**Protocol Studynr. M93SCB**

**Adjuvant chemotherapy with or without intensification with hematopoietic stem cell support in patients with stage II or III breast cancer, involving ≥ 4 axillary lymph nodes**

*A prospective randomized phase III study of the Netherlands Working Party For Autotransplantation in Solid Tumors*

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## 1.0 SUMMARY

This prospective randomized trial investigates the curative potential of very intensive adjuvant chemotherapy in patients with operable stage II or III breast cancer, who have 4 or more tumor-positive axillary lymph nodes and who are under 55 years of age. The adjuvant regimen in the 'experimental arm' consists of four cycles of FEC (5-FU, epidoxorubicin, cyclophosphamide), high-dose combination chemotherapy (cyclophosphamide, thiotepa and carboplatin) with autologous hematopoietic progenitor cell support, locoregional radiotherapy and tamoxifen. The control group receives an identical treatment sequence, except that the high-dose chemotherapy course will be replaced by a 5th course of FEC.

Eligible patients are to be randomized before chemotherapy is initiated. Patients randomized in the 'experimental arm' will undergo peripheral stem cell mobilization employing G-CSF following the third course of FEC.

The study will answer the question whether or not very-high dose chemotherapy with hematopoietic stem cell support should be offered on a routine basis to young patients with high-risk breast cancer as part of an adjuvant therapy strategy. The study is the continuation of a randomized study sponsored by the 'Fonds Ontwikkelingsgeneeskunde' from 1994 to 1995.

## 2.0 BACKGROUND AND INTRODUCTION

### 2.1 Axillary lymph node positive patients

Extensive clinical data demonstrate that the probability of survival at 10 years after diagnosis of breast cancer correlates with the number (N) of involved axillary lymph nodes present at the time of mastectomy. In multivariate analyses, this is the strongest independent predictive factor []. The survival at 10 years is about 70% if N equals 0 and falls below 50% if N is positive, down to 20% if more than three nodes are involved [].

The subdivision of patients with tumor-positive axillary lymph nodes in two subgroups is now generally accepted [2,,]:

1. patients with 1, 2 or 3 positive lymph nodes;

2. patients with $\geq$ 4 positive lymph nodes.

The validity of such a classification has been confirmed by the observation that little difference in disease-free (DFS) and overall survival (OS) exists between patients with either 1, 2 or 3 positive nodes, whereas a striking decrease in DFS and OS is observed when 4 nodes contain tumor [2].

Following locoregional treatment with surgery, women with only 1-3 positive nodes have a 10 year relapse rate of 65%-70%, whereas the corresponding figures in women having > 3 nodes are 84%-86% []. Randomized comparative trials of adjuvant chemotherapy for primary breast cancer have demonstrated an improved disease-free and overall survival for premenopausal stage II patients [3,,]. In a meta-analysis conducted by The Early Breast Cancer Trialists Collaborative Group (EBCTC) [], these results have been confirmed. The annual mortality rate was reduced by 25% for patients below 50 years of age. In general, following adjuvant chemotherapy treatment benefit is observed in all nodal categories, but the final outcome remains inversely related to the number of nodes involved [7]. The differences were most marked in premenopausal patients with 1-3 positive nodes.

These data indicate that despite contemporary adjuvant chemotherapy the prognosis for patients with breast cancer involving $\geq$ 4 axillary lymph nodes remains dismal.

Chemotherapy regimens based on cyclophosphamide, fluorouracil and an anthracycline (doxorubicin or epidoxorubicin) are now accepted by many oncologists as standard first-line chemotherapy for patients with breast cancer. Several studies have demonstrated a relationship between dose intensity and DFS for adjuvant treatment of node positive breast cancer [,]. Abeloff [10], Bonadonna [] and Peters [] have presented preliminary but highly promising findings of new intensive drug regimens in the adjuvant treatment of the prognostically most unfavorable nodal subset.

### 2.2 Dose intensity of chemotherapy in metastatic breast cancer

The prognosis of locally advanced or disseminated breast cancer has improved only little over the last 10 years despite the availability of radiotherapy, chemotherapy and hormonal therapy [].

The optimal chemotherapy combination for breast cancer patients, its timing and dose intensity continue to be subjects of considerable debate. In general, with standard dosed chemotherapy response rates between 50 and 75% can be achieved [,,,], with complete response rates of 20%. Unfortunately, complete responses (CR) do not represent cure in breast cancer since virtually all patients with CR eventually relapse after a median response duration of 16-18 months. The duration of partial remissions is usually reported as 10 months, resulting in a median survival of about 2 years [13].

The quality of response to chemotherapy in metastatic breast cancer has been shown to be closely linked to dose intensity. In a retrospective study of standard dosed chemotherapy regimens, Hryniuk et al. found a definite relationship between response rate and duration and the administered chemotherapy dose []. Several randomized clinical trials in which dose intensity was the most important variable, have shown an increased response rate for regimens with greater dose intensity [,,,], few trials have however demonstrated a significantly increased overall survival [20]. The introduction of hematopoietic growth factors has facilitated the clinical evaluation of the importance of dose intensity. Although higher remission rates have often been associated with an escalation of dose [,,,], corresponding substantial increases in response duration have not usually been observed. The fact that no major survival improvement is detectable after chemotherapy with enhanced dose intensity may be the result of only minor differences in actual dose administered, but could also reflect the lack of any major effect of standard-dosed chemotherapy regimens on survival in metastatic breast cancer.

### 2.3 Rationale for high-dose chemotherapy in breast cancer

Because the dose-limiting toxicity of most chemotherapy is myelosuppression, the administration of high-dose chemotherapy requires supportive care with autologous bone marrow or with peripheral blood stem cells. Employing hematologic growth factors, an approximately 1.5 to 2-fold dose escalation is possible, whereas high-dose chemotherapy with hematopoietic stem cell rescue has allowed a roughly 10-fold increase in dose.

The need to investigate the potential of high-dose chemotherapy followed by hematopoietic stem cell rescue in breast cancer at this time arises from four independent developments in the past decade:

1. The maturation of the technology and supportive treatment required for safe autologous bone marrow support after ablative chemotherapy;

2. The documentation, both in the laboratory and in the clinic, that dose response curves exist for certain drugs in breast cancer [see for reviews references ,,,,,];

3. The availability of hematologic growth factors such as G-CSF and GM-CSF that allow substantial amelioration of bone marrow toxicity associated with high-dose chemotherapy [];

4. The development of peripheral stem cell transplantation, which results in a much more rapid engraftment, associated with a further substantial reduction in duration of the pancytopenic period [].

It has been known for many years that certain drugs have steep dose response curves in the experimental setting [,]. Clinically, dose escalations with bone marrow protection have been found to be curative in acute myeloid leukemia, lymphomas and chronic myelogenous leukemia []. Impressive response rates have been documented in patients with metastatic breast cancer when high-dose chemotherapy was administered with bone marrow support. The rationale for trials using very high-dose chemotherapy with autologous bone marrow support has been reviewed excellently and in depth by Henderson et al. []. Highly informative and argumentative reviews have recently been published by Smith and Henderson [] and by Peters [].

### 2.4 Adjuvant high-dose chemotherapy in patients with stage II and III breast cancer

Most data published on the treatment of breast cancer with high-dose chemotherapy and ABMT are derived from studies of patients having a large tumor load at the time of treatment.

In similar situations of high tumor load, other malignancies such as acute leukemia, germ cell tumors, small cell lung cancer and ovarian cancer have been shown to be incurable. Several malignancies in which only minimal residual disease is present, however, can be cured by high-dose therapy. These include acute leukemia, Hodgkin's disease, intermediate and high-grade non-Hodgkin lymphomas and occasionally germ cell tumors [38,,].

It has become increasingly evident that a crucial principle of the application of high-dose chemotherapy in the autologous transplant setting is to focus on patients who have had no prior chemotherapy, or who are currently responding to treatment at standard dose levels and, finally and most importantly, who have exclusively micrometastatic disease.

A non-randomized study by Peters [12] in 85 patients with 10 or more involved axillary lymph nodes has shown that high-dose chemotherapy can lead to a 5 year disease-free survival of 72%, with a median follow-up 2.5 years. In a well-matched historical control group, the disease-free survival was only 30%. These results have recently been strengthened by a study of the Milano group []. In a Dutch study of Mulder et al. [], 24 breast cancer patients with five or more tumor-positive axillary lymph nodes were treated with induction chemotherapy followed by high-dose chemotherapy and ABMT. The probability of 5 years disease-free survival was 84%, with a median follow-up 36 months. These results are remarkably similar to those of Peters [12].

Three major randomized multi-center studies of high-dose chemotherapy in high-risk breast cancer were in progress at the time of this writing:

- The 'Ontwikkelingsgeneeskunde' study in the Netherlands, which is to continue patient accrual under this protocol. It had randomized over 250 patients by September 1995 (an accrual rate of 180 patiens per year).

- The American study Intergroup-0163/CLB-9082. This study is co-chaired by William Peters (Detroit) and Elizabeth Shpall (Denver). It had recruited over 400 patients by May 1995 and will continue to randomize patients until a 15% survival advantage is detectable. The first preliminary analyses are expected for 1999.

- The American study Intergroup-0121/EST-2190. This study is recruiting relatively poorly (86 patients per year) [] and should finish accrual in 1997 at a patient number of 429. It is chaired by Martin S. Tallman (Chicago).

Unique features of the Dutch (= this) study include:

- *The patient selection* (about two-third of the first 250 patients had 4-9 positive axillary nodes, whereas both American studies are restricted to patients with 10 or more axillary nodes)

- *The high-dose regimen* carboplatin/thiotepa/cycophosphamide. The American studies employ cisplatin/BCNU/cyclophosphamide and cyclophosphamide/thiotepa, respectively. In the Dutch study, the highly toxic BCNU is avoided that caused major lung toxicity in the American study [12].

- *The number of participating centers*. The Dutch study is rapidly accruing in only 10 centers, while the two American studies slowly recruit at 120 centers and 155 centers, respectively. This means that the Dutch centers essentially include all eligible patients, while the American studies only include a small and highly selected subgroup. As a result, the American studies cannot easily be generalized to the whole population.

**2.5 Progress in hematopoietic stem cell support after high-dose chemotherapy**

shown that transplantation with G- or GM-CSF mobilized peripheral blood stem cells results in a complete and durable hematopoietic recovery after high-dose chemotherapy [,]. The development of peripheral blood stem cell transplantation (PSCT) has accelerated in the last few years as a result of the availability of hematopoietic growth factors such as GM- and G-CSF. These growth factors are able to mobilize hematopoietic progenitor cells from bone marrow into peripheral blood, a process already known to occur during the recovery phase following chemotherapy. The advantage of PSCT is the much more rapid restoration of marrow function following transplantation as compared to transplantation with autologous bone marrow alone.

The accelerated hematopoietic recovery is also associated with a marked reduction in platelet and red blood cell transfusions, reduction in the number and duration of fever periods and earlier discharge from the hospital.

Peripheral stem cell transplantation is now an important alternative for autologous bone marrow transplantation. It is reasonable to assume that with PSCT, the treatment related mortality and morbidity will be markedly reduced.

**2.6 Selection of chemotherapy regimens**

We have recently reviewed the high-dose chemotherapy regimens employed in the treatment of solid tumors []. Briefly, alkylating agents have been widely used in intensification regimens for bone marrow transplantation, because myelosuppression is the major dose-limiting toxicity and because these agents have a broad spectrum of activity agains malignant disease. The rationale for multiple-alkylator based high-dose chemotherapy has been convincingly brought forward by Frei et al. [29]:

1. The dose response curves for the alkylating agents in both *in vitro* and *in vivo* experimental systems are steep;

2. Alkylating agents exhibit little cross resistance *in vitro*;

3. Several *in vitro* and *in vivo* studies have demonstrated a substantial synergism for a number of alkylating agents;

4. Because *in vitro* resistance to alkylating agents is usually only of a low degree (5-10-fold), a 5-10-fold dose escalation with hematopoietic stem cell support could be capable to eradicate resistant tumor cell populations;

5. With a combination of alkylators it is possible to create a chemotherapy combination with relatively little extramedullary toxicity.

<u>High-dose chemotherapy regimen</u>

The CTC high-dose chemotherapy regimen (cyclophosphamide 6 g/m2, thiotepa 480 mg/m2, carboplatin 1.6 g/m2) is a well-tolerated regimen without severe organ toxicity []. All three drugs (including carboplatin []) have significant single-agent activity in breast cancer at standard doses. A similar regimen, which contains only half the dose of carboplatin has been employed extensively in breast cancer by the group of Antman []. Based on the findings in a randomized phase II study conducted in the Netherlands Cancer Institute, it was shown that the CTC regimen in conjunction with autologous progenitor cell support is feasible and safe in the adjuvant therapy for breast cancer []. In addition, the pulmonary and bone marrow toxicity of subsequent radiation therapy (an essential component of the treatment for high-risk breast cancer) has been shown to be limited and managable [], while this toxicity has been reported to be severe after other high-dose regimens [12].

<u>Induction chemotherapy</u>

Anthracyclins are generally considered to be the most effective cytotoxic agents in breast cancer. FEC (fluorouracil, epidoxorubicin and cyclophosphamide) and FAC (fluorouracil, doxorubicin and cyclophosphamide) are among the most commonly used anthracyclin-base regimens and have been shown to have equivalent activity in metastatic breast cancer [,]. An important possible advantage of anthracycline-based chemotherapy over CMF in the adjuvant treatment of node positive breast cancer is the limited duration of therapy, while the efficacy is at least equivalent with classical CMF [,].

Epidoxorubicin has been reported to have less cardiotoxicity than doxorubicin [], which is a potentially important property when the agent is incorporated in a treatment strategy together with radiation therapy (with the heart in the radiation port), and with high-dose chemotherapy associated with (reversible) cardiotoxicity.

FEC chemotherapy has also been selected for this protocol because of its proven ability to mobilize peripheral blood stem cells [53] and its ability to induce very high response rates in the up-front chemotherapy of locally advanced breast cancer (over 90% in the Netherlands Cancer Institute study []). In order to have a standard type of chemotherapy in the control arm, an epidoxorubicin dose of 90 mg/m2 was selected, which is slighly lower than has been employed in the Netherlands Cancer Institute experience (120 mg/m2). The cyclophosphamide and fluorouracil doses are unaltered (both 500 mg/m2). The chemotherapy duration will be 15 weeks in both treatment arms (5 subsequent 3-week courses).

## 3.0 OBJECTIVES OF THE STUDY

I. To determine whether very-high dose chemotherapy with autologous stem cell support should be offered to relatively young patients with high-risk breast cancer as part of adjuvant therapy.

II. To compare the toxicity of a standard anthracyclin-based adjuvant chemotherapy consisting of five courses of FEC with 4 courses of FEC followed by very-high dose chemotherapy.

III. The design of the study will allow the evaluation of the potential survival benefit of chemotherapy intensification with autologous hematopoietic stem cell support as a method of preventing relapse. It will also serve to determine their relative costs of these treatment strategies and a cost-effectiveness study will be performed in parallel (see paragraph 11).

## 4.0 ELIGIBILITY CRITERIA

1. Modified radical mastectomy (or breast conserving surgery in some centers) and complete axillary clearance, histologically confirmed stage II A, II B or III A adenocarcinoma of the breast, with $\geq$ 4 involved axillary lymph nodes; the presence of tumor cells near or in the resection margins at microscopic examination is acceptable;

2. Patients who have undergone a tumorectomy as part of a breast conserving procedure will be excluded in some centers because radiation therapists feel that radiotherapy should not be postponed until chemotherapy is concluded.

3. No prior chemotherapy or radiotherapy.

4. No evidence of distant metastases (see section VI. for required investigations);

5. Age $\leq$ 55 years;

6. Performance status (ECOG-ZUBROD) 0 or 1;

7. Normal bone marrow function, WBC $\geq$ 4.0 x 109/l, platelets $\geq$ 100 x 109/l;

8. Adequate renal function (creatinine clearance $\geq$ 60 ml/min.);

9. Adequate hepatic function (serum bilirubin $\leq$ 25 umol/l);

10 Study treatment must begin within 6 weeks of surgery.

11. No other malignancy except adequately treated in situ carcinoma of the cervix or basal cell carcinoma of the skin;

12. No significant prior or concomitant disorder that might interfere with adherence to the intensive treatment regimen, including but not limited to a history of angina, myocardial infarction or heart failure, severe lung function impairment, peptic ulcer disease, etc.;

13. Availability for follow-up.

## 5.0 TRIAL DESIGN

This investigation is a multicenter prospective randomized phase III study.

Please see appendix I for an overview of the study design. Patients eligible for the study will be identified after mastectomy or wide tumor excision with axillary clearance. Following surgery, all patients will receive four courses of cyclophosphamide, epidoxorubicin and fluorouracil. Patients with early progressive disease at any time will be taken off study. The first chemotherapy course must be given as soon as possible after the surgical

procedure, preferably within 3 weeks, but not later than 6 weeks since primary surgery. All radiation therapy (including radiation therapy administered as part of a breast conserving strategy) must be postponed until all chemotherapy has been concluded.

All patients will be randomized before the initiation of chemotherapy.

- The 'standard' treatment arm will include five courses of FEC followed by conventional external beam radiotherapy to the breast or chest wall and to the regional lymph node areas including the axilla and the parasternal area (the latter as indicated by parasternal radionuclide scanning). Modifications of the radiotherapy according to local views are permitted.

- The 'experimental' treatment arm will include four courses of FEC. The third course of FEC will be used for stem cell mobilization in combination with G-CSF followed by peripheral blood stem cell (PBSC) harvest. Three to five weeks after the 4th FEC course, the intensive chemotherapy schedule is begun. It consists of a tri-alkylator regimen of high-dose cyclophosphamide, thiotepa and carboplatin, followed by PBSC reinfusion. After marrow reconstitution, definitive radiotherapy will be administered as in the control treatment arm.

In both treatment arms patients will be treated with tamoxifen (40 mg daily), during two years.

## 6.0 THERAPEUTIC REGIMENS AND TOXICITY

### 6.1 Adjuvant chemotherapy

Adjuvant chemotherapy will consist of FEC

| FEC: (standard dose) | | |
|---|---|---|
| cyclophosphamide | 500 mg/m2 i.v. (push) | day 1\| |
| epidoxorubicin | 90 mg/m2 i.v. (push) | day 1\| q 3 wks. |
| 5-fluorouracil | 500 mg/m2 i.v. (push) | day 1\| |

Dose modifications

Maintaining a rigorous three-week schedule should be attempted. When more than 1 week delay of chemotherapy is necessary, the patient goes off study.

| | day 21 | day 28 |
|---|---|---|
| WBC ≥ 3.0 x 109/l and plat. ≥ 100 x 109/l | 100% | 100% |
| WBC ≥ 2.0 < 3.0 x 109/l | delay 1 week | 75% |
| WBC < 2.0 x 109/l | delay 1 week | off study |
| plat. < 10Mwx 109/l | delay 1 week | off study |

Expected toxicity

The main toxicity of this treatment regimen is reversible bone marrow suppression, usually with only minor depression of platelet counts. Other toxicities include nausea and vomiting (routinely requiring anti-emetics), alopecia, mild mucositis and malaise. Inadvertent extravasation of epidoxorubicin may cause necrotic ulcers. Cyclophosphamide may cause hemorrhagic cystitis, but this is exceptional at the dose level used. Other toxicities may occur, but are uncommon.

**6.2 Hematopoietic stem cell mobilization and harvest**

The peripheral stem cell mobilization and harvest will be done in patients randomized for the high-dose chemotherapy and is planned for the the third course of FEC. The mobilization technique consists of a combined administration of one course of FEC chemotherapy and G-CSF. On day 1 following the third course of FEC chemotherapy G-CSF (filgrastim) will be administered at a dose of 300 :g/day as a daily subcutaneous injection during 10 days.

The peripheral stem cell harvest will be performed as soon as CD34+ mononuclear cells appear in the peripheral blood. See appendix II for more details.

The bone marrow harvest:

In patients from whom it is not possible to harvest sufficient numbers of peripheral stem cells the hematopoietic stem cell rescue must be performed with autologous bone marrow. The bone marrow harvest will be done by multiple aspirations from the iliac crest under general or local anesthesia prior to the fourth course of FEC chemotherapy.

Cryopreservation procedures and quality control checks will be performed according to the local policy (appendix II). Minimum number hematopoietic stem cells required for transplantation:

PSCT : $\geq$ 20 x 104 CFU-GM/kg or CD34+ cells : $\geq$ 3 x 106/kg

BMT : $\geq$ 2 x 104 CFU-GM/kg

**6.3 Intensification of chemotherapy with hematopoietic stem cell support**

High-dose chemotherapy should be started 3-5 weeks after the 4th course of FEC. If the capacity of the treatment center does not allow treatment of the patient within that time period, one of the study coordinators should be contacted.

The high-dose chemotherapy regimen will consist of cyclophosphamide (6 g/m2), thiotepa (480 mg/m2) and carboplatin (1.6 g/m2):

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Conditioning chemotherapy regimen (CTC)

days -6, -5, -4, -3:
- 1500 mg/m2 cyclophosphamide i.v. in 60 minutes
- 6 x 500 mg (total) mesnum i.v.
- 2 x 60 mg/m2 thiotepa in 100 ml D5W or saline in 30-60 minutes i.v.
- 400 mg/m2 carboplatin i.v. in 2 hours

day 0 and +1:
- Hematopoietic stem cell infusion

day 0:
- G-CSF (filgrastim) 300 :g sc daily
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Toxicity and activity of 'CTC':

The CTC regimen in combination with ABMT is known to be relatively well tolerated [50]. As other conditioning regimens, it leads to profound marrow aplasia with severe granulocytopenia (< 0.5 x 109/l) for a median duration of 22 days (range 18-28). This period may be abbreviated by co-administration of G-CSF. Platelet recovery to levels of ≥ 20 x 109/l takes a median of 22 days (range 13-83 days). With PSCT the hematopoietic recovery is markedly accelerated compared to ABMT, granulocyte recovery to levels of 0.5 x 109/l takes a median of 9 days (range 8-17) and platelet recovery to levels of 20 x 109/l takes a median of 13 days (range 7-25). Other toxicities include nausea, vomiting and loose stools on treatment days, and minor mucositis. The single-institution experience in the adjuvant setting for high-risk breast cancer has recently been reported [53].

Only limited information is available about the risk on secondary neoplasms after high-dose or ablative chemotherapy. A recent study in 1631 patients who had underwent an autologous or allogeneous BMT, the cumulative incidence of secondary neoplasms at 10 years after BMT was 3.7% [,].

The majority of all patients receiving high-dose chemotherapy with hematopoietic stem cell support have periods of fever warranting treatment with antibiotics. In approximately half of these episodes, a causal microorganism will be cultured. Treatment related mortality has approached 5% in most series of intensive chemotherapy with autologous bone marrow support, but may be expected to be much lower in this study:

1. Cytotoxic drugs will be used at doses that have not been associated with pulmonary toxicity or hepatic veno-occlusive disease;

2. Peripheral blood stem cell transplantation will be used followed by the administration of G-CSF, resulting in a rapid engraftment of all hematopoietic cell lines;

3. Patients with solid tumors show earlier marrow reconstitution than the heavily pretreated lymphoma patients in most series;

4. The patients in this study all have an excellent performance status and have not previously been subjected to extensive chemotherapy or radiotherapy.

**6.4 Peripheral stem cell infusion**

The minimal period between the end of high-dose chemotherapy and the peripheral stem cell infusion must be 48 hours. The peripheral stem cell infusion may be divided into two parts on day 0 and +1 (appendix IV). In case of a BMT the bone marrow infusion is on day 0.

Following stem cell infusion patients will receive G-CSF (filgrastim) at a dose of 300 :g as a daily subcutaneous injection. The administration starts on the day of the first stem cell infusion (day 0). The G-CSF administration will be discontinued as soon as the W.B.C. count is ≥ 5.0 x 109/l.

**6.5 Hematological support and prophylactic measures**

Supportive care will be given according to local guidelines of the participating institution. Please refer to appendix V for an example of such measures.

**6.6 Radiotherapy**

Radiotherapy should be started as soon as possible after chemotherapy has been completed, whenever possible within 6 weeks after the end of chemotherapy in both treatment arms. In the PSCT arm, adequate bone marrow recovery must have taken place (WBC ≥ 3.0 x 109/l and platelets ≥ 50 x 109/l).

Please note: Radiation therapy will be given according to standard rules of the participating center; it is recommended to use the Manual for Clinical Research in Breast Cancer of the EORTC Breast Cancer

Cooperative Group [] and the Report on Quality Assurance in Center Treatment of Early Breast Cancer []. For further guidelines, please refer to Appendix VI.

**6.7 Hormonal treatment**

Hormonal treatment with tamoxifen, 40 mg per day for two years, will be started after the discontinuation of all chemotherapy, irrespective of the estrogen- and/or progesterone-receptor status of the primary tumor. For the 'conservative' treatment arm, the drug will be started after hematologic recovery from the last (5th) FEC course (and thus prior to radiotherapy). For patients in the 'experimental' arm tamoxifen will start after autologous bone marrow transplantation, when the WBC has returned to 3.0 x 109/l and platelets to 50 x 109/l.

The dose of 40 mg daily has been selected in order to be sure that patients who are still premenopausal after the chemotherapy will have appropriate blood levels of the drug to antagonize the reactive increase of serum oestradiol levels. The value of tamoxifen in this type of adjuvant setting is unclear; the intensive treatment approach of this protocol, however, aims to employ all active treatment modalities up-front, in order to maximize the relapse-free survival rate. Later studies will have to address the contribution of hormonal treatment.

Although the large majority of the premenopausal patients will enter the menopause following the FEC chemotherapy, an imbalance between treatment arms could result from the fact that nearly all patients undergoing autotransplantation will have irreversible ovarian failure. The significance of such an imbalance in menopausal status is uncertain, despite the use of tamoxifen in both treatment arms. Rather than insisting on ovarian ablation in all patients who remain pre-menopausal, the menopausal status after chemotherapy will be considered as a separate covariate in the regression analysis (see statistical considerations).

For this end, the following parameters should be recorded as completely as possible:

- estradiol- and progesterone receptor status of the tumor

- the menopausal status by history before the chemotherapy and before the start of adjuvant tamoxifen and further on, on every visit during follow up

- FSH and 178-estradiol levels before the start of chemotherapy and if premenopausal, before endocrine therapy and every 4 months during and at the end of tamoxifen therapy and 6 and 12 months thereafter and whenever uncertainty about the menopausal state exists.

**7.0 CLINICAL EVALUATIONS, LABORATORY TESTS AND FOLLOW-UP**

**7.1 Overview of tests to be performed**

| Observation | on study | at monthly evaluations | before start of tamoxifen | follow up 4 months | annually |
|---|---|---|---|---|---|
| History & physical examination | x | x | | x | x |
| Menopausal state | x | x | x | x | x |
| Performance, weight | x | x | | x | |
| Hematologya | x | x | | x | x |
| Liver function testsb | x | x | | x | x |
| Serum chemistriesc | x | x | | x | x |
| FSH, 178estradiol | x | | x* | x* | x** |
| Urinalysis | x | | | | |
| Creatinine clearance | x | | | | |
| E.K.G. | x | | | | |
| Mammography | x | | | | x |
| Chest Xray (PA and lat.) | x | | | | x |
| Utrasound exam. liver | x | | | | |
| Isotope bone scand | x | | | | |
| Xray/tomography of bones | x | | | | |
| serum (10 ml), store at 20 EC | x | | | | x |

a Hb, Ht, WBC, platelets (differential when indicated)
b Alk.Phos., gammaGT, SGOT, SGPT, LDH
c Na, K, Cl, BUN, creatinine, protein, albumin
d when the isotope bone scan suggests metastatic disease
* if premenopausal on study
** only if uncerainty exists about menopausal status

**7.2 Follow-up**

After the conclusion of radiotherapy, follow-up frequency will be every 6 weeks in the first year, and every 2 months in the second and third year after the end of treatment. All patients, including those who went 'off study' at any stage, will subsequently be followed for life at intervals determined by the individual investigator.

In case of a relapse, a complete reevaluation must be done to document the pattern of failure. Further treatment is at the discretion of the investigator.

## 8.0 ADMINISTRATIVE CONSIDERATIONS

Patients will be registered and randomized at the Trial Office of the Netherlands Cancer Institute (phone 020-512 2668) as soon as possible after eligibility has been established.

Registration

1. Ensure that informed consent is obtained.

2. Information about: patient's name; age; date of primary surgery; histological diagnosis; number of tumor positive axillary lymph nodes (of total number examined); size of the primary lesion; ER and PR status; menopausal status.

Treatment assignment

Stratification will be done by institution, breast conserving surgery, the presence of 10 or more postive axillary nodes and by menopausal status. The treatment arm will be assigned using minimization techniques.

## 9.0 STATISTICAL CONSIDERATIONS

The major end point of the study is the disease-free survival. Disease-free survival (DFS) is defined as the time from randomization until recurrence or death, whatever occurs first.

A total accrual of 250 patients was achieved in August 1995. The percentage of patients randomized to the high dose therapy/transplantation arm who did not proceed to transplantation was been small (less than 5%). The expected accrual rate has greatly exceeded the first estimates and is currently approximately 15 patients per month. It is therefore reasonable to envisage an accrual of 180-200 patients for 1996 and thereafter.

If **880** patients are entered in this study (440 in each arm) and followed for 5-years the study will have 90% power to detect a true increase of the DFS from 0.30 to 0.40 ("=0.05, 2-tailed test, total number of events=571). Accrual of this number of patients could be achieved (with the curremt accrual rates) by the end of 1998.

Two subgroup analyses are planned: comparison of treatment effect in patients with 4-9 nodes, and the same in patients with $\geq$ 10 axillary lymph node metastases. The estimated 5-year DFS in the 4-9 nodes group is 35% and in the $\geq$ 10 nodes group 20%. In the first part of the study (when 250 patients were entered), 60% of the randomized patients were in the 4-9 nodes group. Hence, approximately 530 of the 880 patients will have 4-9 axillary lymph nodes, and 350 patients will have 10 or more. These numbers will provide over 90% power to detect differences of 15% in DFS in each of the subgroups ("=0.05, 2-tailed).

## 10.0 ETHICAL CONSIDERATIONS

Scientific justification

The prognosis of breast cancer involving $\geq$ 4 axillary lymph nodes is grim, 55-87% of women with primary breast cancer involving 4 or more axillary lymph nodes, will relapse within 5 years of diagnosis.

World-wide experience with intensification of chemotherapy with autologous bone marrow support in breast cancer has essentially confirmed the dose response relationship anticipated by many oncologists on the basis of laboratory data and personal experience. In general, very high response rates with many complete remissions can be obtained in patients with breast cancer who have failed prior conventional chemotherapy regimens or have relapsed after one or more regimens. This group of patients, when treated with conventional second- or higher-line chemotherapy would be expected to achieve response rates of less than 20%, with essentially no complete responses. These findings are very similar to early data in malignant lymphomas. Intensive chemotherapy in the latter disease group is now almost universally accepted as standard approach for patients in first relapse and for poor-prognosis patients as part of the first-line approach.

In phase II studies (Peters, Bonadonna, de Vries) in breast cancer patients with $\geq$ 10 tumor positive axillary lymph nodes, high-dose chemotherapy induces a disease-free survival of 72-85% at 4 years, which appears extremely promising in comparison the historical data. The most urgent questions that must be answered by the studies now being initiated in several centers around the world are:

(1) Is the dramatic improvement in survival as a result of high-dose therapy reproducible in prospective randomized studies?

(2) Which subsets of node-positive breast cancer patients benefit most from this aggressive approach?

Patient information

Patients confronted with the option to be entered in this trial face the prospect of dying of their cancer within one to several years. When randomized in the 'experimental treatment' arm, chances of cure or prolonged relapse-free survival may improve (although it is unknown by how much) but the possibility of serious or even fatal toxicity, although probably very low, must be considered. The decision to participate may thus be a difficult one; it should be facilitated by repeated discussions with the patient and her relatives and/or trusted friend with the physicians responsible for the study, in combination with detailed written patient information.

Liability Insurance

All centers collaborating in this multicenter study have an institutional liability insurance cover, the terms of which include any risks associated with intensive chemotherapy such as administered in this trial. Institutional liability pertains to malpractice and misadventure issues and, clearly, does not extend to outcome in individual patients. The risks related to outcome will be fully disclosed during the patient information procedure (see the previous paragraph).

## 12.0 PUBLICATION OF DATA AND RESULTS

All papers and abstracts will be co-authored by the study coordinators and by one investigator from each center that has contributed one or more patients to the data to be analysed. Full articles on the clinical topics relating to the study will be prepared by the study coordinator(s) and will also be co-authored by the statistician and possibly by the data manager. Publications regarding technology assessment issues will be prepared by the investigators responsible for this topic, but will be co-authored as any other paper (see above). In addition, the manuscripts for these publications will be made available to the study coordinator(s) at least 14 days prior to submission to allow for comments.

Presentations at national or international meetings may be given by investigators from individual centers, but will require the approval of the study coordinator(s) prior to submission in all cases.

These rules will apply exclusively to publications and/or presentations of data that have been collected among more than a single center. Investigators remain free te report in any desired form on patients treated exclusively in their own center.

## 13.0 REFERENCES

**APPENDIX I**

**Overview of the study design**

(tumorectomy) mastectomy

axillary clearance

|

|

≥ 4 tumor positive axillary lymph nodes

|

|

randomization

5 x FEC 2 x FEC

| |

| |

| |

|

| 1 x FEC + G-CSF

| |

| |

|

| PSC harvest

| |

| |

|

| 1 x FEC

| |

| |

|

| CTC + PSCT

| |

| |

| |

| |

.) ) ) ) ) tamoxifen + radiotherapy ) ) ) ) –

**APPENDIX II**

**1. Mobilization procedure**

Prior to the mobilization procedure a Hickman double lumen plasmapheresis catheter (13.5 French) should be placed in the subclavian vein under local anaesthesia.

Peripheral blood stem cells (PBSC) will be mobilized with the third course of FEC chemotherapy followed by the administration of G-CSF (filgrastim) 300 :g subcutaneously during 10 days. The entire mobilization procedure can be performed in an outpatient setting.

FEC G-CSF 300 :g/day s.c.

9 _____

_____|_____9__

1 2 7 8 9 10 11

|_____

stem cell monitoring and hemaphereses

**2. Timing of the peripheral stem cell harvest**

The timing of peripheral stem cell collection is clearly important. Sienna and associates have developed a rapid cytofluorimetry assay of CD34 positive cells using 50 ml of whole blood. The appearance of CD34 positive cells in the peripheral blood can be used as a starting point for leukapheresis (see appendix III).

In the Netherlands Cancer Institute experience, stem cells (operationally defined as CD34+ cells) appear in the peripheral blood as soon as the leucocyte count is rising. This is almost invariably true (> 90%) for patients who have not been heavily pretreated (such as the breast cancer patients in the present study). In practice, hemapheresis for stem cell collection in this patient group can be started as soon as the W.B.C. count is rising and above 3 x 109/l (without monitoring of CD34+ cells in the peripheral blood on days preceding the hemapheresis). This strategy is straightforward and will quite probably result in a successful stem cell harvest. The CD34+ content of the the stem cell harvest must be determined, but this can be done later, at a convenient point in time (see appendix II for technical details of the assay).

Because of the reported higher bleeding tendency when hemaphereses are performed at low platelet counts, the minimum platelet count at the start of the hemapheresis should be > 50 x 109/l (see below for further details). The platelet count will decrease during the procedure.

Start of hemapheresis:

1. CD34+ cells $\geq$ 0.02 x 109/l

or

2. rising W.B.C. counts and total W.B.C. $\geq$ 3 x 109/l

and

3. platelets $\geq$ 50 x 109/l

and

- if platelets $\leq$ 100 x 109/l: determine platelet count after 3 liter processed blood volume

- if platelets > 100 x 109/l: determine platelet count after 6 liter processed blood volume

- Terminate hemapheresis if platelets drop below 40 x 109/l

**3. PBSC harvest**

Initial experience with PBSC collection involved the use of intermittent flow cell separators and some units continue to use these devices. Most groups now use continuous flow cell separators. The most relevant question is whether there is any evidence to suggest that one machine or one technique yields higher levels of PBSC from each leukapheresis. There is no clear evidence that either machine has an absolute advantage. The PBSC harvest product consists of a nearly granulocyte free mononucleated cell product, comparable to the interphase after a Ficoll separation. (See for technical instructions the manual of the factory).

Blood volume to be processed: 10 l maximum per hemapheresis procedure. One to three leukaphereses procedures are usually required.

It is recommended that collections should be obtained in the early morning, to facilitate the further processing by the cryopreservation laboratory during office hours.

**4. Quantitation of PBSC's**

By 'quantitation of the number of PBSC's' by the CFU-GM assay or by a CD34+ determination, a quantitation of committed hematopoietic progenitor cells is in fact meant. No assay exists for the real pluripotent hematopoietic progenitor cell. In the Netherlands Cancer Institute experience, number of infused CD34+ cells is the best predictor of early hematopoietic engraftment of granulocytes and platelets.

Reinfusion of 6 x 106 CD34+ cells per kg body weight (number of cells before freezing) is optimal, and larger cell numbers do not further hasten recovery of platelets and granulocytes. Adequate engraftment has been observed in patients who received between 3 and 6 x 106 CD34+ cells/kg, but the experience with less than 3 x 106 CD34+ cells/kg is limited and if less cells are available, combination with autologous bone marrow reinfusion may be advisable.

For a viability check after freezing, one or more ampoules with cells should be thawed to check viability with the CFU-GM assay or at least with a trypane blue exclusion test. Usually, viability will be 75% or better.

**5. Cryopreservation, thawing and reinfusion of PBSC's**

These procedures will be performed according to local guidelines.

There is uncertainty about the desirable cell concentration for cryopreservation. Probably, the mononucleated cell concentration should not exceed 1 x 108/ml. Because of the high number of mononucleated cells harvested by leukaphereses from peripheral blood compared to a bone marrow harvest (median 250 x 108 vs 15 x 108 mononucleated cells) the total cryopreserved volume will be about 500 cc.

Beginning on day 0 (48 hours after all components of CTC have been administered), half of the total PBSC collection should be reinfused, the second half should be reinfused on day 1.

**6. Autologous bone marrow support**

In cases where PBSC harvest is insufficient (< 3 x 106/kg CD 34+ cells and/or poor viability post freezing) autologous bone marrow should be reinfused (in addition to the available PBSCs), on day 0.

**APPENDIX III**

Flow cytometric estimation of hematopoietic progenitor cells in peripheral blood and stem cell harvest.

Materials

- Isotonic NH4Cl buffer pH 7.4 at 4EC

- Washing buffer PBS/BSA 0.2% (w/v)

- Con IgG 1-FITC

- CD34 FITC (most studies have been carried out with 8G12 FITC from Peter Lansdorp, now commercially available as HPCA-2 FITC from Becton Dickinson = BD

Optional

- Con Ig PE

- CD66 biotin (The antibody CLB gran/10 is commercially available from CLB)

- CD33 PE |

- CD13 PE | these antibodies may be purchased from BD

- HLA-DR PE |

- CD45 RO PE (is present only on uncommitted progenitors)

Equipment

FAC-scan or comparable flow cytometer

Protocol

1. Depletion of platelet rich plasma by centrifugation of 10 ml anticoagulated blood (with for instance EDTA as anticoagulant) 1600 rpm (table centrifuge) for 10 minutes (brake off*)

2. Lysis of the pellet in a 50 ml tube with 25 ml NH4Cl for 10 minutes at 0EC (occasionally shaking)

3. Add PBS/BSA to a final volume of 50 ml

4. Centrifugation, 5 minutes 1700 rpm (brake on)

5. If many erythrocytes are still present in the pellet repeat 2 6 4

6. Resuspend the pellet in PBS/BSA to a cell concentration of 20 x 106/ml

7. Incubate 0.5-1 x 106 cells for 30 minutes at 4EC with antibodies in appropriate dilutions

a. Con IgG 1-FITC + CD66 biotin**

b. CD34 FITC + CD66 biotin

Optional c. CD34 FITC + Con IgG 2a-PE

d. CD34 FITC + CD13 PE

e. CD34 FITC + CD33 PE

f. CD34 FITC + HLA-DR PE

g. CD34 FITC + CD45 RO PE

8. After washing (PBS/BSA) incubation with streptavidine PE (a. and b.) for 20 minutes at 4EC

9. Add 300 :l PBS/BSA to the pellet after the final washing step

10. Acquiring and storing flow cytometric data:

I For the determination of % CD34+ cells in the leukocyte fraction

a. and b.: store the data of at least 20.000 cells measured in list mode

II For the determination of % CD34+ cells in the mononuclear cell fraction

a. and b.: set a live gate using single histogram FL2 on CD66 negative cells (exclusion of CD66 positive granulocytes) and store the data of at least 10.000 CD66 negative cells

III For the determination of phenotype of CD34+ cells

c.-g.: set a live gate using dot plot FL1/SSC*** or single histogram FL1 on CD34+ cells. Store data of at least 1000 cells

11. Analysis of flow cytometric data

I Use 'contour plot analysis' software. Horizontal: FL1. Vertical: SSC or FL2

II Similar analysis as I (FL1/SSC)

III Use 'contour plot analysis' or 'single histogram analysis'. Calculate the percentage of positive cells as well as the mean fluorescence of all cells.

* A similar assay can be carried out with leukapheresis material (300 :l containing about 4-8 x 106 cells), except that only 1-2 ml NH4Cl is used for the lysis of erythrocytes.

** Patients treated with G-CSF have high granulocyte counts. The exclusion of (CD66 positive) granulocytes during the analysis greatly enhances the sensitivity of the assay. When leukapheresis material is tested,which is already depleted from granulocytes it is of course not necessary to use this antibody.

*** CD34 positive cells can easily be recognized as a real population of positive cells by combination of the FL1 signal with the side scatter. The aspecific background FL1 signal of monocytes and granulocytes does not obscure the specific CD34 FL1 signal, as monocytes and granulocytes both have a relatively high side scatter.

This assay is performed on a daily basis in the department of Immunohematology of the CLB (Dr C.E. van der Schoot, 020-512 3390, CLB) and can be requested on CLB form 5.

**APPENDIX IV**

**'C.T.C.' Chemotherapy Course**

| Day | -7 | -6 | -5 | -4 | -3 | -2 | -1 | 0 | 1 |
|---|---|---|---|---|---|---|---|---|---|
| Prehydration 2 L NaCl/12 hrs | x | | | | | | | | |
| **Cyclophosphamide** 1500 mg/m2 i.v. in 500 ml NaCl 0,9% in 1 hr | | x | x | x | x | | | | |
| **Mesnum** 6 x 500 mg in 50 ml NaCl 0,9% start 15 min before first cyclophosphamide dose, thereafter every 4 hrs | | x | x | x | x | | | | |
| **Thiotepa** 60 mg/m2 in 100 ml NaCl 0.9%/30-60 min every 12 hrs two times daily | | x | x | x | x | | | | |
| **Carboplatin** 400 mg/m2 i.v. in 500 ml Gluc 5%/2 hrs | | x | x | x | x | | | | |
| Stem cell reinfusion | | | | | | | | x | |

x

**Additional measures:**

* urine sed. daily

* RR and pulse 4 times daily

* see also appendix V

* hydration during the high-dose chemotherapy 4 L (incl. dissolved chemotherapy)

**APPENDIX V**

**Some Supportive care matters relating to the PSCT procedure**

Pre PSCT screening

- Blood biochemistry, creatinine clearance

- Virus serology (Hepatitis A,B,C; CMV; HIV)

- Toxoplasma serology;

- Allo-antibodies against platelets;

- HLA-typing (only in case of sensibilization against HLA class I antigens);

- OPG; X-thorax; X-sinus;

- Consult dentist; in case of foci on OPG;

- Bacterial inventarisation, 1 week before admission (nose, throat, faeces);

- Control viability and number of CD34+ cells or CFU-GM's.

Medication (or otherwise according to local rules)

- Selective bowel decontamination, start 5 days before admission until granulocytes > 0.3 x 109/l

< Ciproflaxacin 2 dd 500 mg orally (2 dd 200 mg/i.v.)

< Amphotericin B sups 4 dd 5 cc orally

< Chlorhexidine mouth washes

- Streptococci prophylaxis --> start day after ending the high-dose chemotherapy

< Penicillin 4 dd 1 million E

or

< Cloxacillin 4 dd 500 mg (in case of present or previous colonization with staph. aureus)

- Anti-emetics

< a 5-HT3-receptor antagonist

< Dexamethasone 2 dd 10 mg i.v.

< Temesta 3 dd 1 mg

- Other medications

< Vitamin K 2 times weekly 5 mg orally

< folic acid 2 dd 5 mg orally

< Ranitidine 2 dd 150 mg orally (2 dd 50 mg/i.v.)

Blood products support

- Platelet transfusions: if platelet count # 10 x 109/l,

or in case of hemorrhagic diathesis;

- Red blood cell transfusion: according to local policy;

--> During the leucapheresis period (from start G-CSF administration till last leucapheresis) and during the transplantation period (from start high-dose chemotherapy regimen till 4 months after stem cell infusion and good engraftment) all blood products (red blood cells and platelets) must be irradicated with 2500 R before administration.

Hydration during high-dose chemotherapy

Prehydration NaCl 0.9% or NaCl/glucose: 2 L/12 hrs;

Hydration during high-dose chemotherapy: 4 L/24 hrs (including cytostatics).

Laboratory tests

- Daily sodium, potassium, creatinine, glucose, haemoglobin, leuco's, thrombo's;

- Three times weekly complete blood biochemistry;

- Two times weekly check bacterial colonization (nose, mouth, faeces);

- During hematopoietic recovery leucocyte differentiation and reticulocyte, 3 times weekly.

Fever

In case of unexplained fever $ 38E C during the pancytopenic period, start immediately with broad spectrum antibiotics, according to local rules.

**APPENDIX VI**

**Radiation Therapy Guidelines**

Internal mammary nodes

Radiotherapy field of the homolateral lymph nodes: 2 cm above the sternal notch down to the fifth intercostal space with a field of 6 cm wide (1 cm hetero- and 5 cm homolaterally from the midline, also including the medial part of the subclavicular fossa. If the internal mammary node scan is abnormal and shows crossing over or extension outside the previously described field, the field should be adjusted accordingly. The dose will be 50 Gy in 5 weeks at 2 cm depth in 25 fractions with a daily dose of 2 Gy (according to the ICRU report 29). Half to 2/3 of this radiation dose should be delivered with fast electrons (12-14 MeV).

Axilla and supraclavicular region

The field should include sub- and supraclavicular regions and the axilla. The dose is 50 Gy in 5 weeks, in 25 fractions with a daily dose of 2 Gy. Indications for irradiation of the axilla are those situations where there is a high chance of incomplete resection (top of the axilla has tumor positive nodes, very small-free margins, irradicality at the local tumor site). The dose should be specified according to the ICRU report 29. The amount of included lung tissue should be limited, however the sternoclavicular joint should be included.

Breast

The dose should be specified at the intersection of the beam axes in the central plane according to the ICRU 29 prescriptions. Minimum and maximum dosage in the central plane should be > 95% and < 110%. Actual minimum and maximum dose should be registered. Calculation of off axis dose distribution is advised in order to obtain homogeneity. The amount of included lung tissue should be estimated in case of a central lung distance (CLD) of > 3 cm; adaptation of the technique should follow. This CLD can be measured on the simulation or portal film of the tangential beam. Dorsal beam alignment is advised in order to minimize lung irradiation. Lung density correction is recommended. A dose of 50 Gy in 25 fractions is advised. Boost doses should be applied according to local prescriptions.

Chest wall

If a mastectomy has been performed, the chest wall is advised to be irradiated to a dose of 40 Gy in 20 fractions with fast electrons in those situations where there has been a (microscopically) incomplete resection. In general, an energy of 6-8 MeV is sufficient. Utmost care should be taken when energies of $\geq$ 10 MeV are used. The depth of the target volume is to be determined according to a chest wall ultrasound or CT scan defining the anterior surface of the ribs. In case that tangential fields are used, the dose should be specified in the central plane at the intersection of the beams. A maximum of 3 cm CLD is then allowed.

Toxicity

High-dose chemotherapy + ABMT appears to impair the patient's ability to tolerate local-regional radiotherapy.

In a study of Marks [69], 11 of 40 patients developed significant hematologic of pulmonary toxicity. Six of these 11 patients required prolonged treatment interruption or discontinuation. Cardiac, pulmonary and hematologic toxicity requiring treatment interruptions has rarely been reported in large series of irradiated patients, not previously treated with agressive chemotherapy. Although the high incidence of pulmonary toxicity in the study of Marks [69] may be partially related to the BCNU containing high-dose chemo- therapy regimen, this serious side effect will receive particular attention in this study and has to be monitored carefully according to the local protocols.

The incidence of hematologic toxicity associated with radiation therapy is expected to be reduced by the application of peripheral stem cell transplantation. Preliminary experience indicates that part of the toxicity can be prevented by careful treatment planning.

During radiotherapy, a weekly bloodcount must be performed in case the internal mammary nodes and/or the chestwall are irradiated. If the leucocytes and/or platelets show toxicity grade III or IV according the WHO scoring system, the patient should be discussed with the responsible oncologist and/or the study coordinators.

When the patient reports complaints suggestive for radiation pneumonitis, a chest X-ray and pulmonary function tests are mandatory and the patient has to be monitored carefully. When radiation pneumonitis is confirmed it is advised to prescribe corticosteroids at a medium high dose. This therapy is adjusted according to the amelioration of the restrictive defects as measured with (repeat) pulmonary function tests (inclusive TLCO).

Radiation Therapy Consultant:

In case of uncertainty regarding the indication, technique or toxicity of radiation therapy, please contact Dr. J.H. Borger, Dept. of Radiotherapy, Netherlands Cancer Institute, phone 020-512 9111.

Summary Study NR. M93SCB

Adjuvant chemotherapy in patients with stage II or III breast cancer and 4 or more positive nodes

This prospective randomized trial will investigate the curative potential of very intensive adjuvant chemotherapy in patients with operable stage II of III breast cancer, who have 4 or more tumor-positive axillary lymph nodes and who are under 55 years of age. The adjuvant regimen in the `experimental arm' will include four cycles of FEC (5-FU, epidoxorubicin, cyclophosphamide), high-dose combination chemotherapy with hematopoietic stem cell (HSC) rescue, locoregional radiotherapy and tamoxifen. The control group will receive identical treatment, except that the high-dose chemotherapy course will be replaced by a 5th course of FEC.

The patients will be randomized before chemotherapy is initiated. Patients randomized in the `experimental arm' will undergo peripheral stem cell mobilization employing G-CSF following the third course of FEC.

The study will answer the question whether or not very high-dose chemotherapy with hematopoietic stem cell support should be offered on a routine basis to young patients with high-risk breast cancer as part of an adjuvant therapy strategy.

***Samenvatting Studienr. M93SCB***

*Adjuvante chemotherapie met of zonder perifere stamcel transplantatie in patiënten met stadium II of III mamma carcinoom met 4 of meer positieve okselklieren.*

**Patiëntenselectie**

- Gemodificeerde radicale mastectomie met okselklier toilet (in sommige centra mamma sparende chirurgie). Histologisch bewezen stadium IIA, IIB of IIIA mamma carcinoom met $\geq$ 4 positieve okselklieren.
- Mammasparende behandeling: de resectie moet compleet zijn; geen angio-invasieve groei; leeftijd 40 jaar of ouder.
- Geen eerdere chemo- of radiotherapie.
- Geen metastasen op afstand.
- Leeftijd $\leq$ 55 jaar.
- Performance status (WHO) $\leq$ 1.
- WBC $\geq$ 4,0 $10^9$/L

  Thrombocyten $\geq$ 100 $10^9$/L

  Bilirubine $\leq$ 25 $\mu$ mol/L

  Creatinine klaring $\geq$ 60 ml/min

- Start adjuvante chemotherapie binnen zes weken na chirurgie.
- Geen andere maligniteiten in de voorgeschiedenis, met uitzondering van adequaat behandeld cervix carcinoom in situ en/of basaalcel carcinoom van de huid.
- Geen eerdere of huidige ziekte die de protocol behandeling kan hinderen.
- Beschikbaar voor follow-up.
- Informed consent.

**Behandeling**

5 x FEC

R

4 x FEC + PSCT

In beide armen gevolgd door:

- Radiotherapie: parasternaal, axillair, supraclaviculair en thoraxwand.
- Tamoxifen: 20 mg/dag gedurende 4 jaar.

**Adjuvante chemotherapie**

| | | |
|---|---|---|
| Cyclophosphamide | 500 mg/m² i.v. d1 | ⎫ |
| Epidoxorubicine | 90 mg/m² i.v. d1 | ⎬ q 3 weken |
| 5-fluorouracil | 500 mg/m² i.v. d1 | ⎭ |

**Dosis modificaties**

| | dag 21 | dag 28 |
|---|---|---|
| WBC ≥ 3,0 $10^9$/L | | |
| en | 100% | - |
| thrombocyten ≥ 100 $10^9$/L | | |
| WBC ≥ 2,0 < 3,0 $10^9$/L | 1 week uitstel | 75% |
| WBC < 2,0 $10^9$/L | 1 week uitstel | off-study |
| thrombocyten < 100 $10^9$/L | 1 week uitstel | off-study |

-

**Flow chart**

| Parameter | voor behandeling | maandelijkse evaluatie | voor start tamoxifen | follow-up elke 4 mnd | follow-up jaarlijks |
|---|---|---|---|---|---|
| Lichamelijk onderzoek en anamnese | x | x | | x | x |
| Performance status, gewicht | x | x | | x | |
| Hematologie [a] | x | x | | x | x |
| Chemie [b] | x | x | | x | x |
| Urine analyse | x | | | | |
| Creatinine klaring | x | | | | |
| ECG | x | | | | |
| Mammogram | x | | | | x |
| X-thorax | x | | | | x |

| | | | | | | |
|---|---|---|---|---|---|---|
| Echo lever | x | | | | | |
| Botscan | x | | | | | |
| X-skelet [c] | x | | | | | |
| 10 ml serum (bewaren bij -200C) | x | | | | | x |
| Menopausale status | x | | x | x | x | x |
| FSH, 17 B- estradiol | x | | | x | x* | x** |

* indien premenopausaal bij on study

** alleen nodig bij onzekerheid over menopausale status

a: Hb, Ht, WBC, thrombocyten.

b: Alk. fosf., K GT, SGOT, SGPT, LDH, Na, K, Cl, Ureum, Creatinine, totaal eiwit, albumine.

c: Indien bij de botscan verdacht is voor metastasen.

**Randomisatie**

Bij het trialbureau van het AvL, telefoon 020 - 512 2668.