 31-41.
3. Rossi, R., et al., *Assessment of tubular reabsorption of sodium, glucose, phosphate and amino acids based on spot urine samples*. *Acta Paediatr*, 1994. **83(12)**: p. 1282- 6.

PI OS -1			PI OSTEOSARCOMA -1(MODIFIED ST JUDE OS-9) INDUCTION CHEMOTHERAPY: CI: WEEKS 0, 3, 6 (circle week)							Page 1 of 1	
Name Ward			NHI: DoB: Consultant:		Deliver to: Consultant approval given for nursing staff to initiate chemotherapy/...../..... signed _____		Date				
							Height - cm				
							Weight - kg				
							SA - m ²				
Bloods: WCC: N> 1.0, Plts > 100, Hb >80; Electrolytes, Cr and Ur in normal range					ADMINISTRATION						
Day	Date	Time (h)	Medication and dose	Dose	Route	Fluid	Rate	Dr sign	Given by	Check	Time
1		T = -4	Pre-hydration: D4S 1000mL + 30mmol KCL (125mL/m ² /hr for 4 hours)		IVI	<u>1000ml</u> D4S + 30mmol KCL	_____ml/h run rate at 125ml/m ² /h				
		T = -0.5	Mesna 400 mg/m ²		IVI	50 ml D4S + 30mmol KCL	Over 30 mins				
		T = 0	Carboplatin 750 mg/m ²		IVI	In 250mL D5 %	Over 1 hr				
		T = +1	Ifosfamide 2650 mg/m ²		IVI	In <u>100 ml</u> NaCL 0.9%	_____ml/h for 1h				
		T = +2	Post-hydration: D4S 1000mL + 30mmol KCL (125mL/m ² /hr for 22 hours)		IVI	<u>1000ml</u> D4S + 30mmol KCL	_____ml/h run rate at 125ml/m ² /h				
		T= + 4	Mesna 400 mg/m ²		IVI	50 ml D4S + 30mmol KCL	Over 30 mins				
		T = + 8	Mesna 400 mg/m ²		IVI	50 ml D4S + 30mmol KCL	Over 30 mins				
		T = +12	Mesna 400 mg/m ²		IVI	50 ml D4S + 30mmol KCL	Over 30 mins				
2		T= -0.5	Mesna 400 mg/m ²		IVI	50 ml D4S + 30mmol KCL	Over 30 mins				
		T= 0	Ifosfamide 2650 mg/m ²		IVI	In _____ml NaCL 0.9%	_____ml/h for 1h				
		T=+1	Post-hydration: D4S 1000mL + 30mmol KCL (125mL/m ² /hr for 23 hours)		IVI	In <u>1000ml</u> D4S + 30mmol KCL	_____ml/h run rate at 125ml/m ² /h				
		T= + 4	Mesna 400 mg/m ²		IVI	50 ml D4S + 30mmol KCL	Over 30 mins				
		T = + 8	Mesna 00 mg/m ²		IVI	50 ml D4S + 30mmol KCL	Over 30 mins				
		T = +12	Mesna 400 mg/m ²		IVI	50 ml D4S + 30mmol KCL	Over 30 mins				

PI OS -1				PI OSTEOSARCOMA -1 (MODIFIED ST JUDE OS99)								INDUCTION CHEMOTHERAPY: D: WEEK 9				Page 1			
Name NHI: Ward DoB: Consultant:				Deliver to: CHOC				Date											
								Height - cm											
				Consultant approval given for nursing staff to initiate chemotherapy/...../..... signed _____				Weight - kg											
								SA - m2											
Bloods: WCC: N> 1.0, Plts > 100, Hb >80; Electrolytes, Cr and Ur in normal range				ADMINISTRATION															
Day	Date	Time (h)	Medication and dose	Dose	Route	Fluid	Rate	Dr sign	Given by	Check	Time								
1		T=0	Doxorubicin 25 mg/m2		IVI	In 100mL Normal saline	Over 1 hour												
2		T= 0	Doxorubicin 25 mg/m2		IVI	In 100mL Normal saline	Over 1 hour												
3		T=0	Doxorubicin 25 mg/m2		IVI	In 100mL Normal saline	Over 1 hour												

PI OS-1			PI OSTEOSARCOMA-1 (MODIFIED ST JUDE OS 99) POST OPERATIVE CHEMOTHERAPY: DI: WEEKS 14, 23, 32 (circle week) Page 1 of 2									
Name Ward DoB: Consultant:			Deliver to: CHOC				Date					
			Consultant approval given for nursing staff to initiate chemotherapy/...../..... signed _____				Height - cm					
							Weight - kg					
							SA - m ²					
Bloods: WCC: N> 1.0, Plts > 100, Hb >80; Electrolytes, Cr and Ur in normal range			ADMINISTRATION									
Day	Date	Time (h)	Medication and dose	Dose	Route	Fluid	Rate	Dr sign	Given by	Check	Time	
1		T= -4	Pre-hydration: D4S 1000mL + 30mmol KCL (125mL/m ² /hr for 4 hours)		IVI	1000ml D4S + 30mmol KCL	_____ml/h run rate at 125ml/m ² /h					
		T = -0.5	Mesna 400 mg/m ²		IVI	50 ml D4S + 30mmol KCL	Over 30 mins					
		T = 0	Doxorubicin 25 mg/m ²		IVI	In 100 mL Normal Saline	Over 1 hr					
		T = +1	Ifosfamide 2650 mg/m ²		IVI	In 100 ml [#] NaCL 0.9%	_____ml/h for 1h					
		T = +2	Post-hydration: D4S 1000mL + 30mmol KCL (125mL/m ² /hr for 22 hours)		IVI	In 1000ml D4S + 30mmol KCL	_____ml/h run rate at 125ml/m ² /h					
		T = + 4	Mesna 400 mg/m ²		IVI	50 ml D4S + 30mmol KCL	Over 30 mins					
		T = + 8	Mesna 400 mg/m ²		IVI	50 ml D4S + 30mmol KCL	Over 30 mins					
		T = +12	Mesna 400 mg/m ²		IVI	50 ml D4S + 30mmol KCL	Over 30 mins					
2		T=0	Doxorubicin 25 mg/m ²		IVI	In 100mL Normal Saline	Over 1 hr					
		T= +1	Ifosfamide 2650 mg/m ²		IVI	In _____ml [#] NaCL 0.9%	_____ml/h for 1h					
		T=+2	Post-hydration: D4S 1000mL + 30mmol KCL (125mL/m ² /hr for 11 hours)		IVI	In 1000ml D4S + 30mmol KCL	_____ml/h run rate at 125ml/m ² /h					
		T = + 4	Mesna 400 mg/m ²		IVI	50 ml D4S + 30mmol KCL	Over 30 mins					
		T = + 8	Mesna 400 mg/m ²		IVI	50 ml D4S + 30mmol KCL	Over 30 mins					
		T = +12	Mesna 400 mg/m ²		IVI	50 ml D4S + 30mmol KCL	Over 30 mins					

PI OS-1			PI OSTEOSARCOMA -1 (MODIFIED ST JUDE OS 99) INDUCTION CHEMOTHERAPY: DI: WEEKS 14, 23, 32 (circle week) Page 2 of 2									
Name Ward DoB: NHI: Consultant:			Deliver to:				Date					
							Height - cm					
			Consultant approval given for nursing staff to initiate chemotherapy/...../..... signed _____				Weight - kg					
							SA - m ²					
			ADMINISTRATION									
Day	Date	Time (h)	Medication and dose	Dose	Route	Fluid	Rate	Dr sign	Given by	Check	Time	
3		T = -4	Pre-hydration: D4S 1000mL + 30mmol KCL (125mL/m ² /hr for 4 hours)		IVI	<u>1000ml</u> D4S + 30mmol KCL	_____ml/h run rate at 125ml/m ² /h					
		T = -0.5	Mesna 400 mg/m²		IVI	50 ml D4S + 30mmol KCL	Over 30 mins					
		T = 0	Ifosfamide 2650mg/m²		IVI	In 100 <u>ml</u> NaCL 0.9%	_____ml/h for 1h					
		T = +1	Post-hydration: D4S 1000mL + 30mmol KCL (125mL/m ² /hr for 23 hours)		IVI	In <u>1000ml</u> D4S + 30mmol KCL	_____ml/h run rate at 125ml/m ² /h					
		T = + 4	Mesna 400 mg/m²		IVI	50 ml D4S + 30mmol KCL	Over 30 mins					
		T = + 8	Mesna 400 mg/m²		IVI	50 ml D4S + 30mmol KCL	Over 30 mins					
		T = +12	Mesna 400 mg/m²		IVI	50 ml D4S + 30mmol KCL	Over 30 mins					

Fluid volume for Ifosfamide (<2000mg in 50mL NaCL, ≥ 2000mg - 4000mg in 100mL NaCL, ≥4000mg in 200mL NaCL)

Monitor fluid output, if <12ml/kg/4h, give 0.5mg/kg IV.

Dipstick all urines for haematuria: If >2+ haematuria, increase post hyper hydration rate by 25%.

If macroscopic haematuria develops, discontinue ifosfamide, maintain hyper hydration and contact consultant.

PI OS 1.0				PACIFIC OSTEOSARCOMA 1.0 (MODIFIED ST JUDE OS 99) POST-SURGERY CHEMOTHERAPY: CD: WEEKS 20, 29 and 35 (circle)								Page 1	
Name NHI: Ward DoB: Consultant:				Deliver to:			Date						
							Height - cm						
				Consultant approval given for nursing staff to initiate chemotherapy/...../..... signed _____			Weight - kg						
							SA - m ²						
<i>Bloods: WCC: N> 1.0, Plts > 100, Hb >80; Electrolytes, Cr and Ur in normal range</i>				ADMINISTRATION									
Day	Date	Time (h)	Medication and dose	Dose	Route	Fluid	Rate	Dr sign	Given by	Check	Time		
1		T=0	Carboplatin 750 mg/m²		IVI	In 250mL 5% Dextrose	Over 1 hour						
		T=+1	Doxorubicin 25 mg/m²		IVI	In 100mL Normal Saline	Over 1 hour						
2		T = 0	Doxorubicin 25 mg/m²		IVI	In 100mL Normal saline	Over 1 hour						

