

EURO-B.O.S.S

EUROpean Bone Over 40 Sarcoma Study

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

This document is intended to describe a collaborative study in patients aged 41 to 65 years with high grade sarcoma of bone and to provide information for entering patients. The trial committee does not intend it to be used as an aidmemoire or guide for treatment of non-registered patients. 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 has received clearance from their ethical committee.

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

PREFACE

The trial EUROBOSS is a multicentre prospective study for patients older than 40 years with highly malignant spindle cell sarcoma of bone. Because of the low incidence of bone sarcomas, multiinstitutional collaborations are essential to address important questions concerning diagnosis and treatment. The participating intergroups cover a population of approximately 200 million people and together these organizations claim to provide an adequate patient volume to explore the aims of the current study.

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

The study is open to collaboration with other Groups or Institutions, after agreement of all participating groups.

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

Protocol chairman and

ISG co-ordinator

Stefano Ferrari

Dept. of Chemotherapy

Istituto Ortopedico Rizzoli

stefano.ferrari@ior.it

SSG co-ordinator:

Sigbjørn Smeland

Dept. of Oncology

Norwegian Radium Hospital

sigbjorn.smeland@klinmed.uio.no

COSS co-ordinator:

Stefan Bielack

Dept. of Pediatric Oncology

University Hospital of Münster

coss@uni-muenster.de

INTERGROUP DATA CENTRE:

Sezione di Chemioterapia. Istituto Ortopedico Rizzoli, via Pupilli 1 40136 Bologna, Italy.

Phone: +39-051-6366199, Fax: +39-051-6366277.

E-mail: chemioterapia@ior.it.

Data managing: Annalisa Nobile

Scandinavian Sarcoma Group (SSG)

SSG co-ordinator: Sigbjørn Smeland

SSG Secretariat: Regional Tumor Registry, University Hospital of Lund, SE-221 85 Lund, Sweden.

Phone: +46-46-177555, Fax: +46-46-188143

E-mail: evy.nilsson@cancerepid.lu.se

Data managing: Evy Nilsson

Cooperative Osteosarcoma Study Group (COSS)

COSS co-ordinator: Stefan Bielack

COSS secretariat: Cooperative Osteosarkomstudienegruppe (COSS), Olgahospital, Klinik für Kinder- und Jugendmedizin- Pädiatrie 5 (Onkologie, Hämatologie, Immunologie, Allgemeine Pädiatrie, Gastroenterologie, Rheumatologie) – Bismarckstraße 8, D-70176 Stuttgart, Germany.

Phone: +49-711-278 73881/73877, Fax: +49-711-278 73882

E-mail: coss@olgahospital-stuttgart.de

Italian Sarcoma Group (ISG)

Protocol chairman and ISG co-ordinator: Stefano Ferrari

ISG Clinical Trial Office, Istituto Ortopedico Rizzoli, via Pupilli 1 40136 Bologna, Italy. Phone: +39-051-63.66.400 Fax: +39-051-6366400.

E-mail: emanuela.marchesi@ior.it.

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1. TREATMENT SCHEDULE

ADJUVANT

CDP ADM	IFO CDP	IFO ADM	CDP ADM	IFO CDP	IFO ADM
0	3	6	9	12	15
CDP ADM	IFO CDP	IFO ADM			
18	21	24	week		

CDP = Cisplatin 100 mg/m², 48 hour continuous infusion iv; ADM = Adriamycin 60 mg/m², 24 hours iv; IFO = Ifosfamide 3 g/m²/day iv, two days.

NEOADJUVANT

PREOPERATIVE CHEMOTHERAPY

CDP ADM	IFO CDP	IFO ADM	Surgery	
0	3	6	9	week

CDP = Cisplatin 100 mg/m², 48 hour continuous infusion iv; ADM = Adriamycin 60 mg/m², 24 hours iv; IFO = Ifosfamide 3 g/m²/day iv, two days.

POSTOPERATIVE CHEMOTHERAPY (GR)

CDP ADM	IFO CDP	IFO ADM	CDP ADM	IFO CDP	IFO ADM	
10	13	16	19	22	25	week

CDP = Cisplatin 100 mg/m², 48 hour continuous infusion iv; ADM = Adriamycin 60 mg/m², 24 hours iv; IFO = Ifosfamide 3 g/m²/day iv, two days.

POSTOPERATIVE CHEMOTHERAPY (PR)

CDP ADM	MTX	IFO CDP	MTX	IFO ADM	MTX	
10	13	14	17	18	21	week
CDP ADM	MTX	IFO CDP	MTX	IFO ADM		
22	25	26	29	30		week

CDP = Cisplatin 100 mg/m², 48 hour continuous infusion iv; ADM = Adriamycin 60 mg/m², 24 hours iv; IFO = Ifosfamide 3 g/m²/day iv, two days. MTX = Methotrexate 8 g/m², 4 hours IV.

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 (ADM), cisplatin (CDP), and ifosfamide (IFO) are the four drugs with proven efficacy against osteosarcoma. They have been used according to different schedules in chemotherapy protocols adopted in large monocentric and multicentric studies (4-9). Due to the peak of incidence of osteosarcoma in the second decade of life (2), the studies reported in the literature usually include 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 ADM, 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 recommend (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 chemo sensitivity, and similar ultra structural 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 (ADM), ifosfamide (IFO), and methotrexate (MTX) (21-27).

Chondrosarcoma is not a chemo sensitive 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 behaviour 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 spindle cell 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 randomised 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 (ADM), 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 ADM, 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 (ADM, 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 postoperative chemotherapy treatment or only an adjuvant chemotherapy. In case of immediate surgery, patients will receive an adjuvant treatment with the 3-drug regimen (CDP-ADM-IFO).

Since the observational character of the study, also patients who meet the inclusion criteria and will receive chemotherapy treatments according to Institutional guidance can be registered in the study.

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.

The 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 (death, 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

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.

Recruitment is foreseen for an additional **two years, that is until Dec. 31st, 2014.**

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 Data Centre (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 Excel database and will send files with new patients and updated cases to the intergroup secretariat every six months. The Intergroup Data Centre will paste data in the common Excel 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 information requested for the common database (see list of data required).

6. PUBLICATION

Data relating to EUROBOSS 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 will be provided within 5 years after the completion of the projected patient accrual.

7. “RESOURCE GROUP”

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 EUROBOSS working group has formed a “*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*”.

ISG Resource Group:

Per problemi inerenti l’ interpretazione del protocollo e la sua applicazione verrà contattato il coordinatore dello studio, fatto salvo che la gestione clinica del paziente resta in carico al Centro che lo ha in cura.

8. ETHICAL CONSIDERATIONS

1. EUROBOSS is a non-randomised phase II-III 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 ISG/COSS/SSG “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. CRITERIA FOR ELIGIBILITY

1. Histologically proven diagnosis of high-grade sarcoma of bone of any site.
2. Histologic 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, adriamycin, and ifosfamide
6. Written informed consent

10. CRITERIA 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 $< 70 \text{ ml/min}$

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, creatinine clearance, 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 scans
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, creatinine clearance, 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, creatinine clearance, 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

Chemotherapy-related late effects follow-up:

Physical examination, Complete blood count, Serum creatinine, Na, K, Mg, P, Bilirubin, Transaminases, Alkaline Phosphatase, LDH, Creatinine Clearance, Tmp/GFR.

Echocardiography with evaluation of Left Ventricular Ejection Fraction or fractional shortening rate of the left ventricle

Audiogram.

The frequency of the above examinations is established by each Group according to their standards, but it is mandatory that the tests to investigate chemotherapy –related late effects are done at least on a yearly basis.

Tumor-related follow-up:

Physical examination

Conventional x-rays of the primary lesion, and CT scans of the lungs (conventional X-rays of the chest are allowed).

Additional exams when clinically indicated.

The frequency of the above examinations is established by each Group according to their standards, but it is mandatory that in the first 4 years of follow-up, lung metastases are searched for every three months with CT-scans, or every two months when chest X-rays are used. In the subsequent years of follow-up up to the 10th year every six months.

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. Creatinine clearance before cycle with each 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 ADM, 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, ADM, IFO require a minimum number of 3×10^9 /L leukocytes (or 1×10^9 /L of neutrophils), and of 100×10^9 /L platelets. Cycles with MTX require a minimum number of 0.5×10^9 /L neutrophils (or 2×10^9 /L leukocytes), and of 80×10^9 /L platelets.

Renal function

Cycles with CDP, IFO require serum creatine levels in a normal range. Cycles with MTX require a creatinine clearance value > 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 ADM. Before each cycles with ADM 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 ADM is not administered, and the patient undergoes additional tests to assess the cardiac function. In case of no evidence of cardiac dysfunction ADM is administered. A $> 10\%$ reduction of the ejection fraction (compared to the baseline) contraindicates further ADM administration. Despite a reduction of the ejection fraction, ADM can be delivered (short infusion) with the use of dexrazone (cardioxane) if considered of clinical relevance.

Antiemetic treatment

Each Institution will decide the antiemetic treatment, but the use of 5HT3 antagonists and dexametazone is recommended for the cycles with CDP, ADM, and IFO.

13.1 G-CSF

G-CSF support will be used according to the ASCO recommendation (34). G-CSF should be added in the next course if there is a delay in starting chemotherapy because of prolonged neutropenia or neutropenic fever (temp. $>38.5^{\circ}\text{C}$ and a nadir in the white blood counts $<1.0 \times 10^9/\text{l}$). G-CSF is not necessary after chemotherapy with MTX.

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

13.2 CHEMOTHERAPY

Cisplatin (CDP)

Dose: 100 mg/m²

Infusion: intravenously over 48-72 hours, dissolved in basal solution

Basal solution: 0.9% NaCl with KCl 15 mEq/L and Mg 3mEq/L

Prehydration: Basal solution 500 mL/m² over 2 hours

Hydration: Basal solution 2 L/m²/24hours

Posthydration: Basal solution 500 mL/m² over 2 hours

Adequate hydration and magnesium replacement according to the Groups standards are allowed

Course CDP/ADM: CDP is given before the administration of ADM

Course IFO/CDP: CDP starts on day 3, after infusion of IFO on day 1 and 2

Doxorubicin (ADM)

Dose: 60 mg/m²

Infusion: intravenously over 24 hours, dissolved in 2.000 mL 0.9% NaCl

Course CDP/ADM: ADM starts after the 48-72 hour infusion of CDP

Course IFO/ADM: ADM starts on day 3, after infusion of IFO on day 1 and 2

Ifosfamide (IFO)

Dose: 6/m². (3g/m²/day for two days)

Infusion: intravenously over 1-2 hours, dissolved in 500 mL 0.9% NaCl

Prehydration: intravenously over 1 hour 500 mL 0.9% NaCl with MESNA 400 mg/m

Posthydration: : intravenously 0.9% NaCl 2L/m² with MESNA 3g/m²/day with bicarbonate 3 mEq//Kg/day and KCl 0.5 mEq/Kg/day.

Adequate hydration and MESNA according to the Groups standards are allowed

Course IFO/CDP: IFO is delivered on days 1-2 and is given before CDP
Course IFO/ADM: IFO is delivered on days 1-2 and is given before ADM

Methotrexate

Dose: 8 mg/m²

Infusion: intravenously over 4 hours (T0-T4), dissolved in basal solution

Basal solution: 1 L of basal solution contain 0.9% NaCl with KCl 20 mEq and Bicarbonate 60 mEq

Prehydration: Basal solution 500 mL/m² over 2 hours

Hydration: T0-T24 Basal solution 2.5 L/m²

Alkalinization: T0-T24 bicarbonate 4 mEq/kg

In the following 24 hours (T25-T-48) hydration with IV basal solution 2 L/m²

Adequate hydration and alkalinization according to the Groups standards are allowed

Lederfolin: Starting from T24 8 mg/m² every 6 hours for 11 administration (up to T84)

Leukovorin: 15 mg/m² x 12 times are allowed.

Serum MTX measurement: suggested at T4, mandatory at T24 –T48 and up to serum levels <0.2 μM.

13.3 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/ADM 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/ADM 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)

14. 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 procol 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.

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 (alfa) 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.

15. REFERENCES

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