

Scandinavian Sarcoma Group  
& Oncologic center  
Lund, Sweden

# **EUROBOSS I**

## **A European treatment protocol for bone-sarcoma in patients older than 40 years**

This document describes a collaborative study in patients aged 41 to 65 years with high-grade bone sarcoma and provides information for entering patients into the protocol. The trial committee does not intend it to be used as an aidmemoire or guide for treatment of non-registered patients. Protocol amendments may be necessary; these will be circulated to known participants in the trial, but institutions entering patients are advised to contact the appropriate study centers to confirm the correctness of the protocol in their possession. Before entering patients clinicians must ensure that the study protocol is approved by their respective ethical committee.

Due to their rarity, the treatment of the tumors object of the present study is recommended only in centers experienced in bone sarcomas.

## **PREFACE**

The trial EUROBOSS 1 is a multicentre prospective study for patients older than 40 years with high-grade bone sarcoma. Because of the low incidence of bone sarcomas, multiinstitutional collaborations are essential to address questions concerning diagnosis and treatment. The current participating intergroups (ISG, COSS and SSG) cover a population of approximately 200 million people, and together these organisations claim to provide an adequate patient volume to explore the aims of the current study. The trial is open for participation by other internationally recognised osteosarcoma groups or institutions provided agreement from the other groups.

The present EUROBOSS I protocol is based on the experience of the participating intergroups in the treatment of bone sarcomas and their past and present osteosarcoma protocols.

A working committee consisting of the three intergroup co-ordinators (Stefano Ferrari, Stefan Bielack and Sigbjørn Smeland) have initiated this protocol:

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## SCANDINAVIAN SARCOMA GROUP

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 co-operation. Accordingly, the Scandinavian Sarcoma Group was founded in 1979 with the aim to improve the prognosis for sarcoma patients within Scandinavia. Its work has led to a systematic organisation of sarcoma treatment, with guidelines for diagnosis, pathology, and treatment now generally accepted by all tumour centers in Scandinavia.

The first Scandinavian non-randomised neo-adjuvant chemotherapy trial for high-grade osteosarcoma localised to the extremities, SSG II, was based on the Rosen T-10 protocol and was carried out during 1982–1989. The protocol represented a breakthrough in the treatment of osteosarcoma in Scandinavia with a > 40% improvement in outcome compared to historical controls. The second osteosarcoma trial (SSG VIII), using a more aggressive preoperative combination chemotherapy, high-dose methotrexate, doxorubicin and cisplatin opened in 1990 and was closed in 1997. The outcome analysis of the SSG VIII study shows a further improvement of 10% in long-time survival. The first joint Italian/Scandinavian study, ISG/SSG I, activated March 1997, was undertaken to explore the effect of maximum dose-intensive chemotherapy including high-dose ifosfamide scheduled for all patients. The protocol was closed by September 2000 and replaced by our currently ongoing SSG XIV protocol.

**The SSG version of the EUROBOSS-1 protocol has been completed by the following five SSG members (here defined as intergroup members):**

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

The EUROBOSS I protocol will be activated by September 2002.

Lund, August 2002

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## **1. TREATMENT SCHEDULE**

## 2. INTRODUCTION

Wide surgical removal of the neoplastic lesion combined with adjuvant or neoadjuvant chemotherapy is currently considered the “standard” in the management of patients with osteosarcoma (1-3). Methotrexate (MTX), doxorubicin (DOX), cisplatin (CDP), and ifosfamide (IFO) are the four drugs with proven efficacy against osteosarcoma that have been used according to different schedules in chemotherapy protocols adopted in large monocentric and multicentric studies (4-9). Since the incidence of osteosarcoma peaks in the second decade of life (2), the studies reported in the literature usually involve patients younger than 40 years of age treated with dose intensive chemotherapy protocols (4-9).

Only a few studies contain data on the use of chemotherapy in patients older than 40 years with high grade osteosarcoma (10-16). In the retrospective EMSOS study (15), forms of 486 patients from 13 different centres were evaluated. Here it was shown that secondary osteosarcoma (post radiation osteosarcoma and Paget’s osteosarcoma), as well as patients older than 60 have a very poor prognosis. Moreover, it was shown an advantage in terms of prognosis for those patients who received some kind of chemotherapy. Unfortunately the study did not provide details on the different chemotherapy protocols used. In the COSS experience (16), 54 osteosarcoma patients 40-68 years old were more likely to present with axial tumor, secondary osteosarcomas, a prolonged history of symptoms compared to their younger counterparts. Also they were more likely to experience a delayed start of treatment. An age of 40 years or older was associated with inferior overall and event-free survival probabilities (55% and 42% at 5 years and 42% and 37% at 10 years). In multivariate analysis, however, age was not a prognostic factor, rather, the poor outcome seems to be due to the predilection for unfavorable sites. In fact, the corresponding survival figures for the >40 year old patients with extremity tumors (including both localized and primary metastatic tumors) were 59% and 50% at 5 years and 56% and 32% at 10 years. An Italian study (14) reported the results obtained in a selected population of 29 patients aged 40-60 with non-metastatic osteosarcoma of the extremity. They were treated with adequate surgery and adjuvant chemotherapy with DOX, CDP and IFO obtaining an 8-yr OS of 62%. The remaining studies (10-13) gave few data on this topic.

The proven efficacy of the chemotherapy regimens in children and adolescents with osteosarcoma would suggest the use of the same antineoplastic drugs also in older patients. Among the latter the use of the dose intensive chemotherapy protocols, may however be complicated by concomitant diseases (co-morbidity). Furthermore, physiological changes occur with aging, including decreased cardiovascular performance, decreased haematopoietic tissue activity as well as decreased renal function with implications for drug toxicity (17). On the other hand, age itself can not be considered a sufficient parameter to exclude patients from chemotherapy but “exclusions should be based on physiologic functional parameters, such as measures of renal, liver, and marrow function, or performance status” (18-19).

The vast majority of the osteosarcoma chemotherapy protocols are specifically planned for adolescents and children. Dose and schedule adjustments are to be made in planning chemotherapy protocols for older patients, especially for renally excreted agents, and for cardiotoxic drugs, and a strict hemopoietic support with hemopoietic growth factors is recommended (19-20).

Due to their rarity, a “standard” treatment option is not established for the non-osteogenic, non Ewing’s tumors of bone: Fibrosarcoma, Malignant Fibrous Histiocytoma (MFH), Leiomyosarcoma, Dedifferentiated Chondrosarcoma, Angiosarcoma. The wide surgical removal of the primary lesion is the cornerstone of the treatment also for these tumors (1), but the role played by the chemotherapy, and the antineoplastic drugs to be used is still under discussion.



A similar chemosensitivity, and similar ultrastructural characteristics have been reported for MFH, Fibrosarcoma, Leiomyosarcoma suggesting that these tumors can be effectively treated with multidrug chemotherapy protocols as for osteosarcoma based on cisplatin (CDP), doxorubicin (DOX), ifosfamide (IFO), and methotrexate (MTX) (21-27).

Chondrosarcoma is not a chemosensitive tumor (1), but a high-grade non-cartilaginous sarcoma can develop within a pre-existing chondrosarcoma (2). The dedifferentiated component usually shows the characteristics of MFH or osteosarcoma with a more aggressive and malignant behavior than that of the cartilaginous component. (2). Despite a wide surgical resection, distant metastases develop. Scant data come from the literature on the type of chemotherapy used, but usually the protocols were based on drugs active against the dedifferentiated component (28).

The rarity of high-grade bone sarcomas requires collaborative trials in order to establish the most effective drugs, the dose, and the duration of chemotherapy treatment. For osteosarcoma and MFH we have substantial data on the key role of the chemotherapy in the management of these tumours (especially in patients younger than 40). Little is known about the activity of chemotherapy in patients with rarer histologic subtypes (fibrosarcoma, leiomyosarcoma, angiosarcoma of bone, dedifferentiated chondrosarcoma), also characterised by an aggressive metastatic behaviour. In the current trial, all patients are scheduled to receive similar treatment with the same chemotherapy regimen. With a common treatment for all histological subtypes, in addition to obtain general information of efficacy and feasibility, the protocol opens for separate sub-analyses according to the different histologic categories included

### **3. AIMS AND GENERAL PROTOCOL DESIGN**

The present study is a first step of a process to establish the standard chemotherapy treatment with the aim to improve outcome for patients with these rare tumours. For this reason the study will be a non-controlled clinical trial.

In this regard, the study aims to determine the feasibility of intensive chemotherapy in this age group, and/or separate efficacy analyses according to the different histologic categories and whether the number of patients recruited by the co-operating groups permits future randomized studies.

#### **Primary aim**

To evaluate clinical outcome and chemotherapy-related toxicity in patients 41-65 years old with high-grade bone sarcoma treated with a three drug chemotherapy regimen containing adriamycin (DOX), cisplatin (CDP) and ifosfamide (IFO), and the addition of methotrexate (MTX) to poor histologic responders.

#### **Secondary aims**

To evaluate the histologic response to preoperative chemotherapy based on DOX, CDP and IFO in high-grade bone sarcomas in patients 41-65 years, and to evaluate the prognostic significance of this histologic response.

#### **Treatment Strategy**

Wide surgical removal of the tumor with the addition of a systemic treatment based on the antineoplastic drugs active against osteosarcoma (DOX, CDP, IFO, MTX). The use of radiation therapy will be given to patients with unresectable tumors. It is recommended in patients who

underwent inadequate surgical removal of the tumor. The addition of radiation therapy can not compensate for an adequate surgical treatment.

All the patients eligible for the study will receive the planned systemic treatment. Depending on clinical features, and feasibility of adequate surgical removal of the tumor, patients may receive primary chemotherapy followed by a post operative chemotherapy treatment or only an adjuvant chemotherapy. In case of immediate surgery, patients will receive an adjuvant treatment with the 3-drug regimen (CDP-DOX-IFO). In patients who will receive primary chemotherapy, the histologic response will be evaluated. **The evaluation of the histologic response will be performed in referral centers. Each group will indicate the different referral centers for the pathology.** following grading systems are allowed: Huvos system, SSG (30), Salzer-Kuntschik system, COSS (31), and percentage of necrosis system, ISG (32).

For the patients with an histologic response graded Huvos I, Salzer-Kuntschik 5-6 or less than 50% necrosis, MTX will be added in the post operative phase in case of adequate glomerular function (defined as creatinine clearance > 70 ml/min).

### **Start of the protocol**

The protocol will be active after approval by the appropriate ethic's committee of at least two of the participating groups.

### **Withdrawal**

In case of withdrawal of two groups the protocol will be closed early.

## **4. EVALUATION CRITERIA AND ESTIMATED PATIENT NUMBER**

### **Clinical outcome**

*Date of study entry:* date of the diagnostic biopsy

*Event-free survival (EFS):* calculated from the date of study entry to the date of first adverse event (distant or local recurrence, secondary malignancy or treatment related death) or last follow-up. Patients who never achieve a complete surgical remission have to be considered as an event on day 1 from biopsy.

*Progression-free survival (PFS):* calculated from the date of study entry to the date of tumor progression or last follow-up. (Clinical and/or radiological suspicion of local progression before surgery is not considered as progression)

*Disease-free survival (DFS):* calculated from the date of surgery of primary lesion and metastases, if present, to the date of distant or local recurrence or last follow-up.

*Metastasis-free survival (MFS):* calculated from the date of surgery of primary lesion and metastases, if present, to the date of distant recurrence or last follow-up.

*Overall survival (OS):* calculated from the date of study entry to the date of death or last follow-up.

*Chemotherapy toxicity:* chemotherapy toxicity will be graded and recorded according to NCI expanded common toxicity criteria (version 2.0-March 1998) (33).

**Estimated number of patients:** Patients will be enrolled over a three-year period for an estimated number of patient/year of 45.

**Pathologic review:** A panel of pathologists from the participating groups will review the histopathologic sections of biopsies and of the resected tumors.

## **5. DATA COLLECTION**

### **Common database**

A common database will be created at the intergroup secretariat (Sezione di Chemioterapia-Rizzoli; Bologna, Italy), and reports will be sent to the various group secretariats to collect all the informations (see enclosed list of data required) required from all the participating centres. Each group secretariat will enter the data into the Excell database and will send files with new patients and updated cases to the intergroup secretariat every six months.

The Intergroup secretariat will paste data in the common Excell database and will send this updated file to all the group secretariats.

### **Case Report Form**

Each group will prepare CRFs reporting data on the patients enrolled according to their standards. The only requirement of forms is to contain the informations requested for the common database.

## **6. PUBLICATION**

Data relating to EUROBOSS 1 must not be reported or published without prior consultation with the study chairmen. Any publication arising from the trials will have as its authors those who have produced the paper and acknowledgement to the intergroup members.

A final report of EUROBOSS 1 will be provided within 5 years after the completion of the projected patient accrual.

## 7. “RESOURCE GROUPS”

In a multi-center study employing aggressive poly-drug chemotherapy as an integrated part of a multi-disciplinary treatment, 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 participating groups have formed their “*Resource Group*”. Its task is to aid each treating physician to solve these problems. 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* 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. ETHICAL CONSIDERATIONS**

1. EUROBOSS I is a non-randomized phase II study based on the experience from previous osteosarcoma protocols of the participating intergroups (ISG, COSS, SSG) and the experience from recent medical literature.
2. Before the start of treatment, the patients will be informed about the nature of the disease, the treatment plan, its benefits and the 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 EUROBOSS “Resource Group” of specialists is established to assist in such situations.
5. Before entering patients clinicians must ensure that the study protocol has received clearance from their ethical committee.

## **9. CRITERIAE FOR ELIGIBILITY**

1. Histologically proven diagnosis of high-grade sarcoma of bone of any site and stage.
2. Any of the following histological types: osteosarcoma (high-grade surface, central primary and secondary), fibrosarcoma, malignant fibrous histiocytoma, leiomyosarcoma, dedifferentiated chondrosarcoma, angiosarcoma.
3. Age: 41 - 65
4. Normal bone marrow, hepatic, cardiac and renal function
5. Absence of contraindications to the use of cisplatin, doxorubicin and ifosfamide
6. Written informed consent

## **10. CRITERIAE FOR EXCLUSION**

1. Planned chemotherapy and/or follow-up not feasible
2. Previous chemotherapy treatment, which contraindicates the use of one or more drugs, included in the present protocol
3. Previous chemotherapy treatment for the current tumor
4. White blood count  $< 3.0 \times 10^9/L$ , and platelets  $< 100 \times 10^9/L$
5. Creatinine clearance  $< 70$  ml/min
6. Left ventricular ejection fraction  $< 55\%$  or fractional shortening rate of the left ventricle  $< 28\%$
7. Serum transaminases and bilirubin  $> 2$  times the normal values
8. ECOG performance status  $> 2$
9. Chondrosarcoma or small/round cell bone sarcoma including mesenchymal chondrosarcoma and Ewing's family tumors.

## **11. PRETREATMENT INVESTIGATIONS AND FOLLOW-UP**

### **Baseline**

1. Medical history and physical examination
2. Complete blood count
3. Serum creatinine, Na, K, urinalysis, GFR, TmP/GFR, bilirubin, transaminases, alkaline phosphatase (optional bone specific alkaline phosphatase), LDH.
4. Audiogram
5. EKG
6. Estimation of left ventricular ejection fraction (LVEF) with cardiac ultrasound or radionuclide ventriculography (MUGA) before first course of doxorubicin treatment
7. Conventional X-rays of the primary lesion
8. CT and MRI scan of the primary lesion
9. Total bone scan
10. CT scan of the chest
11. Additional investigations when clinically required

### **Before surgery\***

1. Physical examination
2. Complete blood count
3. Serum creatinine, Na, K, Mg., GFR, TmP/GFR, bilirubin, transaminases, alkaline phosphatase (optional bone specific alkaline phosphatase), LDH
4. Conventional X-rays of the primary lesion
5. CT and MRI scan of the primary lesion
6. CT scan of the chest
7. Additional investigations when clinically required

\*For those patients treated with primary chemotherapy.

### **End of treatment (about 4 weeks after chemotherapy completion)**

1. Physical examination

2. Complete blood count
3. Serum creatinine, Na, K, Mg, GFR, TmP/GFR, bilirubin, transaminases, alkaline phosphatase (optional bone specific alkaline phosphatase), LDH
4. Audiogram
5. Estimation of left ventricular ejection fraction (LVEF) with cardiac ultrasound or radionuclide ventriculography (MUGA) before first course containing doxorubicin
6. Conventional X-rays of the primary lesion
7. CT scan of the chest
8. Additional investigations when clinically required

## **12. FOLLOW-UP**

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 at each visit.
4. GFR and TmP/GFR 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.



## **13. CHEMOTHERAPY ADMINISTRATION**

### **13.0 General consideration**

#### **Before each cycle of chemotherapy**

1. Physical examination
2. Complete blood count, serum creatinine, Na, K, Mg, transaminases, alkaline phosphatase, LDH, urinalysis. GFR before each cycle with MTX. Tmp/GFR before each cycle with ifosfamide
3. After MTX administration: complete blood count, serum creatinine, Na, K, Mg, transaminases, serum MTX levels, urinalysis
4. After each cycle of chemotherapy with DOX, CDP, IFO: complete blood count, from day 9 to 16, on alternate days are suggested, but longer intervals are allowed if clinically feasible.
5. Additional investigations when clinically required.

#### **Bone marrow function**

Cycles with CDP, DOX, IFO require a minimum number of  $3 \times 10^9$ /L leukocytes (or  $1 \times 10^9$ /L of neutrophils), and of  $100 \times 10^9$ /L platelets. Cycles with MTX require a minimum number of  $2 \times 10^9$ /L leukocytes (or  $0.5 \times 10^9$ /L neutrophils), and of  $80 \times 10^9$ /L platelets.

#### **Renal function**

Cycles with CDP, IFO require serum creatinine levels in a normal range. Cycles with MTX require a GFR  $> 70$  ml/min. Episodes of reversible renal toxicity do not contraindicate further administrations of CDP and IFO. Persistent reduction of Tmp/GFR and electrolyte disturbances contraindicates the administration of IFO and CDP. Delayed MTX excretion with renal toxicity, even if reversible, is a contraindication to further MTX administrations.

#### **Cardiac function**

An EF  $> 55\%$  (or fractional shortening rate of the left ventricle  $>28\%$ ) is mandatory for the use of DOX. Before each cycles with DOX physical examination and EKG (optional) and before the last cycle an echocardiogram or MUGA-scan is required. In case of clinical signs or changes in EKG suggesting a possible heart dysfunction DOX is not administered, and the patient undergoes additional tests to assess the cardiac function. In case of no evidence of cardiac dysfunction DOX is administered. A  $> 10\%$  reduction of the ejection fraction (compared to the baseline) contraindicates further DOX administration. Despite a reduction of the ejection fraction, DOX can be delivered (short infusion) with the use of dexrazone (cardioxane) if considered of clinical relevance.

#### **Antiemetic treatment**

The antiemetic treatment will be decided by each Institution, but the use of 5HT3 antagonists and dexametazone is recommended for the cycles with CDP, DOX, IFO.

### 13.1 G-CSF

G-CSF support is mandatory (within ISG and SSG) after each course with IFO/DOX, IFO/CDP or CDP/DOX chemotherapy. G-CSF support is not necessary after MTX.

G-CSF is administered as a subcutaneous injection or i.v. infusion once daily at a dose of 300µg to patients < 80 kg and otherwise 480µg. 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  $5.0 \times 10^9/l$ .

### 13.2 Cisplatinum (CDP/DOX, IFO/CDP)

#### General considerations

CDP (cisplatinum) is administered in combination with doxorubicin (CDP/DOX) or (IFO/CDP).

Drug interactions: Aminoglycosides may augment the nephrotoxicity of cisplatinum.

*Blood check-ups on second day of cisplatinum infusion:* GOT, GPT (=ASAT, ALAT), creatinine, Mg, Ca, Na, K and P.

**Basal solution:** 0.9% NaCl with 20 mmol KCl/L and 3 mmol Mg/L.

a. *Prehydration:* 1000 ml of basal solution for 2 hours.

b. *Cisplatinum dose:* 50 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:* 2000 ml of basal solution should be given over a 12 hours period.

d. *Diuresis:* If < 800 ml in 6 hours, give furosemide 10-20 mg.

### 13.3 Doxorubicin (CDP/DOX, IFO/DOX)

Doxorubicin (DOX) is administered in combination with cisplatinum (IFO/DOX) or cisplatinum (CDP/DOX). DOX is started day 3 in both courses.

Doxorubicin (DOX) 60 mg/m<sup>2</sup> (CDP/DOX) is given as a 24 hours continuous infusion in 1 000 ml 5% glucose.

### 13.4 Ifosfamide (IFO/CDP, IFO/DOX)

*Blood check-ups 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:** 0.9% NaCl with 40 mmol NaHCO<sub>3</sub>/L + 20 mmol KCl/L.

a. *Prehydration and alkalinization:* Infuse 500 ml basal solution with Mesna 400 mg/m<sup>2</sup> over a 1 hour period.

b. **Dose:** The doses of ifosfamide is 3000 mg/m<sup>2</sup>/24 hours, each for two consecutive days, giving a total dose of ifosfamide of 6 000 mg/m<sup>2</sup>. Ifosfamide is resolved in 500 ml basal solution and infused in 2 hours.

c. **Postifosfamide alkalinization and mesna administration:** Immediately following the ifosfamide infusion: mesna 3 000 mg/m<sup>2</sup> in 2000 ml/m<sup>2</sup> basal solution in 22 hours.

e. **Diuresis:** If <400 ml/m<sup>2</sup> in 6 hours, give furosemide 10-20 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, 2000 ml/8hours with 1000mg/m<sup>2</sup> mesna should be infused until the urine clears. The ifosfamide infusion should then be (re)started.

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

f. **Additional alkalinization:** 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 minutes.

g. **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, 2000ml/8 hours with 1 000mg/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!

### 13.5 Methotrexate

High-dose Methotrexate is given post-operatively to poor responders only.

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

a. **Daily blood checks after starting the MTX infusion and until the serum MTX is <0.2 μmol/L:** GOT, GPT (= ASAT, ALAT), Na, K, S-creatinine.

b. *Prealkalinization and prehydration*: Use the following solution i.v.: 500 ml/m<sup>2</sup> 5% glucose with 100 mmol NaHCO<sub>3</sub>/L and 20 mmol KCL/L over a period of 60 minutes.

c. *Dose of methotrexate*: 8000 mg/m<sup>2</sup>

d. *Methotrexate* should be dissolved in 500 ml of 5 % glucose with 40 mmol NaHCO<sub>3</sub>/L and 20 mmol KCl/L. This methotrexate solution is infused over 4 (four) hours.

e. *Total fluid input/day until serum MTX concentration <0.2 µmol/L*

(T<sub>0</sub>-T<sub>24</sub>): 2 500 ml/m<sup>2</sup> (including prealkalinization, methotrexate infusion and oral fluids)

(T<sub>24</sub>-T<sub>48</sub>): 2 000 ml/m<sup>2</sup>

(T<sub>48</sub>-T<sub>72</sub>): 2 000 ml/ m<sup>2</sup>

(T<sub>72</sub>-T<sub>96</sub>): 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.

f. *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<sub>84</sub>. It is sufficient to give leucovorin until six (6) hours after the methotrexate concentration has fallen below 0.2 µmol/L.

g. *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<sub>4</sub> sample), and then at least at T<sub>24</sub> and every 24th hour until serum MTX is <0.2 µmol/L.

h. *Diuresis*: Give furosemide 10-20 mg if diuresis <400 ml/m<sup>2</sup>. 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.

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

j. *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.

## 14. DOSE ADJUSTMENTS

### **Methotrexate**

No dose reduction. In case of delayed MTX excretion and concomitant nephrotoxicity the following cycles of MTX are omitted.

### **Ifosfamide/cisplatin course**

If neutropenic (neutrophils  $<0,5 \times 10^9/l$ ) fever reduce following IFO/CDP cycle: IFO 75%, if repeated: 50%

If negligible myelosuppression with reduced dose: back to previous dose level.

If creatinine  $> 120 \mu\text{mol/l}$  following CDP: reduce the next dose to 75%. Omit CDP if repeated.

Peripheral neuropathy  $\geq$  Grade 3: omit CDP (sensory loss or paresthesia interfering with activities of daily living)

### **Ifosfamide/doxorubicin course**

If neutropenic (neutrophils  $<0,5 \times 10^9/l$ ) fever: reduce following IFO/DOX cycle: IFO 75%, if repeated: 50% If negligible myelosuppression with reduced dose: back to previous dose level.

### **Cisplatin/doxorubicin cycle**

If neutropenic (neutrophils  $<0,5 \times 10^9/l$ ) fever reduce following CDP/DOX cycle: CDP 75%, if repeated 50%.

If negligible myelosuppression with reduced dose: back to previous dose level.

If creatinine  $> 120 \mu\text{mol/l}$  following CDP: reduce the next dose to 75%. Omit CDP if repeated.

Peripheral neuropathy  $\geq$  Grade 3: omit CDP (sensory loss or paresthesia interfering with activities of daily living)

## 15. SERIOUS ADVERSE EVENTS, STOPPING RULES

### Adverse events

Death (other than death of disease) under treatment or within 12 months from the end of treatment will be regarded as adverse event, unless it is proven that there is no relation with therapy, e.g. traffic accidents.

Life-threatening treatment-related complications, i.e. CTC grade 4 toxicity of the following categories are regarded to be adverse events: cardiac, renal, hepatic\*, central nervous, peripheral nervous, skin.

CTC grade 4 neutropenia (and neutropenic infection), thrombocytopenia which resolve and do not have life-threatening consequences are to be expected with the protocol presented here and are not regarded as serious adverse events.

Any life-threatening event; however, must be reported (see SAE form) immediately, i.e. within the next working day, and followed up, regardless whether it falls within the categories listed above or not. All participating groups (institutions) will be notified about important toxicities according to GCP guidelines.

\* except following methotrexate chemotherapy

### Stopping rules

Toxic deaths: The expected toxicity is mainly based on previous experiences of the participating groups in chemotherapy protocols applied to a younger population (4, 6, 8). In the current protocol a dose adaptation of the drugs has been planned due to the age of patients included.

Interim analyses on severe acute toxicity (grade 4 other than haematologic toxicity and mucositis) and toxic deaths will take place twice a year by the "Resource group".

Log rank and crude percentage comparison tests will compare deaths not related to the underlying malignant disease to historical control in patients aged <41 years. If any of these tests is significant at  $p < 0.001$ , 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; then a full analysis will be considered. Based on previous experience (4, 6, 8) in younger patients the limit percentage has been set at 3%. The type 1 error (alpha) has been fixed equal to 0.05.

Example:

Number of treated patients	K	Pobs
20	3	15%
50	5	10%
100	6	6%

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

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

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## **II APPENDIX**

1. Participating centers within SSG
2. Patient information
3. Reporting of serious adverse events
4. Management of methotrexate toxicity and delayed methotrexate excretion
5. Calculation of renal tubular reabsorption of phosphate – TmP/GFR
6. WHO performance status
7. Associated research projects
8. Guidelines for pathology
9. Guidelines for surgery
10. Guidelines for radiotherapy

## 1. Participating centers and referral centers within SSG

(Referral centers are marked in bold)

		Responsible Pathologist	Responsible Orotopedic surgeon
<b>Sweden</b>			
<b>Karolinska Hospital</b>	<b>Stockholm</b>	<b>J Wejde</b>	<b>O Brosjö</b>
<b>Sahlgrenska University Hospital</b>	<b>Gothenburg</b>	<b>LG Kindblom</b>	<b>B Gunterberg</b>
University Hospital	Uppsala		
University Hospital	Umeå		
University Hospital	Linköping		
<b>University Hospital</b>	<b>Lund</b>	<b>H Domansky</b>	<b>A Rydholm</b>
<b>Finland</b>			
<b>University Hospital</b>	<b>Helsinki</b>	<b>T Böhling</b>	<b>A Kivioja</b>
University Hospital	Turku		
University Hospital	Tampere		
University Hospital	Kuopio		
University Hospital	Oulo		
<b>Norway</b>			
<b>The Norwegian Radium Hospital</b>	<b>Oslo</b>	<b>B Bjerkehagen</b>	<b>G Follerås</b>
Haukeland University Hospital	Bergen		
University Hospital (St. Olav)	Trondheim		
Univeristy Hospital	Tromsø		

**The evaluation of histologic response will be performed at the referral centers.  
A conclusion that a tumour is in-operable must be done at a referral center.**

## **2. Patient Information**

### **EURO-BOSS 1**

#### **An European treatment protocol for high-grade bone sarcoma in patients older than 40 years.**

You have recently been diagnosed with bone cancer. Primary bone tumours are very rare diseases, and in particular in your age group. The knowledge and the current standard therapy are mainly based on studies in children and adolescent, in which the use of modern chemotherapy has significantly improved survival. Evidence exists that this therapy is also effective in adult patients, but due to their rarity as up to now no firm conclusion can be made. This study aims to answer some of these questions. A collaboration between several European groups covering a population of more than 200 million should allow enough information to be obtained to make progress in the knowledge and treatment also for adult patients.

The planned chemotherapy according to this protocol is very intensive. We have made some adjustments to treatment given to younger patients since it is well known that normal changes occur with ageing including decreased bone marrow and kidney activity. In addition, we have included guidelines for dose adjustments during therapy to safely modify your treatment if necessary.

Acute side-effects almost always follow intensive chemotherapy. For you, these will include nausea, hair loss and bone marrow suppression. Those are all reversible and we will give you supportive medicine to reduce your discomfort. Due to the expected bone marrow toxicity you will be carefully monitored with blood tests between the cycles. Patients with low white blood cell counts harbour a high risk of developing serious and life-threatening infections. Infections start with fever and you will before starting therapy receive oral and written information with strict guidelines on how to react upon fever in periods with low blood values.

Intensive chemotherapy also has a significant risk of development of late organ complications. The most common include impaired function of heart, kidney and your sense of hearing. Men have a high risk of developing infertility but the sexual hormone production is generally not affected. Routinely all patients will go through specified investigation to ensure proper organ functions before, during and after completion of therapy. If necessary, treatment will be adjusted according to changes in organ function during therapy.

Your participation in this project will not change your therapy or require additional investigations since we consider the protocol as the current standard management of patients with bone tumours at your age group. With your participating you allow us to collect clinical data, blood

samples and tumour tissue for the present and possible future studies. Selected clinical data will be recorded anonymously and stored in a common study-database which is placed at the Rizzoli Institute in Bologna, Italy. 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. By signing the formula below, you accept your willingness to participate and confirm that adequate information has been given.

Dr. Sigbjørn Smeland

Chairman of osteosarcoma studies/Principal Investigator

Scandinavian Sarcoma Group

### **3. Reporting serious adverse events**

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 Tumor Registry, University Hospital of Lund, S-221 85 Lund, Sweden**

**Tel. +46-46-177555**

**Fax. +46-46-188143**

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

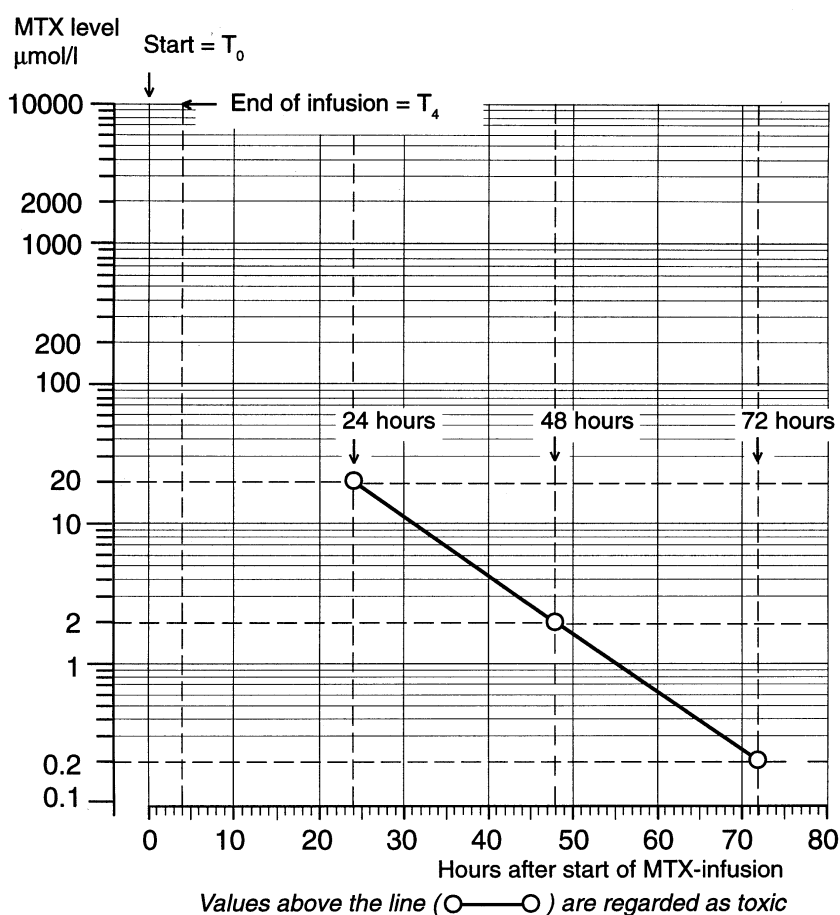
This must be done by fax within 24 hours of the initial observation of the events. Details should be documented on the specified Serious adverse event form. The study secretariat will forward all Serious adverse event report within 24 hours of receipt to all appropriate persons. A complete report must follow the initial report within 10 days.

## 4. Management of methotrexate toxicity and delayed methotrexate excretion

### 1. 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 within 24 hours 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.

### 2. 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. 19.

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 hours 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  $\text{pH} < 7$ .

## 5. Calculation of renal tubular reabsorption of phosphate – TmP/GFR

The ratio of the renal tubular maximum reabsorption rate of phosphate to the glomerular filtration rate (TmP/GFR) is used to monitor renal tubular function after administration of potential toxic chemotherapeutics (i.e. ifosfamide)

Calculation of TmP/GFR requires the calculation of the fraction tubular reabsorption of phosphate (TRP).

$$\text{TRP} = 1 - \left\{ \left( \frac{U_p}{P_p} \right) \times \left( \frac{P_{cr}}{U_{cr}} \right) \right\}$$

$U_p$  : urine phosphate

$P_p$  : plasma phosphate

$P_{cr}$  : plasma creatinine

$U_{cr}$  : urine creatinine

**If TRP is  $\leq 0.86$ :** Phosphate reabsorption is at its maximum and there is a linear relationship between changes in plasma phosphate and excretion. TmP/GFR is therefore given by the relation:

$$\text{TmP/GFR} = \text{TRP} \times P_p$$

**If TRP is  $> 0.86$ :** There is a curvilinear relationship between changes in plasma phosphate and excretion which fits a rectangular hyperbola. TmP/GFR is given by the relation:

$$\text{TmP/GFR} = 0,3 \times \text{TRP} / \{1 - (0,8 \times \text{TRP})\} \times P_p$$

TmP/GFR is measured in mmol/L. Reference ranges in patients 40-65 years are:

Male 0,90-1,35 mmol/L

Female 0,88-1,42 mmol/L

References:

1. Barth JH, Jones RG and Payne RB. Calculation of renal tubular reabsorption of phosphate: the algorithm performs better than the nomogram. *Ann Clin Biochem* 2000; **37**: 79-81
2. Payne RB. Renal tubular reabsorption of phosphate (TmP/GFR): indications and interpretation. *Ann Clin Biochem* 1998; **35**: 201-206

## **6. WHO performance status: ECOG**

- 0**      Able to carry out all normal activity without restriction
- 1**      Restricted in physically strenuous activity but ambulatory and able to carry out light work
- 2**      Ambulatory and capable of self-care but unable to carry out any work; up and about more than 50 % waking hours
- 3**      Capable of only limited self-care; confined to bed or chair more than 50% of waking hours
- 4**      Completely disabled; cannot carry on any self-care; totally confined to bed or chair

## **7. Associated research projects**

### **Micrometastases (only for patients with osteosarcoma)**

#### **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 tumor cell isolation, using monoclonal antibodies TP-3 and 9.2.27 in combination with Dynabeads<sup>R</sup>.
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 tumor 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 tumor 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 tumor 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 tumor 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% (11/18pts) 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 tumors had tumor cells in BM, none in PBL. Among patients with overt metastases at primary diagnosis 92% (11/12) 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 / Dept. 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 Dept. of Tumor Biology, Norwegian Radium Hospital, will perform the tumor 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 Tumor Biology, Norwegian Radium Hospital.

### **1.5. Practical aspects of sampling**

Samples will be obtained from each patient, preferably at 1) initial diagnosis, 2) at the time of primary surgery following preoperative chemotherapy, 3) at 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 tumor. If possible, fresh tumor 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 tumor 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 "tumor-markers".

### 1.7. Shipment of samples

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

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## **1.0 INFORMED CONSENT FOR PATIENTS REGARDING THE RESEARCH PROJECT**

### **”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 Micrometastasis 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



## 8. 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. 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.

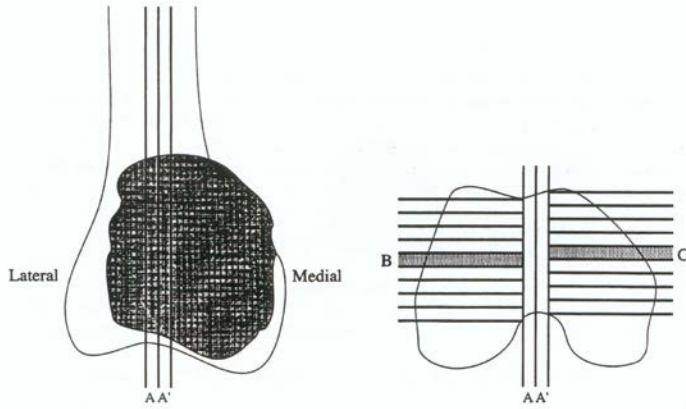


Fig. 1

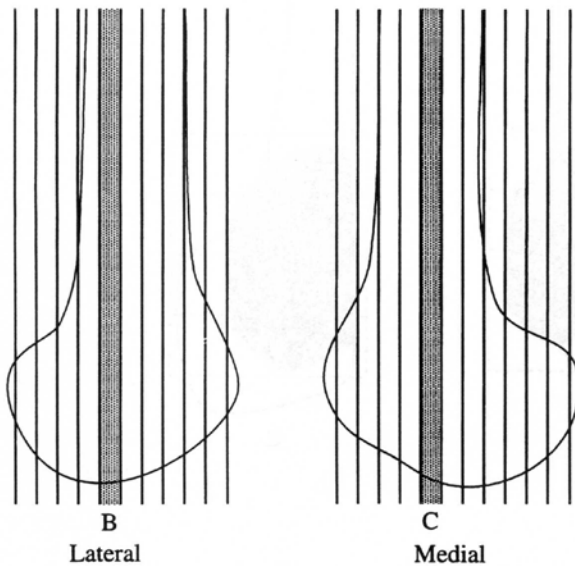


Fig. 2

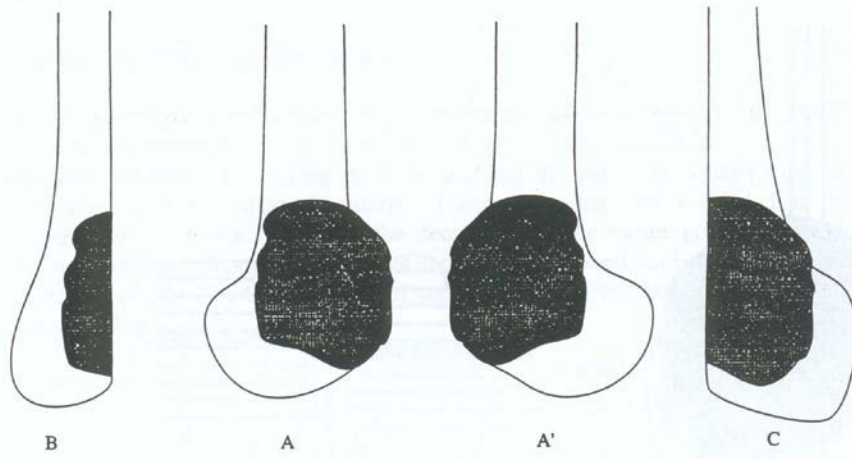


Fig. 3

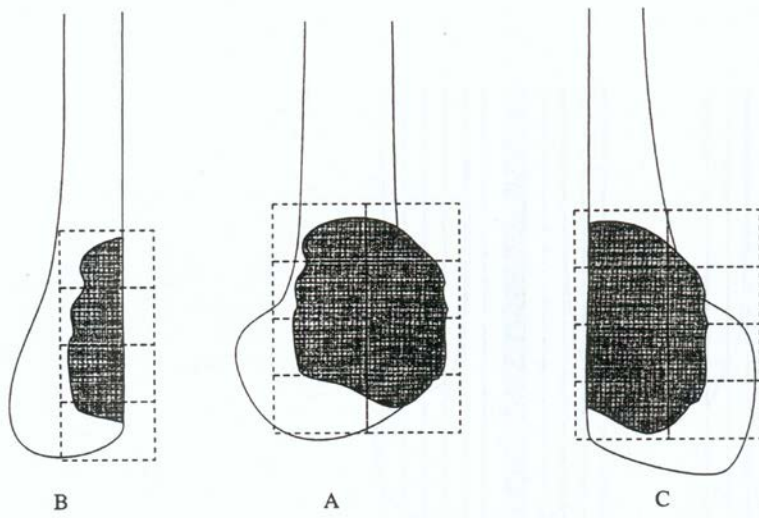


Fig. 4

## Grading of tumour response:

Grading of tumour response by assessment of treatment induced tumour necrosis is mainly based on examination of tumour specimen from children or young adults treated with neoadjuvant chemotherapy for highly malignant osteosarcoma. For most trials the cut-off between good and poor responders has been set at around 90% necrosis. In the current protocol less intensive neoadjuvant chemotherapy is given and different types of bone sarcomas with an expected poorer response to chemotherapy are included. For the actual age group (41-65 years) a potential highly toxic salvage therapy (high-dose methotrexate) is prescribed. Therefore, the definition of poor histologic response in this protocol is defined as little or no effect of chemotherapy identified.

Evaluation of prognostic impact of histologic response to preoperative chemotherapy is a secondary aim of this study. For SSG, tumour necrosis should be assessed according to SSG's modification of Huvos system.

Four histological grades are used:

- |           |  |
|-----------|--|
| Grade I   | Unaffected tumour with little or no identified effects   |
| Grade II  | Areas of affected tumour tissue detected<br>And one or both of the following criteria:<br>> 10% of examined tumour area reveal <i>unquestionable</i> viable tumour or<br>one or more areas of unaffected viable tumour exceed 2.5 mm in largest diameter |
| Grade III | < 10% of examined tumour area reveal <i>unquestionable</i> viable tumour and<br>No single area of unaffected viable tumour exceed 2.5 mm in largest diameter   |
| Grade IV  | No histologic evidence of viable tumour identified within the specimen.  |

With *unaffected* means a morphologic appearance closely resembling that of the pre-treatment 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.

### **Poor response:**

Poor response will correspond to a **grade I** response as defined above.

### **Good response:**

All others

In the case of several tumour manifestations (i.e. metastatic disease), all resected specimens should be assessed for histologic response. The overall response will be decided by the poorest response reported at any site.

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

## 9. GUIDELINES FOR SURGERY

Because of the complexity of the current 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 an oncologist. Follow-up discussions during the treatment are necessary.

Surgery is carried either at the start of treatment or after one cycle of chemotherapy, and within 21 days after completion of preoperative chemotherapy, as soon as possible after leucocyte (neutrophils  $>1.0 \times 10^9/L$  and platelets ( $\geq 100 \times 10^9/L$ ) recovery. Note that re-evaluation before surgery with chest X-ray and X-ray + CT/MRI of the involved bone are mandatory before surgery (see pp. 22 and 84).

### 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. **A conclusion that a tumour is in-operable must always be done at a referral center.**

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.

*Surgery of primary tumor:* Localized patients. The aim of the surgery is the removal of the tumor with wide surgical margins. The surgical planning is based on clinical data and radiographic examinations performed before start of chemotherapy and before surgery. If a limb salvage surgical procedure with wide surgical margins is not feasible, an amputation is recommended. No fixed guidelines can be claimed for the type of reconstruction.

*Patients with metastases at presentation:* In case of unresectable metastatic disease, a surgical removal of primary tumor with inadequate surgical margins can be accepted. When the metastases are considered resectable, the surgical procedure must be planned to achieve a wide removal of primary tumor.

*Surgery of the metastases:* Surgical resection of the metastatic lesions is always recommended when a complete surgery (removal of all evident metastatic disease, with no tumor tissue at the resection margins on histologic examination) can be planned on the basis of the radiographic

examinations performed before surgery. Whenever possible, surgical removal of the primary tumor and metastases should be performed at the same time to achieve an early removal of the macroscopic disease, and to reduce the delay in delivering chemotherapy after surgery.

For lung surgery, sternotomy or lateral thoracotomy is left to the discretion of the thoracic surgeon. In case of unilateral metastases on CT scan, it is recommended to surgically explore also that the controlateral side. In case of complete remission of lung metastases on CT scan after preoperative chemotherapy, the lung should nevertheless be explored surgically.

### **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

*Radical margin:* The whole compartment is removed.

*Wide margin:* A cuff of healthy tissue all around the tumour is included in the specimen.

*Marginal margin:* The excision is performed close to the tumour capsule and through the reactive zone in one or several planes.

*Intralesional margin:* (“Debulking surgery”). The excision is in one or several planes performed through the tumour.

## 10. GUIDELINES FOR RADIOTHERAPY

Surgical removal of all tumour tissue at any site should always be attempted and is the only proven way to achieve local control. In selected cases, however, radiotherapy plays an important role; i.e. when the mutilation from a surgical procedure seems unacceptable, when the tumour is unresectable for technical and/or medical reasons, or when the resection margins following surgery are involved judged by histopathological examination. Only tumours of malignancy grade 3 and 4 are included in this treatment proposal.

The patients treated with *post-operative irradiation* should receive an eq. total dose of 56-62 Gy in 2 Gy's fraction where margins are microscopically involved, and 64-70 Gy where macroscopic tumour tissue is left behind. For *definitive radiotherapy* of an inoperable osteosarcoma a radiation dose of 70Gy or more should always be attempted.

Selected institutions may advocate the use of intraoperative electron boost irradiation or brachytherapy by high-dose rate after loading techniques in cases where macroscopic tumour tissues are left behind or where the surgical margins obviously are inadequate.

### 4.1 Practical guidelines for delivery of radiotherapy

#### 4.1.1. Treatment equipment

High-energy photons generated by a linear accelerator should be used to treat deep-seated tumours; with a recommended radiation quality between 5 and 15 MV. If the target volume exceeds to the surface of the *patient*, adequate dose coverage should be obtained using bolus material rather than a mixed beam technique.

A three-dimensional computerised dose planning with inhomogeneity corrections shall be performed based on CT-scans performed on a flat table top. The CT-acquisition must cover all organs at risk as well as the entire target volume.

A multiple field technique, with optimal beam entry directions and beam weights, should be applied to obtain a homogenous dose to the PTV while at the same time minimise the dose to organs at risk. Normal tissue sparing should be attempted by field shaping using customised blocks (individually cut) or with a multileaf collimator.

Virtuell or conventional simulation procedures are mandatory for all fields. The position of all shielding blocks should be indicated on the simulation films or on BEV-plots as overlays on DDR's.

#### 4.1.2. Treatment equipment and verification

- Simulator port films or Beams Eye View-plots (BEV-plots) as overlay on Digital Reconstructed Radiographs (DDR).
- Treatment verification (portfilm or Electronic Portal Imaging (EPI) at the beginning, in the middle, and at the end of the treatment.
- Measurement of entrance dose or other equivalent methods to ensure that the correct calculated dose is given to the patient.
- Radiation treatment charts as well as the dose plan and port films shall be saved.

#### 4.1.3 Abbreviations (Source: ICRU Report 50)

GTV (Gross Tumour Volume) is the gross tumour extension; either palpable or visible/demonstrable by imaging techniques. Its delineation should preferentially be done in collaboration with a radiologist.

CTV (Clinical Target Volume) contains a demonstrable GTV and/or sub-clinical microscopic malignant disease. Original tumour extension should guide the delineation of CTV. Ideally this should be done in collaboration with the treating surgeon. In axial tumours a safety margin of 2 cm added to GTV should be attempted. For an extremity osteosarcoma a margin of 4-5 cm may be advisable.

PTV (Planning Target Volume) is a geometrical concept defined to select appropriate beam sizes and beam arrangements, taking into considerations the net effect of all the possible geometrical variations. Margins, 0,5-1,0 cm should be added to the CTV to take into account the effects of organ and patient movements and inaccuracies in beam and patient set-up in order to ensure that the prescribed dose is actually absorbed within the CTV.

#### 4.1.4. Fractionation

1.8 - 2.0 Gy/fraction given as 1 fraction per day and 5 fractions per week.

In case of bank holidays or machine breakdowns, the overall treatment time might be extended where the indication is adjuvant, whereas in case of macroscopic tumour tissue an accelerated compensation should be considered.

#### 4.1.5. Dose homogeneity

A maximum dose variation within the PTV between 95-105% according to the dose plan should be attempted. Hot spots outside the PTV with a maximum of 110% are acceptable only if total volume is less than 10 cm<sup>3</sup>. Moreover, single *hot spots* should not exceed 5 cm<sup>3</sup>.

#### 4.1.6. Organs at risk & Tolerance doses for normal tissues

All structures that may be associated with serious late toxicity should be delineated and dose-volume-histograms generated. The following maximum radiation doses should obtain:

Medulla spinalis (more than 5 cm) 45 Gy

Medulla spinalis (below 5 cm) 50 Gy

Brain tissue 60 Gy

N.opticus/chiasma 50 Gy

Intestine 50 Gy, depending on partial volume

Liver 20 Gy total – 50 Gy if less than ¼ volume is irradiated

Kidney 20 Gy (> 1/3)

Heart 30 Gy

Lung 20 – 60 Gy depending on partial volume

Urinary bladder 60 Gy

## 4.2 Follow up



The standard guidelines pointed elsewhere in this protocol should be followed. Particular emphasis should be placed on establishing whether a local recurrence, represents an “in field” central relapse or develops outside field or as an “edge” reminence.

CTC-score / RTOG-score vs. SOMA-lent guidelines should preferentially be used for score normal tissue complication rates.

### **4.3 Quality assurance (QA)**

Co-operative group multicenter clinical trials require means to guarantee uniformity of treatment procedures and QA is a prerequisite to evaluate patients entered from various institutions. A major deviation from the protocol may jeopardise the ability to answer questions addressed in the trial.

#### 4.3.1. Objectives

The aim of this QA part of the protocol is to ensure uniformity of all radiotherapy data for each patient. Specifically, this means;

- To establish a uniform description of the radiation therapy given in terms of volumes, doses and fractionation
- To evaluate compliance with the radiotherapy instructions
- To help enable a correct evaluation of the endpoints in the trial
- To create a platform for evaluation of reactions in healthy tissue, to radiation alone or in combination with the chemotherapy administered

#### 4.3.2. Elements of the QA

A final treatment evaluation of each single patient after completion of radiotherapy shall be performed. A responsible physicist will check the following parameters:

- Patient immobilisation
- 3D dose planning
- Dose prescription according to ICRU 50 and beam calibrations according to the IAEA Technical Report No. 277 or TRS 398
- Fractionation
- Volumes of GTV, CTV and PTV
- Field data for all fields
- Dose distribution in a transversal plane in or close to the centre of GTV
- Dose distribution in transversal, sagittal and frontal planes in or close to the centre of PTV
- Dose-volume histogram for all defined volumes of interest

- Copy of the treatment chart.

A questionnaire shall be filled in by the radiation oncologist at the completion of the treatment and sent to the Study Secretariat (Oncologic Centre, Lund for SSG-patients).

