Patient selection for high-dose chemotherapy in stage II and IV breast cancer

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Chapter 2.

Dose-intense chemotherapy for locally advanced breast cancer

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Summary

The availability of hematopoietic growth factors has allowed a range of feasibility and uncontrolled studies with high-dose chemotherapy (with or without stem cell support) to take place. Preliminary data from some randomized studies are now available as well. Dose-intensive chemotherapy appears to be effective in downstaging the tumor. Only a minority of patients achieve a pathologic complete remission and additional therapeutic options to control minimal residual disease are urgently needed. There are few indications that high-dose chemotherapy is superior to conventional dose therapy in terms of relapse-free or overall survival. Although the results of most studies are premature or unknown at this time, a modest but clinically significant survival advantage may still emerge.

Introduction

Definition

No uniform definition exists for the term ‘locally advanced breast cancer’, but it usually refers to stage III disease [1] and thus covers about 10 to 30% of all patients with newly diagnosed breast cancer. Stage IIIA disease includes tumors over 5 cm in size (T3), with or without regional lymph node metastases, or tumors associated with axillary lymph node metastases fixed to each other or to other structures (N2). Stage IIIB disease refers to tumors of any size that extend to the chest wall or invade the skin (T4) or to the presence of ipsilateral internal mammary lymph node metastases (N3). Inflammatory breast cancer is included in stage IIIB, but carries a worse prognosis. Although metastases to the ipsilateral supraclavicular lymph nodes are classified as M1 disease, many investigators consider these tumors without other distant metastases as locally advanced disease.

Established principles of management

The majority of patients with stage III breast cancer have distant micrometastases and they will die of their disease when systemic treatment is withheld. Analysis of the natural course of locally advanced disease in patients who lived between 1805 and 1933, yielded a mean survival time of 2.7 years (range 3 months to 18 years) [2]. With modern multimodality approaches, local tumor control can be achieved in 80 to 90% of patients, and 10-year survival rates of 30 to 40% are common [1]. Interestingly, the incorporation of tamoxifen in the systemic part of the treatment appears to be even more crucial for long-term survival than chemotherapy [3].

Aims of treatment

Locally advanced breast cancer is no longer a uniformly fatal disease, but a clear need still exists for improvement of the long-term survival rate. Because most patients die of distant metastases, better systemic treatment is urgently required. One important strategy to achieve this has been to increase the dose-density of chemotherapy with or without the incorporation of novel agents. Quality-of-life issues, however, are becoming increasingly important as long-
term survival increases. Dose-dense chemotherapy may allow efficient downstaging of the tumor when administered before local therapy, making breast-conserving approaches available to more women [4,5,6,7].

On the other hand, intensive chemotherapy may also result in more long-term toxicity, such as anthracycline-caused cardiotoxicity [8,9], second malignancies, or a recently recognized form of central neurotoxicity. Van Dam et al. [10•] found in a cross-sectional study, that patients who had undergone high-dose therapy performed significantly worse at neuropsychological testing than patients who had received conventional dose adjuvant chemotherapy. Because the neuropsychological abnormalities persisted for at least 2 years after the conclusion of chemotherapy, it is possible that these changes are irreversible [10]. Little information is available about second tumors other than breast cancers in this patient group, but this may change as long-term survival improves.

**Possible advantages of primary chemotherapy**

In addition to downstaging of the tumor, primary systemic combination therapy has several other potential advantages. In theory, one of these could be that early treatment of micrometastases is beneficial and that local effects may be more pronounced when the blood supply has not been compromised as a result of therapy. Importantly, systemic chemotherapy prior to local treatment allows the assessment of pathological response to chemotherapy. A number of studies have investigated the predictive value of several biological tumor properties with respect to pathological response, prognosis and disease free survival. Willsher et al. [11] found an increased likelihood of response to preoperative chemotherapy when the tumor was Her-2/neu oncogene negative. This finding was consistent with findings from previous studies [12]. Other studies have focused on BCL-2 expression [13] and other biological markers, such as protein p53, P-glycoprotein, micro vessel density and Ki-67 antigen expression in locally advanced breast cancer. Some of these markers may eventually be helpful in determining the optimal treatment strategy in individual patients.

**Dose-intense treatment without progenitor cell reinfusion**

Now that recombinant human hematopoietic growth factors have become available, a large number of feasibility studies and other uncontrolled trials have been reported that attempt to increase the dose-intensity, defined as the amount of chemotherapy administered per unit of time (Table 1).

With conventional dose chemotherapy given before local therapy, clinical response-rates of 70 to 90% can be achieved, and pathological response rates of 10% are routinely found when surgery follows chemotherapy. With prolonged chemotherapy, a 28% pathological response rate has been described [14] and with dose-intense therapy pathological complete response rates of even 17 to 36% have been reported [15].
### Randomized studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Regimen</th>
<th>Number of Patients/stage</th>
<th>Clinical Response Rate (%)</th>
<th>Pathologic Response Rate (%)</th>
<th>Follow-up (median or mean) (months)</th>
<th>5-year DFS (%)</th>
<th>5-year OS (%)</th>
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</thead>
<tbody>
<tr>
<td>Levine et al [26••]</td>
<td>Postsurgery arm a: CMF arm b: CEF</td>
<td>710</td>
<td>59</td>
<td>CMF:53</td>
<td>CMF:77</td>
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<td></td>
<td>arm b: CEF</td>
<td>arm a: 359</td>
<td>arm b: 351</td>
<td>stage II and III</td>
<td>CEF:63</td>
<td>CEF:70</td>
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<td></td>
<td>arm a: FCE x 6</td>
<td>448</td>
<td>27</td>
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<tr>
<td></td>
<td>arm b: CEF 6</td>
<td>+ tamoxifen</td>
<td></td>
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<tr>
<td>Therasse et al [25]</td>
<td>arm a: initial surgery → surgery</td>
<td>272</td>
<td>124</td>
<td>arm a: ± 60</td>
<td>arm b: ± 60</td>
<td></td>
<td></td>
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<tr>
<td>Mauriac et al [5]</td>
<td>arm a: 3x VM/3xMithV1</td>
<td>118</td>
<td>≥14 years</td>
<td>arm a: 11</td>
<td>arm a: 38</td>
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<td>arm b: 3x MithV1</td>
<td>arm a: 138</td>
<td>arm a: 45</td>
<td>arm b: 21</td>
<td>arm b: 35</td>
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<tr>
<td></td>
<td>arm b: 3x MithV1</td>
<td>arm b: 134</td>
<td>arm b: 34</td>
<td>arm c: 23</td>
<td>arm c: 41</td>
<td></td>
<td></td>
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<tr>
<td>Konin and Hart [16]</td>
<td>arm a: RT</td>
<td>94</td>
<td>arm a: 60</td>
<td>(pCR: 10)</td>
<td>arm a: 37</td>
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<tr>
<td></td>
<td>arm b: RT → CMF (12x) + tamoxifen</td>
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<td>(pPR: 65)</td>
<td>arm b: 47</td>
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<td>arm a: CEF x 6</td>
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<td>arm b: 34</td>
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<td>Cunningham et al [17]</td>
<td>arm a: CVFMP</td>
<td>55</td>
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<td></td>
<td>arm b: 34</td>
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<tr>
<td></td>
<td>arm a: Adriamycin x4</td>
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<td>arm b: Adriamycin x4</td>
<td>arm b: 37</td>
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<tr>
<td></td>
<td>arm b: Adriamycin x4</td>
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</table>

### Non-randomized studies

<table>
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<tr>
<th>Study</th>
<th>Regimen</th>
<th>Number of Patients/stage</th>
<th>Clinical Response Rate (%)</th>
<th>Pathologic Response Rate (%)</th>
<th>Follow-up (median or mean) (months)</th>
<th>5-year DFS (%)</th>
<th>5-year OS (%)</th>
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<tr>
<td></td>
<td>Regimen b: FAC'84</td>
<td>pIR:83</td>
<td>pIR:64</td>
<td>pIR:58</td>
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<td>Karlsson et al [18]</td>
<td>Prior to surgery: FEC(4-6x)</td>
<td>128</td>
<td>cCR:5</td>
<td>37</td>
<td>36</td>
<td>49</td>
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<td></td>
<td>Surgery + RT</td>
<td>stage II-IV</td>
<td>cPR:55</td>
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<tr>
<td></td>
<td>FEC (3-5x) + tamoxifen</td>
<td>stage II-IV</td>
<td>cPR:55</td>
<td></td>
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</tr>
<tr>
<td></td>
<td>MVAC (5-6x)</td>
<td>cPR:60</td>
<td>cPR:11</td>
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<td></td>
<td></td>
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<tr>
<td>Honkoop et al [45•]</td>
<td>A (x 4-6) + GM-CSF</td>
<td>42</td>
<td>cCR:50</td>
<td>32</td>
<td>at 2 years</td>
<td>78</td>
<td></td>
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<tr>
<td></td>
<td>MVAC(x 6)</td>
<td>cPR:48</td>
<td>at 2 years</td>
<td></td>
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<td>If inoperable after first FAC: FAC → RT/CMF → if possible surgery → FAC</td>
<td>stage IIIa:67</td>
<td>pCR:63</td>
<td></td>
<td></td>
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<td></td>
<td>stage IIIb:73</td>
<td>pPR:12</td>
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</tbody>
</table>

pPR= pathological partial remission, pCR= pathological complete remission, pIR= pathological incomplete response, cCR= clinical complete response, cPR= clinical partial remission, LABC= locally advanced breast cancer
A= Adriamycin, C= Cyclophosphamide, E= Epirubicin, F= 5-Flourouracil, M= Methotrexate, M= Mitomycin C, Th= Thiotepa, V= Vincristine, Vi= Vindesine, RT= Radiotherapy

### Table 1. Recent (1998 and later) studies of dose-intensive chemotherapy without progenitor cell reinfusion in locally advanced breast cancer

1 Two different FAC dosages
2 Stage IV included only ipsilateral supraclavicular lymph nodes
Clinical response, but particularly pathological complete response, has been associated with improved long-term survival [7,21]. This association, which has been confirmed by other investigators [22] may allow pathological complete response to become a useful intermediate end point for clinical studies in locally advanced breast cancer.

Although the results of early studies of upfront chemotherapy in breast cancer appear to be encouraging, brief follow-up and a lack of control groups make definitive conclusions difficult [15,23,24]. Results from only a few randomized studies have been published.

Preliminary results are now available from an international phase III study supported by the European Organization for Research in Cancer Therapy (EORTC), the US National Cancer Institute (NCI) of the National Institute of Health, and the Swiss Group for Clinical Cancer Research (SAKK). Findings from this study of neo-adjuvant dose-intensive chemotherapy in locally advanced breast cancer were reported at the 1998 meeting of the American Society of Clinical Oncology (ASCO) in Los Angeles, CA [25]. The trial randomized subjects in two treatment arms 1) conventional dosage of 5-fluorouracil, epirubicin and cyclophosphamide or 2) intensive epirubicin, and cyclophosphamide with granulocyte colony-stimulating factor (G-CSF) support. Four hundred and forty-eight patients with locally advanced breast cancer were included in the study, which took place from 1993 to 1996. The local treatment consisted of radiation therapy and/or surgery, and tamoxifen 20 mg/day was administered until progression. The dose-intensive regimen was feasible and was well-tolerated, but its years of progression-free survival rate was not significantly better than that in the conventional arm. There was, however, a trend in favor of the dose-intensive arm. Further results of this trial are awaited.

An important study supporting the concept of dose intensity has been reported from the NCI clinical trials group [26]. Seven hundred and ten patients with stage II or III breast cancer were randomized to receive either classical CMF (cyclophosphamide, methotrexate, and 5-fluorouracil) adjuvant chemotherapy following surgery or an intensified regimen: of cyclophosphamide 75 mg/m², orally on days 1 to 14, and epirubicin, 60 mg/m², plus 5-fluorouracil, 500 mg/m² (CEF) both intravenously, on days 1 and 8 of a 28-day cycle. The CEF regimen was shown to be superior, both in terms of disease-free survival (63% vs 53%, p=0.09) and overall survival (77% vs 70%, p=0.03). The intensified CEF regimen was, however, clearly more toxic and required prophylactic antibiotics in an effort to limit hospitalization for neutropenic fevers. Five episodes of subsequent acute leukemia were observed in patients receiving this intensified chemotherapy regimen. This study not only involved a higher dose-intensity in the experimental arm, but also employed an anthracycline while the conventional arm did not. Evidence is accumulating that anthracyclines in adjuvant chemotherapy regimens may be associated with improved long-term outcomes [27].
### Table 2.
Recent (1998 and later) studies of high-dose chemotherapy in stage III/high-risk stage II breast cancer

**Dose-intense treatment with progenitor cell reinforcement**

High-dose chemotherapy with hematopoietic progenitor cell support has become a frequently employed treatment modality in locally advanced breast cancer [24]. The development of peripheral blood progenitor cell support has decreased the morbidity and mortality of the transplant procedure and has allowed the administration of a single dose or even several courses of very high-dose chemotherapy (Table 2).

<table>
<thead>
<tr>
<th>Study</th>
<th>Number of patients</th>
<th>Patient selection</th>
<th>High-dose regimen</th>
<th>Strategy</th>
</tr>
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<tr>
<td><strong>Randomized studies</strong></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Hortobagyi et al [33]</td>
<td>78</td>
<td>&gt;10+lymphnodes</td>
<td>Cyclophosphamide</td>
<td>Late intensification</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt;4+lymphnodes after CT</td>
<td>Etoposide</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Cisplatin</td>
<td></td>
</tr>
<tr>
<td>Rodenhuis et al [32*]</td>
<td>81</td>
<td>Infraclavicular lymphnodes</td>
<td>CTC¹</td>
<td>Late intensification</td>
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<tr>
<td><strong>Non-randomized studies</strong></td>
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</tr>
<tr>
<td>Schwartzberg et al [28]</td>
<td>96</td>
<td>Stage II/III</td>
<td>CTCb</td>
<td>Late intensification</td>
</tr>
<tr>
<td>Basser et al [36]</td>
<td>99</td>
<td>Stage II/III</td>
<td>3x Epirubicin</td>
<td>Early intensification</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Cyclophosphamide</td>
<td></td>
</tr>
<tr>
<td>Hohaus et al [35]</td>
<td>91</td>
<td>Stage II/III</td>
<td>Paclitaxel</td>
<td>Early intensification</td>
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<td></td>
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<td>Stage IV</td>
<td>Ifosfamide</td>
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<td></td>
<td></td>
<td>Epirubicin</td>
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</tr>
<tr>
<td>Kuyu et al [31]</td>
<td>35</td>
<td>Stage III/IBC²</td>
<td>CTCb</td>
<td>Late intensification</td>
</tr>
<tr>
<td>Cagnoni et al [30]</td>
<td>30</td>
<td>IBC</td>
<td>CPB³</td>
<td>Late intensification</td>
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<tr>
<td>Viens P et al [29]</td>
<td>17</td>
<td>IBC</td>
<td>Mitoxantrone, Cyclophosphamide</td>
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<td>Melphalan</td>
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</tbody>
</table>

¹ CTC:C=cyclophosphamide, T=thiotepa, C=carboplatin
² IBC=inflammatory breast cancer
³ CPB:C=cyclophosphamide, P=cisplatin, B=BCNU
**Late intensification**

'Late intensification' is the term used for strategies in which a number of conventional dose courses of chemotherapy are administered, followed by a final course of high-dose chemotherapy.

Cagnoni et al. [30] treated 30 patients with inflammatory breast cancer with high-dose chemotherapy between 1993 and 1997. Twenty-three patients received neo-adjuvant chemotherapy before high dose chemotherapy (22 patients received a doxorubicin-containing regimen). Eighteen patients also had adjuvant chemotherapy after surgery but before high dose chemotherapy. Most patients had surgery before the high dose chemotherapy, but three patients underwent surgery afterwards. High-dose chemotherapy followed this regimen: cyclophosphamide 1875 mg/m$^2$/d for 3 days, cisplatin 165 mg/m$^2$ continuously for 72 hours immediately followed by carmustine 600 mg/m$^2$ (referred to as CPB). After this treatment, radiotherapy was started, and tamoxifen was given if the estrogen receptor was positive. The mean follow-up after high-dose chemotherapy was 19 months. The major non-hematological toxicity was drug-induced lung injury, which responded to corticosteroid therapy. At the time of reporting, eight relapses had occurred, of which five were local. The overall and disease free survivals could not yet be analyzed meaningfully, but 70% of the patients were still alive and free of disease. Although the follow-up on this study is limited, the results are encouraging and appear to justify further randomized studies.

At the 1998 ASCO meeting, Kuyu et al. [31] reported updated results of a study performed between 1992 and 1997, that involved 35 patients treated for locally advanced breast cancer (stages IIIA/IIIB and inflammatory breast cancer). All patients received doxorubicin-based chemotherapy, and mastectomy was performed when possible. All patients received the high-dose chemotherapy regimen CTCb: cyclophosphamide 6000 mg/m$^2$, thiotepa 500 mg/m$^2$ and carboplatin 800 mg/m$^2$, with all drugs given by continuous infusion over 96 hours from day -7 to day -4. Thirty-four patients received radiotherapy to the chest wall and regional nodes. This multimodality treatment was given in different sequences. The median follow-up was 36 months. Thirteen patients relapsed, and eight died. Seven of the nine patients who underwent mastectomy had residual disease, and three of these relapsed. The 3-year disease-free and overall survivals were 58% and 67%, respectively.

The first results of two randomized studies of high-dose chemotherapy in high-risk breast cancer were reported in 1998 (one only in abstract to date). Rodenhuis et al. [32] performed a randomized trial in 97 women aged under 60 years with breast cancer and extensive axillary node involvement, as determined by a tumor-positive infraclavicular lymph node biopsy. The patients received three courses of upfront chemotherapy, consisting of cyclophosphamide 500 mg/m$^2$, epirubicin 120 mg/m$^2$ and 5-fluorouracil 500 mg/m$^2$ (FE$^{120}$C), once every 3 weeks. After surgery, the 81 patients with responsive or stable disease were randomized to either another course of FE$^{120}$C or to high-dose chemotherapy (cyclophosphamide 6 g/m$^2$, thiotepa 480 mg/m$^2$, carboplatin 1600 mg/m$^2$) with stem cell support. At 49 months of follow-up, the 4-year overall and relapse free survival for the 97 patients were 75 and 54% respectively, but there was no difference between the two therapy arms (Figures 1 and 2).
Figure 1. Study design of a randomized study of high-dose chemotherapy in the adjuvant treatment of locally advanced breast cancer
From Rodenhuis et al. [32*] with permission
The authors conclude that until the benefit of high-dose chemotherapy is confirmed by large phase III trials, this treatment modality should only be used in randomized studies. Hortobagyi et al. [33] performed a randomized trial in patients with breast cancer with either 10 or more lymph node metastases, or at least four tumor-positive lymph nodes after four courses of neoadjuvant 5-fluorouracil, doxorubicin and cyclophosphamide. The patients were randomized to receive either two cycles of high-dose cyclophosphamide 5250 mg/m$^2$, etoposide 1200 mg/m$^2$ and cisplatin 265 mg/m$^2$ followed by autologous stem-cell transplantation or to no further treatment. Treatment was completed with radiotherapy and tamoxifen for a 5-year period (Figure 3).

No differences were evident in 4-year disease free survival (55% vs 48%) or overall survival (68% vs 60%).
**Figure 3.**

Study design of randomized trial of high-dose chemotherapy versus standard therapy by Hortobagyi et al. [33]

DFS-disease-free survival (at 4 years) ER= estrogen-receptor positive FAC=5-fluorouracil, Adriamycin (doxorubicin), and cyclophosphamide; OS-overall survival; PBSCT-peripheral blood stem cell transplantation

- Resectable tumor
- ≥10 tumor positive lymphnodes after surgery
- >4 residual lymph-nodes after neoadjuvant chemotherapy

FAC x8

- 2 x high-dose chemotherapy
cyclophosphamide
etoposide
cisplatin+PBSCT
  - DFS 52%
  - OS 64%
- No further chemotherapy
  - DFS 51%
  - OS 63%
- Radiotherapy
tamoxifen (if ER+)
Multiple cycles high-dose chemotherapy up-front

Immediate high-dose chemotherapy (without prior conventional-dose chemotherapy) has been attempted in several studies. This strategy aims to prevent the induction of chemotherapy-resistance with relatively low dosages, which could reduce the ability of high-dose therapy to eradicate all residual tumor cells.

Gianni et al. [34] explored the concept of high-dose sequential chemotherapy in stage III and high-risk stage II breast cancer. In this study, three supposedly non-cross-resistant drugs (cyclophosphamide 7 g/m², methotrexate 8 g/m² and melphalan 200 mg/m²) were given sequentially at high-dose over a very short duration. The methotrexate was combined with vincristin and cisplatin. This type of treatment was reasonably well tolerated and could be completed in a median of 70 days. This approach is currently being evaluated in a randomized trial.

Hohaus et al. [35] studied sequential high-dose therapy consisting of two cycles of ifosfamide (12 g/m²), carboplatin (900 mg/m²) and epirubicin (180 mg/m²) with peripheral stem-cell support. Fifty-one patients with stage II/III and 10 or more positive lymph nodes and 40 patients with metastatic disease were treated with high-dose chemotherapy. Stem cells were collected after induction therapy. Sixty-eight patients received two cycles of ifosfamide/epirubicin, and 23 patients received one cycle paclitaxel/ifosfamide/epirubicin. In the adjuvant treatment they found a probability of disease free survival of 64% at 47 months.

Basser et al. [36] designed a regimen of multiple (three) cycles of high dose epirubicin (200 mg/m²) and cyclophosphamide (4 g/m²) with stem-cell and filgrastim support once every 21 or 28 days. Progenitor cells were collected before the start of the chemotherapy, following mobilization with cytokines (filgrastim or stem-cell factor). Ninety-two of the 99 patients completed all three cycles. The main toxicities were severe reversible neutropenia and mucositis. Dose intensification by reducing the interval from 28 to 21 days did not cause more toxicity. Three patients developed cardiac failure, but the mean ejection fraction was lowered by only 4%. At 60 months, the disease free and overall survival rates were 64 and 53%, respectively.

Preliminary results of three randomized studies of high dose chemotherapy in high risk breast cancer

Three additional randomized studies of high-dose chemotherapy in high-risk breast cancer were reported at the 1999 ASCO meeting in Atlanta, GA. Peters et al. [37] described a multi-center-randomized study of 783 patients with primary breast cancer and 10 or more tumor-positive lymph nodes. All of the patients were initially treated with four cycles of cyclophosphamide, Adriamycin (doxorubicin: Pharmacia and Upjohn, Bridgewater, NJ) and 5-fluorouracil (CAF). Patients were randomized to receive either high-dose chemotherapy with cyclophosphamide 5625 mg/m², cisplatin 165 mg/m² and BCNU 600 mg/m² (CPB) and progenitor cell support, or more conventionally-dosed chemotherapy consisting of the same agents in a lower dosage. The treatment was completed with radiotherapy and tamoxifen. At 37 months the disease-free and overall survival rates
were 68% and 78% in the high-dose group, and 64% and 80% in the intermediate dose group, respectively. In the high-dose group, 7.4% treatment-related deaths were observed, while no deaths occur in the conventional-dose group.

Bezwoda et al. [38] performed a randomized trial of 154 women with high risk breast cancer defined as T1-3a. Ten or more involved lymph nodes or tumors greater than or equal to 5 cm and seven to nine tumor positive lymph nodes and at least one additional poor prognostic factor. The patients were randomized to either receive high-dose chemotherapy (cyclophosphamide 4400 mg/m², mitoxantrone 45 mg/m², VP-16 1500 mg/m²) with stem-cell support or standard CAF courses (cyclophosphamide, Adriamycin or epirubicin, and 5-fluorouracil). Two cycles of high-dose chemotherapy were given at a 6-weeks intervals. At 5-years follow-up, 25% of the 75 patients in the high-dose regimen group had relapsed, as did 66% of the 79 patients in the standard dose group. The mortality rates were 17% in the high-dose group versus 35% in the standard dose arm. Thus, results from this small study suggest a marked advantage of tandem high-dose therapy over standard anthracyclin-based chemotherapy in the adjuvant treatment of high-risk breast cancer.

Finally, the Scandinavian Breast Cancer Study Group [39] reported the results of a randomized study of 525 women with high-risk breast cancer. Women in this study were randomized to receive either a relatively intensive regimen of 9 courses ‘tailored’ 5-fluorouracil, epirubicin, and cyclophosphamide (FEC), with the chemotherapy dose adjusted according to the lowest leukocyte count, along with G-CSF support, or three cycles of FEC followed by high-dose chemotherapy (CTCb) with stem-cell support. After a median follow-up of 20 months, 50 relapses and 40 deaths had occurred in the ‘tailored FEC’ arm and 78 relapses and 40 deaths in the high-dose group. Eight patients died in the ‘tailored FEC’ group from secondary acute leukemia or myelodysplastic syndrome, and two therapy-related deaths were seen in the high-dose therapy group. Clearly, this study did not indicate a beneficial effect for high-dose therapy over maximally intensive anthracyclin-based therapy with G-CSF support, although it points to the marked leukemogenic potential of high cumulative doses of anthracyclines.

The information now available is insufficient to determine whether high-dose chemotherapy represents a step forward in the management of high-risk or locally advanced breast cancer. The results of most reported studies do not suggest an improvement, but the data are still immature, and only a single has been reported in a peer-reviewed journal.

High-dose chemotherapy employing new agents

Systemic treatment for breast cancer is still far from satisfactory, and dose-intensification alone does not appear to be the breakthrough technology it was once hoped to be. The combination of multiple treatment approaches remains essential, and the incorporation of new chemotherapeutic agents into dose-intense regimens is an active avenue of research. The most important new agents for breast cancer include the taxanes, paclitaxel and docetaxel; the vincamine, vinorelbin and several new agents that inhibit thymidylate synthetase.
Dose-intensive regimens of paclitaxel, for example, are under development [40]. The integration of paclitaxel [41] or docetaxel [42] in dose-dense chemotherapy is now under intense scrutiny. Hudis et al [43] treated 42 patients with resected breast cancer and four or more lymph node metastases with nine cycles of chemotherapy: three cycles of doxorubicin, 90 mg/m$^2$, followed by three cycles of paclitaxel, 250 mg/m$^2$, in 24 hours, and cyclophosphamide, 3 g/m$^2$ (all at 2 week intervals). All courses were given with G-CSF support on days 3 through 10. Postmenopausal women received tamoxifen 20 mg for 5 years. No treatment-related deaths occurred and no cardiologic toxicity was seen. After a median follow-up of 48 months, 19 of the patients had relapsed and 10 % had died. The disease-free survival rate was 78%.

Conclusions

Dose intensive chemotherapy, particularly when applied prior to surgical treatment, appears to be effective in the down-staging of patients in order to make breast conserving surgery possible even for larger tumors. There are few indications at this time, that high-dose therapy with peripheral blood progenitor cell transplantation offers substantial benefit over conventional-dose therapy, but the statistical power of the available studies is rather limited and worthwhile survival advantage may still emerge with longer follow-up. Further data from the large American and European randomized studies of high-dose therapy in high-risk breast cancer must be awaited.

The experience of the past few years has shown that many patients can be rendered macroscopically disease-free by chemotherapy, even before local treatment is given. At microscopic examination, however, the large majority of specimens show residual microscopic disease and the still considerable distant failure rate attests to the inability of current chemotherapy to eradicate distant micrometastases as well. Thus, chemotherapy as it is now practiced is effective for cytoreduction, but additional treatment for microscopic residual disease is urgently required to obtain cure. In some patients, prolonged use of tamoxifen may fulfill this role. Some authors believe that non-specific treatments such as the use of GM-CSF may aid in developing an effective cellular immune-response against residual tumor cells [44,45•], but the evidence is slim. It is hoped that the dramatic advances in understanding of the molecular mechanics of the cellular immune response may aid in the development of immunological treatments for minimal residual disease in the next few years. In addition, inhibition of angiogenesis or blocking of mechanisms for local tumor invasion (e.g. metalloproteinase-inhibitors) could aid in prevention of tumor progression and recurrence after dose-intense chemotherapy is administered as cytoreduction.
References and Recommended Reading

Recently published papers of particular interest have been highlighted as

- of importance
- of major importance


Results from this study show that patients who receive high-dose chemotherapy as a part of their adjuvant chemotherapy for high-risk breast cancer have significantly more neuropsychologic abnormalities than patients who receive conventional dose adjuvant therapy. These abnormalities may be irreversible.
Dose intensive chemotherapy for LABC


This study documents that a complete pathologic response after upfront chemotherapy in locally advanced breast cancer correlates strongly with relapse-free survival. A pathologic complete response could serve as a substitute end point for clinical studies.


This large randomized trial compares CMF and an intensified CEF regimen in patients with stage II and III breast cancer. There is a clear survival advantage for dose-intensive treatment.


This is the first randomized trial of high-dose chemotherapy in high-risk breast cancer published in a peer-reviewed journal. In the 81 patients randomized, there was no benefit for the high-dose chemotherapy arm, but the statistical power of the study was too low to detect a relapse-free survival advantage of less than 30%.


This randomized trial showed no benefit for high-dose chemotherapy over conventional therapy in adjuvant treatment of high risk breast cancer.

Gianni AM, Siena S, Bregni M. Efficacy, toxicity, and applicability of high-dose sequential chemotherapy as adjuvant treatment in operable breast cancer with 10 or more involved axillary nodes: five-year results. J Clin Oncol 1997; 15: 2312-2321


Bezwoda WR. Randomised, controlled trial of high dose chemotherapy (HD-CNVp) vs. Standard Dose CAF chemotherapy for high risk, surgically treated, primary breast cancer. Proc Am Soc Clin Oncol 1999; 18: abstract 4


42 Gradishar WJ. Docetaxel as neoadjuvant chemotherapy in patients with stage III breast cancer. Oncology (Huntington) 1997; 11: 15-18


This study describes the prognostic roles of clinical and pathologic characteristics in patients with locally advanced breast cancer who received anthracyclin-based neoadjuvant chemotherapy with growth factor support.