# Is There a Role for Intensive Therapy in Breast Cancer?

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With reference to survival, polychemotherapy has been demonstrated to be statistically significantly more effective than monochemotherapy both in the adjuvant setting and in the metastatic situation. Breast cancer demonstrates a dose-response relationship. Chemotherapy used in the conventional dose range should be given with adequate dose-intensity both in the adjuvant setting and for metastatic patients. More dose-intensive combinations are almost always associated with a higher response rate in patients' metastatic disease, but these results have seldom been translated into an improved survival. For marrow requiring high-dose therapy, repeated phase II studies have demonstrated the possibility of a survival tail, which may be due to stage migration and patient selection. At present we have at least 13 ongoing phase III studies in the adjuvant setting and at least 5 ongoing studies in the metastatic situation. These studies will give a definite answer on whether marrow-supported high-dose therapy is better than conventional therapy or if alternative approaches using tailored therapy will result in an equivalent outcome. In the future we must make better use of the present arsenal of drugs and examine the marked inter-individual variations in pharmacokinetic profiles for the drugs. We have to tailor the therapy to the tumour biological profile, in both the primary tumour and metastases with appreciation of heterogeneity and tumour progression. Based on these prerequisites, therapy can be either dose-intensive or in some instances continuous using lower doses.

The background, clinical dose-response and dose-intensity data on human breast cancer are reviewed. The article includes discussions of pharmacokinetic considerations and data on the potential of individually tailored chemotherapy aimed at increasing the dose-intensity without simultaneously enhancing the side effects.

## BACKGROUND

Studies of the receptor-positive human breast carcinoma cell line MCF 7 have revealed a marked dose-response effect for different alkylating agents; melphalan, thiotepa, cisplatin and cyclophosphamide (1). The demonstrated synergism between thiotepa and the cyclophosphamide metabolite partly supports the clinical use of the high-dose regimen $CTC_b$ (cyclophosphamide, thiotepa, carboplatin) for breast cancers (2). A dose-response relationship has been demonstrated for other human in vitro cell lines including murine leukaemia cells (3, 4). The importance of dose is underlined by the fact that in certain animal models a 20% dose reduction will result in a 50% reduction in cure rate (5, 6).

Most solid tumours, including breast cancer, are characterized by marked tumour cell heterogeneity, most likely also reflected by differences in proliferation rate of the cancer cells within a solid tumour mass. This makes the in vivo situation in humans with many cancer cells in $G_0$ far from comparable with the in vitro situation with a much larger proportion of cell proliferation (7). Accordingly, one should be very cautious when interpreting and transferring in vitro data to the human situation, at least with reference to response patterns for different cytostatics and demonstrated steep dose-response curves.

With reference to the clinical situation, one high-dose chemotherapy regimen with marrow support has been calculated to result in a median tumour cell kill of $10^5$ to $10^6$ cells (8). In accordance with this, a double high-dose procedure should result in 12 logs of cell kill (8). However, this is probably incorrect, because of the complex cellular resistance factors in solid tumour masses together with the demonstrated inter-patient variability in plasma pharmacokinetics (9–12). Furthermore, in the clinical setting a follow-up of the double high-dose procedure with marrow support has been demonstrated in an indirect comparison not to be superior to the single high-dose procedure (13).

## PRESENT THERAPY STRATEGIES FOR TREATMENT OF METASTATIC DISEASE

Most oncologists consider the treatment of this group of patients to be strictly palliative, while other therapy optimists may even consider some patients in this situation as

potential candidates for therapy strategies with curative intent (14). For patients with receptor-positive breast cancer cells the standard therapy will include several lines of hormonal therapy, if the patients respond to this type of therapy. Finally, however, all patients will progress on hormonal therapy. In this situation some patients will have a larger tumour burden than when the hormonal therapy was initiated. This will then most likely result in a more marked tumour cell heterogeneity, probably related to enhanced problems with resistance to chemotherapy.

An alternative strategy would be to use up-front aggressive chemotherapy aiming at maximal tumour cell reduction to avoid development of drug resistance. This will result in a minimal tumour burden in the responding patients, and for those with hormone receptor-positive tumours endocrine therapy may be more beneficial in this situation, while this type of therapy has been demonstrated to be curative for micrometastases, e.g. adjuvant tamoxifen therapy (15).

## PHARMACOKINETIC CONSIDERATIONS AND TAILORED THERAPY

Most cytostatics demonstrate a marked inter-patient variability in clearance/systemic exposure with many multiples (10, 12). For many of the commonly used cytostatics limited or no correlations have been demonstrated between pharmacokinetics and body surface area (16), (reviewed in Gurney (10)) (11). Furthermore, so far no correlation has been demonstrated between body surface area and liver function. Correlations have been demonstrated between pharmacokinetic factors and tumour response for some haematological malignancies and certain solid tumours (reviewed in Gurney (10)). Positive correlations have been found for many cytostatics between pharmacokinetic variables and toxicity (reviewed in Gurney (10)).

These considerations may be of importance in interpreting studies aimed at answering dose-response and dose-intensity questions. Owing to the marked variation in clearance/systemic exposure, patients randomized to the high-dose arm may actually (pharmacokinetic reasons) have received a dose corresponding to the lower dose level tested in the randomized study and vice versa (10). Thus, it is not unlikely that many of the dose-response and dose-intensity studies have been too underpowered to be able to answer the question about whether there is a dose-response relationship for human breast cancer in vivo. This may be one explanation for individual studies tending to be negative with reference to survival, while a recent overview of prospective and randomized trials demonstrated a positive survival benefit for a higher dose-intensity using polychemotherapy versus a lower dose-intensity (17). However, a significant dose-response effect could not be demonstrated for monochemotherapy (17).

Furthermore, in overview analyses of controlled and randomized studies, monochemotherapy has been demonstrated to give a statistically significantly worse survival outcome compared with polychemotherapy, both in the adjuvant situation and in the treatment of metastatic disease (18, 19).

The marked variations in pharmacokinetics from one individual to another as well as the fact that the best effect by adjuvant therapy is seen in individuals with marrow toxicity are the basis for some of the background facts and prerequisites for exploring the use of chemotherapy tailored for each individual (20). In addition, one should remember that the doses used in phases II and III studies and for clinical routine are based on a phase I study with inclusion of triplets of patients at each dose level. In the case of severe toxicity in one of these three individuals at a certain dose level, three to six more patients are included at this dose level. In normal circumstances the maximum tolerated dose and the dose to be used for further clinical exploration in phase II and phase III will be discovered in 14 to 30 patients (21). Furthermore, to add to the complexity, most patients in phase I are frequently severely ill and may have been exposed to different cytotoxic agents and radiotherapy before participating in a phase I study. This may have altered their renal and hepatic function with reference to the handling of the new cytotoxic agent, perhaps not reflected by the conventional laboratory tests. Based on the inter-patient variation in clearance/systemic exposure by a factor of 2 to 11, it is not unreasonable to be rather sceptical with reference to the limited number of patients used in phase I to identify the 'correct' dose level for the future development of a cytotoxic compound. A more rational approach would be to define a dose range based on the phase I data, to be further explored in phases II and III. Accordingly, in clinical routine a dose range should also be used. It could be added that pharmacokinetic evaluations are used for anti-convulsants, anti-depressants, certain antibiotics, digoxin, theophylline and neuroleptic drugs but not for cytostatics, with the exception of methotrexate, despite 'all' cytostatics having narrow therapeutic indexes (9).

Based on the marked inter-patient variation in pharmacokinetic parameters, we have developed a tailored FEC regimen given with G-CSF support with ciprofloxacin as prophylactic antibiotic (12, 22). The epirubicin dose range from 38 mg/m$^2$ to 120 mg/m$^2$ and the cyclophosphamide dose has a span of from 450 mg/m$^2$ to 1800 mg/m$^2$ (22). The 5-fluorouracil (5-FU) dose was not elevated above the normal range, because the mucositis side effects associated with this compound could be a major disadvantage and most likely would have increased the risk of granulocytopenic infections. This tailored FEC regimen has been tested in the metastatic situation, as preoperative therapy for locally advanced breast cancer and as adjuvant therapy in one arm of the randomized SBG 9401 study (Lindman et al. unpublished data, Karlsson et al. unpublished data) (22). The use of individual tailoring to marrow toxicity is further supported by recent studies demonstrating the best outcome for

patients with toxicity on standard chemotherapy (20, 23). Based on the first 89 patients in the A-arm of the SBG 9401 adjuvant study, we found that for 73% to 94% of the courses there were no differences in NCI toxicities between the two highest dose levels and the four lowest dose levels (22). On the down side, we have eight (0.0319; 95% conf. interval 0.0102–0.0536) patients with, most likely, therapy-related acute myeloid leukaemia/myelodysplastic syndrome in this tailored arm with 251 randomized patients after 23.7 months of median follow-up in the SBG 9401 study (Scandinavian Breast Cancer Study Group 9401 (24), ASCO 1999). This should be compared with patients receiving a dose-intensive CEF (cyclophosphamide, epirubicin, 5-FU) regimen, escalated in a conventional manner without G-CSF support to all patients in this arm (25). In this study 5 patients (0.014; 95% conf. interval 0.0018–0.027) developed leukaemia out of the 356 randomized to the CEF arm (25). The outcome in this study will be described under the next heading.

## DOSE-RESPONSE IN THE CONVENTIONAL DOSE RANGE

*Adjuvant therapy*

A retrospective study from Milan revealed that patients receiving the highest cumulative doses of CMF had a statistically significantly improved disease-free survival (26). Partly complementary and contradictory results have also been obtained by other retrospective studies analysing dose intensity. In a Finnish study of 148 patients, treated with cyclophosphamide, doxorubicin and oral ptorafur with and without tamoxifen, patients with more marked bone marrow toxicity were described as having a statistically significantly better disease-free- ($p = 0.01$) and overall ($p = 0.04$) survival. Partly in accordance with this finding, the International Breast Cancer Study Group revealed in a retrospective analysis of 1350 patients that those receiving 65% to 84% of prescribed dose tended to have a better disease-free survival ($p = 0.07$) and a significantly better overall survival ($p = 0.03$) (23). Patients treated with = 85% of the prescribed dose or a lower dose than 65% of intended dose using the classical CMF regimen fared worse (23). Taken together, these studies strongly indicate that patients receiving standard doses without toxicity, most likely on account of a more rapid clearance of the cytostatics, are being under-treated. Extrapolation of the data indicates that in this situation these patients should receive increased doses. On this background it is rather strange that almost no treatment protocol contains instructions for dose escalation, despite the fact that they all contain information on how to decrease the dose when patients experience toxicity.

In a prospective study, 1550 patients were randomized to high, moderate or low doses in the conventional dose range of cyclophosphamide (300 mg/m$^2$–600 mg/m$^2$), doxorubicin (30 mg/m$^2$–60 mg/m$^2$) and 5-FU (300 mg/m$^2$–600 mg/m$^2$) (27). The high-dose arm had the same total dose as the moderate dose arm, which was delivered with two-thirds of the dose intensity compared with the high-dose arm. At 9 years' follow-up disease-free survival ($p = 0.001$) and overall survival ($p = 0.004$) were statistically significantly superior for the high-/moderate-dose arm compared with the low-dose arm (27).

In another phase III study the investigators studied the escalation of cyclophosphamide to 1200 mg/m$^2$ per course compared with the standard dose of 600 mg/m$^2$ with a maintained doxorubicin dose 60 mg/m$^2$ in all three arms (28). We could not demonstrate any difference in relapse-free- or overall survival between the three arms (28). Based on this study, it is reasonable to conclude that conventional escalation of cyclophosphamide within the conventional dose range does not add any benefit, at least not when a total dose of less than 5 g/m$^2$ is used.

In a prospective and randomized study of 565 node-positive patients, escalation of epirubicin from 50 mg/m$^2$ to 100 mg/m$^2$ in the FEC combination (5-FU, epirubicin, cyclophosphamide) resulted in a survival improvement from 70% to 80% ($p = 0.002$) at 5 years' follow-up (29).

Furthermore, the benefit gained by adding an intensified epirubicin-based therapy is highlighted in the randomized study of 710 patients comparing dose-intensive CEF, with epirubicin 60 mg/m$^2$ given on days 1 and 8, compared with classical CMF given with the same schedule (25). The anthracycline-containing arm resulted in an absolute survival improvement of 7% ($p = 0.03$) at 59 months medium follow-up (25).

In a recently reported study, based on Kaplan-Meier estimates at 18 months, the addition of three courses of paclitaxel to four courses of doxorubicin and cyclophosphamide in 3170 patients was associated with a statistically significantly improved disease-free- and overall survival (30). The absolute survival benefit was 2% ($p = 0.039$) and the improvement in disease-free survival was 4%, from 86% to 90% ($p = 0.0077$). A major concern is whether the improved survival is due to the additional taxoid (or taxen) or just due to the fact that these patients received seven courses, giving a higher total chemotherapy dose compared with the four courses of doxorubicin–cyclophosphamide. The doxorubicin doses in the three arms were 60 mg/m$^2$, 75 mg/m$^2$ or 90 mg/m$^2$, while cyclophosphamide was given at a standard dose of 600 mg/m$^2$ in all three arms. No differences were disclosed in-between the different doxorubicin arms (30). Further data will emerge in the future while an intergroup study in the United States is comparing these doxorubicin levels in a study comprising 3000 patients. So far, no data are available from this study (reviewed in Zujewski et al. (31)).

Based on these observations the standard dose of doxorubicin should be 60 mg/m$^2$, the corresponding epirubicin dose should most likely be in the range of 90 mg/m$^2$ to 120

mg/m$^2$, and cyclophosphamide should be given at 600 mg/m$^2$, if patients are treated with an anthracycline-based combination regimen in clinical routine.

*Metastatic situation*

Eighteen prospective and randomized studies concerning dose response have been identified (32–49); a more marked dose-intensity concept was evident in 9 of these studies (32–34, 38, 39, 42, 43, 46, 48).

As expected from the preclinical experiments, a higher dose intensity in the metastatic setting is almost always associated with an increased objective response rate. However, this increased response rate has been translated into an improved survival in only a few studies (35, 38, 43, 48).

The classical, oral CMF regimen has been demonstrated to be statistically significantly superior compared with the 3-weekly intravenous CMF regimen with reference to overall survival (38).

Epirubicin at 40 mg/m$^2$, 60 mg/m$^2$, 90 mg/m$^2$ or 135 mg/m$^2$ was investigated in a randomized study of 287 women with metastatic breast cancer (32). The response rate and time to progression increased when the epirubicin dose was increased from 40/60 mg/m$^2$ to 90 mg/m$^2$, but no benefit was found above this level. No association could be demonstrated between the recorded pharmacokinetic variables and efficacy parameters, but correlations were demonstrated for the observed side effects (32).

Furthermore, in support of a dose-response relationship, even in vivo, is the fact that breast cancer patients with refractory disease on conventional chemotherapy, then receiving very high doses of chemotherapy requiring marrow support may obtain objective tumour regressions and some of them will even obtain a complete remission (50). However, these responses are usually very short lived with a duration of only a few months. Accordingly, at present, patients with refractory breast cancers to conventional therapy cannot be recommended the high-dose procedure outside the framework of a controlled study.

## HIGH-DOSE THERAPY

The demonstrated dose-response effect in different model systems for breast cancer, the demonstrated synergism in vitro for two alkylating agents, the lack of proven cross-resistance and the selection of drugs with different non-haematological toxicities were the major rationales for investigating high-dose chemotherapy with autologous haematological bone marrow stem-cell support to breast cancer patients and other solid tumour types (1) (reviewed in Zujewski et al. (31)). The most commonly used high-dose regimens explore the alkylating agents in doses 5 to 30 times the conventional doses given without cytokine or bone marrow support (reviewed in Zujewski et al. (31)).

A search through the database at the National Library of Medicine, PubMed gave 1502 hits on January 4, 1999 for the combination of high-dose chemotherapy and breast cancer and the corresponding number of hits for autologous bone marrow and breast cancer was 489. The number of English language articles in the area of autologous stem-cell rescue/high-dose chemotherapy for breast cancer has expanded exponentially, at least during the early years of the 1990s (31).

Breast cancer is probably the most common indication today in North America for the use of autologous marrow-supported high-dose chemotherapy and it is also commonly used in Europe, but with marked variations between different countries (51, 52). Furthermore, in recent years there has been a relative switch from high-dose therapy in patients with metastatic disease to the use of this type of therapy approach in the adjuvant setting (49) (reviewed in Zujewski (31)). However, so far, the scientific support for this type of strategy is for both indications limited to many pilot, phase I/II studies and three randomized studies, two smaller studies with less than 100 patients included, respectively, and one study is so far only presented at ASCO in 1996 (8, 13, 53–71).

*High-dose therapy in the metastatic setting*

The repeated message from the uncontrolled high-dose studies in the metastatic setting is the possibility of 'a survival tail' compared with conventional chemotherapy for this group of patients (reviewed in Zujewski et al. (31), reviewed in Bergh (72)). This was also demonstrated in a randomized study of 90 patients with metastatic breast cancer receiving up-front mitoxantrone-based, high-dose chemotherapy repeated twice compared with 6 to 8 courses of mitoxantrone-based chemotherapy given in the conventional dose range (55). This study was updated in 1998, demonstrating a sustained overall survival at five years or more in the order of 20% (73, 74). However, the main problem with this study is that only those patients who responded to therapy were given tamoxifen. Thus a much higher proportion of the patients in the high-dose arm received tamoxifen, which could explain the difference observed in the study. In addition, the conventional arm was not considered to be optimal (74). The South African authors have also previously demonstrated a considerably higher response rate with the conventional arm than in this randomized high-dose study (75). Despite these critical comments, it would not be unreasonable if high-dose chemotherapy programs were demonstrated to be superior for certain subgroups of patients with metastatic breast cancer compared with chemotherapy delivered in the conventional dose range. Whether the possible high-dose therapy should be given up-front to avoid the development of cellular drug resistance is still to be proven, compared with the more common strategy of selecting those patients responding to conventional induction chemotherapy.

In a previous study of 94 patients with primary chemotherapy-sensitive metastatic breast cancer, we

demonstrated a survival at 5 years of around 30%–40% (64) according to Kaplan-Meier calculations. In most cases these patients received induction chemotherapy with FAC (5-FU, doxorubicin, cyclophosphamide) or FEC (5-FU, epirubicin, cyclophosphamide). Upon a demonstrated complete or partial response on the induction regimen, the patients received high-dose therapy with $CTC_b$ (6000 mg/$m^2$ cyclophosphamide, 500 mg/$m^2$ thiotepa, 800 mg/$m^2$ carboplatin) and 23 patients also received a double high-dose procedure with melphalan at 140 to 180 mg/$m^2$ preceding the $CTC_b$ regimen (64). The $CTC_b$ and melphalan treatments were both given with autologous stem-cell support; 9 patients received only bone marrow, 7 patients received the combination of bone marrow and peripheral-blood stem cells and 78 patients received only peripheral-blood stem cells. This variation in autologous stem-cell support was a reflection of the fact that the study was carried out from January 1, 1991 to December 1, 1996, during the rapid introduction of the use of peripheral-blood stem cells. This was motivated by the demonstrated potential to reduce the neutropenic and thrombocytopenic phase after the high-dose procedure, thus increasing the safety and reducing the costs (76–78).

Today we have at least five ongoing randomized studies investigating whether high-dose chemotherapy with marrow support is superior to conventional chemotherapy (see Table 1). The problem is that patient recruitment for these studies was slow and this may have introduced an unwanted selection bias of patients with relatively indolent metastatic breast cancer, while high-dose therapy is frequently used as a clinical routine at many institutions in the USA and Europe (reviewed in Zujewski et al. (31)), (52). With reference to selection bias, Rahman and coworkers have pointed out the risk that the demonstrated survival tail by high-dose chemotherapy may be explained by patient selection (79). Long-term follow-up of patients treated at the M.D. Anderson Cancer Centre with standard FEC disclosed a survival tail; 263 (16.6%) out of 1581 patients received an initial complete response, and 49 (3.1%) patients remained in complete remission at 5 years (80). In this context one should remember that these data were not based on an unselected and population-based cohort.

*Adjuvant high-dose therapy*

In the adjuvant setting an early phase II study demonstrated a markedly improved relapse-free survival compared with historical controls (81). An improvement in relapse-free survival from 30% to around 70% at 5 years' median follow-up was described, ((81), and personal communication). In many institutions the use of high-dose programs has been associated with a much more thorough staging of the patients. New routines with skeletal and bone marrow investigations together with CT examinations of other organs will very likely lead to stage migration and thus selection of patients with better prognoses (22). This may thus explain the positive results from uncontrolled high-dose studies in the adjuvant setting (51, 52, 72, 81).

One small randomized study has so far been presented (68). Eighty-one patients from an initial 97 patients were randomized between a dose-intensive epirubicin 120 mg/$m^2$ combination versus high-dose therapy with $CTC_b$ without a proven difference in outcome (68). These data strongly indicate that the difference in outcome is not as large as indicated from the comparisons with historical controls, but this study must be considered to be underpowered if we are to detect a more realistic difference in outcome. Accordingly, the Dutch group along with 12 other collaborative groups is presently running or has just completed the inclusions in these studies (see Table 1) (reviewed in Zujewski et al. (31)), (Scandinavian Breast Cancer Study Group 9401 (24), submitted to ASCO 1999). The target sample sizes for these studies range from 200 to 1000 patients (reviewed in Zujewski et al. (31)), making it possible to detect smaller and potentially important differences in outcome.

## TOXICITIES BY HIGH-DOSE THERAPY

The 100-day post-transplant mortality has decreased from 22% to 5%, according to the registry data for the time period 1989 to 1995 (51). This can probably be explained by the use of peripheral-blood stem cells combined with the fact that high-dose therapy is given relatively more frequently in the adjuvant setting and to patients with locoregional disease. The safety of high-dose therapy in the adjuvant setting using peripheral-blood stem cells is underlined by the fact that in the SBG 9401 study we have only 2 (0.7%) therapy-related deaths in the high-dose arm consisting of 274 patients, in this two-armed study with 525 randomized patients (Scandinavian Breast Cancer Study Group 9401 (24), presented in the name of SB69401 — Jonas Bergh was presenter at the ASCO meeting.

In our study of 94 patients with metastatic disease, two patients died from chemotherapy-related complications, corresponding to a therapy mortality at 100 days of 2.2% (64). Previous studies using the $CTC_b$ regimen or melphalan combined with $CTC_b$ have demonstrated a toxic death rate of from 1% to 13% (13, 53, 69, 82). In an early study reported in 1988 (67), the regimen containing BCNU instead of thiotepa has been associated with a much higher risk of lung toxicity and a reported toxic death rate of 23%. However, this high toxic death rate is probably not relevant for the present situation when $CTC_b$ is used combined with peripheral-blood stem-cell support, along with the fact that chemotherapy-sensitive patients are selected for the present high-dose procedure, thus decreasing the risk of fatal outcome even in the metastatic situation.

In summary, when using marrow-supported, high-dose chemotherapy the common toxicities include; infections, hepatic veno-occlusive disease, drug-induced pulmonary side effects, renal dysfunction, haemorrhagic cystitis, CNS side effects, and secondary malignancies possibly related to the therapy (83), (reviewed in Zujewski et al. (31)). The described reduced intellectual capacity of patients receiving high-dose therapy in the adjuvant setting with the $CTC_b$ regimen used in the Dutch study raises major concern (83). The group from Holland used a higher dose of the potentially neurotoxic drug carboplatin, 1600 mg/m$^2$ versus 800 mg/m$^2$, which may be one explanation for their findings. However, other groups, including SBG 9401, have not run/reported the use of prospective psychometric studies which may be required in order to determine the described loss in intellectual capacity.

**Table 1**

*Ongoing randomized high dose chemotherapy studies in the adjuvant and metastatic setting*

| Disease setting | Trial No./sponsor | HDC/ASCR arm | Control arm | Sample size/accrual as of 6/1/97 |
|---|---|---|---|---|
| Adjuvant therapy for stage II/III disease. No. of involved axillary lymph node | | | | |
| 4–9 | S9623/(SWOG, CALGB, ECOG, NCCTG) | AC × 4, HDC/ASCR: CTCb or CPB | HDSC: A × 3, Tx × 3, C × 3 (only G-CSF support) | 1000/105 |
| ≥10 | INT-0121/(ECOG, SWOG) | CAF × 6, HDC/ASCR: CT | CAF × 6 | 534/460 |
| ≥10 | INT-0163/(CALGB, SWOG, NCIC) | CAF × 4, HDC/ASCR: CPB | CAF × 4, CPB (only G-CSF support) | 760/684 |
| Disease setting | Sponsor | HDC/ASCR arm | Control arm | Target sample size |
| Adjuvant therapy for stage II and/or III disease. No. of involved axillary lymph node | | | | |
| ≥4 | Milan/Italy | HDSC/ASCR: C × 1, VM × 1, E × 2, LP × 1 | E × 3, CMF × 6 | 200 |
| ≥4 | NWPFAST | CEF × 4, HDC/ASCR: CTCb | 'CEF' × 5 | 880 |
| >4 | ACG | LAM × 4, HDC/ASCR: CT | LAM × 4, CMF × 8 | 550 |
| 4–9 | Response Technologies | A × 4, HDC/ASCR: CTCb | A × 4, CMF × 8 | 246 |
| ≥5 | SBG 9401 | CEF × 3, HDC/ASCR: CTCb | 'CEF' × 9 | 500 |
| ≥8 | PEGASE | CEF × 4, HDC/ASCR: CMtL | CEF × 4 | 240 |
| ≥10 | IBCSG | HDSC/ASCR: EC × 3 | EC/AC × 4, CMF × 3 | 210 |
| ≥10 | GABG | EC = 4, HDC/ASCR: CTMt | EC × 4, CMF × 3 | 420 |
| ≥10 (stage II only) | GABG-IMG | EtlCE × 2, HDC/ASCR: EtlCb | EC × 4, CMF × 3 | 320 |
| ≥10 (stage III only) | GABG-IMG | EC × 3, HDC/ASCR: Ccb × 1, Tmt × 1 | EC × 3, CMF × 3 | 300 |
| Metastatic disease (stage IV) | Duke University | AFM × 2-4, HDC/ASCR: CBP | AFM × 2-4, at relapse: HDC/ASCR: CBP | 80 |
| | PEGASE | CEF × 4, HDC/ASCR: CT | CEF | 180 |
| | NCIC | A or Tx × 4, HDC/ASCR: CMtCb × 2 | Continue A (to dose limit) or Tx (9 cycles) | 192 |
| | PBT-01/(Philadelphia Group, ECOG, SWOG, NCCTG) | CMF/CAF × 4-6, HDC/ASCR: CTCb | CMF/CAF × 4-6, CMF × 2 y | 587/516 |

'FEC': Tailored FEC (22)
(Modified from Zujewski et al. (30)).

## HIGH-DOSE CHEMOTHERAPY—FUTURE DIRECTIONS

If this type of therapy in randomized studies can be demonstrated to be significantly better than non-marrow-supported chemotherapy, many important questions will have to be answered. Previous studies have demonstrated the risk for tumour cell contamination of the harvested peripheral-blood stem cells (84). The detection of micrometastases is associated with many technical pitfalls and the techniques used need to be standardized and validated (85). The positive selection of CD34+ bone marrow stem cells together with the negative selection of marrow contaminating breast cancer cells may be beneficial (86–88). However, this may not be a way forward, while it has recently been demonstrated that there is no difference in outcome between those patients with or without bone marrow micrometastatic disease receiving high-dose therapy (89).

Another interesting option could be the use of high-dose therapy with allogenic marrow support combined with the adoption of modern immunomanipulatory and vaccination procedures to treat remaining micrometastatic disease after high-dose chemotherapy (90–92).

Of course, one should not forget the pharmacokinetic considerations, as discussed in a previous paragraph, when designing future high-dose regimens. At optimal the drug selection should of course be based on the tumour biological profile rather than on the histological patterns in the primary tumour. The predictive data on the oncogene c-erbB-2 and the tumour suppressor gene p53 is just the beginning of a new and interesting era with, it is hoped, a more rational way to select drugs and therapy principles (93–97).

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