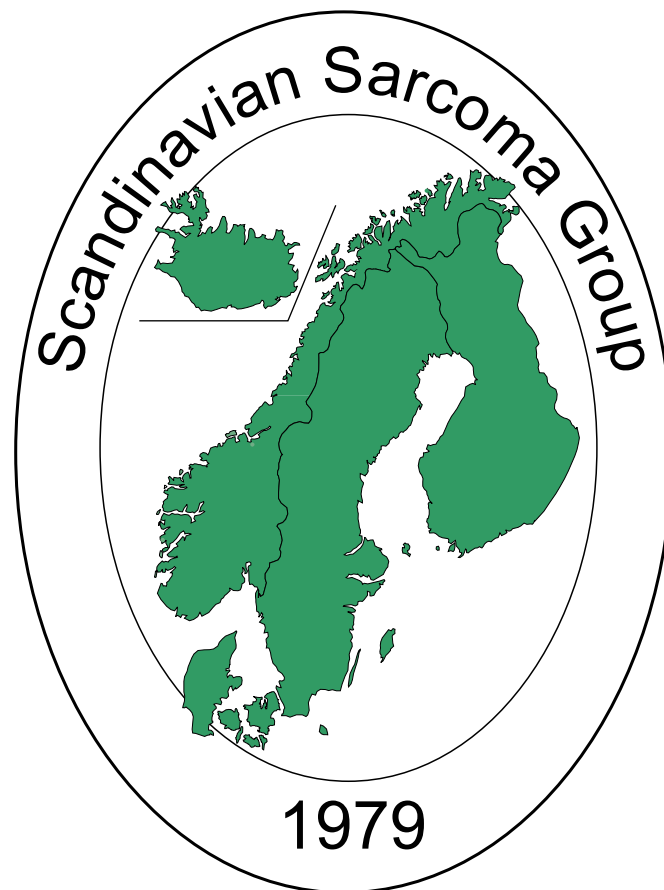


Scandinavian Sarcoma Group and  
Oncologic Center, Lund, Sweden

## SSG XIV

**A Scandinavian treatment research protocol  
for extremity localized high-grade osteosarcoma**



*Date of activation February 1, 2001*

## SSG XIV

### **A Scandinavian treatment and research protocol for extremity localized high-grade osteosarcoma**

Trial SSG XIV is a Scandinavian multicenter, prospective study exploring the efficacy of combination chemotherapy and surgery in patients with resectable, high grade osteosarcoma of the extremities. This non-randomized study is open to all specialized cancer centers that comprise the SSG network, and that fulfills all the protocol criteria and complies with the other requirements for inclusion in the study (see commitment form).

All patients with osteosarcoma treated according to this program must be reported to the Scandinavian Sarcoma Group secretariat.

This protocol is prepared by the Working Committee of the Scandinavian Sarcoma Group

### **Important modification of the SSG XIV protocol according to the osteosarcoma chemotherapy group, Oslo-meeting, June 1<sup>st</sup> 2001:**

Increase the fluid intake day 1 on high-dose methotrexate (p 17) from 1500 ml/m<sup>2</sup> to 2000 ml/m<sup>2</sup>.

Increase the volume and infusion time for the posthydration following cisplatin infusion from 500 ml/m<sup>2</sup> in 2 hours of basal solution (p 22) to 2000 ml/m<sup>2</sup> in 24 hours.

The doxorubicin-infusion is given as a 4 hours infusion simultaneously with cisplatin posthydration starting 2 hours after stop 48 hours cisplatin infusion.

*See also page 19.*

## Preface

The Scandinavian countries (Denmark, Finland, Iceland, Norway and Sweden) have total a population of about 25 million. They possess similar social structures, a modern medical service covering all inhabitants as well as an effective registration system for all cancer patients. This serves as a good basis for cooperation. Accordingly the Scandinavian Sarcoma Group was founded in 1979. The aim was to improve the prognosis for sarcoma patients within the Scandinavia. Its work has led to a systematic organization of sarcoma treatment, with guidelines for diagnosis, pathology, and treatment now generally accepted by all tumour centers in Scandinavia.

The first non-randomized neo-adjuvant chemotherapy trial for high-grade osteosarcoma localized to the extremities, SSG II, was based on the Rosen T-10 protocol and was carried out during 1982–1989. The second osteosarcoma trial (SSG VIII), using more aggressive preoperative combination chemotherapy, high-dose methotrexate, doxorubicin and cisplatin started in 1990 and was closed in 1997. The first joint Italian/Scandinavian study, ISG/SSG I, was activated in March 1997 and closed September 2000. The present SSG XIV protocol replaces the ISG/SSG I protocol. It is based on the SSG VIII protocol with some modifications based on the experience from the ISG/SSG I protocol and currently available literature.

A working committee consisting of four members has completed the present protocol. The following members have participated:

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Printing and distribution of the final protocol will be arranged by the Oncologic Center in Lund.

The SSG XIV protocol will be activated February 1, 2001.

Lund January 25, 2001

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### Research protocol

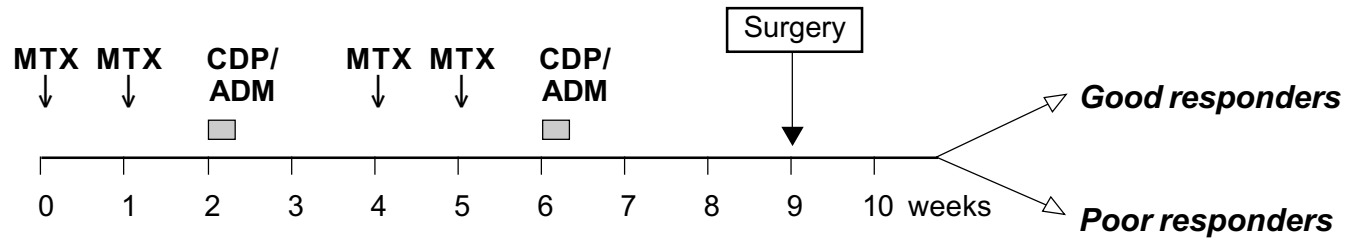
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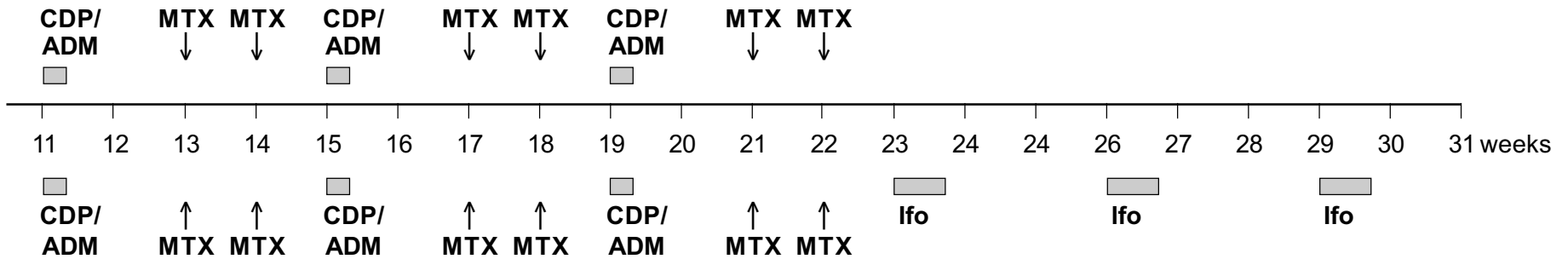
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1. Treatment schedule

Scandinavian osteosarcoma protocol, SSG XIV



Good responders



Poor responders

<b>MTX</b>	Methotrexate	12 000 mg/m <sup>2</sup>
<b>CDP</b>	Cisplatin	45 mg/m <sup>2</sup> /day × 2 days
<b>ADM</b>	Adriamycin	75 mg/m <sup>2</sup>
<b>Ifo</b>	Ifosfamide	2 000* mg/m <sup>2</sup> /day × 5 days

\* Increase dose by 20% if no grade IV neutropenia or thrombocytopenia followed previous Ifo-course

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### 2. Introduction

The use of aggressive combination chemotherapy has significantly improved the survival of patients with high-grade osteosarcoma (1–7), and simultaneously the frequency of limb salvage surgery has increased from 20% to 90% (8). A dose-response relationship for individual chemotherapeutic agents has been demonstrated (9–12), and maintaining a high dose intensity throughout the treatment seems of major importance for the outcome (13–15).

Histologic response to preoperative chemotherapy is generally agreed to be the most important prognostic factor in non-metastatic osteosarcoma (16–19). It is based on the assumption that the local treatment effect on the macrotumour reflects the effect on the micrometastases in the lungs. The information of histological tumour necrosis is used to modify chemotherapy for poor responders to improve outcome. However, the therapeutic benefit of this strategy is disputed and the only documented success so far is the Rizzoli experience from IOR-NEO 2 protocol. By adding ifosfamide and etoposide to the group of poor responders a similar outcome as for good responders was obtained (20). A pathological peer review of the SSG VIII material has demonstrated an unacceptable problem of reproducibility with a more than 20% change between the original and the revised pathological report (usually from good to poor responders). With the grading system for histological response used in the ISG/SSG I protocol, only 15% of the patients were classified as good responders (21), which is, to stratify post-operatively chemotherapy, an unsatisfactory low fraction of patients in a treatment group. The SSG pathology group has therefore for the current protocol made a new two-grade system for histological response. This is based on the previous used Huvos system with minor modification to make it more reproducible. With the experience from the pathological peer review a maximum of 70% of the patients treated according to the current SSG XIV protocol are expected to be poor responders.

The former Scandinavian SSG VIII protocol was based on a three-drug regimen preoperatively, methotrexate, doxorubicin and cisplatinum, with unchanged treatment for good responders and ifosfamide based therapy to poor responders postoperatively. The overall eight years survival of 68% is comparable to the best published results.

The recently terminated protocol, ISG/SSG I, was undertaken to explore the potential of highly aggressive chemotherapy. Maximal doses of all the known effective drugs, methotrexate, doxorubicin, cisplatinum and ifosfamide were given up-front to all patients. Preliminary data presented at the first joint Italian/Scandinavian meeting at Capri September 2000 demonstrated that the protocol gives no major advantages in terms of metastasis-free survival, but more toxicity than previous protocols. This probably reflects the relatively low protocol compliance, also compared to the ISG/SSG pilot study (21). The protocol was terminated in Italy and Scandinavia by September 2000.

The current protocol, SSG XIV, is based on the former SSG VIII protocol, with some distinct modifications. Based on the experience from the ISG/SSG I protocol a tailored use of methotrexate at dose 12–14 g/m<sup>2</sup> will be given to all patients. The data from the SSG VIII demonstrates that the VIG regimen (vepeside, ifosfamide and G-CSF support) is not an effective salvage therapy to poor responders with a 28% difference at eight years in event-free survival for good and poor responders. Moreover, for the patients with a changed revised pathology report of tumour necrosis (from good to poor responders) outcome is dependent of treatment (primary report) rather than necrosis (revised report). The conclusion is that the three-drug combination of methotrexate, doxorubicin and cisplatinum is effective and superior to the VIG regimen in this group of primary poor responders.



Based on the experience from the SSG VIII protocol and the published results from the Italian IOR-NEO 2 study, the study committee has decided to add three courses of dose-escalated ifosfamide as salvage therapy to the group of poor responders. The ifosfamide is a supplement to the three-drug regimen, and the courses are placed at the end of the chemotherapy to not interfere with the dose intensity of the other drugs.

### **3. Aims and general protocol design**

SSG XIV is a Phase II study for patients with high-grade osteosarcoma confined to the extremities. It is a multiagent chemotherapy protocol based on the previous SSG VIII protocol and experiences from the ISG/SSG I protocol and the currently available literature.

The principal aims of the study are to:

- 1.** Evaluate the histological tumour response, relapse-free survival and overall survival rates.
  - a.** Increase the percentage of good histologic responders from 30% to 50%.
  - b.** Increase the overall survival at 5 years from 68% to 80%.
  - c.** Increase the survival for poor responders to the level of good responders.
- 2.** Study long term toxicity and complications, particularly renal function, in view of the extensive use of potentially nephrotoxic agents (HDMTX, Ifosfamide, Cisplatinum).
- 3.** Monitor the relative importance of previously suggested prognostic factors (age, sex, tumour site, tumour volume, serum LDH and alkaline phosphatase, serum MTX) and potentially new (micrometastases detection). The purpose is to identify factors facilitating future differentiation to risk-adapted treatment.

## 4. Comments regarding the choice of agents and combinations

### High-doses of methotrexate (MTX)

The baseline dose is 12 000 mg/m<sup>2</sup>. The previous ISG/SSG I protocol was the first large scale multi-institutional study to prescribe an individually adjusted MTX dose based on serum measurements. This principle will be continued in SSG XIV. The dose of MTX will be increased if the serum concentration at 4 hours (measured just before the end of infusion) in the previous course was below 1 000 µmol/L.

### Cisplatinum (CDP) and doxorubicin (ADM)

Both agents are given as long term infusions to reduce nephrotoxicity and ototoxicity (cisplatinum) as well as cardiotoxicity (doxorubicin) in a similar manner as ISG/SSG I protocol. This is of particular importance since the patient group consists mainly of children and adolescents. The dose of cisplatinum in each course is the same as in the SSG VIII protocol (90 mg/m<sup>2</sup>/48 h). It is reduced from 120 mg/m<sup>2</sup>/48 h employed in the ISG/SSG I, aiming at the optimal dose intensity. Cisplatinum will be administered intravenously. The cumulative doxorubicin dose is 375 mg/m<sup>2</sup> for all patients (both good and poor responders).

### Postoperative Ifosfamide to poor responders

ISG/SSG I was the first prospective multi-centre study to include high-dose Ifosfamide in the preoperative treatment to all patients. The outcome for the patients maintaining an optimal dose intensity were excellent, but due to the overall poor protocol compliance the survival data of the ISG/SSG I study, is not better than previous protocols with less/without Ifosfamide. Based on the experience with the Rizzoli IOR-NEO 2 protocol three courses of dose-escalated Ifosfamide starting at a dose of 2 g/m<sup>2</sup> × 5 post-operatively will be given to the poor responders. The dose of Ifosfamide is escalated by 20% in the next course if no grade IV neutropenia ( $\leq 0,5 \times 10^9/L$ ) or thrombocytopenia ( $\leq 25 \times 10^9/L$ ) occurs. The Ifosfamide courses are placed at the end of the chemotherapy to avoid reduction in the dose intensities of the other drugs.

## 5. Organization

### The study secretariat is located in Sweden:

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## 6. Publication

The individual participating institutions are free to publish their own data. However, a main purpose is to publish the SSG patient materials together. In this process, the list of authors will be worked out in collaboration between the working committee and the SSG publication ombudsman.

## 7. SSG XIV “Resource Group”

In a multi-center study employing aggressive poly-agent chemotherapy as part of a multi-disciplinary treatment and multi-agent chemotherapy, unforeseen situations and complications that may not be sufficiently covered in the protocol are anticipated. In an attempt to minimize protocol violations and to ensure uniform handling of such situations, the SSG XIV working group has formed a “Resource Group”. Its task is to aid each treating physician solving these problems. Such problems include toxicity/safety in connection with HDMTX treatment, etc. In the event of a problem, the clinician should contact a member of the resource group from his own country who, in turn, will assist either directly or arrange a telephone conference with some or all members of the group. Chemotherapy problems should be solved within 24–48 hours, whereas surgical problems may require consultation with X-rays, etc. Written documentation regarding the problem’s nature and solution should be sent to the clinician in question, to all members of the resource group and should be included in the patient’s file at the study secretariat.

In the case of a *serious adverse event* (p. 26) the study secretariat will forward the incoming report from the responsible physician to all the appropriate members of the “Resource group”.

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## 8. Associated research projects

The SSG XIV study expects to recruit approximately 20 new patients per year. Within SSG the micrometastasis research project was started with the ISG/SSG I protocol. Sampling of peripheral blood and bone marrow to study micrometastasis will be continued in the SSG XIV protocol.

This research project is optional and not a prerequisite for participation in the clinical study. However, participating centers are encouraged to join the research project and, in order for their patients to be eligible for the clinical study, each participating institution must fill in the contract form (Appendix 1), stating whether or not it will join the associated project.

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## 9. Ethical considerations

1. SSG XIV is a non-randomized phase II study based on the experience from previous osteosarcoma protocols of the SSG and the experience from recent medical literature.
2. Before the start of treatment, the patients (and/or parents) will be informed about the nature of the disease, the treatment plan and the effects and side-effects, according to the standard procedures in each country.
3. The outcome and side effects of the treatment will be recorded and reported in the international literature.
4. The physician responsible for the individual patient may deviate from the protocol or may terminate treatment for various medical reasons on medical indications. The SSG provide a “Resource Group” of specialists to assist in such situations.

## 10. Criteriae for eligibility

1. Histologically proven extremity localized osteosarcoma of high-grade malignancy (grade III or IV).
2. The diagnosis must be made by open or coarse needle biopsy.
3. The tumour must arise in the marrow or at the bone surface.
4. Only patients with localized disease are eligible. The use of CT scan of the chest and total bone scan is mandatory to exclude metastases.
5. No previous treatment should have been given for osteosarcoma.
6. Age  $\leq 40$  years.
7. Normal hepatic and renal function.
8. White blood count  $\geq 3.0 \times 10^9/L$  and platelets  $\geq 100 \times 10^9/L$ .
9. Chemotherapy must be started within four weeks after the histological diagnosis.
10. Patient registration form must be accompanied by representative histology slides (for verification of diagnosis) and conventional anterior/posterior and lateral X-rays of the entire involved bone (for estimation of tumour volume).
11. A completed "Institution's commitment form" (Appendix) must be submitted to the secretariat for each individual patient.
12. The patient must be informed about the nature of the disease and the effects and side-effects of the treatment in accordance with the standard procedure in each country.

## 11. Criteriae for exclusion

1. Non-extremity localised osteosarcoma.
2. Metastatic disease.
3. Previous malignancy other than basal cell carcinoma of the skin and in situ/non-invasive carcinoma of the cervix.
4. Paraosteal osteosarcoma.
5. Secondary osteosarcoma (e.g. following Paget's disease or irradiation).
6. Medical contraindications to the cytostatic agents and dose levels in question.
7. Planned chemotherapy and/or follow-up not feasible.
8. Patient's refusal to participate in the treatment program.

## 12. Pretreatment investigations

### Mandatory requirements:

1. Complete medical history and physical examination (including date and nature of first symptoms and body height, weight and surface area).
2. Open surgical (preferable) or large core needle biopsy (representative slides should be sent to the study secretariat on registration).
3. Laboratory studies:
  - a. Complete blood count (Hb, white blood counts with differential, Trc).
  - b. Serum creatinine, GFR estimation using the methodology of the individual institution, ALP, LDH, total bilirubin, liver transaminases and cystatin C.
  - c. Serum Na, K, Mg and P.
  - d. Hepatitis serology A, B, C.
4. Radiological and scintigraphic studies:
  - a. A–P and lateral conventional X-rays of the entire involved bone (copies should be sent to the study secretariat on registration).
  - b. MRI of the entire involved bone and/or CT scan of the tumour area.
  - c. A–P and lateral chest X-rays.
  - d. CT scan of the chest with contiguous slices and maximum thickness of 8 mm.
  - e. Total bone scan, preferably with a dynamic study of the primary tumour area.
5. Audiogram before first course of cisplatin treatment.
6. Electrocardiogram (ECG).
7. Estimation of left ventricular ejection fraction (LVEF) with cardiac ultrasound or radionuclide ventriculography (MUGA) before first course of doxorubicin treatment.

### Recommended investigations (optional):

8. Sperm count is recommended in all patients where it is feasible. Furthermore, these patients should be offered an option of sperm banking prior to chemotherapy.

## 13. Reevaluation before surgery (week 8)

### Mandatory investigations:

1. Complete physical examination.
2. Laboratory studies:
  - a. Complete blood count (Hb, white blood counts with differential count, Trc).
  - b. Serum creatinine, GFR estimation, ALP, LDH, total bilirubin, liver transaminases and cystatin C.
  - c. Serum Na, K, Mg and P.
3. Radiological studies:
  - a. A–P and lateral conventional X-rays of the entire involved bone.
  - b. MRI of the entire involved bone and/or CT scan of the tumour area.
  - c. A–P and lateral chest X-rays.
4. Electrocardiogram.

### Recommended investigations (optional):

5. CT scan of the chest.
6. Total bone scan, preferably with dynamic study of the primary tumour area.

## 14. Investigations at the end of treatment

Mandatory investigations:

1. Complete physical examination.
2. Laboratory studies:
  - a. Complete blood count (Hb, white blood counts with differential, Trc).
  - b. Serum creatinine, GFR estimation, ALP, LDH, total bilirubin, liver transaminases and cystatin C.
  - c. Serum Na, K, Mg and P.
3. A–P and lateral chest X-rays.
4. Estimation of left ventricular ejection fraction (LVEF) with cardiac ultrasound or radionuclide ventriculography (MUGA).
5. Audiogram.
6. Hepatitis serology A, B, C.

**Recommended investigations (optional):**

7. CT scan of the chest.
8. Sperm count in patients with sufficient sexual maturation.

## 15. Follow-up after end of treatment

Patients should be followed at 3 months intervals for 3 years, at 4 months intervals during the 4th and 5th years, and then at yearly intervals until 10 years after treatment was completed.

Mandatory investigations at follow-up:

1. Complete physical examination.
2. A–P and lateral chest X-rays at each visit. The CT scan of the chest is optional as routine, but it must always be done if chest X-ray shows metastasis or is inconclusive.
3. Blood count (Hb, white blood counts, Trc), transaminases, ALP, LDH, serum creatinine, Na, K, Mg, P and cystatin C at each visit.
4. GFR estimation at 3 months, 6 months, at 6 month intervals during the second and third years, and then yearly.
5. Estimation of left ventricular ejection fraction (LVEF) with cardiac ultrasound or radionuclide ventriculography (MUGA) at 6 months 12 months and then at 3 years intervals.
6. Audiogram one year after the completion of therapy.
7. Bone scan and plain X-rays on clinical suspicion of bone metastases; if inconclusive supplement with MRI and CT.

**Recommended investigations (optional):**

8. Sperm count 3 years after the end of treatment in patients with sufficient sexual maturation.

## 16. Chemotherapy administration

**NOTE:** All infusion volumes are specified per m<sup>2</sup> of body surface area to facilitate correct adjustments for each individual patient.

### 16.1 General considerations

**Bone marrow function:** CDP/ADM and Ifo courses are started if neutrophil count is  $\geq 1.0 \times 10^9/L$  and platelet count is  $\geq 100 \times 10^9/L$ . MTX courses are started if neutrophil count is  $\geq 0,5 \times 10^9/L$  and platelet count is  $\geq 60 \times 10^9/L$ .

**Renal function:** Serum creatinine must be measured before each course of MTX, Ifo and CDP, and must be within normal range (if in doubt, measure GFR). In general, with a normal estimation of GFR, chemotherapy should be given with no reduction in dose, even with a previous history of nephrotoxicity to the prescribed drug. GFR is measured before start of treatment, before surgery, and at the end of treatment. GFR is measured by Cr-EDTA, Iohexol clearance, or equivalent methods.

### 16.2 Guidelines for G-CSF

G-CSF support will be used according to the ASCO recommendation (24). G-CSF should be added in the next course if there is a delay in starting chemotherapy because of prolonged neutropenia or neutropenic fever (temp.  $>38.5$  °C and a nadir in the white blood counts  $<1.0 \times 10^9/L$ ). G-CSF is not necessary after chemotherapy with MTX.

G-CSF is administered as a subcutaneous injection or i.v. infusion once daily. The dose is 5 µg/kg.

Administration of G-CSF should be started 48–72 hours after termination of chemotherapy and 7–8 daily doses are recommended. G-CSF must be discontinued at least 24 hours before starting the next course of chemotherapy and it should be stopped when the total white blood count exceeds  $5.0 \times 10^9/L$ .

*SSG institutions are obliged to use filgrastim.*

### 16.3 High-doses of methotrexate

MTX is started day 1 week 0, 1, 4, 5, 13, 14, 17, 18, 21, 22

**Drug interactions:** Avoid simultaneous use of the following drugs because of the risk of interactions: penicillin, NSAID probenecid, sulfamethoxazole trimethoprim and salicylic acid.

1. **Blood check:** Before starting MTX infusion: GFR (according to p. 14, 15), hemoglobin, white blood counts, neutrophil count, platelets, albumin, liver enzymes and total bilirubin, Na, K. After starting the MTX infusion and until the serum MTX is  $<0.2$  µmol/L, the following blood tests should be done daily: GOT, GPT (= ASAT, ALAT), Na, K, S-creatinine.
2. **Prealkalinization and prehydration:** Use the following solution i.v.: 250 ml/m<sup>2</sup> glucose 5% with 100 mmol NaHCO<sub>3</sub>/L and 20 mmol KCL/L over a period of 30 minutes.
3. **Dose of methotrexate:** 12 000 mg/m<sup>2</sup>, increase by 2 000 mg/m<sup>2</sup> if four (4) hour methotrexate concentration was  $<1$  000 µmol/L in the previous course.
4. **Methotrexate** should be dissolved in 500 ml/m<sup>2</sup> of NaCl 0.9% with 40 mmol NaHCO<sub>3</sub>/L and 20 mmol KCl/L. This methotrexate solution is infused over 4 (four) hours.



**5. Total fluid input/day until serum MTX concentration  $<0.2 \mu\text{mol/L}$**

( $T_0 - T_{24}$ ): 1 500 ml/m<sup>2</sup> (including prealkalinization, methotrexate infusion and oral fluids)

( $T_{24} - T_{48}$ ): 2 000 ml/m<sup>2</sup>

( $T_{48} - T_{72}$ ): 2 000 ml/m<sup>2</sup>

( $T_{72} - T_{96}$ ): 2 000 ml/m<sup>2</sup>

For all i.v. fluid in the posthydration, use 5% glucose with 40 mmol NaHCO<sub>3</sub>/L + 20 mmol KCl/L.

**6. From  $T_{24}$ , the patient should receive at least 1 500 ml/m<sup>2</sup>/24 hours as i.v. fluid to keep the urine alkaline.**

**7. Leucovorin (folinic acid) rescue:** 8 mg/m<sup>2</sup> intravenously or orally every 6<sup>th</sup> hour, beginning 24 hours after starting the methotrexate infusion. Normally, leucovorin is given by eleven (11) doses until  $T_{84}$ . It is sufficient to give leucovorin until six (6) hours after the methotrexate concentration has fallen below 0.2  $\mu\text{mol/L}$ .

**8. Determinations of serum methotrexate levels:** Capillary or venous blood (not taken from the vein used for the methotrexate infusion). Blood samples for methotrexate concentrations should be taken just *before* the end of the methotrexate infusion ( $T_4$  sample), and then at least at  $T_{24}$  and every 24th hour until serum MTX is  $<0.2 \mu\text{mol/L}$ .

**9. Diuresis:** Give furosemide 0.5–1.0 mg/kg if diuresis  $<300 \text{ ml/m}^2$  in 6 hours the first 24 hours and  $<400 \text{ ml/m}^2$  in 6 hours during the following 24 hour periods. The maximum dose of furosemide is 20 mg. If the total fluid volume is increased to 3 000 ml/m<sup>2</sup>/24 hours because of delayed MTX excretion, the minimum level of diuresis should be increased to 600 ml/m<sup>2</sup> in 6 hours.

**10. Additional alkalinization:** If the urine pH is  $<7$  give 2 mmol NaHCO<sub>3</sub>/kg during 30 minutes.

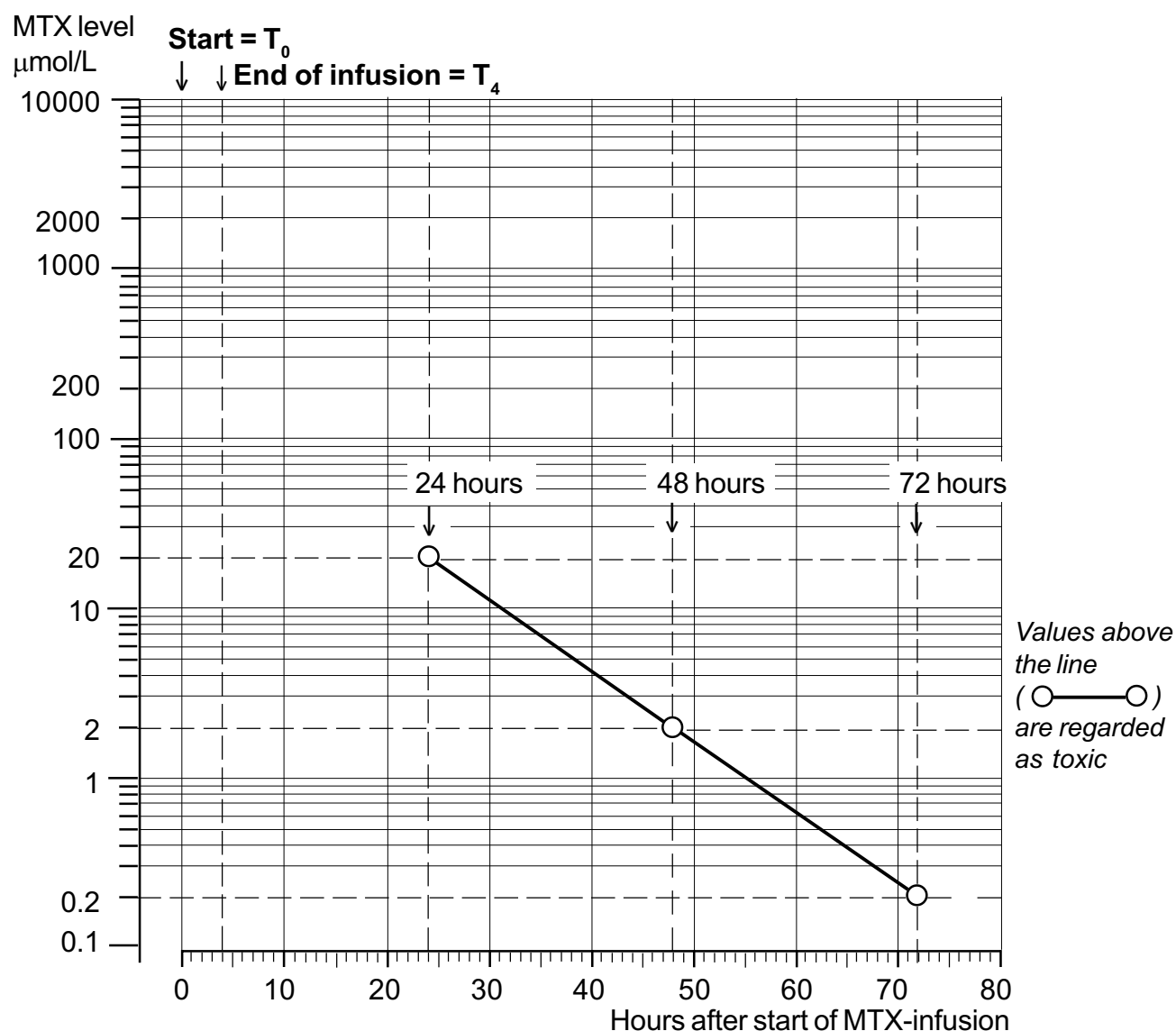
**11. Monitoring MTX and fluid volume:** All serum MTX values, i.v. and oral fluids, diuresis, urinary pH, supplemental NaHCO<sub>3</sub> and furosemide should be listed on a detailed chart to ensure accurate monitoring of MTX clearance and fluid balance.

## 16.4 Management of MTX toxicity and delayed MTX excretion

### General considerations

Prompt intervention will prevent severe toxicity. Severe toxicity is anticipated if there is a greater than 100% rise in the serum creatinine level 24 hours within after start of the methotrexate infusion and/or the serum methotrexate levels are in the “toxicity range“ on the MTX excretion curve (see below). Patients in this situation should be treated by continued hydration and alkalinization of the urine with 3 000 ml/m<sup>2</sup>/24 h of 5% glucose with 40 mmol NaHCO<sub>3</sub>/L and 20 mmol KCl/L. In this case, the minimum diuresis should be increased to 600 ml/m<sup>2</sup>/6h. Increase the dose of leucovorin as described below. The administration of potassium should be carefully monitored, depending on renal function. Body weight, fluid input and output and blood pressure should be monitored. Blood counts, serum creatinine, liver transaminases, ALP, bilirubin and serum methotrexate levels should be measured daily. If increased serum-creatinine, kidney function should be evaluated with GFR. Records should be kept of the clinical course. Always ensure that the patient is not taking other medications which interfere with methotrexate binding or excretion. If stomatitis and myelosuppression are severe enough to delay subsequent chemotherapy courses, then rescue should be continued for one additional day in subsequent MTX courses, i.e. 5 additional doses of leucovorin after the serum MTX is <0.2 µm.

### Methotrexate excretion curve



### Adjustment of leucovorin dose during delayed methotrexate excretion

$$\text{Total daily dose of leucovorin (mg)} = \frac{\text{Patient's actual serum MTX} \times \text{standard daily dose of leucovorin}}{\text{Upper limit of serum MTX for the actual day and time}}$$

The upper limit of decline in serum MTX levels as a function of time is shown in the MTX excretion curve, p. 18.

The upper limit of serum MTX	at 24 hours is	20 $\mu\text{m}$
	at 48 hours is	2 $\mu\text{m}$
	at 72 hours is	0.2 $\mu\text{m}$

*Example:*

If the 48 hour methotrexate level was 40  $\mu\text{m}$ , the leucovorin dose should be adjusted to:

$$\frac{32 \text{ mg/m}^2 \times 40}{2} = 640 \text{ mg/m}^2/24 \text{ hours by continuous i.v. infusion}$$

It is possible to reduce the dose of leucovorin on the following days in relation to the reduction in S-MTX.

When the S-MTX level is in the range of 0.9 – 0.2  $\mu\text{m}$ , give leucovorin in doses of 8  $\text{mg/m}^2$  orally every 6 hours until one dose after the serum level is <0.2  $\mu\text{m}$ .

**Note:** Always continue to monitor urine pH and give more  $\text{NaHCO}_3$  if  $\text{pH} < 7$ .

## MANAGEMENT OF METHOTREXATE-TOXOCITY

(Jon Helgestad, Bergen)

As supplement to the guidelines in the protocol the following points, during the working committee of the SSG meeting, Oslo, June 2001, were emphasised.

### Before start HDMTX the following criteria must be fulfilled

#### *Liver function*

The liver enzymes GOT, GPT (=ASAT, ALAT) should not be > 10 times highest normal level before start of HDMTX.

#### *Mucositis*

No clinical sign of mucositis is accepted before start HDMTX.

As outlined in the protocol, previous slow methotrexate excretion and/or transient nephrotoxicity is no reason to withheld further methotrexate therapy. There is a substantial variation of methotrexate excretion also for individual patients and methotrexate nephrotoxicity is only rarely permanent. With restoration of kidney function (normal GFR) HDMTX should be given in full doses as scheduled.

With severe nephrotoxicity/delayed excretion one may consider megadoses (1  $\text{g/m}^2/\text{day}$ ) of leucovorin as a continuous infusion. Hemodialysis is occasionally necessary to treat acute kidney failure, but does not eliminate MTX faster. In terms of acute life-threatening toxicity (kidney, CNS) the biological effect of MTX can be stopped immediately with Carboxypeptidase. It was previously available through participation in a toxicity study coordinated by Prof Uno Bode in Bonn. Due to problems with drug delivery the trials is currently closed.

**16.5**  
**Osteosarcoma SSG XIV**  
**Order sheet**  
**Methotrexate (MTX)**

Name (first & family name)  
 Date of birth (day, month, year)

At ordering see the SSG XIV protocol.  
**Fill in this order sheet completely!**

Upon participation in the research project; Fill in *sampling protocols* and *fluid lists!*

Weight: ..... kg Length: ..... cm Body surface area: ..... m<sup>2</sup>

Date for start of this Methotrexate course, day ..... month ..... year .....

**1. Prealcalinisation**

This patient shall have i.v. infusion: ..... ml glucose 5% with 100 mmol NaHCO<sub>3</sub>/litre and 20 mmol KCl/litre during 30 min.

Start of prealcalinisation T - 0.5: hour ..... min ..... Nurse sign. ....

End of prealcalinisation T0: hour ..... min ..... Nurse sign. ....

**2. Methotrexate**

This patient shall have i.v. infusion: ..... mg Methotrexate dissolved in ..... ml NaCl 0.9 % with 40 mmol NaHCO<sub>3</sub>/litre and 20 mmol KCl/litre during 4 hours.

Start of Methotrexate T0: hour ..... min ..... Nurse sign. ....

End of Methotrexate T4: hour ..... min ..... Nurse sign. ....

**3. Posthydration**

Glucose 5% with 40 mmol NaHCO<sub>3</sub>/litre + 20 mmol KCl/litre as i.v. infusion

	Start	Sign.	End	Sign.
From T4 until T24 infuse ..... ml	..... day hour min	.....	..... hour min	.....
From T24 until T48 infuse ..... ml	..... day hour min	.....	..... hour min	.....
From T48 until T72 infuse ..... ml	..... day hour min	.....	..... hour min	.....
From T72 until T96 infuse ..... ml	..... day hour min	.....	..... hour min	.....

*If posthydration is changed, document and sign in a special list.*

**4. Antidote.** This patients  oral/  i. v. leucovorin dose: ..... mg/dose.

Leucovorin dose changed to ..... mg/dose. Date ..... Time .....

The leucovorin dose is documented and signed on the opposite side of this order sheet.

Leucovorin is given every sixth (6:th) hour from T24 until T84. 11 doses of Leucovorin are usually given. Alternatively until 6 hours after S-MTX <0,2 µmol/litre.

**5. Methotrexate concentration measurements**

S-MTX is monitored at T4 (*just before end of infusion*), and at least T24 and every 24th hour thereafter until the S-MTX <0,2 µmol/liter.

The concentration is monitored on the opposite page. Attending physician must follow the MTX elimination. By delayed elimination the protocol, for change of hydration and leucovorin dose, must be followed.

**6. Diuresis and extra alcalinisation**

If diuresis < ..... ml/6 hours give ..... mg Furosemide.

If urine-pH <7 ..... mmol NaHCO<sub>3</sub> shall be administered during 30 minutes.

Furosemide and extra NaHCO<sub>3</sub> is documented and signed on the opposite page.

Attending physician responsible for this order, *signature*: .....

Contra signature of this order, *signature*: .....

Order sheet, Methotrexate (cont')

Hour	Time day/hour/min	MTX-conc. µmol/L	Leocovorin dose, mg Nurse sign	Furosemide dose / time Nurse sign	Extra. NaHCO <sub>3</sub> mmol / time Nurse sign
T 4	/ /	*	<del>                    </del>	/	/
T 18	/ /		<del>                    </del>	/	/
T 24	/ /	*		/	/
T 30	/ /			/	/
T 36	/ /			/	/
T 42	/ /			/	/
T 48	/ /	*		/	/
T 54	/ /			/	/
T 60	/ /			/	/
T 66	/ /			/	/
T 72	/ /	*		/	/
T 78	/ /			/	/
T 84	/ /			/	/

\*Mandatory

## 16.6 Cisplatinum (CDP/ADM)

### General considerations

CDP(cisplatinum) is administered only in combination with doxorubicin (CDP/ADM). CDP is started day 1 weeks 2, 6, 11, 15, 19.

Drug interactions: Aminoglycosides may augment the nephrotoxicity of cisplatinum.

*Blood check-ups* before starting cisplatinum: Hemoglobin, white blood counts, neutrophil counts, platelets, albumin, liver enzymes including bilirubin, creatinine, Mg, Ca, Na K, P and cys C.

On second day of cisplatinum infusion: GOT, GPT (=ASAT, ALAT), creatinine, Mg, Ca, Na, K and P.

### Basal solution for infusion of cisplatinum:

0.9% NaCl with 20 mmol KCl/L and 1.5 mmol Mg/L.

- a. *Prehydration*: 500 ml/m<sup>2</sup> of basal solution for 2 hours.
- b. *Cisplatinum dose*: 45 mg/m<sup>2</sup>/day is administered in 2 000 ml/m<sup>2</sup>/day of basal solution as a continuous infusion for 2 days (48 hours).

**NOTE:** CaCl<sub>2</sub> must *not* be infused together with cisplatinum in the same infusion line because it causes the formation of stable CaSO<sub>4</sub> complexes of that block the catheter.

- c. *Posthydration*: 500 ml/m<sup>2</sup> of basal solution should be given over a 2 hours period.
- d. *Diuresis*: If <400 ml/m<sup>2</sup> in 6 hours, give furosemide 0.5 – 1.0 mg/kg. The maximum dose of furosemide is 20 mg.

## 16.7 Doxorubicin (CDP/ADM)

Doxorubicin (ADM) is administered only in combination with cisplatinum (CDP/ADM). ADM is started day 3 immediately following the cisplatinum posthydration, at weeks 2, 6, 11, 15, 19.

Doxorubicin (ADM) 75 mg/m<sup>2</sup> (CDP/ADM) is given as a 4 hours continuous infusion in 1 000 ml 5% glucose.

**16.8**  
**Osteosarcoma SSG XIV**  
**Order sheet**  
**Cisplatin and Doxorubicin (CDP/ADM)**

Name (first & family name)  
 Date of birth (day, month, year)

At ordering see the SSG XIV protocol.  
**Fill in this order sheet completely!**

Upon participation in the research project; Fill in **sampling protocols** and **fluid lists!**

Weight: ..... kg Length: ..... cm Body surface area: ..... m<sup>2</sup>

Date for start of this course, day ..... month ..... year .....

**Basal solution for Cisplatin administration**

NaCl 0.9% with: 20 mmol KCl/litre and 1.5 mmol Mg/litre

**1. Prehydration (before Cisplatin)**

This patient shall have i.v. infusion: ..... ml basal solution during 2 hours.

Start of prehydration T-2: hour ..... min ..... Nurse sign. ....

End of prehydration T0: hour ..... min ..... Nurse sign. ....

**2. Cisplatin**

Dose for this patient: ..... mg Cisplatin. This dose is dissolved in ..... ml basal solution and is administered during 48 hours.

It is divided in two portions of which the first is administered during the first 24 hours (T0 – T24), and the second during the following 24 hours (T24 – T48)

This patient shall have i. v. infusion: ..... mg Cisplatin in: ..... ml basal solution/24 hours. This is administered twice (during 2 consecutive 24 hour periods).

Day 1: Start of Cisplatin T0: ..... hour ..... min ..... Nurse sign. ....  
 End of Cisplatin T24: ..... day ..... hour ..... min ..... Nurse sign. ....

Day 2: Start of Cisplatin T24: ..... day ..... hour ..... min ..... Nurse sign. ....  
 End of Cisplatin T48: ..... hour ..... min ..... Nurse sign. ....

**3. Posthydration (after Cisplatin)**

This patient shall have i.v. infusion: ..... ml basal solution during 2 hours.

Start of posthydration T48: ..... day ..... hour ..... min ..... Nurse sign. ....

End of posthydration T50: ..... hour ..... min ..... Nurse sign. ....

**4. Diuresis:** If diuresis < ..... ml/6 hours give ..... mg Furosemide.

**5. Doxorubicin**

When combined with Cisplatin (CDP1/ADM1), Doxorubicin is given directly after the posthydration after Cisplatin. If Doxorubicin is given as single drug; start at this item.

This patient shall have i.v. infusion: ..... mg Doxorubicin in ..... ml glucose 5% during 4 hours.

Start of Doxorubicin T50: hour ..... min ..... Nurse sign. ....

End of Doxorubicin T54: hour ..... min ..... Nurse sign. ....

Attending physician responsible for this order, *signature* .....

Contra signature of this order, *signature* .....

## 16.9 Ifosfamide

**Ifo is started day 1, at weeks 23, 26, 29 for poor responders only.**

**Blood check-ups** before start of Ifosfamide: Hematocrit, white blood counts, neutrophils, platelets, albumin, liver enzymes, including bilirubin, Na, K, Mg, Ca, creatinine, GFR before Ifo week 23. Uristix for hematuria

Daily: Hematocrit, white blood counts, platelets, venous acid/base (or serum bicarbonate), uristix, creatinine, Na, K, Ca, Mg, GOT and GPT (=ASAT, ALAT).

**Basal solution:** 5% glucose with 40 mmol NaHCO<sub>3</sub>/L + 20 mmol KCl/L.

- 1. Prehydration and alkalization:** Infuse 500 ml/m<sup>2</sup> over a 2 hours period.
- 2. Dose:** The doses of Ifosfamide and of mesna for the first course are 2 000 mg/m<sup>2</sup>/24 hours, each for five consecutive days, giving a total dose of both Ifosfamide and Mesna of 10 000 mg/m<sup>2</sup>. The doses of Ifosfamide and Mesna are escalated by 20% in the next course if no grade IV neutropenia or thrombocytopenia occurs.
- 3. Ifosfamide/Mesna infusion:** Ifosfamide and Mesna are infused i.v. in 2 000 ml/m<sup>2</sup>/24 hours of basal solution.
- 4. Postifosfamide alkalization and Mesna administration:** Following the Ifosfamide/Mesna infusion on day 5: Mesna 1 000 mg/m<sup>2</sup> in 1 000 ml/m<sup>2</sup> basal solution in 8 hours. Alternatively, Mesna 500 mg/m<sup>2</sup> and NaHCO<sub>3</sub> 500 or 1 000 mg may be given orally 4 and 8 hours after the Ifosfamide-Mesna infusion. The dose of Mesna is increased in parallel with the escalation of the Ifosfamide dose (se above).
- 5. Diuresis:** If <400 ml/m<sup>2</sup> in 6 hours, give furosemide 0.5–1.0 mg/kg. The maximum dose of furosemide is 20 mg. Check for hematuria every 24 hours. With macroscopic hematuria or microscopic hematuria (+++ or more) confirmed by microscopic examination (≥10 red blood cells/field), Ifosfamide should be withheld and basal solution, 1 000/ml/m<sup>2</sup>/8 hours with 1 000–1 440 mg/m<sup>2</sup> Mesna should be infused. The Ifosfamide infusion should then be re-started.

**NOTE:** Uristix may be falsely negative or positive during treatment with Ifosfamide.

- 6. Additional alkalization:** If urine pH <7 or venous acid/base indicates metabolic acidosis (serum bicarbonate <21 mmol/L), give 2 mmol NaHCO<sub>3</sub>/kg intravenously during 30 min.
- 7. Treatment and prophylaxis for Ifosfamide-induced CNS toxicity:** The cause of Ifosfamide-induced acute encephalopathy is unknown. It may be dose-dependent and may be aggravated by metabolic acidosis. The condition is reversible. The commonest symptom of mild CNS toxicity is undue somnolence, which usually does not require specific measures other than to keep the serum bicarbonate levels >21 mmol/L. The Ifosfamide infusion should not be interrupted. **Severe encephalopathy** is recognized by disorientation, visual and cognitive disturbances, undue fear, nightmares, hallucinations or even convulsions. The symptoms usually start insidiously and slowly increase. The Ifosfamide infusion should be stopped and treatment instituted with methylene blue 50 mg i. v. every 8 hours together with infusion of basal solution, 1 000/ml/m<sup>2</sup>/8 hours with 1 000–1 440 mg/m<sup>2</sup> Mesna. Metabolic acidosis must be corrected according to recommendation above. The symptoms generally disappear quickly and 2–3 methylene blue infusions usually suffice. This Ifo course should not be re-started.

In subsequent Ifo courses, prophylactic treatment with oral methylene blue 50 mg × 3 daily should be given when starting Ifosfamide. This will usually prevent further CNS toxicity (23).

Methylene blue is a non-toxic agent. Its exact mechanism of action in this context is not precisely known.

**NOTE:** Methylene blue is not routinely available in hospital pharmacies and must be purchased in advance in institutions giving Ifo treatment!



**16.10**  
**Osteosarcoma SSG XIV**  
**Order sheet**  
**Ifosfamide (Ifo)**

Name (first & family name)  
 Date of birth (day, month, year)

At ordering see the SSG XIV protocol.  
**Fill in this order sheet completely!**

Upon participation in the research project; Fill in **sampling protocols** and **fluid lists!**

Weight: ..... kg Length: ..... cm Body surface area: ..... m<sup>2</sup>

Date for start of this Ifosfamide course, day ..... month ..... year .....

**Basal solution for prehydration, alcalinisation and Ifosfamide/Mesna infusion**

Glucose 5% with 40 mmol NaHCO<sub>3</sub>/litre + 20 mmol KCl/litre.

**1. Prehydration and alcalinisation**

This patient shall have: ..... ml basal solution during 2 hours

Start of prehydration T-2 (time): ..... Nurse sign. ....

End of prehydration T0 (time): ..... Nurse sign. ....

**2. Ifosfamide/Mesna infusion**

Ifosfamide and Mesna are mixed in the same basal solution which is administered intravenously during five (5) consecutive 24 hour periods.

This patient shall have i.v. infusion ..... mg Ifosfamide/24 hours and  
 ..... mg Mesna/24 hours mixed in ..... ml basal solution/24 hours.

*This is repeated during (5) consecutive 24 hour periods.*

Day 1: Start of Ifosfamide/Mesna T0: ..... hour ..... min ..... Nurse sign.....

End of Ifosfamide/Mesna T24: *day* hour ..... min ..... Nurse sign. ....

Day 2: Start of Ifosfamide/Mesna T24: ..... hour ..... min ..... Nurse sign.....

End of Ifosfamide/Mesna T48: *day* hour ..... min ..... Nurse sign. ....

Day 3: Start of Ifosfamide/Mesna T48: ..... hour ..... min ..... Nurse sign.....

End of Ifosfamide/Mesna T72: *day* hour ..... min ..... Nurse sign. ....

Day 4: Start of Ifosfamide/Mesna T72: ..... hour ..... min ..... Nurse sign.....

End of Ifosfamide/Mesna T96: *day* hour ..... min ..... Nurse sign. ....

Day 5: Start of Ifosfamide/Mesna T96: ..... hour ..... min ..... Nurse sign.....

End of Ifosfamide/Mesna T120: *day* hour ..... min ..... Nurse sign. ....

**3. Posthydration with Mesna**

This patient shall have ..... mg Mesna in ..... ml basal solution during 8 hrs

Start of posthydration T120: ..... hour ..... min ..... Nurse sign. ....

End of posthydration T128: *day* hour ..... min ..... Nurse sign. ....

**4. Diuresis and extra alcalinisation**

If diuresis < ..... ml/6 hours give ..... mg Furosemide.

If urine-pH <7 ..... mmol NaHCO<sub>3</sub> shall be administered during 30 minutes.

Attending physician responsible for this order, *signature*: .....

Contra signature of this order, *signature*: .....

## 17. Serious adverse event

### 17.1 Definition

An adverse event is defined as any untoward medical occurrence or experience in a patient or clinical investigation which occurs following the administration of the trial medication regardless of the dose or causal relationship. A *serious adverse event* is defined as any undesirable experience occurring to a patient, whether or not considered related to the protocol treatment. A serious adverse event which is considered related to the protocol treatment is defined as a *serious adverse drug reaction*. Adverse events and adverse drug reactions which are considered as serious are those which results in:

- Death
- A life-threatening event (i.e. the patient was at immediate risk of death at the time the reaction was observed)
- Hospitalization or prolongation of hospitalization
- Persistent or significant disability/incapacity
- A congenital anomaly/birth defect
- Any other medically important condition

WHO/CTC grade 4 neutropenia (and neutropenic infection), thrombocytopenia, mucositis, diarrhoea or hepatic toxicity (the latter, following methotrexate only) which resolve and do not have life-threatening consequences are to be expected with the protocol and are not regarded as serious adverse events. Any life-threatening event, however, must be reported immediately (see below).

### 17.2 Reporting procedure

All serious adverse events, related or not to the study treatment, occurring during the treatment period or within 30 days after the last protocol treatment administration, must be reported to the main study secretariat:

Regional Tumour Registry, Lund University Hospital, SE-221 85 Lund, Sweden

Tel. +46-46-17 75 55

Fax. +46-46-18 81 43

E-mail: [evy.nilsson@cancerepid.lu.se](mailto:evy.nilsson@cancerepid.lu.se)

This must be done by fax within 24 hours of the initial observation of the events. Details should be documented on the specified “Serious adverse event” form. The study secretariat will forward all serious adverse event report within 24 hours of receipt to all appropriate persons.

A complete report must follow the initial report within 10 days.

### 17.3 Minimal information required (See Form 10)

- The protocol number, the patient identification
- The onset date of the event
- A description of the event
- The category of the event
- The suspected causal relationship
- The outcome of the event

### 17.4 Stopping rules for the study protocol due to toxic deaths

Interim analyses on severe acute toxicity and toxic deaths will take place twice a year by the “Resource group”.

Log rank test and crude percentage comparison tests will compare deaths not related to the underlying malignant disease to historical control (i.e. the SSG VIII material, 3 cases in 116 patients). If any of these tests is significant at  $p < 10^{-4}$ , the conclusion will be that there is a relative excess of toxic deaths; then a full analysis will be considered

Crude percentage will also be compared to the theoretically acceptable toxic death rate. If the lower boundary of the 99.9% confidence interval of the observed percentage is above this limit, the conclusion will be that there is an absolute excess of toxic deaths in this group; then a full analysis will be considered. Based on previous experience of toxic deaths observed in SSG VIII (0.86%) the limit percentage has been set at 1%. The type 1 error ( $\alpha$ ) has been fixed equal to  $10^{-3}$ .

Example:

To conclude that  $p_{\text{obs}} \geq 1\%$  with  $\alpha = 10^{-3}$

Number of treated patients	K	P <sub>obs</sub>
20	4	20%
50	5	10%
100	7	7%

K: number of toxic deaths leading to the conclusion of an absolute excess of toxic deaths.

If the analysis conclude that there is an absolute excess of toxic deaths, the study will be stopped immediately by the study co-ordinators

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Scandinavian Sarcoma Group  
& Oncologic Center, Lund, Sweden

## **SSG XIV**

### **Research protocol**

## **Informed consent for patients and their parents regarding the research projects**

### **“Detection of micro metastasis in osteosarcoma”**

You have recently been diagnosed with a type of bone cancer, osteosarcoma. Modern treatment of this disease has indeed improved the cure rates. Before effective cytostatics were available, approximately 20% of the patients without detectable spread at the time of operation were cured. In contrast today close to 70% of osteosarcoma patients are cured.

Modern combination chemotherapy given to osteosarcoma patients is very intensive. In addition to the acute adverse effects there is also a significant risk for the development of late complications. An aim in the international research community is to optimise the combination of drugs and their doses (so called “risk adapted therapy”) so that the most aggressive combinations are reserved for those patients that really need it. Presence of metastatic disease is a known risk factor relapse and will imply more aggressive chemotherapy. We know from historical data that most patients with osteosarcoma have metastatic spread at the time of primary diagnosis. The problem is that the majority of these patients only have micrometastasis, that is lesions that are so small that they can not be identified with current diagnostic modalities (X-rays, etc.). We are with the current methods not able to distinguish between patient with micrometastatic spread and patients without metastatic disease. The consequence is that all patients receive the similar intensive chemotherapy. In an aim to identify patients with microscopic spread we have embarked upon a common Scandinavian Research protocol linked to our current osteosarcoma treatment; “The Micro-metastasis Project”.

The Norwegian Radiumhospital has developed special techniques to disclose single tumour cells that are spread from the primary tumour in blood and bone marrow. The aim of the research project is to collect materials from a number of patients so that we can learn if the detection of these tumour cells is of prognostic value and could aid our treatment of the individual patients.

Your participation in the project implies that we need to draw a bone marrow aspirate and a sample of peripheral blood. These will be done before the start of chemotherapy, at the time of definite surgery for the primary tumour and when the adjuvant chemotherapy is completed. Also patients experiencing relapses will be candidates. We will aim to do these procedures when you are under general anaesthesia for primary biopsy, implantation of venous access port, etc. In cases where general anaesthesia will not be given, you will receive local anaesthesia, as is the routine procedure for several other groups of patients.

You and your relatives should decide your participation in this study. If you do not want to participate, this will of course have no consequences for the treatment you will receive. You are also free to withdraw from the study, at any time, without any further justification. You and your relatives accept your willingness to participate and confirm that information has been given by signing the formula below.

*Øyvind S. Bruland*  
Professor of Clinical Oncology  
Research Project Leader

*Sigbjørn Smeland*  
Sr. Consultant  
Protocol Chairman

## 1. Micrometastasis in patients with osteosarcoma

*Co-ordinator: Professor Ø. S. Bruland, Oslo*

### 1.1 Aims

1. To collect samples of mononuclear cells derived from peripheral blood and bone-marrow aspirates of patients with various biological subtypes and clinical stages of osteogenic sarcoma (OS).
2. To evaluate the feasibility of immunomagnetic positive tumour cell isolation, using monoclonal antibodies TP-3 and 9.2.27 in combination with Dynabeads®.
3. To generate hypotheses in relation to the use of such methods as a prognostic tool in OS patients on the basis of findings in this study.
4. To explore the biological role of circulating tumour cells in OS.

### 1.2 Background

The current management of OS is fraught with difficult dilemmas (22). In particular, overtreatment and long-term sequelae among cured patients are of major concern.

OS is considered a systemic disease characterized by the presence of sub-detectable tumour spread at primary diagnosis in the vast majority of patients. Adjuvant chemotherapy is a cornerstone in the current multi-modal management. However, OS displays considerable heterogeneity with regard to metastatic capacity and chemosensitivity. The current outcome may well be further improved by individualizing the treatment. Up to now it has not been possible to identify subgroups with different prognoses of patients and better methods for “biological staging” are needed. The presence of circulating tumour cells may well be a new prognostic factor. If consensus with regard to prognostic factors can be achieved, the stage might be set for exploring “risk-adapted therapy” in OS (22).

A method for immunomagnetic isolation and detection of tumour cells present in mononuclear cell suspensions from bone marrow (BM) aspirates and peripheral blood (PBL) will be applied. Two monoclonal antibodies, known to be reactive with osteosarcoma cells, but not with normal hematopoietic cells are used in this rosetting technique. Based on the cumulative experience (now 43 OS-patients) from The Norwegian Radium Hospital over a ten years period, it was decided to include “micrometastases” as one of the research projects in the protocols ISG/SSG I & II. It has been decided to continue this study also in the SSG XIV protocol. The aim is to increase the number of samples so that any conclusion regarding the potential clinical significance of micrometases can be drawn faster.

In SSG/SSG I & II each center was encouraged to freeze down mononuclear cells from BM and PBL blood to be sent to Oslo for subsequent testing. “Rizzoli” supplied samples for analyses from 29 OS-patients—“Lund” four; samples that now are under analysis.

The specimens from patients treated at The Norwegian Radium Hospital were analyzed directly after the sampling, whereas frozen materials have been used from the two other institutions. Using fresh materials 61% (11/18 patients) of “classical” OS-patients were positive in BM, only one positive in PBL. Interestingly, none of the BM-negative patients have suffered a relapse with a mean follow up of 47 months, whereas three did so in the BM-positive cohort (one dead of disease, one alive with multiple metastases and one in CR, salvaged with thoracotomy)—mean follow up 45 months. Two out of four with axial primary tumours had tumour cells in BM, none



in PBL. Among patients with overt metastases at primary diagnosis 92% (11/12 patients) had positive BM-samples, and usually a very high number of rosettes were recovered. Five of the nine patients with relapsed metastatic disease (56%) had positive BM. Two of the four negative patients had several years of disease free interval from primary treatment and detection of a solitary lung metastasis, and both are alive NED at six years follow up (25).

The analysis of frozen samples seemingly give conflicting results in as much as fewer of the patients score positive. The number of mononuclear cells recovered after thawing are generally much lower making a direct comparison difficult.

### 1.3 Organization

Data in the study will be collected by the Clinical Research Branch / Department of Oncology, Norwegian Radium Hospital; it will be based on information given in the enclosed registration form and data from the central register of the protocol. The Department of Tumour Biology, Norwegian Radium Hospital, will perform the tumour cell isolation assays without knowledge of clinical information.

### 1.4 Clinical material

Peripheral blood (20 ml heparinized blood) and bone marrow aspirates (10–20 ml) will be collected into tubes containing heparin (heparin coated Vacutainer etc.). Material will then be transferred to tubes for shipment, as overnight express postal service. This material will be supplied each center. The preparation of mononuclear cells and testing with the rosetting assay will be performed at the Department of Tumour Biology, Norwegian Radium Hospital.

### 1.5 Practical aspects of sampling

Samples will be obtained from each patient, preferably at

1. initial diagnosis
2. the time of primary surgery following preoperative chemotherapy
3. the end of treatment.

If a relapse is diagnosed and surgical removal of metastases is planned, renewed sampling is highly recommended.

Samples can often be obtained simultaneously with a surgical procedure. This is an advantage especially in younger patients. Blood and bone marrow should be drawn before manipulating the tumour. If possible, fresh tumour material should also be frozen for subsequent comparative studies.

Mark each tube with:

- Patient's initials
- Birth date
- Sampling date
- *BM* (bone marrow), *PB* (peripheral blood)

## 1.6 Future prospects

A relationship seemingly exists between the presence and number of isolated tumour cells and clinical stage and progression of the disease. The results obtained are promising for the use of this sensitive method in selecting patients to receive individualized therapeutic intervention, for monitoring effects of systemic treatment, and as part of patient follow up programs.

The extra samples of cryo-preserved material are available for exploring improved bead-technology and/or PCR assays. Plasma samples are collected for evaluating the usefulness of novel “tumour-markers”.

## 1.7 Shipment of samples

*It is mandatory to contact Prof. Bruland before sending the material!*

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## Appendix, Treatment protocol

### 1. Investigation and follow-up flowsheet

**NOTE:** Follow-up after end of treatment. Patients should be followed at 3 month intervals for 3 years, at 4 month intervals during the 4<sup>th</sup> and 5<sup>th</sup> years, and then yearly until 10 years after end treatment.

	Pre-treatment	Pre-surgery	End of treatment	Every follow-up	Other (see comments)
Physical examination	×	×	×	×	
Std. blood Sample*	×	×	×	×	
S-creatinine, Na, K, Mg,P, Cys-C	×	×	×	×	
GFR	×	×	×		× At 3 months, 6 months, at 6 months interval up to 3 years, then yearly
Hepatitis serology	×		×		
X-rays of involved bone	×	×		×	
MRI and/or CT of involved bone	×	×			
Chest X-ray	×	×	×	×	
CT of chest	×	(×)	(×)	(×)	× On suspicion of lung-metastases on chest X-ray
Bone scan	×	(×)			× On suspicion of bone-metastases
Audiogram	×		×		× One year after treatment
ECG	×	×	(×)		(×) (Every 3 years after treatment)
LVEF (Cardiac ultrasound, Mugascan)	×		×		× At 3 months, at 6 months, and then every 3 years after treatment
Sperm count	(×)		(×)		(×) (3 years after treatment)

× = mandatory (×) = recommended

\* Includes: Hb, white blood counts with differential, Trc, creatinine, ALP, LDH, total bilirubin, transaminases, Na, K, Mg

## 2. Guidelines for pathology

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### Handling of specimens

In the case of amputation specimens skin and soft tissue not infiltrated by the tumour should be removed and larger blood vessels should be examined for possible tumour thrombosis.

In all types of specimens, note the relationship between tumour, bone, articular cartilage, epiphysis, surrounding soft tissues, and resection margins. Make a statement about the margins (intralesional, marginal, wide, radical) and give measurements in cm. Sample bone marrow from the resection site.

The bone containing the tumour should be sectioned in a plane that will optimally identify residual viable tumour tissue. The bone should be cut longitudinally into halves with a band saw. Saw an additional 3–4 mm thick longitudinal slice from one of the halves and an additional slice from the other half for a large section A'. Take photographs of the sawing lines and slices (**Figs. 1–3**). Saw the remaining two halves into 3–4 mm thick slices perpendicular to the above planes and take additional photographs. Choose the two slides that contain most tumour tissue. If the tumour tissue is very soft, it is better to precut it with a large knife as deeply as possible before sawing.

Fix the slices overnight and divide the tumour areas into pieces of appropriate size (**Fig. 4**). Use an ink pen for drawing the lines on the tissue. Take photographs and make a drawing and number the separate areas. Saw along the lines and put the pieces in formalin for 1–2 days. Decalcify, if necessary, the pieces using fast decalcifiers for preservation of tissue. Note that the decalcifying time varies greatly from piece to piece. Avoid overdecalcification. The pieces should be processed, embedded, cut and stained using routine methods. The total number of sections depends on the size of the tumour.

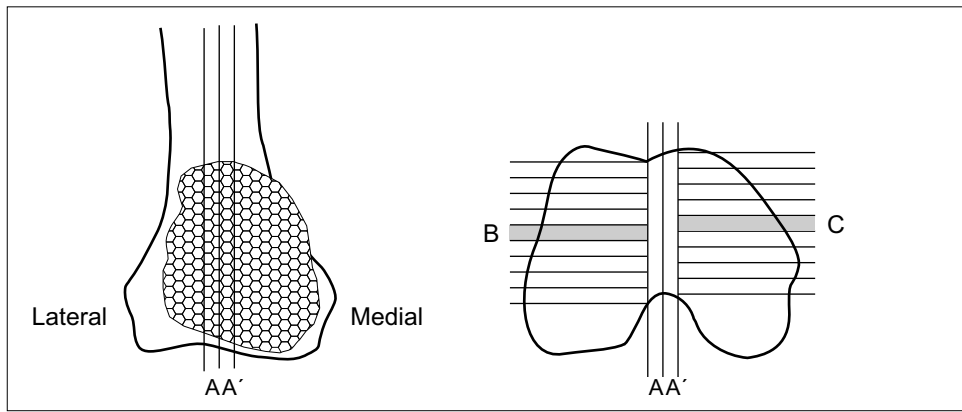


Figure 1.

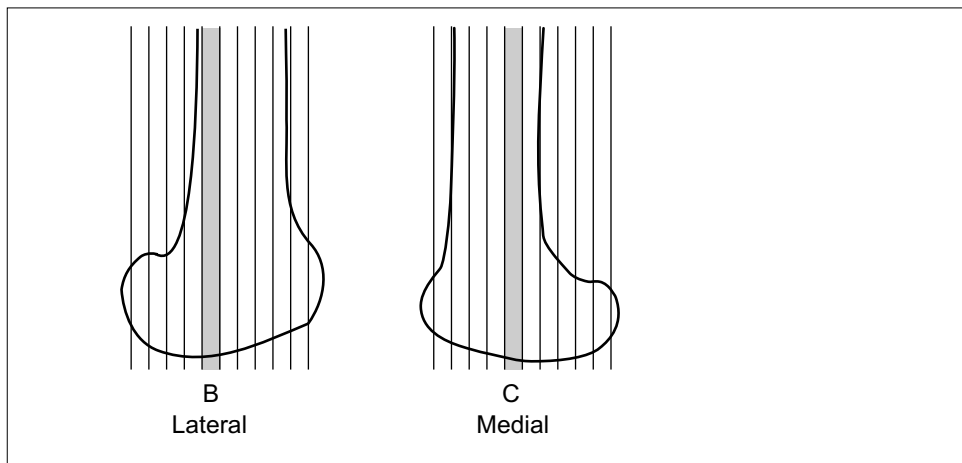


Figure 2.

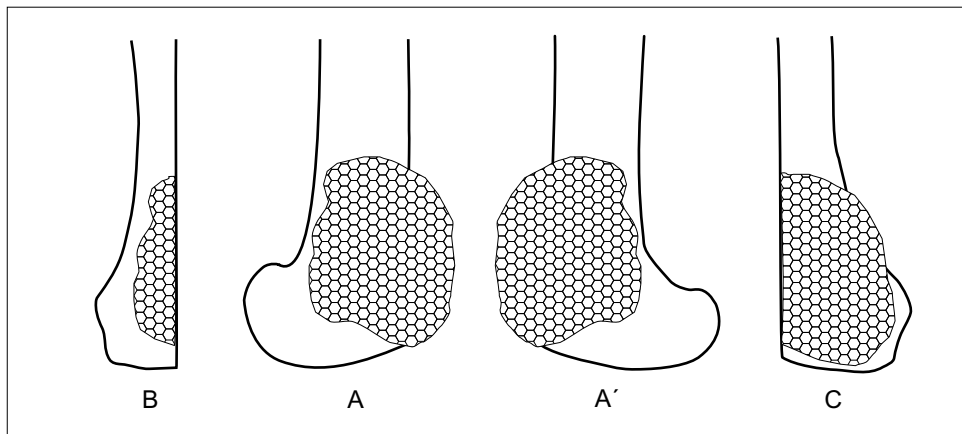


Figure 3.

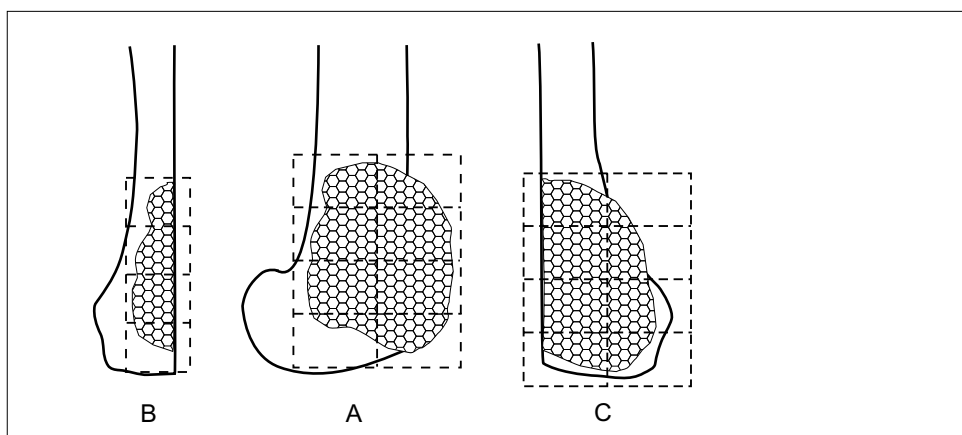


Figure 4.

## Grading of tumour response

### **Good response: Fulfilling the following two criteria:**

1. <10% of examined tumour area reveal *unquestionable* viable tumour.
2. No single area of *unaffected* viable tumour exceed 2.5 mm in largest diameter.

### **Poor response: Fulfilling one or both of the following two criteria:**

1. One or more areas of *unaffected*, viable tumour >2.5 mm in largest diameter.
2. >10% of the examined tumour area show *unquestionable viable* tumour.

With *unaffected* means a morphologic appearance closely resembling that of the pretreatment biopsy.

With *unquestionable viable* means various degrees of response, including decreased cellularity, and signs of maturation with bone and cartilage matrix production, but with remaining clearly viable tumour cells.

The location of residual tumour (intramedullary, periosteal, soft tissue) should be indicated in the report.

Scattered, single large cells with hyperchromatic nuclei, in a background of granulation tissue is not considered to represent *unquestionable viable* tumour. A dense bone matrix with small pyknotic nuclei in lacunae is not either considered *unquestionable viable* tumour.

### 3. Guidelines for orthopaedic surgery

Because of the complexity of the SSG XIV protocol (aggressive combination chemotherapy and surgery), the whole treatment program should be planned in tumour board, with a pathologist and/or a cytologist, a diagnostic radiologist, and orthopedic surgeon, and a pediatric or an adult oncologist. Follow-up discussions during the treatment are necessary.

Surgery is carried out after two cycles of chemotherapy, and within 21 days after completion of preoperative chemotherapy, as soon as possible after leucocyte recovery (neutrophils  $>1.0 \times 10^9/L$  and platelets  $(\geq 100 \times 10^9/L)$ ). Note that re-evaluation before surgery with chest X-ray and X-ray + MRI and/or CT of the involved bone are mandatory before surgery.

#### Biopsy

The location of the diagnostic biopsy is crucial. At later surgery the biopsy tract must be included *en bloc* with the specimen. A misplaced biopsy may greatly complicate the definitive surgery, Hence the diagnostic biopsy should be planned and performed by the surgeon who will be responsible for the definitive surgery.

If a coarse needle biopsy is done, location of the biopsy tract has to be tattooed.

#### Surgery

The surgical planning should be based on clinical data and radiographic examinations (plain radiographs, scintigraphy, CT, MRI, and possibly angiography) performed before start of chemotherapy and just before surgery. The surgeon should try to assess the tumour response, feasibility of a limb-saving surgical procedure, and need for bone-, joint-, vascular-, and soft tissue reconstruction. No fixed guidelines can be claimed for either the choice or extent of local tumour surgery, nor type of reconstruction.

The tumour should preferably be excised with a wide surgical margin. If a limb-saving procedure with wide surgical margin is not possible, an amputation has to be considered. However, a marginal margin may be acceptable in good responders. Amputation is a surgical procedure and has to be classified according to the obtained surgical margin.

#### Evaluation of surgical margin

After intra- or postoperative macroscopical examination of the specimen, where any area with supposed inadequate margin is marked, the specimen should be cross sectioned serially and margins examined microscopically (see “Guidelines for pathology”).

**Surgical margins** are defined according to Enneking

1. *Radical margin*: The whole compartment is removed.
2. *Wide margin*: A cuff of healthy tissue all around the tumour is included in the specimen.
3. *Marginal margin*: The excision is performed close to the tumour capsule and through the reactive zone in one or several planes.
4. *Intralesional margin*: (“Debulking surgery”). The excision is in one or several planes performed through the tumour.

#### 4. Submission of forms

Form	Contents	Reporting
<b>Institution's commitment</b> Form 1		Completed by responsible principal investigator
<b>Registration</b> Form 2	Patient data, date of biopsy, localization of tumour, date of start of chemotherapy	Completed by pediatrician or oncologist
<b>Pathology report I</b> Form 3	Primary diagnostic procedure	Completed by pathologists
<b>On-study</b> Form 4	Patient data, primary tumour status, type of surgery	Completed by pediatrician or oncologist latest four weeks after surgery
<b>Pathology report II</b> Form 5	Final diagnosis, tumour response	Completed by pathologists
<b>Preoperative chemotherapy flow-sheet</b> Form 6A <b>Toxicity flow-sheet</b> Form 6B	Details of each preoperative therapy cycle, patient data, date, and dose of chemotherapy and toxicity data	Completed by pediatrician or oncologist
<b>Postoperative chemotherapy flow-sheet</b> Form 7A <b>Toxicity flow-sheet</b> Form 7B	Details of each postoperative therapy cycle, patient data, date, and dose of chemotherapy and toxicity data	Completed by pediatrician or oncologist
<b>Chemotherapy flow-sheet</b> Form 8A <b>Toxicity flow-sheet</b> Form 8B	Details of ifosfamide courses (poor responders only) and toxicity data	Completed by pediatrician or oncologist
<b>Follow-up</b> Form 9	Clinical evaluation of patients from time of diagnosis	Completed by a examining physician at each follow-up visit
<b>Serious adverse event</b> Form 10	Details of the event	Completed by principal investigator

**NOTE:** The following forms are sent to the SSG secretariat.

**Form 1, 2 and 3** together with anteroposterior and lateral X-rays of the primary tumour-involved bone and histological slides of the primary tumour are sent *one week after start of chemotherapy*.

**Form 4, 5, 6A, 6B, 7A and 7B** are sent *3 weeks after end of pre-/postoperative chemotherapy*.

**Form 8A and 8B** are sent *3 weeks after completed postoperative chemotherapy*.

**Form 9** is sent *immediately after end of follow-up visit*.

**Form 10** are sent within 24 hours of the initial observation of the event.



Osteosarcoma SSG XIV

**Institution's commitment**

**Form 1**

Name (first & family name)

Date of birth (day, month, year)

Send to:  
SSG secretariat  
Regional Tumour Registry  
Lund University Hospital  
SE-221 85 LUND  
Sweden

Department: ..... Hospital: .....

City: ..... Country: .....

This form is a prerequisite for patient eligibility in SSG XIV and should be completed and sent to the secretariat, together with the following:

1. Anteroposterior and lateral X-rays of the primary tumour-involved bone.
2. Representative histological slides of the primary tumour.

The above named institution and department(s) commit themselves to participate in the clinical SSG XIV study and will comply with the scheduled investigations, treatment and follow-up.

yes  no

### **Associated research projects**

(optional)

The above named institution and department(s) agree to participate in the following research projects associated with the SSG XIV protocol:

Micrometastases  yes  no

.....  
day month year

.....  
Name and signature of the responsible principal investigator

Osteosarcoma SSG XIV  
**Registration**

**Form 2**

Name (first & family name)  
Date of birth (day, month, year)

Send this form after start of chemotherapy to:  
SSG secretariat  
Regional Tumour Registry  
Lund University Hospital  
SE-221 85 LUND  
Sweden

Hospital and department

Date Day Month Year

Physician

- Enclosed are:**
1. An anterior – posterior – lateral X-ray of the primary tumour involved bone
  2. Histological representative slides of diagnostic material
  3. Institution commitment form

Date of biopsy Day Month Year

Tumour site:

High-grade osteosarcoma  yes

Start of chemotherapy Day Month Year

Send to:  
SSG secretariat  
Regional Tumour Registry  
Lund University Hospital  
SE-221 85 LUND  
Sweden

Department: ..... Hospital: .....

City: ..... Country: .....

Pathologist: ..... Sign.: .....

Biopsy number: .....

**Diagnosis**

Initial diagnosis, date: day ..... month ..... year ..... based on:

Open biopsy

Troacar biopsy

Fine needle aspiration biopsy

Additional methods used in diagnostics, specify: .....

.....

.....

.....

.....

**Diagnosis; Subtype**

**Grade**

<input type="checkbox"/> Classic osteoblastic osteosarcom	<input type="checkbox"/> Grade 3
<input type="checkbox"/> Fibroblastic osteosarcoma	<input type="checkbox"/> Grade 4
<input type="checkbox"/> Chondroblastic osteosarcoma	<input type="checkbox"/> Other, specify: .....
<input type="checkbox"/> Telangiectatic osteosarcoma	.....
<input type="checkbox"/> Small cell osteosarcoma	
<input type="checkbox"/> Non-classifiable osteosarcoma	
<input type="checkbox"/> Periosteal	
<input type="checkbox"/> Intraosseus	

Necrosis present:     yes     no

Osteosarcoma SSG XIV

**On-study**

**Form 4**

Name (first & family name)  
Date of birth (day, month, year)

Send to:  
SSG secretariat  
Regional Tumour Registry  
Lund University Hospital  
SE-221 85 LUND  
Sweden

Hospital and department	Physician	Date	Day	Month	Year
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**Patient data**

Age			years	Sex:	<input type="checkbox"/> male	<input type="checkbox"/> female
Duration of symptoms, month     (Time interval from first symptom to pathologic confirmation of diagnosis)						
Site:	<input type="checkbox"/> proximal	<input type="checkbox"/> mid	<input type="checkbox"/> distal			
Metastatic site(s):	<input type="checkbox"/> lung	<input type="checkbox"/> skeleton	<input type="checkbox"/> other, specify; .....			
Soft tissue involvement:	<input type="checkbox"/> no	<input type="checkbox"/> yes				

**Investigations prior to treatment**

Plane X-ray:	<input type="checkbox"/> performed	<input type="checkbox"/> not performed										
CT of involved bone:	<input type="checkbox"/> performed	<input type="checkbox"/> not performed										
MRI of involved bone:	<input type="checkbox"/> performed	<input type="checkbox"/> not performed										
Bone scan:	<input type="checkbox"/> solitary lesion	<input type="checkbox"/> multiple lesions	<input type="checkbox"/> not performed									
Chest x-ray:	<input type="checkbox"/> normal	<input type="checkbox"/> prob benign	<input type="checkbox"/> prob malign	<input type="checkbox"/> not performed								
CT of lung:	<input type="checkbox"/> normal	<input type="checkbox"/> prob benign	<input type="checkbox"/> prob malign	<input type="checkbox"/> not performed								
Alkaline phosphatase						..... (specify unit)	LDH					..... (specify unit)

**Chemotherapy**

<b>Cycle 1 completed</b>						<b>Cycle 2 completed</b>					
<input type="checkbox"/> MTX	<input type="checkbox"/> MTX	<input type="checkbox"/> CDP/ADM	Day	Month	Year	<input type="checkbox"/> MTX	<input type="checkbox"/> MTX	<input type="checkbox"/> CDP/ADM	Day	Month	Year
<input type="checkbox"/> yes	<input type="checkbox"/> no	Date				<input type="checkbox"/> yes	<input type="checkbox"/> no	Date			

**Surgery**

<input type="checkbox"/> Resection	<input type="checkbox"/> Amputation	<input type="checkbox"/> Rotation plasty	<input type="checkbox"/> Reconstruction	Date	Day	Month	Year
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**Type of reconstruction**

<input type="checkbox"/> Allograft	<input type="checkbox"/> Vascularized graft	<input type="checkbox"/> Endoprosthesis	<input type="checkbox"/> Other, specify; .....
------------------------------------	---	---	--

Final report including photograph  
(Polaroid picture or slide)

Send to: SSG secretariat  
Regional Tumour Registry  
Lund University Hospital  
SE-221 85 LUND  
Sweden

Department: ..... Hospital: .....

City: ..... Country: .....

Pathologist: ..... Sign.: .....

Number of specimen: .....

**Primary tumour**

<b>Macroscopy</b>	
Tumour localization: .....	
Tumour size (three dimensions) : ..... cm × ..... cm × ..... cm	
Margins: <input type="checkbox"/> intralesional <input type="checkbox"/> marginal <input type="checkbox"/> wide <input type="checkbox"/> radical	
<b>Microscopy</b>	
Final diagnosis	Chemotherapy response:
<input type="checkbox"/> Classical osteoblastic osteosarcoma	<input type="checkbox"/> Poor response
<input type="checkbox"/> Fibroblastic osteosarcoma	<input type="checkbox"/> Good response
<input type="checkbox"/> Chondroblastic osteosarcoma	
<input type="checkbox"/> Telangiectatic osteosarcoma	
<input type="checkbox"/> Small cell osteosarcoma	
<input type="checkbox"/> Non-classifiable osteosarcoma	
Number of blocks: .....	Whole tumor section available: <input type="checkbox"/> Yes <input type="checkbox"/> No

Comments: .....

Sending institution (if not same as above): .....

Osteosarcoma SSG XIV  
**Chemotherapy flow-sheet**

**Form 6A**

Name (first & family name)  
 Date of birth (day, month, year)

Send to:  
 SSG secretariat  
 Regional Tumour Registry  
 Lund University Hospital  
 SE-221 85 LUND  
 Sweden

Hospital and department

Date Day Month Year

Physician

**Preoperative chemotherapy**

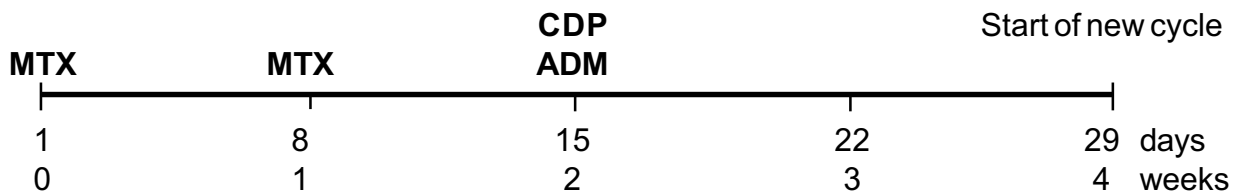
Year: .....

Weight: ..... kg

Height: ..... cm

Body surface: ..... m<sup>2</sup>

Cycle No: .....



	Start	Nadir	Start	Nadir	Start	Nadir	
Date, D/M/Y							
WBC							
Tromb							
Hb							
<b>Given doses</b>							
MTX, mg							
MTX, mg							
CDP, mg							
ADM, mg							

**MTX** = Methotrexate    12 000 mg/m<sup>2</sup>

**CDP** = Cisplatin        45 mg/m<sup>2</sup> /day × 2 days

**ADM** = Adriamycin    75 mg/m<sup>2</sup>

Osteosarcoma SSG XIV  
**Chemotherapy toxicity flow-sheet Form 6B**

Name (first & family name)  
 Date of birth (day, month, year)

Submit this form together with Form 6A to:

SSG secretariat  
 Regional Tumour Registry  
 Lund University Hospital  
 SE-221 85 LUND  
 Sweden

Preoperative cycle No: .....

	MTX			MTX			CDP/ADM					
Date	Day	Month	Year	Day	Month	Year	Day	Month	Year			
Delay	<input type="checkbox"/> yes	<input type="checkbox"/> no		<input type="checkbox"/> yes	<input type="checkbox"/> no		<input type="checkbox"/> yes	<input type="checkbox"/> no				
Reduction	<input type="checkbox"/> yes	<input type="checkbox"/> no		<input type="checkbox"/> yes	<input type="checkbox"/> no		<input type="checkbox"/> yes	<input type="checkbox"/> no				
Transaminase*	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4
Creatinine*	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4
Stomatitis*	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4
Low Bicarb.	<input type="checkbox"/> yes	<input type="checkbox"/> no		<input type="checkbox"/> yes	<input type="checkbox"/> no		<input type="checkbox"/> yes	<input type="checkbox"/> no				
Fever	<input type="checkbox"/> yes	<input type="checkbox"/> no		<input type="checkbox"/> yes	<input type="checkbox"/> no		<input type="checkbox"/> yes	<input type="checkbox"/> no				
Hospitalization	<input type="checkbox"/> yes	<input type="checkbox"/> no		<input type="checkbox"/> yes	<input type="checkbox"/> no		<input type="checkbox"/> yes	<input type="checkbox"/> no				
Transfusion Erythrocyt	<input type="checkbox"/> yes	<input type="checkbox"/> no		<input type="checkbox"/> yes	<input type="checkbox"/> no		<input type="checkbox"/> yes	<input type="checkbox"/> no				
Transfusion Platelets	<input type="checkbox"/> yes	<input type="checkbox"/> no		<input type="checkbox"/> yes	<input type="checkbox"/> no		<input type="checkbox"/> yes	<input type="checkbox"/> no				
G-CSF	<input type="checkbox"/> yes	<input type="checkbox"/> no		<input type="checkbox"/> yes	<input type="checkbox"/> no		<input type="checkbox"/> yes	<input type="checkbox"/> no				

\* According to NCIC CTG Expanded common toxicity criteria

Toxicity grade	1	2	3	4
Transaminase	$\leq 2.5 \times N$	$2.6-5.0 \times N$	$5.1-20.0 \times N$	$>20.0 \times N$
Creatinine	$<1.5 \times N$	$1.5-3.0 \times N$	$3.1-6.0 \times N$	$>6.0 \times N$
Stomatitis	painless ulcers, erythema, or mild soreness	painful erythema, edema, or ulcers but can eat	painful erythema, edema, or ulcers, and cannot eat	mucosal necrosis and/or req parenteral or enteral support, dehydration





Osteosarcoma SSG XIV  
**Chemotherapy toxicity flow-sheet Form 7B**

Name (first & family name)  
 Date of birth (day, month, year)

Submit this form together with Form 7A to:

SSG secretariat  
 Regional Tumour Registry  
 Lund University Hospital  
 SE-221 85 LUND  
 Sweden

Postoperative cycle No: .....

	CDP/ADM			MTX			MTX									
Date	Day	Month	Year	Day	Month	Year	Day	Month	Year							
Delay	<input type="checkbox"/>	yes	<input type="checkbox"/>	no	<input type="checkbox"/>	yes	<input type="checkbox"/>	no	<input type="checkbox"/>	yes	<input type="checkbox"/>	no				
Reduction	<input type="checkbox"/>	yes	<input type="checkbox"/>	no	<input type="checkbox"/>	yes	<input type="checkbox"/>	no	<input type="checkbox"/>	yes	<input type="checkbox"/>	no				
Transaminase*	<input type="checkbox"/>	1	<input type="checkbox"/>	2	<input type="checkbox"/>	3	<input type="checkbox"/>	4	<input type="checkbox"/>	1	<input type="checkbox"/>	2	<input type="checkbox"/>	3	<input type="checkbox"/>	4
Creatinine*	<input type="checkbox"/>	1	<input type="checkbox"/>	2	<input type="checkbox"/>	3	<input type="checkbox"/>	4	<input type="checkbox"/>	1	<input type="checkbox"/>	2	<input type="checkbox"/>	3	<input type="checkbox"/>	4
Stomatitis*	<input type="checkbox"/>	1	<input type="checkbox"/>	2	<input type="checkbox"/>	3	<input type="checkbox"/>	4	<input type="checkbox"/>	1	<input type="checkbox"/>	2	<input type="checkbox"/>	3	<input type="checkbox"/>	4
Low Bicarb.	<input type="checkbox"/>	yes	<input type="checkbox"/>	no	<input type="checkbox"/>	yes	<input type="checkbox"/>	no	<input type="checkbox"/>	yes	<input type="checkbox"/>	no				
Fever	<input type="checkbox"/>	yes	<input type="checkbox"/>	no	<input type="checkbox"/>	yes	<input type="checkbox"/>	no	<input type="checkbox"/>	yes	<input type="checkbox"/>	no				
Hospitalization	<input type="checkbox"/>	yes	<input type="checkbox"/>	no	<input type="checkbox"/>	yes	<input type="checkbox"/>	no	<input type="checkbox"/>	yes	<input type="checkbox"/>	no				
Transfusion Erythrocyt	<input type="checkbox"/>	yes	<input type="checkbox"/>	no	<input type="checkbox"/>	yes	<input type="checkbox"/>	no	<input type="checkbox"/>	yes	<input type="checkbox"/>	no				
Transfusion Platelets	<input type="checkbox"/>	yes	<input type="checkbox"/>	no	<input type="checkbox"/>	yes	<input type="checkbox"/>	no	<input type="checkbox"/>	yes	<input type="checkbox"/>	no				
G-CSF	<input type="checkbox"/>	yes	<input type="checkbox"/>	no	<input type="checkbox"/>	yes	<input type="checkbox"/>	no	<input type="checkbox"/>	yes	<input type="checkbox"/>	no				

\* According to NCIC CTG Expanded common toxicity criteria

Toxicity grade	1	2	3	4
Transaminase	≤2.5 × N	2.6–5.0 × N	5.1–20.0 × N	>20.0 × N
Creatinine	<1.5 × N	1.5–3.0 × N	3.1–6.0 × N	>6.0 × N
Stomatitis	painless ulcers, erythema, or mild soreness	painful erythema, edema, or ulcers but can eat	painful erythema, edema, or ulcers, and cannot eat	mucosal necrosis and/or req parenteral or enteral support, dehydration

<b>Osteosarcoma SSG XIV</b> <b>Chemotherapy flow-sheet</b>		<b>Form 8A</b>		Name (first & family name) Date of birth (day, month, year)	
Send to: SSG secretariat Regional Tumour Registry Lund University Hospital SE-221 85 LUND Sweden					
Hospital and department				Date Day    Month    Year	
Physician					

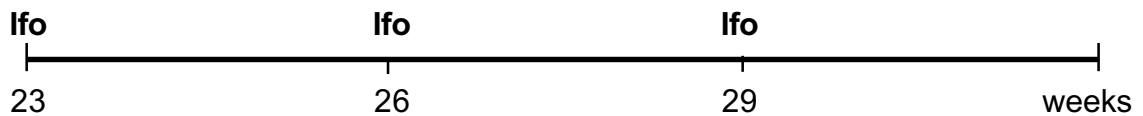
**Postoperative chemotherapy  
Poor responders – Ifosfamide**

Year: .....

Weight: ..... kg

Height: ..... cm

Body surface: ..... m<sup>2</sup>



	Start	Nadir	Start	Nadir	Start	Nadir
Date, D/M/Y						
WBC						
Tromb						
Hb						
<b>Given doses</b>						
lfo, mg						
lfo, mg						
lfo, mg						

**lfo** = Ifosfamide    2 000 – 2 400 mg/m<sup>2</sup> / day × 5 days

Osteosarcoma SSG XIV  
**Chemotherapy toxicity flow-sheet Form 8B**

Name (first & family name)  
 Date of birth (day, month, year)

Submit this form together with Form 8A to:

SSG secretariat  
 Regional Tumour Registry  
 Lund University Hospital  
 SE-221 85 LUND  
 Sweden

**Postoperative chemotherapy  
 Poor responders**

	Ifo			Ifo			Ifo					
Date	Day	Month	Year	Day	Month	Year	Day	Month	Year			
Delay	<input type="checkbox"/> yes	<input type="checkbox"/> no		<input type="checkbox"/> yes	<input type="checkbox"/> no		<input type="checkbox"/> yes	<input type="checkbox"/> no				
Reduction	<input type="checkbox"/> yes	<input type="checkbox"/> no		<input type="checkbox"/> yes	<input type="checkbox"/> no		<input type="checkbox"/> yes	<input type="checkbox"/> no				
Transaminase*	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4
Creatinine*	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4
Stomatitis*	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4
Hematuria*	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4
Low Bicarb.	<input type="checkbox"/> yes	<input type="checkbox"/> no		<input type="checkbox"/> yes	<input type="checkbox"/> no		<input type="checkbox"/> yes	<input type="checkbox"/> no				
Fever	<input type="checkbox"/> yes	<input type="checkbox"/> no		<input type="checkbox"/> yes	<input type="checkbox"/> no		<input type="checkbox"/> yes	<input type="checkbox"/> no				
Hospitalization	<input type="checkbox"/> yes	<input type="checkbox"/> no		<input type="checkbox"/> yes	<input type="checkbox"/> no		<input type="checkbox"/> yes	<input type="checkbox"/> no				
Transfusion Erythrocyt	<input type="checkbox"/> yes	<input type="checkbox"/> no		<input type="checkbox"/> yes	<input type="checkbox"/> no		<input type="checkbox"/> yes	<input type="checkbox"/> no				
Transfusion Platelets	<input type="checkbox"/> yes	<input type="checkbox"/> no		<input type="checkbox"/> yes	<input type="checkbox"/> no		<input type="checkbox"/> yes	<input type="checkbox"/> no				
G-CSF	<input type="checkbox"/> yes	<input type="checkbox"/> no		<input type="checkbox"/> yes	<input type="checkbox"/> no		<input type="checkbox"/> yes	<input type="checkbox"/> no				

\* According to NCIC CTG Expanded common toxicity criteria

Toxicity grade	1	2	3	4
Transaminase	$\leq 2.5 \times N$	$2.6-5.0 \times N$	$5.1-20.0 \times N$	$>20.0 \times N$
Creatinine	$<1.5 \times N$	$1.5-3.0 \times N$	$3.1-6.0 \times N$	$>6.0 \times N$
Stomatitis	painless ulcers, erythema, or mild soreness	painful erythema, edema, or ulcers but can eat	painful erythema, edema, or ulcers, and cannot eat	mucosal necrosis and/or req parenteral or enteral support, dehydration
Hematuria	micro only	gross, no clots	gross -clots	req transfusion

**Osteosarcoma SSG XIV**

**Follow-up**

**Form 9**

Name (first & family name)  
Date of birth (day, month, year)

Send to:  
SSG secretariat  
Regional Tumour Registry  
Lund University Hospital  
SE-221 85 LUND  
Sweden

Hospital and department

Date Day Month Year

Physician

**Clinical evaluation**

Date of evaluation	Day	Month	Year			
Physical examination	<input type="checkbox"/> no	<input type="checkbox"/> yes	GRF			ml/min
Chest X-ray	<input type="checkbox"/> no	<input type="checkbox"/> yes	LVEF			%
CT of chest	<input type="checkbox"/> no	<input type="checkbox"/> yes				
X-ray of the primary tumor site	<input type="checkbox"/> no	<input type="checkbox"/> yes				
Bone scan	<input type="checkbox"/> no	<input type="checkbox"/> yes				
Alkaline phosphatase					..... (specify unit)	LDH
						..... (specify unit)

**Status**

Tumour status						
<input type="checkbox"/> No evidence of disease	<input type="checkbox"/> Local recurrence	<input type="checkbox"/> Distant metastasis				
<input type="checkbox"/> Death	Date	Day	Month	Year	Autopsy	<input type="checkbox"/> no <input type="checkbox"/> yes
<input type="checkbox"/> Died from osteosarcoma	<input type="checkbox"/> Died with osteosarcoma from other cause					
<input type="checkbox"/> Died from treatment related complications	<input type="checkbox"/> Died NED from other causes, specify; .....					

**In case of distant metastase(s)**

Lung	<input type="checkbox"/> no	<input type="checkbox"/> yes	<input type="checkbox"/> unilateral	<input type="checkbox"/> bilateral	
Liver	<input type="checkbox"/> no	<input type="checkbox"/> yes	Number of metastases		
Bone	<input type="checkbox"/> no	<input type="checkbox"/> yes	Number of metastases		
<input type="checkbox"/> Other, specify; .....					

**Treatment for relapse**

<input type="checkbox"/> Curative intent	<input type="checkbox"/> Palliative intent
Treatment plan:	<input type="checkbox"/> chemotherapy <input type="checkbox"/> surgery <input type="checkbox"/> other, specify; .....

Osteosarcoma SSG XIV  
**Serious adverse event**

**Form 10**

Name (first & family name)  
Date of birth (day, month, year)

Send to:  
SSG secretariat  
Regional Tumour Registry  
Lund University Hospital  
SE-221 85 LUND  
Sweden

Hospital and department

Date Day Month Year

Physician

Course information: .....

.....

Description of event: .....

.....

Outcome of the event: .....

.....

Present status: .....

.....

Concomitant medications: .....

.....

Category of event: .....

.....

- Suspected causal relationship:
- unrelated
  - unlikely
  - possible
  - probable
  - definite