Scandinavian Sarcoma Group
&
Oncologic center
Lund, Sweden

An Italian – Scandinavian treatment protocol for metastatic and pelvic osteosarcoma

ISG/SSG II is an Italian – Scandinavian joint multicenter, prospective study for evaluation of combination chemotherapy and high–dose chemotherapy followed by autologous bone–marrow transplantation for patients with overt pelvic or metastatic osteosarcoma at diagnosis. The study is not randomized and it is open to any specialized cancer center which is part of the ISG/SSG network, and which fulfills the protocol criteria and complies with the requirements for inclusion in the study (see commitment form).

All patients with metastatic and pelvic osteosarcoma treated according to this program should be reported to the Scandinavian Sarcoma Group secretariat.

Prepared by the Scandinavian and Italian Sarcoma Group Working Committee

PREFACE

The Scandinavian countries (Denmark, Finland, Iceland, Norway and Sweden) have a total population of about 24 million. They possess similar social structures, a modern medical service covering all inhabitants and 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 of the Group was to improve the prognosis for sarcoma patients in the area. This work has led to improvements in the organization of treatment; guidelines for diagnosis, pathology, and treatment have been established and are now generally accepted by tumor centers in Scandinavia.

Our first non–randomized neo–adjuvant chemotherapy trial for highly malignant osteosarcoma localized to the extremities employed the Rosen T–10 protocol (SSG II) and was conducted during 1982–1989 (4). The second osteosarcoma trial (SSG VIII), using more aggressive preoperative combination chemotherapy (i.e.) high–doses of methotrexate, adriamycin (doxorubicin) and cisplatinum started in 1990, and was replaced by the ISG/SSG I study on February 28, 1997.

Because of the low incidence of osteosarcoma, multiinstitutional collaboration is essential in dealing with important questions concerning treatment. The Italian Sarcoma Group and the Scandinavian Sarcoma Group prefer collaboration between relatively few population–based institutions, together providing an adequate patient volume. In addition to our aims concerning clinical treatment results, the current project means collaboration in clinical and basic research, including an analysis of new prognostic factors (micrometastases and multidrug resistance).

Because of the evidence of dose response and dose intensity effects in osteosarcoma, high–dose chemotherapy with stemcell rescue (PBSC) is an interesting approach, which has not yet been explored. In the ISG/SSG I high–dose treatment with PBSC has been scheduled for patients with metastatic relapse, and in the current protocol the same approach is introduced for patients with poor prognostic features at initial presentation, i.e. patients with metastases or pelvic primary tumors.

The working group responsible for the design of the present protocol has consisted of

Dr. Thor A. Alvegård
Dept. of Oncology
University Hospital
SE–221 85 Lund

Dr. Gaetano Bacci
Dept. of Chemotherapy
Istituto Ortopedico Rizzoli
Via Pupilli 1
IT–40136 Bologna

Dr. Adalberto Brach del Prever
Dept. of Pediatric Oncology
University of Torino
Children Regina Margherita Hospital
P.zza Polonia 94
IT–10126 Torino

Dr. Carl Blomqvist
Dept. of Oncology
University Hospital
FI–00290 Helsinki

Dr. Stefano Ferrari
Dept. of Chemotherapy
Istituto Ortopedico Rizzoli
Via Pupilli 1
IT–40136 Bologna

Dr. Piero Picci
Istituto Ortopedico Rizzoli
Via Pupilli 1
IT–40136 Bologna

Dr. Gunnar Sæter
Dept. of Oncology
Norwegian Radium Hospital
NO–0310 Oslo

Dr. Amelia Tienghi
Medical Oncology Division
City Hospital
Via Missiroli 10
IT–48100 Ravenna

Dr. Thomas Wiebe
Dept. of Pediatric Oncology
University Hospital
SE–221 85 Lund

Dr. Tom Wiklund
Dept. of Radiotherapy and Oncology
University Hospital
FI–00290 Helsinki

Dr. Torgil Möller
Southern Swedish Regional Tumor Registry
University Hospital
SE–221 85 Lund

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

The ISG/SSG II protocol will be activated March 1, 1998.

Lund, February 28, 1998

Organization
of the Italian Sarcoma Group

Laboratorio di Ricerca Oncologica
Istituti Ortopedici Rizzoli
Via di Barbiano 1/10
40136 Bologna – Italy
Tel. +39–51–6366757 Fax +39–51–584422
E–mail stafflab@oncolabrizzoli.tizeta.it
Secretary: Dott.ssa Alba Balladelli

Chairman:	P. Picci, Bologna	Program committee:
Vice chairmen:	G. Bacci, Bologna	M. Campanacci, Bologna
	M. Carli, Padova	A. Madon, Torino
	M. Mercuri, Bologna	M. Marangolo, Ravenna
Secretary:	F. Gherlinzoni, Bologna	G. Paolucci, Bologna
		G. Schiliro, Catania

Subcommittees

Oncology (Adult)
G. Bacci, Bologna
A. Comandone, Torino
S. Frustaci, Aviano
A. Tienghi, Ravenna

Oncology (Pediatric)
G. Bernini, Firenze
A. Brach del Prever, Torino
M. Carli, Padova
L. Cordero di Montezemolo, Torino
B. De Bernardi, Genova
M.T. Di Tullio, Napoli
P. Rosito, Bologna

Statistics
A. Cazzola, Bologna
R. Rondelli, Bologna
D. Serraino, Aviano

Orthopaedic Surgery
S. Boriani, Bologna (Osp.Maggiore)
R. Capanna, Firenze
F. Gherlinzoni, Bologna
V. Ippolito, Brescia
M. Mercuri, Bologna
V. Zucchi, Milano

Radiotherapy
E. Barbieri, Bologna
A. De Paoli, Aviano
E. Emiliani, Ravenna
P. Olmi, Firenze
U. Ricardi, Torino
G. Sotti, Padova

Stem Cell Transplantation
L.B. Faulkner, Firenze
S. Frustaci, Aviano
R. Miniero, Torino
A. Pession, Bologna
A. Prete, Bologna
A. Tienghi, Ravenna

Central Surgery
P. Borasio, Torino
A. Briccoli, Modena
F. Di Filippo, Roma
M. Guglielmi, Padova
L. Solaini, Ravenna

Pathology
F. Bertoni, Bologna
A. Carbone, Aviano
M. Forni, Torino
A. Franchi, Firenze
V. Ninfo, Padova

Tumor Biology
N. Baldini, Bologna
G. Basso, Torino
A. Colombatti, Aviano
A.L. Pession, Bologna
A. Rosolen, Padova
G. Tonini, Genova

Protocols Chairmen

Osteosarcoma (Localized):	G. Bacci, Bologna, M. Mercuri, Bologna, A. Tienghi, Ravenna
Osteosarcoma (Advanced):	A. Brach del Prever, Torino, A. Comandone, Torino, A. Briccoli, Modena
Ewing's sarcoma (Standard risk):	P. Rosito, Bologna, S. Ferrari, Bologna, G. Frezza, Bologna
Ewing's sarcoma (High risk):	A. Pession, Bologna, E. Emiliani, Ravenna, A Tienghi, Ravenna
Adult soft tissue sarcomas (Localized):	F. Gherlinzoni, Bologna, S. Ferrari, Bologna,S. Frustaci, Aviano
Adult soft tissue sarcomas (Advanced):	A. Comandone, Torino, A. De Paoli, Aviano, P. Olmi, Firenze
Pediatric soft tissue sarcomas:	M. Carli, Padova, M. Guglielmi, Padova, G. Sotti, Padova
Multidrug resistance in O.S.:	N. Baldini, Bologna
Pharmacokinetics and toxicity in O.S.:	S. Ferrari, Bologna, A Comandone, Torino
Micrometastases in O.S.:	M. Manfrini, Bologna

Organization
of the Scandinavian Sarcoma Group

Scandinavian Sarcoma Group Secretariat
Southern Swedish Regional Tumor Registry
University Hospital
S–221 85 LUND
Phone: +46–46–177555, Fax: +46–46–188143
E–mail evy.nilsson@cancerepid.lu.se
Secretaries: Evy Nilsson and Ingrid Dahlberg

Chairman:	T.A. Alvegård, Lund	Program committee:	T.A. Alvegård, Lund
Vice Chairmen:	H. Bauer, Stockholm		H. Bauer, Stockholm
	C. Blomqvist, Helsinki		C. Blomqvist, Helsinki
Secretary:	G. Sæter, Oslo		L.G. Kindblom, Gothenburg
Vice Secretary:	A. Rydholm , Lund		U. Nilsonne, Stockholm
			G. Sæter, Oslo
Honorary:	N.O. Berg, Lund	Publication:	A. Walløe, Bergen
	B. Stener, Gothenburg		T.A. Alvegård, Lund
	L. Angervall, Gothenburg		I. Elomaa, Helsinki
Data management	T. Möller, Lund		L.G. Kindblom, Gothenburg
and epidemiology:	H. Olsson, Lund		O. Myhre-Jensen, Aarhus
Statistician	H. Anderson, Lund		U. Nilsonne, Stockholm

Subcommittees

Central registry
Chairman:
H. Bauer, Stockholm
Coordinators:
P. Gustafson, Lund
C. Trovik, Bergen
T. Wiklund, Helsinki

Epidemiology
Chairman:
H. Olsson, Lund
Coordinators:
L. Hardell, Örebro

Diagnostic radiology and nuclear medicine
Chairman
N. Egund, Copenhagen
Coordinators:
V. Söderlund, Stockholm
M. Winderen, Oslo

Morphology (Pathology and cytology)
Chairman:
L.G. Kindblom, Gothenburg
Coordinator:
M. Åkerman, Lund

Tumor Biology
Chairman:
N. Mandahl, Lund
Coordinators:
S. Knuutila, Helsinki
F. Mertens, Lund

Surgery
Chairman:
A. Rydholm, Lund
Coordinator:
G. Follerås, Oslo

Chemotherapy
Chairman:
H. Strander, Stockholm
Coordinators:
G. Sæter, Oslo
T. Wiebe, Lund

Clinical Pharmacology
Chairman
T. Skärby, Lund

Radiotherapy
Chairman:
C. Blomqvist, Helsinki
Coordinator:
I. Turesson, Uppsala

Past and present protocols chairmen	**Oncology**	**Surgery**	**Pathology**	**Radiotherapy**
Osteosarcoma: SSG II, SSG VIII, ISG/SSG I, ISG/SSG II	G. Sæter, Oslo T.A. Alvegård, Lund	O. Brosjö, Stockholm	T. Holmström, T. Böhling, Helsinki	
Ewing's sarcoma: SSG IV, SSG IX	I. Elomaa, Helsinki T. Wiklund, Helsinki	O. Brosjö, Stockholm	M. Åkerman, Lund	C. Blomqvist, Helsinki
Localized soft tissue sarcoma: SSG I	T.A. Alvegård, Lund	A. Rydholm, Lund	L. Angervall, Gothenburg N.O. Berg, Lund	C. Blomqvist, Helsinki
Advanced soft tissue sarcoma: SSG X, SSG XII	T.A. Alvegård, Lund G. Sæter, Oslo C. Blomqvist, Helsinki	J. Høie, Oslo	A.E. Stenwig, Oslo H. Willén, Lund	C. Blomqvist, Helsinki I. Turesson, Uppsala
SSG Central Registry: SSG VII	T.A. Alvegård, Lund	H. Bauer, Stockholm P. Gustafson, Lund	L.G. Kindblom, Gothenburg M. Åkerman, Lund	C. Blomqvist, Helsinki, I. Turesson, Uppsala

CONTENTS

1. TREATMENT SCHEDULE

2. INTRODUCTION

Following the introduction of aggressive chemotherapy with various combinations of high–dose methotrexate (MTX), doxorubicin (ADM), cisplatin (CDP) and ifosfamide (IFO), the long–term outcome for patients with localized, high–grade osteosarcoma has improved dramatically, with survival rates rising from about 15% to 70% (1–6). Treatment results have shown gradual improvement with increasing aggressiveness of the chemotherapy, and the importance of *dose–response relationships* and *dose intensity* has been demonstrated both at the level of tumor response and survival (4,7–10). In the current Italian–Scandinavian cooperative protocol for localized extremity osteosarcoma (ISG/SSG I), an optimalization of chemotherapy is attempted through dose escalation of the most active agents, individualization of MTX dose on the basis of serum levels, and prolonged drug infusion to reduce long term toxicity.

Despite the improvements seen with chemotherapy in osteosarcoma, the results for patients with overt metastatic disease at diagnosis remain poor, with overall survival in the 20–25% range (2,5,11,12). However, aggressive chemotherapy in combination with complete metastasectomy has a curative potential, and following metastatic relapse these treatment modalities can be shown to be of independent prognostic value for a favorable outcome (5,11). Other groups with poor prognosis include patients with tumors localized outside the extremities, particularly in the pelvis. In these patients, an increased metastatic potential may be related to a large tumor volume (13), and failure of local control also contributes to an inferior prognosis (14–16). Although other non–extremity localizations are also associated with poor prognosis, this group of patients are considered too heterogeneous as regards age and possibilities for primary tumor management to be suitable for an aggressive and rigidly scheduled protocol (16).

Due to the evidence of dose–response and dose intensity effects in osteosarcoma, high–dose chemotherapy with stem cell rescue (PBSC) is an interesting approach that has so far not been explored. In the ISG/SSG I protocol high–dose treatment with PBSC has been scheduled for patients with metastatic relapse, in the current protocol the same approach is introduced for patients with a poor prognostic features at initial presentation, i.e. patients with overt pelvic or metastases primary tumors.

3. AIMS AND GENERAL PROTOCOL DESIGN

(for treatment outline see p. 8)

ISG/SSG II is a prospective phase II study for patients with metastases from high–grade osteosarcoma at initial presentation and patients with pelvic localization irrespective of stage. It is an aggressive multiagent chemotherapy protocol directed towards an optimal choice of chemotherapeutic agents and maximal dose levels, in combination with primary tumor surgery and metastasectomy. The protocol is modified from the ISG/SSG I study, is based on the same choice of chemotherapeutic agents and incorporates high–dose chemotherapy with peripheral blood stem cell (PBSC) rescue.

The objectives of the study are:

1. In all patients with detectable metastases at initial presentation, to increase 5–year overall survival from 20% to 40%.

2. In patients who undergo complete metastasectomy, to increase 5–year overall survival from 40% to 60%.

3. In patients with operable pelvic osteosarcomas, to increase 5–year overall survival from approx. 30% to a level approaching that of extremity tumors (60%), and to increase local control from <50% to 80%.

4. To evaluate the prognostic importance of histologic response to preoperative chemotherapy in the primary tumor and metastatic lesions.

5. To evaluate whether patients who remain inoperable after the initial 6 chemotherapy courses can be converted to operability by high–dose chemotherapy with PBSC.

The ISG/SSG II study will be active from March 1, 1998. The estimated accrual per year is 15–20 patients with metastases and 7–10 patients with pelvic tumors. The study is expected to accrue patients for four years, giving a total number of 60–80 patients with metastases and 30–40 patients with pelvic tumors. The results will be evaluated by comparison to historical controls in the ISG and SSG databases.

4. COMMENTS REGARDING THE CHOICE OF CYTOSTATIC AGENTS AND COMBINATIONS

The preoperative regimen is the same as in ISG/SSG I, since further intensification is not feasible and because some patients have uncertain lung nodules, which can not be confirmed as metastases before thoracotomy.

High–dose methotrexate (MTX). The baseline dose is 12 g/m^2. The MTX dose is modified based on serum measurements, and the dose is escalated if the serum concentration at 4 h (end of infusion) in the previous course was below 1000 µmol/l.

Cisplatin (CDP) and doxorubicin (ADM). Both agents are given as long term infusions to reduce nephrotoxicity, ototoxicity (cisplatin), and cardiotoxicity (doxorubicin). This is of particular importance since the patient population largely consists of older children and adolescents. Cisplatin will be administered intravenously.

High–dose ifosfamide (Ifo). Recent results suggest that ifosfamide is one of the most active agents in osteosarcoma (3,5,17,18) and published as well as unpublished preliminary data from ISG and SSG indicate that high–dose ifosfamide may be particularly active (18,19). An Ifo dose of 15 g/m^2 has been chosen, given as a continuous infusion over 5 days. The pilot study preceding ISG/SSG I indicated that the short term toxicity is acceptable (see ISG/SSG I protocol for pilot data pp. 16–17).

High–dose chemotherapy with peripheral stem cell rescue (PBSC). ISG/SSG II is to our knowledge the first prospective study to include high–dose chemotherapy with PBSC rescue for patients with poor prognosis on conventional therapy; i.e. patients with metastases at presentation or pelvic primary tumor. This approach appears attractive based on the dose–response data and pharmacokinetic data available in osteosarcoma. High–dose treatment with carboplatin and etoposide is chosen due to a suitable toxicity profile, and recent data indicate activity of etoposide against bone and soft tissue sarcomas (5,20,21). Also, preliminary results from a "window" study conducted at Memorial Sloan Kettering Cancer Center demonstrates carboplatin activity in osteosarcoma (22).
High–dose chemotherapy is scheduled relatively early in the postoperative phase to reduce cumulative toxicity. The shortening of the postoperative treatment is partly compensated for by a double transplant approach.

Timing of PBSC harvest and choice of mobilizing regimen. Preliminary data both from ISG, SSG and other (23) institutions indicate that in osteosarcoma, PBSC harvest should be performed early in the chemotherapy sequence to secure adequate yields. In an ISG/SSG pilot series of approx. 10 patients, high–dose ifosfamide with G–CSF has been a suitable mobilizing regimen in most patients (yields of 4.0–8.0 $x10^6$ CD34+ cells/kg), but problems regarding PBSC mobilization has been encountered in some cases. Therefore, to avoid reduction in stem cell reserve before mobilization, G–CSF support should be avoided if possible in the first CDP1/ADM1 course, and the G–CSF dose after the Ifo mobilization course is 10 ug/kg/day. Two aphareses are generally necessary. Pilot results from the University Hospitals in Torino and Helsinki indicate that the mobilizing regimen for relapsed patients in the ISG/SSG I protocol (CyE^1 = cyclophosphamide/etoposide) give good PBSC yields, and one CyE^1 course is thus scheduled for all ISG/SSG II patients in the initial postoperative phase, so that further PBSC harvest can be attempted at this point if the initial yields are low.

Toxicity – results of the pilot study

In relation to the conventional part of the chemotherapy a large pilot series (82 patients) was conducted before the activation of ISG/SSG I (see pp. 16–17 in the ISG/SSG I protocol for details). The conclusion was that the protocol had relatively severe hematologic toxicity, but it was feasible with good dose intensity. Data on renal toxicity have shown reversible changes in tubular function, and a reduction in glomerular function in 50% of the patients that is of unknown duration (short follow–up). The toxicity data has so far not warranted changes in the ISG/SSG I study. Interim data from the ISG/SSG I study will be reviewed by the principal investigators every 6 months to allow protocol amendments to avoid unacceptable toxicity, and these results will of course also be of importance for ISG/SSG II. It should however be emphasized that patients entered in ISG/SSG II have a very poor prognosis on conventional treatment, and that the acceptability of toxicity must be evaluated accordingly.

So far, approx. 8 patients have undergone high–dose chemotherapy with HDE^2C and PBSC rescue, and all patients have had relatively rapid marrow recovery. Apart from one patient who developed a transient toxic dilatation of the small intestine (possibly due to carboplatin neurotoxicity), no undue toxicity has been seen.

5. ORGANIZATION

The main study secretariat is located in Sweden:

Regional Tumor Registry, University Hospital of Lund, SE–221 85 Lund, Sweden
Tel. +46–46–177555
Fax. +46–46–188143
E–mail evy.nilsson@cancerepid.lu.se

A register of ISG patients will be kept at Istituto Ortopedico Rizzoli, Via Pupilli 1, IT–40136 Bologna, Italy. All the Italian patients will be registered in the ISG register and its data will be sent to the main study secretariat in Sweden.

Tel.: +39–51–6366829 (Dr. Bacci)
+39–51–6366759 (Dr. Picci)
Fax.: +39–51–6366277 (Dr. Bacci)
+39–51–584422 (Dr. Picci)
E-mail picci@pt.tizeta.it

6. PUBLICATION

Both the ISG and SSG groups will have access to the entire database, and individual institutions are free to publish their own data. However, a main purpose is to publish the ISG and SSG patient materials together. In this process, the list of authors will be worked out in a collaboration between the principal investigators of ISG and the SSG publication committee.

7. ISG/SSG II "RESOURCE GROUP"

When running a multicenter study with multimodality treatment and multi–agent chemotherapy, unforeseen situations and complications may occur which may not be sufficiently covered in the protocol. In an attempt to minimize protocol violations and to ensure uniform handling of such situations, the ISG/SSG II working group has formed a "*Resource Group"* whose task will be to help the local clinician solving these problems.
Thus, 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.

Members of the Resource Group and Principal Investigators in the ISG/SSG II study

Chemotherapy:

Dr. Gaetano Bacci
Dept. of Chemotherapy
Istituto Ortopedico Rizzoli
Via Pupilli 1
IT–40136 Bologna
Tel +39–51–6366829
Fax +39–51–6366277

Dr. Gunnar Sæter
Dept. of Oncology
Norwegian Radium Hospital
Montebello
NO–0310 Oslo
Tel +47–22–934000
Fax +47–22–934553
Email: Gsaeter@online.no

Dr. Thor Alvegård
Dept. of Oncology
University Hospital
SE–221 85 Lund
Tel +46–46–177555
Fax +46–46–188143
Email:
Thor_Andreas.Alvegard@onk.lu.se

Dr. Thomas Wiebe
Dept. of Pediatric Oncology
Lund University Hospital
SE–221 85 Lund
Tel +46–46–171097
Fax +46–46–145459
Email:
Thomas.Wiebe@Barn.Lund.ltskane.se

Dr. Stefano Ferrari
Dept. of Chemotherapy
Istituto Ortopedico Rizzoli
Via Pupilli 1
IT–401 36 Bologna
Tel +39–51–6366829
Fax +39–51–6366277

Dr. Tom Wiklund
Dept. of Oncology
University Central Hospital
Haartmansgatan 4
FI–00290 Helsinki
Tel +358–9–4711
Fax +358–9–4714203

Dr. Amelia Tienghi
Medical Oncology Division
City Hospital
Via Missiroli 10
IT–48100 Ravenna
Tel +39–544–409217
+39–544–409245
Fax +39–544–409330

Dr. Adalberto Brach del Prever
Dept. of Pediatric Oncology
University of Torino
Children Regina Margherita Hospital
P.zza Polonia 94
IT–10126 Torino
Tel +39–11–3135222
Tel +39–11–3135245
Fax +39–11–6635695
Fax +39–11–3135487

Surgery:

Dr. Rodolfo Capanna
Chirurgia Oncologica
Ricostruttiva
C.T.O. Carreggi
Largo Palagi 1
IT–50139 Florence
Tel +39–55–4278072
+39–55–4278191
Fax +39–55–4278396

Dr. Otte Brosjö
Dept. of Orthopedics
Karolinska Hospital
SE–171 76 Stockholm
Tel +46–8–7292000
Fax +46–8–7294699

Dr. Mario Mercuri
1st Orthophaedic Clinic
Istituti Ortopedici Rizzoli
Via Barbiano 1/10
IT–40136 Bologna
Tel +39–51–6366841
Fax +39–51–331710

Dr. Gunnar Follerås
Dept. of Surgery
Norwegian Radium Hospital
Montebello
NO–0310 Oslo
Tel +47–22–934000
Fax +39–51–6446417

Dr. Aarne Kivioja
Dept. of Orthopedics
University of Helsinki
FI–00260 Helsinki
Tel +358–9–4711
Fax +358–9–4717481
Fax +47–22–934553
Email: Aarne.Kivioja@Helsinki.Fi

Dr. Antonio Briccoli
Dept. of Pathology Surgery
University of Modena
Via del Pozzo 71
IT–41100 Modena
Tel +39–59–422110
Fax +39–59–360159

8. ASSOCIATED RESEARCH PROJECTS

As a continuation of the ISG/SSG I study for localized osteosarcoma of the extremities, the following research projects are also part of ISG/SSG II:

1. The detection of micrometastatic disease in bone marrow and peripheral blood using monoclonal antibodies and immunobeads. Desired time points for sampling are before start of preoperative chemotherapy, at surgery, at the end of treatment and at later relapses.

2. Study of P–glycoprotein expression in tumor tissue at the following time points: before start of preoperative chemotherapy (primary tumor biopsy), at surgery (viable primary tumor and metastases) and at biopsy and surgery for subsequent relapses.

These research projects may give important knowledge regarding micrometastatic dissemination and chemotherapy resistance in patients with poor prognosis on conventional treatment, and will also generate new knowledge when compared to patients with localized extremity tumors treated according to ISG/SSG I.

Principal investigators and study secretariats:

1. Micrometastases:

Dr. Øyvind Bruland
Dept. of Oncology
Norwegian Radium Hospital
Montebello
NO–0310 Oslo
Norway
Tel +47–22–934000
Fax +47–22–934553

2. P–glycoprotein:

Dr. Nicola Baldini
Istituto Ortopedico Rizzoli
Via Pupilli 1
IT–40136 Bologna
Italy
Tel +39–51–6366759
Fax +39–51–584422
E-mail GIS2278@IPERBOLE.BOLOGNA.IT

For further details, please consult the ISG/SSG I protocol.

9. ETHICAL CONSIDERATIONS

1. ISG/SSG II is a non–randomized phase II study based on ISG and SSG experience, and on experiences in the recent medical literature.

2. Before the start of treatment, the patients (and/or parents) should 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 effects and side–effects of the treatment as well as the collection and registration of data 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 ISG and SSG provide a "Resource Group" of specialists to assist in such situations.

10. ELIGIBILITY CRITERIA

1. Histologically proven osteosarcoma of high malignancy grade (grade III or IV), with primary tumor localization in the pelvis or with metastases at initial presentation irrespective of primary tumor localization.

2. The diagnosis must be made by open or coarse needle biopsy.

3. Tumor origin should be in the marrow or on the bone surface.

4. No previous treatment given for osteosarcoma.

5. Age <40 years.

6. Normal hepatic and renal function.

7. WBC $\geq 3.0 \times 10^9$/l and platelets $\geq 100 \times 10^9$/l.

8. Chemotherapy must be started within four weeks from the histological diagnosis.

9. The patient registration form must be accompanied by representative histology slides (for verification of diagnosis) and conventional front and lateral x–rays of the entire involved bone (for estimation of tumor volume).

10. The Institution Commitment Form has been completed and submitted to the secretariat (for each individual patient).

11. 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. EXCLUSION CRITERIA

1. Previous malignancy other than basal cell carcinoma of the skin and in situ/non–invasive carcinoma of the skin or cervix.

2. Periosteal and paraosteal osteosarcoma.

3. Secondary osteosarcoma (e.g., following Paget's disease or irradiation).

4. Medical contraindications to the cytostatic agents and dose levels in question.

5. Planned chemotherapy and/or follow–up not feasible.

6. Patient's declining to participate in the treatment program.

12. PRETREATMENT INVESTIGATIONS

(see also flow–sheet in Appendix 1, p. 37)

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 or large coarse needle biopsy (representative slides should be sent to the study secretariat on registration). The diagnosis should be confirmed by two pathologists.

3. Laboratory studies:
   a. Complete blood count (Hemoglobin, white blood counts with differential, platelets)
   b. Serum creatinine, GFR estimation using the methodology of the individual institution, ALP, LDH, total bilirubin and liver transaminases
   c. Serum Na, K, and Mg
   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. CT and/or MRI scan of the entire involved bone
   c. A–P and lateral chest x–rays
   d. CT scan of the chest
   e. Total bone scan, preferably with dynamic study of the primary tumor area

5. Audiogram before first course of cisplatinum treatment.

6. Electrocardiogram (ECG).

7. Cardiac ultrasound, with estimation of left ventricular ejection fraction (LVEF), before first course of adriamycin treatment.

Recommended investigations (optional):

1. Sperm count. It is recommended that a sperm count be performed in all patients where it is feasible, and that these patients be offered sperm banking prior to chemotherapy.

13. RE–EVALUATION BEFORE SURGERY (week 11)

(see also flow–sheet in Appendix 1, p. 37)

Mandatory investigations:

1. Complete physical examination

2. Laboratory studies:
   a. Complete blood count (Hemoglobin, white blood cells with differential count, platelets)
   b. Serum creatinine, GFR estimation, ALP, LDH, total bilirubin and liver transaminases
   c. Serum Na, K, and Mg

3. Radiological studies:
   a. A–P and lateral conventional x–rays of the entire involved bone
   b. CT and/or MRI scan of the entire involved bone
   c. A–P and lateral chest x–rays
   d. CT scan of the chest

4. Electrocardiogram

Recommended investigations (optional):

1. Total bone scan, preferably with dynamic study of the primary tumor area

NOTE: In patients who are judged inoperable after preoperative chemotherapy, postoperative treatment including high–dose chemotherapy with PBSC is administered as scheduled, and these patients are re–evaluated after the second HDE^2C cycle with CT and/or MRI scans of all involved areas. If at least marginal surgery is judged possible, surgery is performed after recovery from the second HDE^2C cycle. In case of residual non–resectable disease, the patient is evaluated for experimental treatment after consultation with the Resource Group.

14. INVESTIGATIONS AT THE END OF TREATMENT (2 months after last therapy)

(see also flow–sheet in Appendix 1, p. 37)

Mandatory investigations:

1. Complete physical examination

2. Laboratory studies:
   a. Complete blood count (Hemoglobin, WBC with differential, platelets)
   b. Serum creatinine, GFR estimation, ALP, LDH , total bilirubin and liver transaminases
   c. Serum Na, K, Cl and Mg

3. A–P and lateral chest x–ray

4. CT scan of chest

5. Audiogram

6. Hepatitis serology A, B, C

Recommended investigations (optional):

1. Total bone scan

2. Sperm count in patients with sufficient sexual maturation

15. FOLLOW–UP (after end of treatment)

(see also flow–sheet in Appendix 1, p. 37)

Patients should be followed at 2 month intervals for 3 years, at 4 month intervals during the 4th and 5th years, and then at 6 month intervals until 10 years after the end of treatment.

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 (Hemoglobin, white blood counts, platelets), transaminases, ALP, LDH and serum creatinine at each visit.

4. Serum creatinine, GFR estimation at 4 month interval during the first year, at 6 month intervals during the second and third years, and then yearly.

5. Cardiac ultrasound with estimation of left ventricular ejection fraction at 6 months 12 month and then at 3 year 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 CT and/or MRI.

Recommended investigations (optional):

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

16. ADMINISTRATION OF "CONVENTIONAL" CHEMOTHERAPY

(see chemotherapy flow sheet on p. 8)

NOTE: Infusion volumes are specified per m^2 of body surface area in order to facilitate necessary adjustments for children. For adults, infusion volumes are generally given according to a body surface area of 2.0 m^2.

16.0 General considerations

Bone marrow function: CDP1/ADM1, CDP1, ADM2 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 $\geq 1.0 \times 10^9$/l and platelet count is $\geq 60 \times 10^9$/l.

16.1 General guidelines for G–CSF

G–CSF support is necessary following Ifo, ADM2 and CyE[1] courses. The second CDP1/ADM1 course should also be supported with G–CSF, but the first CDP1/ADM1 course should if possible be given *without* G–CSF support to secure a good PBSC yield after the next Ifo course. G–CSF is not used following MTX chemotherapy.

G–CSF is given as a subcutaneous injection once daily. The dose for children is 5 ug/kg. Adults are given 300 ug if body weight is <80 kg and 480 ug if body weight is >80 kg.

G–CSF administration starts 48–72 hours after termination of chemotherapy and the 7–8 doses are recommended. G–CSF must be discontinued at least 24 hours before the start of the next chemotherapy course and is stopped if total WBC count exceeds 10.0 x 10^6/l.

SSG institutions are obliged to use Filgrastim.

NOTE: Recommendations concerning the use of G–CSF in connection with peripheral stem cell (PBSC) harvest and HDE[2]C chemotherapy are presented in separate guidelines (p. 31).

16.2 High–dose methotrexate (MTX1 courses)

MTX1 is started day 1 week 0 and 6.

Drug interactions: Avoid simultaneous use of the following drugs because of the risk of interactions: penicillin, NSAID, probenecid, sulfamethoxazole and trimethoprim, as well as organic acids such as salicylic acid.

a. *Blood check*: Before starting MTX infusion: Creatinine, GFR (according to p. 18), hemoglobin, white blood cells, neutrophil count, platelets, albumin, liver enzymes and total bilirubin, Na, K. After starting the MTX infusion and until the serum MTX is <0.2 umol/l, the following blood tests should be done daily: Bilirubin, transaminases, Na, K, S–creatinine.

b. *Prealkalinization and prehydration:* Use the following solution i.v.: 250 ml/m^2 glucose 5% with 100 mmol $NaHCO_3$/l and 20 mmol KCL/l over a period of 30 minutes.

c. *Dose of methotrexate:* **MTX1** 12 000 mg/m^2, increase by 2 000 mg/m^2 if four (4) hour (at the end of infustion) methotrexate concentration <1 000 μmol/l in the previous course.

d. *Methotrexate* should be dissolved in 500 ml/m^2 of NaCl 0.9% with 40 mmol $NaHCO_3$/l and 20 mmol KCl/l. This methotrexate solution is infused during 4 (four) hours (T_0–T_4).

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

(T_0–T_{24}): 1 500 ml/m^2 (including prealkalinization, methotrexate infusion and oral fluids)
(T_{24}–T_{48}): 2 000 ml/m^2 (including oral fluids)
(T_{48}–T_{72}): 2 000 ml/ m^2 (including oral fluids)
(T_{72}–T_{96}): 2 000 ml/ m^2 (including oral fluids)

For all i.v. fluid in the posthydration, use 5% glucose with 40 mmol $NaHCO_3$/l + 20 mmol KCl/l.

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

f. *Leucovorin (folinic acid) rescue:* 8 mg/m^2 intravenously or orally every 6th hour, beginning 24 hours after start of methotrexate infusion. Normally, leucovorin is given by eleven (11) doses until T_{84}. It is sufficient to give leucovorin until six (6) hours after methotrexate if the 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_4 sample), and then at least at T_{24} and every 24th hour until serum MTX is <0.2 μmol /l.

h. *Diuresis:* Give furosemide 0.5–1.0 mg/kg if diuresis <300 ml/m^2 in 6 hours the first 24 hours and <400 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^2/24 hours because of delayed MTX excretion, the minimum level of diuresis should be increased to 600 ml/m^2 in 6 hours.

i. *Additional alkalinization:* If the urine pH is <7 give 2 mmol $NaHCO_3$/kg during 30 minutes.

j. *Monitoring MTX and fluid volume:* All serum MTX values, i.v. and oral fluids, diuresis, urinary pH, supplemental $NaHCO_3$ and furosemide should be listed on a detailed chart to ensure accurate monitoring of MTX clearance and fluid balance.

16.3 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 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 (below). Patients in this situation will be treated by continued hydration and alkalinization of the urine with 3 000 ml/m^2/24h of 5% glucose with 40 mmol $NaHCO_3$/l and 20 mmol KCl/l. In this case, the minimum diuresis should be increased to 600 ml/m^2/6h. 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, 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

3. Adjustment of leucovorin dose during delayed methotrexate excretion

Total daily dose of leucovorin (mg) = Patient's actual serum MTX x standard daily dose of leucovorin / 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. 21.

The upper limit of serum MTX at 24 hours is 20 µM
at 48 hours is 2 µM
at 72 hours is 0.2 µM

Example:
If the 48 hour methotrexate level was 40 µM, the leucovorin dose should be adjusted to:

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

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 µM, give leucovorin in doses of 8 mg/m^2 orally every 6 hours until the serum level is <0.2 µM after one dose.

Note: Always continue to monitor urine pH and give more $NaHCO_3$ if pH < 7.

Order sheet methotrexate

Hour	Time day/hour/min.	Mtx-conc. µmol/lit	Leocovorin dose mg Nurse sign	Furosemide Time, dose Nurse sign	Extra. $NaHCO_3$ Time, mmol Nurse sign.
T4	/ /	*			
T18	/ /				
T24	/ /	*			
T30	/ /				
T36	/ /				
T42	/ /				
T48	/ /	*			
T54	/ /				
T60	/ /				
T66	/ /				
T72	/ /	*			
T78	/ /				
T84	/ /				

*Mandatory

16.5 Cisplatin (CDP1/ADM1 courses)

General considerations

CDP1/ADM1 courses are started day 1 week 1 and 7.

Drug interactions: Aminoglucosides 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 and K.
On second day of cisplatinum infusion: liver enzymes including bilirubin, creatinine, Mg, Ca, Na and K.

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^2 of basal solution for 2 hours.

b. *Cisplatinum dose:* 60 mg/m^2/day (CDP1/ADM1 courses) is administered in 2 000 ml/m^2/day of basal solution as a continuous infusion for 2 days (48 hours).

NOTE: CaCl must *not* be infused together with cisplatinum in the same infusion line because it causes the formation of a stable complex of $CaSO_4$ that blocks the catheter.

c. *Posthydration:* 500 ml/m^2 of basal solution should be given over a 2 hour period.

d. *Diuresis:* If <400 ml/m^2 in 6 hours, give furosemide 0.5–1.0 mg/kg. The maximum dose of furosemide is 20 mg.

16.6 Doxorubicin (ADM1 and ADM2 courses)

ADM1 is administered only in combination with cisplatinum (CDP1/ADM1). ADM1 is started day 3 immediately following the cisplatinum posthydration weeks 1 and 7. ADM2 is started day 1 weeks 15 and 21.
Adriamycin (doxorubicin) 75 mg/m^2 (CDP1/ADM1) or 90 mg/m^2 (ADM2) is given as a 24 hour continuous infusion in 1 000 ml 5% glucose, see order sheet p. 26.

Order sheet cisplatin och doxorubicin

16.8 High–dose ifosfamide (Ifo courses)

Ifo is started day 1 week 4 and 10.

Blood check–ups before start of ifosfamide: Hemoglobin, white blood counts, neutrophils, platelets, albumin, liver enzymes including bilirubin, Na, K, Mg, Ca, creatinine, GFR before Ifo week 26 and 32, Uristix for hematuria.
Daily: Hematocrit, white blood counts, platelets, venous acid/base (or serum bicarbonate), uristix, creatinine, Na, K, Ca, Mg, liver enzymes including bilirubin.
Basal solution: 5% glucose with 40 mmol $NaHCO_3$/l + 20 mmol KCl/l.

a. *Prehydration and alkalinization:* Infuse 500 ml/m^2 over a 2 hour period.

b. *Dose:* The doses of ifosfamide and of mesna are 3 000 mg/m^2/24 hours, each for 5 consecutive days, giving a total dose of both ifosfamide and mesna of 15 000 mg/m^2.

c. *Ifosfamide/Mesna infusion:* Ifosfamide and mesna are infused i.v. in 2 000 ml/m^2/24 hours of basal solution.

d. *Postifosfamide alkalinization and mesna administration:* Following the ifosfamide/mesna infusion on day 5: mesna 1 500 mg/m^2 in 1 000/ ml/m^2 basal solution in 8 hours. Alternatively, mesna 500 mg/m^2 and $NaHCO_3$ 500 or 1 000 mg may be given orally 4 and 8 hours after the ifosfamide–mesna infusion.

e. *Diuresis:* If <400 ml/m^2 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. If ++ or more for blood, ifosfamide should be withheld and normal saline should be infused i.v. until the urine clears. The ifosfamide infusion should then be started again.

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 $NaHCO_3$/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 dosedependent and may be aggravated by metabolic acidosis (24–26). 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. 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 3x daily should be given when starting ifosfamide. This will usually prevent further CNS toxicity (26), as noted in patients at Norwegian Radium Hospital and at Sahlgrenska Hospital, Gothenburg.

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!

Order sheet ifosfamide

16.10 Cyclophosphamide/Etoposide (CyE^1 course)

Cyclophosphamide: Cyclophosphamide in the dose of 4 000 mg/m^2 is given as a 3 hour continuous intravenous infusion, together with Uromitexan in the same dose (4 000 mg/m^2). Cyclophosphamide and Uromitexan is dissolved in 500 ml 5% glucose.

Posthydration: 3 000 ml/m^2/day during 21 hours. Use 5% glucose with 40 mmol Na/l and 20 mmol K/l.

E^1: Etoposide in the dose of 200 mg/m^2/24 hours is given as a continuous infusion over 72 hours (total dose 600 mg/m^2). Etoposide is dissolved in 1 500 ml/m^2/24 hours of 0.9% NaCl (total fluid volume over 72 hours 4 500 ml/m^2). Start the infusion, when the posthydration after cyclophosphamide is completed.

G–CSF administration and PBSC–harvest If CyE^1 is given without PBSC mobilization, the G–CSF dose is 5 µg/kg. If CyE^1 is given to mobilize PBSC, G–CSF 10 µg/kg/day is started 48 hours after the termination of chemotherapy. If the yield is insufficient (<4x10^6 CD34+ cells/kg), consider a second CyE^1 conditioning cycle before HDE^{2}C treatment. The mobilization of CD34+ cells into peripheral blood is monitored and CD34+ cells are harvested according to local routines.

17. HIGH–DOSE ETOPOSIDE/CARBOPLATIN WITH PERIPHERAL STEM CELL RESCUE (HDE^{2}C with PBSC rescue)

General comments

Dose limiting toxicity from single high–doses of etoposide consists of mucositis (stomatitis, diarrhea) and from single doses of carboplatin of neuropathy (peripheral neuropathy, ototoxicity), nephrotoxicity, and hepatic toxicity.

Toxicity data from double high–dose treatment using HDE^{2}C with PBSC are derived from three phase 1–2 studies on adult germ cell tumors and one pediatric study on mixed tumors. In one study, high–dose therapy was part of the primary therapy (30), whereas in the three others high–dose therapies were parts of salvage therapies, frequently after extensive use of platinum containing chemotherapy. Thus, data from the previous studies can to some extent be extrapolated to the current protocol.
The studies in pretreated patients aimed at optimizing treatment by increasing the doses of carboplatin (27) or of carboplatin and etoposide (28–29).

In the first study the maximal tolerated dose (MTD) of carboplatin was 2 100 mg/m^2 and the etoposide dose was 2 250 mg/m^2 given as a short infusion (28). No second line treatment could be given to 21% of the patients because of toxicity. The treatment related mortality was 19% (multiorgan failure, CNS hemorrhage, myocardial infarction, VOD, sudden death). Non–lethal toxicity consisted of delayed nausea and vomiting, mucositis requiring morphine treatment, peripheral neuropathy, ototoxicity, transient nephrotoxicity and transiently elevated transaminases. Most patients also needed supplements of Mg.

In the second study, carboplatin dose was based on the glomerular filtration rate, (GFR), using the AUC formula, mentioned by Calvert, and etoposide was set at 1 200 mg/m^2 as a short infusion. Doses were increased from AUC 15 mg x min/ml to MTD of 30 mg x min/ml. This corresponds to total MTX doses of 1 515–3 650 mg (median 2 910 mg). 12 of 23 patients received a second cycle after 2–3 months. The mortality was 13% (sepsis, renal failure, lung toxicity and enterocolitis). Non–lethal toxicity consisted of cardiac (congestive heart failure) and central nervous toxicity (seizures).

In the pediatric study (29), carboplatin was increased from 1 200 to 2 100 mg/m^2 and etoposide from 960 to 1 500 mg/m^2. Two high–dose treatments were given to 44% of the patients. Hepatotoxicity was doselimiting. Four of 25 patients died of toxicity (CNS hemorrhage, sepsis and enterocolitis). Recommended doses for further studies were carboplatin 2 100mg/m^2 and etoposide 1 500 mg/m^2.
Based on these studies, and on the type of severe toxicity that is deemed acceptable, any chosen dose level for this protocol may well be inaccurate. Our current recommendation is high pretreatment doses of the patient population. The doses of carboplatin per m^2 should be calculated. However, dosing based on GFR is now used more frequently and may prove advantageous. However, this method is affected by the method employed to determine GFR (CrEDTA, creatinine clearance based on 24h urine collection or serum creatinine level). Moreover, in pediatric patients the adequacy of basing the dose on the AUC remains to be determined.
Since etoposide was not included in the previous therapy, dosing of etoposide should probably have priority over carboplatin.

Only moderate doses of carboplatin should be used initially, but then the amount can be gradually increased by adjusting the protocol after regularly assessing the response to treatment.

Pre–therapy investigations

These should include: body weight, audiogram, chest X–ray, ECG, blood type, Hemoglobin, white blood counts, platelets, creatinine, GFR, Na, K, Ca, Mg, P, urate, albumin, glucose, liver enzymes, bilirubin, CRP, sedimentation rate and urine sediment.
Cultures from the pharynx, stools and urine.
Serology for CMV, hepatitis A, B, C, HIV, virus antibody screening and EBV.
Lung function and echocardiography are optional investigations that may be included.

Check–up before second HDE^{2}C and PBSC

This check–up should include: body weight, audiogram, chest X–ray, ECG, blood type, Hemoglobin, complete white blood count, platelets, creatinine, GFR, Na, K, Ca, Mg, P, urate, albumin, ALAT, alkaline phosphatase (ALP), lactate dehydrogenase (LDH), gamma GT, bilirubin, CRPsedimentation rate and urine sediment.
Cultures from the pharynx, stools and urine.
Lung function and echocardiography are optional investigations that may be included.

Check–up during the HDE^{2}C and PBSC treatment

Check–up should include: creatinine *twice daily (watch out for rapid development of progressive renal failure).*
Na, K, Cl, Ca, Mg and P *daily*.
Complete blood count, CRP, ALAT, ALP, bilirubin and LDH *every other day*.

Check–up after HDE^{2}C and PBSC treatment until discharge

Controls should include: Hemoglobin, white blood counts, platelets, CRP *daily* until ANC >1.0x10^9/l and platelets >50x10^9/l (determined after the patient has received no transfusion for three days and has no infection.
Creatinine, K, Na, Cl and Mg *daily*.
Creatinine, K and Na should be determined again on the afternoon of PSCT.
ASAT, ALAT and bilirubin every other day.

Controls after discharge

Controls should include: complete blood count and CRP twice weekly until neutrophil count >1x10^9/l and platelets >100x10^9/l in two consecutive samples.

These are guidelines that may be modified according to the routines in the high–dose treatment units in individual centers.

Mobilization and harvest of peripheral blood stem cells (PBSC)

Mobilization is performed after the first Ifo course, and second mobilization is added after CyE^1 if the first yield was insufficient to support two HDE^2C courses (<4.0 x 10^6 CD34+ cells/kg). G–CSF 10 ug/kg is started at 48 hours after the termination of chemotherapy. Pilot data show that the optimal time point for apharesis is not easy to standardize and that the appearance of CD34+ cells in peripheral blood must be followed frequently for optimal timing of apharesis. 2–3 days of apharesis may be necessary.

High–dose etoposide/carboplatin with PBSC–rescue

Carboplatin 375 mg/m^2/day, 2 hour infusion, days –6, –5, –4, –3.
The dose of carboplatin is adjusted in case of decreased GFR.

GFR (ml/min/1.73m^2)	Carboplatin dose
<30	no carboplatin
30–59	50% reduction
60–79	25% reduction
>80	full dose

Etoposide (E^2) 450 mg/m^2/day, continuous infusion, days –6, –5, –4, –3.

PBSC–rescue on day 0.
The optimal number of CD34+ cells to be infused is >2x10^6/kg patient body weight.

G–CSF starting day +1 until ANC $\geq$1x10^9/l for three consecutive days or $\geq$10x 10^9/l once.

Administration

Carboplatin is dissolved in 5% glucose. Etoposide in the concentration of not more than 0.4 mg/ml is dissolved in 0.9% NaCl.
Hydration 3 000 ml/m^2/day; aiming for diuresis of 600ml/m^2/6 hours from start of therapy until 24 hours after cessation of the chemotherapy infusion.
Alkalization of Urine: U–pH>7.
Antiemetic therapy as practiced locally.
Prophylactic antibiotics as practiced locally.
Mg should be supplemented carefully.
Leucocyte depleted, irradiated blood products.
The second cycle is identical with the first, and should be given when the patient has fully recovered from the first one and has not experienced an unacceptable degree of toxicity. The minimum interval between the cycles is 4 weeks.

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Appendix 1

OSTEOSARCOMA ISG/SSG II

INVESTIGATION AND FOLLOW–UP FLOW–SHEET

NOTE: Follow–up after end of treatment. Patients should be followed at 2 month intervals for 3 years, at 4 month intervals during the 4th and 5th years, and then at 6 month intervals until 10 years after end of treatment.

	Pre treatment	Pre–surgery	End of treatment	Every follow–up	Other (see comments)	Comments
Physical examination	X	X	X	X		
Std. blood sample1	X	X	X	X		
S–creatinine,	X	X	X	X		
GFR	X	X	X		X	See p. 18
Hepatitis serology	X		X			
X–rays of involved bone	X	X		X		
CT and/or MRI of involved bone	X	X				
Chest x–ray	X	X	X	X		
CT of chest	X	(X)3	(X)3	(X)	X	On suspicion of lung metastases on chest x–ray
Bone scan	X	(X)				On suspicion of bone metastases
Audiogram	X		X		X	One year after treatment
ECG	X	X	(X)		(X)	(every 3 years after treatment)
Cardiac ultra–sound/LVEF2	X		X		X	at 3 months, 6 months and then every 3 years after treatment
Sperm count	(X)		(X)		(X)	(3 years after treatment)

X = mandatory (X) = recommended

1. Includes: Hb, white blood counts with differential, Trc, creatinine, ALP, LDH, total bilirubin, transaminases, Na, K, Mg
2. Left ventricular ejection fraction
3. Mandatory for patients with detectable metastases at diagnosis

Appendix 2

GUIDELINES FOR HANDLING OF TUMOR SPECIMENS FOLLOWING CHEMOTHERAPY

Chairmen:

Dr. Franco Bertoni
Istituto Ortopedico Rizzoli
Via Pupilli 1
40136 Bologna
Italy
Tel +39–51–632111
Fax +39–51–6361202

Dr. Teddy Holmström
Barnmorskeinstitutet
Sofielundsgatan 5A
00610 Helsinki
Finland
Tel +358–9–70811
Fax +358–9–7570930

Coordinators:

Dr. Tom Böhling
Dept. of Pathology
Haartman Institute
University of Helsinki
P.O. Box 21
00014 Helsinki
Finland
Tel +358–9–43461
Fax +358–9–4346700

Dr. Helena Willén
Dept. of Pathology
University Hospital
221 85 Lund
Sweden
Tel +46–46–173419
Fax +46–46–143307

Dr. Anna E. Stenwig
Norwegian Radium Hospital
Dept. of Pathology
Montebello
0310 Oslo
Norway
Tel +47–22–934000
Fax +47–22–730164

Grading of tumor response

Gross examination should preferably be performed by the surgeon and pathologist together.

In the case of *amputation specimens* skin and soft tissue not infiltrated by the tumor should be removed and larger blood vessels should be examined for possible tumor thrombis, which should be photographed.
In both types of specimens, bone and articular cartilage to the epiphysis, to the surrounding soft tissues and to the resection margin should be investigated and documented. Make a statement about the margins (intralesional, marginal, wide, radical). Bone marrow from the resection site and from tissue removed from the tumor specimen should be investigated.

Specimens to be taken from the tumor

The tumor containing bone should be sectioned in a plane that will optimally identify residual viable tumor tissue. The bone should be cut longitudinally into halves with a bandsaw (should be a model used by butchers). 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 if you process them. 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 tumor tissue. If the tumor tissue is very soft, it is better to precut it with a large knife as deeply as possible before sawing.
Place the two longitudinal and two perpendicular slices in 10 per cent buffered formalin. Samples needed for other investigations can be taken from the remaining tumor tissue.

Further handling of tumor slices

Fix slices overnight and divide the tumor 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 equally numbered bottles of 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 tumor, but may be considerable.

Figure 1

Figure 2

Figure 3

Figure 4

Grading of tumor response

Examine the slices one by one and use the (drawing) map to mark areas of necrosis and vital tumor respectively. Planimetry of each respective area, should be performed in order to report the result in a per cent mode.

Full chemotherapy response is equivocal to areas of acellular tumor osteoid, necrotic and/or fibrotic material, whereas no response means unaffected tumor tissue. "Necrosis" means absence of neoplastic cells. They may have disappeared completely or may have formed "ghost cells" without preserved of nuclear–cytoplasmic details. Tumor necrosis is followed by ingrowth of granulation tissue, fibrosis and hemosiderin deposition. Previous experience shows that viable tumor is most likely to persist in the invaded soft tissues, cortex, subcortex, ligaments or around areas of hemorrhage. Notably, osteosarcoma often necrotize spontaneously in the middle of the tumor.

Good responders: Total necrosis, or than 10 foci containing not more than 30 cells/focus.
The number if viable tumor cell foci should be determined and classified as grades III (<10 foci) or grade IV (no viable cells).

Poor responders: All other cases, including those with only one area which is bigger than the focus defined above.

The same criteria should be used for evaluating the response in metastases.

Resected metastase(s)

Metastasectomy should be evaluated with respect to tumor margins (i.e. intralesional, marginal, wide) and the number of metastases should be noted. The same criteria for grading of tumor response after pre–operative chemotherapy should be used as for the primary tumor.

Appendix 3
GUIDELINES FOR ORTHOPAEDIC SURGERY

Because of the complexity of this treatment protocol (aggressive combination chemotherapy and surgery), the whole treatment program should be planned in a tumor board, with pathologists and/or cytologists, diagnostic radiologists, orthopedic surgeons, pediatricians, and oncologists.

Surgery is carried out after two cycles of ISG/SSG II chemotherapy (i.e. MTX1, CDP1/ADM1, Ifo) and within 21 days after completion of the preoperative chemotherapy, as soon as possible after leucocyte (neutrophiles $>1.0x10^9/l$ and platelets ($\geq$ $100x\ 10^9/l$) recovery. Please, note that re–evaluation before surgery with chest x–ray and x–ray + CT/MRI of the involved bone is mandatory before surgery (see pp. 18 and 37).

Biopsy

The location of the diagnostic biopsy is crucial. The biopsy tract must be included *en bloc* with the specimen at subsequent surgery. A misplaced biopsy may greatly complicate the definitive surgery, Hence the diagnostic biopsy should be planned and performed by the surgeon 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 tumor 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 tumor surgery, nor type of reconstruction.

The tumor 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 tumor is included in the specimen.

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

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

Appendix 4
GUIDELINES FOR THE RESECTION OF METASTASES

For patients with *detectable lung metastases at diagnosis,* surgical removal of the primary tumor and the metastases should preferably be performed at the same time, i.e. in the orthopedic procedure preceding unilateral thoracotomy, bilateral thoracotomy, or sternotomy. The Rizzoli Institute has considerable experience in performing such contemporary procedures, and have not experienced unacceptable complications. However, it is recognized that the policies of individual institutions may differ, and that removal of the primary tumor and the metastases in the same surgical session may not be feasible in all centers.

Thus, the minimum requirement is that *all surgery should be performed within the course of one week.* Chemotherapy should preferably resume within 10-14 days from the last surgical procedure.

Surgical methods

For lung surgery, the choice of sternotomy or lateral thoracotomy is left to the thoracic surgeon. It should be stressed that in the case of unilateral metastases on CT scan, it is recommended that the contralateral side is also explored surgically, as occult non–visualized metastases could be identified in up to 30% of patients. Both lungs should preferably be explored at the same time, and maximally within the course of one week. In cases where lung metastases go into complete remission on CT scan during preoperative chemotherapy, the lung should nevertheless be explored surgically, as foci of viable tumor may still be identified and removed (5).

When operable and within the setting of curative treatment, *extrapulmary (usually skeletal) metastases* should be removed with a wide margin, although a marginal procedure may also be acceptable.

It is not possible to accurately define what are the criteriae for a situation with curative treatment intent, as opposed to a palliative situation. This evaluation will to a large extent depend on the resectability of the metastatic lesions, or in some cases the possibility of reclassification to resectability following a good chemotherapy effect.

If in doubt, contact the Resource Group.

Appendix 5
SUBMISSION OF FORMS

FORM	CONTENTS	REPORTING
Institution's commitment Form 1		Completed by responsible principal investigator
Registration form 2	Patient data, date of biopsy, localization of tumor, localization of metastasis, date of start of chemotherapy	Completed by pediatrician or oncologist
Pathology report I Form 3	Primary diagnostic procedure	Completed by pathologists
On–study Form 4	Patient data, primary tumor status, type of surgery	Completed by pediatrician or oncologist latest four weeks after surgery
Pathology report II Form 5	Final diagnosis, tumor response of primary tumor and metastatic disease	Completed by pathologists
Chemotherapy flow–sheet Form 6A (preoperative treatment) Form 6B	Details of each preoperative therapy cycle, patient data, date, and dose of chemotherapy and toxicity data	Completed by pediatrician or oncologist
Chemotherapy flow–sheet Form 7A Form 7B	Details of postoperative good responders chemotherapy and toxicity data	Completed by pediatrician or oncologist
Chemotherapy flow–sheet Form 8A Form 8B	Details of chemotherapy, before metastasectomy and (relapse) toxicity data	Completed by pediatrician or oncologist
Follow–up Form 9	Clinical evaluation of patients from time of diagnosis	Completed by a examining physician at each follow–up visit

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

I. Form 1, 2 and 3 together with anteroposterior and lateral x–rays of the primary tumor–involved bone and histological slides of the primary tumor are sent *one week after start of chemotherapy.*
II. Form 4, 5, 6A and 6B are sent *3 weeks after end of preoperative chemotherapy*.
III. Form 7A, 7B are sent *3 weeks after completed postoperative chemotherapy*.
IV. Form 8A and 8B are sent *3 weeks after metastasectomy.*
V. Form 9 are sent *immediately after end to follow–up visit.*