A Systematic Overview of Chemotherapy Effects in Breast Cancer

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A systematic review of chemotherapy trials in several tumour types was performed by The Swedish Council of Technology Assessment in Health Care (SBU). The procedures for the evaluation of the scientific literature are described separately (Acta Oncol 2001; 40: 155–65). This synthesis of the literature on chemotherapy for breast cancer is based on 233 randomised studies, 9 meta-analysis of randomised studies, a population-based cohort study and 18 overviews/retrospective analyses including a total of 155 243 patients. The conclusions reached can be summarised into the following points:

Adjuvant treatment

- There is solid scientific support from randomised studies that adjuvant polychemotherapy at 10 years will result in an absolute mortality reduction for patients younger than 50 years by 12% for node positive (34% relative mortality reduction corresponding to an estimated median survival prolongation of several years) and 6% for node negative patients. For women aged 50 to 69 years, the corresponding figures for node positive and node negative patients are 6% and 2%, respectively (approximately 11% relative mortality reduction).
- Anthracycline-containing combinations result in an absolute survival benefit at five years of 3% compared with non-anthracycline based polychemotherapy.
- There are indications that the taxane paclitaxel may further improve the survival compared with anthracyclines. However, the limited data preclude conclusions for the routine care.
- The addition of tamoxifen to chemotherapy further enhances the survival benefit for receptor positive subgroups.
- The roles of more dose-intensive regimens, including high-dose therapy with stem cell support, are presently studied in randomised investigations. The data presented so far are conflicting but they do not in general support high-dose therapy.
- Quality of life, based on analyses of randomised studies, demonstrate that adjuvant polychemotherapy has an initial detrimental effect, but long-term follow-up of treated patients demonstrates no impairment of quality of life compared with untreated patients.
- Polychemotherapy in standard doses should be offered to premenopausal node positive patients, and the corresponding post-menopausal group with a receptor-negative breast cancer and to node negative patients with high risk factors. Polychemotherapy should be combined with tamoxifen to all patients with receptor-positive tumours. Due to a need of more knowledge in this field, patients should be included in investigational protocols.

Locally advanced breast cancer

- Based on current knowledge, treatment of patients with locally advanced breast cancer should include neoadjuvant/preoperative polychemotherapy since there is evidence from controlled studies that such therapy will statistically significantly increase the number of patients who can be offered breast-conserving surgery. Indirect comparisons also demonstrate survival improvements, but the scientific support is equivocal.

Metastatic breast cancer

- The median survival for patients with metastatic disease treated with conventional chemotherapy doses and regimens is 12 to 24 months.

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- Retrospective cohort studies indicate that the use of non-anthracycline containing chemotherapy compared with no chemotherapy might add a survival gain of six to nine months. However, this estimation is based on equivocal data.
- Based on overview data, polychemotherapy results in a statistically significant survival gain compared with single-agent therapy.
- Based on repeated randomised studies, the addition of anthracyclines increases the response rate and statistically significantly improves the survival compared with non-anthracycline containing chemotherapy, except for CMF combined with prednisone/prednisolone, which will statistically significantly improve the survival compared with some anthracycline combinations.
- Second line therapy using vinorelbine or docetaxel is statistically significantly better than other regimens with a time to progression and survival benefit in the order of one to three months based on few randomised studies. The role, if any, of third line therapy is yet to be demonstrated.
- In the metastatic setting, conventional chemotherapy improves the quality of life.
- In standard care, first line therapy should contain an anthracycline and second line therapy using vinorelbine or docetaxel could be offered to selected patients failing first line therapy.
- Based on numerous randomised studies, breast cancer demonstrates a positive dose-response relationship both in the adjuvant situation and for metastatic disease. However, in the conventional dose-range there seems to be a plateau in the dose-response curve, with no further survival gains for higher doses.
- High-dose therapy with bone marrow support might result in further increases in antitumour effects with the potential of increasing survival, but additional phase III studies are required before this can be recommended for routine care.
- The growth factors G-CSF and GM-CSF reduce chemotherapy-induced hematological toxicity. So far their use has given no proven effect on survival.
- There is no support that unspecif ic immunomodulation improves the outcome in breast cancer. A clinical benefit from monoclonal HER-2 antibodies is suggested but needs further confirmation.

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Methodological issues

The studies analysed in this report have been identified via systemic computerised search on MedLine back to the 1960s. Unfortunately, many uncontrolled studies had wrongly been classified as controlled studies in the MedLine database and essential phase III studies were not identified, but were identified via reviews and personal knowledge. With reference to the adjuvant studies we have almost exclusively relied on data from the Oxford group responsible for the already critically reviewed data for 'Early Breast Cancer Trialists' Collaborative Group' (1, 2). Finally, the conclusions are mainly based on randomised studies and overviews of them. Phase II data are mentioned, but never classified and were not a basis for the conclusions.

Basic aspects of breast cancer

Breast cancer is the most common malignant disease for females in northern Europe and north America, corresponding to an age-corrected annual incidence of 100 to 120 per 100000 females. Alternatively expressed, one in eight to one in 12 women will risk contracting breast cancer during her lifetime. The incidence for males is roughly 1/100 of the female number. In 1996, 5843 new cases with female breast cancer were diagnosed in Sweden. The age-corrected incidence, compensating for ageing, has almost doubled since the start of the Swedish cancer registry in 1959. The median age for new breast cancer diagnosis is 60 to 64 years. The mortality number is now around 1600 per year, and has been fairly constant during recent years despite an increasing incidence.

Around 70% of the breast cancers in the Uppsala county between the age of 40 to 69 were diagnosed via a population-based screening program (3). Thus, the fraction of early cancers will be higher in Sweden compared with countries without early detection programmes, which may influence the proportion of patients who become candidates for adjuvant therapy.

Essentially all malignant breast tumours are carcinomas; nine of ten are ductal carcinomas while one of ten is a lobular carcinoma. The remaining 1–2%, not considered here, consist of cystosarcoma phyllodes, malignant non-Hodgkin's lymphoma or primary skin cancers. The clinical and histopathological TNM staging (primary tumour size, regional lymph node status combined with presence or absence of distant metastases; Table 1) provides important prognostic information.

Furthermore, analysis of certain other factors may yield statistically significant prognostic information for groups of patients, but so far not on an individual level (Table 2). Prognostic factors giving information on the efficacy of certain oncological therapy modalities are better denoted as predictive factors, e.g. the oestrogen and progesterone receptor positive breast cancers have a 50 to 70% chance to respond to hormonal therapy, while the corresponding figure for the receptor negative cancer is only 5–10%. A number of other investigational predictive factors are now under evaluation (4–7).

Treatment principles

Therapy of primary, operable, breast cancer involves the use of surgery with or without radiotherapy and with or without adjuvant systemic therapy. Breast conservative surgery supplemented with radiotherapy is the standard procedure for all unifocal cancers less than 3–4 cm in size, giving equivalent survival results as more aggressive surgical procedures (8). A tumour larger than 5 cm or a smaller tumour with signs of locally advanced disease (T3/T4, N2,

Table 1
TNM classification of breast cancer

Clinical staging	
T	Primary tumour
Tis	Cancer in situ
T1	Tumour <2 cm, a = without and b = with fixation to muscle or muscle fascia
T2	Tumour >2 cm, <5 cm, a and b as T1
T3	Tumour >5 cm, a and b as T1
T4	Tumour fixed to chest wall or skin
N	Regional lymph nodes
N0	No palpable axillary lymph nodes
N1	Palpable movable axillary lymph nodes
N2	Axillary lymph nodes fixed to one another or other structures
N3	Lymph nodes supra- or infraclavicular
M	Distant metastasis
M0	No distant metastasis
M1	Distant metastasis

Histopathologic staging (pTNM)	
T	Primary tumour
Tis	Cancer in situ
T1	Tumour <2 cm, a = without and b = with fixation to muscle or muscle fascia. Further categorised: i <0.5 cm, ii >0.5 cm <1 cm, and iii ⩾1 cm <2 cm.
T2	Tumour >2 cm, <5 cm, a and b as T1
T3	Tumour >5 cm, a and b as T1
T4	Tumour fixed to chest wall or skin
N	Regional lymph nodes
N0	No axillary lymph node metastasis
N1	Axillary lymph node metastasis, a = micrometastasis <0.2 cm and b = visible metastasis depending on size i–iv.
N2	Axillary lymph nodes fixed to one another or other structures
N3	Lymph nodes supra- or infraclavicular
M	Distant metastasis
M0	No distant metastasis
M1	Distant metastasis

Stage grouping	
Stage 0	Tis, N0, M0
Stage I	T1, N0, M0
Stage IIA	T0, N1, M0
	T1, N1, M0
	T2, N0, M0
Stage IIB	T2, N1, M0
	T3, N0, M0
Stage IIIA	T0, N2, M0
	T1, N2, M0
	T2, N2, M0
	T3, N1, M0
	T3, N2, M0
Stage IIIB	T4, any N, M0
	Any T, N3, M0
Stage IV	Any T, any N, M1

N3) are currently often offered neo-adjuvant chemotherapy.

The use of postoperative radiotherapy will statistically significantly reduce the risk for local relapse (8–12). In addition, results from two randomised studies also demonstrated a statistically significant survival advantage by adding loco-regional radiotherapy to chemotherapy compared with adjuvant chemotherapy only (13, 14). This survival benefit has later been confirmed in a meta-analysis of 18 trials (odds ratio, 0.83; 95% CI, 0.74–0.94) (15).

Adjuvant systemic therapy (polychemotherapy, ovarian ablation or Tam), results in statistically significant survival improvements compared with only loco-regional therapy modalities (8). The selection of adjuvant therapy modality is dependent on the tumour biological characteristics of the cancer combined with the patient's age, general condition and own preferences.

Therapy of metastatic breast cancer involves the use of a wide range of cytostatics and hormonal agents, radiotherapy, surgery and bisphosphonates in addition to what is designated 'best supportive care'. Metastatic breast cancer is generally considered as an incurable disease using conventional dosages, but a modest survival prolongation might be achieved, as discussed below.

A long list of cytostatics have been tested in patients with metastatic breast cancer (Table 3). Their anti-tumoural activities have mostly been identified in phase II studies, sometimes validated in phase III studies. Drugs demonstrated to be effective in the metastatic setting are frequently used in the adjuvant setting, which seems reasonable although drug resistance related factors might differ between those settings. Abbreviations are shown in Table 4.

The objective response rate in the advanced setting of single agents is between 10–70%, the highest figures recorded for the anthracyclines Doxo and Epi, Vino and the taxanes (16–18). The majority of the drugs were tested in pilot/phase I and II studies already in the 1960s as single agents. Single-agents have sooner or later been incorporated and explored in an almost endless number of different combinations.

ADJUVANT CHEMOTHERAPY

Results from the 1990 overview

The results from 133 randomised and controlled trials involving 75000 women were published as ten-year follow-up figures in 1992 (1). The observed effects of adjuvant chemotherapy were derived from around 18000 women participating in different randomised studies of different size and quality, but they all compared no systemic chemotherapy vs systemic chemotherapy therapy with the same type of loco-regional therapy. The loco-regional therapy in both arms was always surgery, sometimes with the addition of radiotherapy. The results demonstrated that

Table 2

Prognostic factors used in routine care

TNM stage
Histological grading system
Sex steroid receptors (oestrogen and progesterone)
Ploidy
S-phase

adjuvant hormonal therapy (tamoxifen or oophorectomy) and polychemotherapy statistically significantly enhanced the ten-year survival compared with only local or loco-regional therapy (Table 5). Furthermore, the survival differences in favour of systemic adjuvant therapy vs no therapy increased during the follow-up time between five to ten years. Polychemotherapy was significantly better than single-agent chemotherapy. Twelve months of adjuvant polychemotherapy was no better than six months. Short term/peri-operative therapy with Cyclo had survival benefits, but these were inferior compared with CMF based polychemotherapy. The absolute mortality reduction is in the order of 8% to 12% using conventional strategies with Tam to postmenopausal women with receptor positive tumours and polychemotherapy to receptor negative breast cancer or lymph node positive breast cancer in the premenopausal group.

A general problem with all types of adjuvant therapy is the marked overtreatment, i.e. those patients who received the therapy and who would have been cured even without adjuvant therapy. Depending on selection criteria for adjuvant therapy this group is, in the Swedish environment and using present criteria for selection of patients for adjuvant

Table 3

Single agents with activity in breast cancer

Alkylating agents	Anti metabolites	Mitotic inhibitors
Cyclophosphamide (M)	Methotrexate (M)	Vincristine (M)
Ifosfamide (M)	5-Fluorouracil (M)	Vinorelbine (A)
Melphalan (W)		Vindesine (W)
Thiotepa (M)		
Chlorambucil (W)		
Cisplatin (M)		
Carboplatin (W)		
Antibiotics	**Taxanes**	**Others**
Doxorubicin (A)	Paclitaxel (A)	Etoposide (W)
Epirubicin (A)	Docetaxel (A)	CPT 11 (W)
Mitomycin C (M)		Gemcitabine (M)
Mitoxantrone (M)		BCNU
Bisantrene (W)		Carmustine (W)

(A) Very active compound; > 50 per cent response rate.
(M) Moderately active compound; 20–50 per cent response rate.
(W) Weakly active compound; < 20 per cent response rate.
(Adopted from: Cancer: Principles & Practice of Oncology, Eds de Vita, Hellman & Rosenberg, p 1604, 1997).

Table 4

Abbreviations

AC = doxorubicin, cyclophosphamide
Adriamycin® = doxorubicin
Cyclo = cyclophosphamide
CFP = cyclophosphamide, 5-fluorouracil, prednisone
CFPMV = cyclophosphamide, 5-fluorouracil, prednisone, methotrexate, vincristine
Cis = cisplatin
CMF = cyclophosphamide, methotrexate, 5-fluorouracil
CMFP = cyclophosphamide, methotrexate, 5-fluorouracil, prednisone
CMFVP = cyclophosphamide, methotrexate, 5-fluorouracil, vincristine, prednisone
CNF = cyclophosphamide, mitoxantrone, 5-fluorouracil

DC = doxorubicin, cyclophosphamide
Doce = docetaxel
Doxo = doxorubicin
EC = epirubicin, cyclophosphamide
Epi = epirubicin
FAC = 5-fluorouracil, adriamycin, cyclophosphamide
FAI = 5-fluorouracil, doxorubicin, ifosfamide
FEC = 5-fluorouracil, epirubicin, cyclophosphamide
5-FU = 5-fluorouracil
FNC = 5-fluorouracil, mitoxantrone, cyclophosphamide
FuMi = 5-fluorouracil, mitomycin C
FVP = 5-fluorouracil, vincristine prednisone
G-CSF = granulocyte colony stimulating factor
GM-CSF = granulocyte macrophage colony stimulating factor
Ida = idarubicin
Melph = melphalan
Meth = methotrexate
MF = melphalan, 5-fluorouracil
MFVP = methotrexate, 5-fluorouracil, vincristine, prednisone
Mito = mitoxantrone
Mit C = mitomycin C
MMM = mitoxantrone, methotrexate, mitomycin C
Mpa = medroxyprogesterone acetate
Pacl = paclitaxel
PE = cisplatin, etoposide
PMF = prednimustine, methotrexate, 5-fluorouracil
Predn = prednisone
Tam = tamoxifen
VAC = vincristine, doxorubicin, cyclophosphamide
VATH = vinblastine, doxorubicin, thiotepa, halotestin
Vinbl = vinblastine
Vincr = vincristine
Vinde = vindesine
Vino = vinorelbine
VM = vinblastine, mitomycin C
VP = vincristine, prednisone
Vp16 = etoposide

EBCTCG = Early Breast Cancer Trialists' Collaborative Group
IBCSG = International Breast Cancer Study Group
LABC = Locally Advanced Breast Cancer
MTD = Maximum Tolerated Dose
NSABP = National Surgery Adjuvant Breast and Bowel Project
QoL = Quality of Life
Q-TWIST = Time without symptoms and toxicity

SBG = Scandinavian Breast Group

Table 5

Proportional and absolute improvements in 10-year survival from treatment of 100 middle-aged women with stage II breast cancer

Allocated treatment	Proportional reduction in annual mortality	Absolute reduction in 10-year mortality per 100 women treated % (SD)
Age > 50 yr		
(i) Polychemotherapy alone (eg, > 6 mo CMF)	12 (4)	5 (2)
(ii) Tam alone (for a median of 2 yr)	20 (2)	8 (1)
(iii) Polychemotherapy + Tam	30 (5)	12 (2)
Age < 50 yr		
(i) Polychemotherapy alone	25 (5)	10 (3)
(ii) Ovarian ablation alone	28 (9)	11 (4)
(iii) Polychemotherapy + ovarian ablation	30–40? [1]	12–16? [1]

From the 1990 overview, EBCTCG, 1992.
[1] Denotes equivocal data.

therapy, in the order of 30% to 70% of the patients. However, the acute and late side-effects of conventional adjuvant polychemotherapy have been fewer than expected (1, 2, 8). Furthermore, the survival benefit by adjuvant polychemotherapy has most likely been underestimated in previous studies compared with present practice, e.g. the present use of better anti-emetics resulting in higher actually given doses and more dose-intensive regimens.

Better prognostic and predictive factors, including drug resistance factors to tailor therapy for each individual patient, are warranted to diminish over- and undertreatment.

Results from the 1995 overview

The 15-year follow-up data were presented in Oxford in September 1995 and published in 1998 (2). Only randomised trials started before 1990 were included in the 1995 overview, 6900 references were scanned by the EBCTCG team in Oxford, England. In this overview, our comments and conclusions are based on the data from EBCTCG.

Sixty-nine randomised polychemotherapy trials were identified: 17723 women in 47 studies comparing no chemotherapy vs prolonged polychemotherapy; 6104 patients in 11 studies with shorter vs longer duration of chemotherapy and 5942 patients in anthracycline-based regimens vs CMF in 11 trials (2). Thus, this material consists of 29769 women and 10395 deaths were recorded. Corresponding figures for the 1990 overview were 11000 and 3500, respectively. With the inclusion of 47 trials comparing several months of polychemotherapy vs non-chemotherapy, the relative mortality reduction was 15.3% (2.4; $p < 0.00001$). The percentage figure given after the relative mortality reduction represents two standard deviations.

The estimated absolute gain at 10 years is 11.5% for the premenopausal node positive group, 7.1% for the node negative group, while the corresponding figures for the postmenopausal group are 3.2 and 2.4%, respectively (Table 6) (2).

The relative mortality reduction has also been subanalysed in relation to age at diagnosis of primary breast cancer. Younger patients tend to have better effects in mortality reduction by adjuvant polychemotherapy compared with elderly women (Table 7).

The relative effect by adjuvant polychemotherapy was best for the premenopausal group with a low oestrogen receptor content in the primary cancer (Table 8). A relatively less marked effect was seen in women above the age of 50 with oestrogen-rich primary cancers.

The combination of Tam and chemotherapy resulted in relative survival improvements of 11% for the combined group compared with Tam alone (19) (Table 9). No additional effect, not even a detrimental one, was seen for patients younger than 50 years with primary cancers with a low oestrogen receptor content (not shown).

The addition of an anthracycline adds a small, but statistically significant absolute survival benefit of 2.7% ($p = 0.02$) compared with CMF based regimens (2). Furthermore, one recently reported study on 710 patients demonstrates a statistically significant absolute survival gain of 7% ($p = 0.03$) at 59 months median follow-up in the comparison between dose intensive CEF and classical and per oral CMF (20). Similar significant survival gains have been disclosed for premenopausal node positive and high risk node negative patients in the randomised Danish-Swedish study on 1120 patients between FEC and CMF given with the three-weekly intravenous schedule (21). However, no benefit could be demonstrated for the postmenopausal group.

The use of higher than conventional doses with support of autologous stem cells has been explored in several recent studies. The results of these high-dose trials will be described in a separate section below.

Table 6

Absolute survival advantages for node negative patients without risk factors (good prognosis), intermediate risk and node positive patients – estimated figures

	Prognostic group	Survival		
		Allocated polychemo (%)	Adjusted control (%)	Absolute mortality reduction (%)
<50 years	Good prognosis	(96.1)	(95.0)	1.1
5 years follow-up	Intermediate risk	(86.6)	(83.4)	3.2
	Node positive	(68.4)	(62.0)	6.4
<50 years	Good prognosis	(92.6)	(90.0)	2.6
10 years follow-up	Intermediate risk	(78.3)	(71.2)	7.1
	Node positive	(53.3)	(41.8)	11.5
50–69 years	Good prognosis	(95.6)	(95.0)	0.6
5 years follow-up	Intermediate risk	(84.1)	(82.5)	1.6
	Node positive	(71.1)	(68.4)	2.7
50–69 years	Good prognosis	(91.0)	(90.0)	1.0
10 years follow-up	Intermediate risk	(69.2)	(66.8)	2.4
	Node positive	(49.1)	(45.9)	3.2

From the 1995 overview, EBCTCG, 1998 (2).

The use of taxanes, Pacl and Doce, are presently explored in the adjuvant setting. Very early data, with a median follow-up of only 18 months indicated a statistically significant absolute survival benefit of 2% ($p = 0.04$) in a study of 3170 node positive patients. All patients received four courses of the base-line therapy, Cyclo combined with three different dose levels of Doxo (60 mg/m^2, 75 mg/m^2, 90 mg/m^2) (+ G-CSF) (22). Half of the patients received Pacl for three courses at 175 mg/m^2. All receptor positive patients received adjuvant Tam. The major drawback with this study is that four courses of chemotherapy are compared with eight courses of chemotherapy. A recent update at an NIH Breast Cancer Consensus Conference on Adjuvant Therapy, Bethesda, November 1–3, 2000, with a median follow-up of 52 months, both the mortality reduction and the overall survival benefit of Pacl have decreased ($p = 0.08$).

Follow-up of the adjuvant trials – non-breast cancer deaths

Non-breast cancer deaths were recorded in 3.1% and 3.3% in the polychemotherapy and control groups, respectively (Table 10). Thus, adjuvant polychemotherapy using standard CMF must be considered as relatively safe with reference to secondary deaths. This fact is important in the context of risk for overtreatment.

Serious long-term side-effects by adjuvant therapy

The relative risk of a secondary malignancy (excluding contralateral breast cancer and skin cancer) was 1.29 in a retrospective analysis of 2465 breast cancer patients who had received adjuvant CMF-based therapy, with a medium follow-up of 12 years (23). Three patients developed acute non-lymphocytic leukaemia (cumulative risk 0.23% + 0.15%, relative risk 2.3). Contradictory results have been presented based on a study population of 1113 early breast cancer patients. The frequency of a new primary malignancy was 1% in the chemotherapy group ($p < 0.0003$) compared with 6% in the radiotherapy group and 5% in the group with surgery alone (24).

The enhancement by the combination of radio- and chemotherapy with reference to the risk of developing acute leukemia is further underlined in another large retrospective study of 1474 breast cancer patients treated with an anthracycline-containing combination, 12 of 14 cases had received the combination (25). In the randomised study comparing intensive FEC and classical CMF, with 710 randomised patients, five patients with leukaemia/myelodysplastic syndrome (MDS) were diagnosed in the FEC arm (20).

Furthermore, in the SBG 9401 study with 525 randomised patients treated with G-CSF supported and dose-intensive FEC therapy or conventional FEC followed by marrow supported high-dose therapy, ten patients in the dose-intensive FEC arm developed acute myeloid leukaemia (AML) or MDS (26, 27, see also below for an update).

The use of the Mito/prednimustine combination for breast cancer therapy resulted in a 25% cumulative risk for AML/MDS after three to four years (28). A similar cumulative risk figure of 16% was demonstrated for the Epi-Cis combination (28).

To put this into perspective, one should note that alkylating agents given for more than 12 cycles in the therapy of Hodgkin's disease have been demonstrated to result in a cumulative risk of AML/MDS in the order of 37% after ten years (28). These prolonged treatments with combinations containing alkylating agents have not, however, been

Table 7

Polychemotherapy vs no adjuvant therapy. Mortality in relation to age

Age at diagnosis	Deaths/patients		Polychemo deaths		Relative mortality reduction (% ± SD)	Absolute mortality reduction (%)
	Allocated polychemo (%)	Adjusted control (%)	Obs-Exp	Variance of O–E		
<40	238/694 (34.3)	268/675 (39.7)	−34.2	106.6	27 ± 8	5.4
40–49	514/1 629 (31.6)	602/1 531 (39.3)	−79.3	249.1	27 ± 5	7.7
50–59	1 183/3 362 (35.2)	1 313/3 411 (38.5)	−80.7	529.2	14 ± 4	3.3
60–69	1 212/3 394 (35.7)	1 298/3 413 (38.0)	−44.3	522.6	8 ± 4	2.3
70+	103/307 (33.6)	120/302 (39.7)	−0.8	39.6	–	6.1
Total	3 250/9 386 (34.6)	3 601/9 332 (38.6)	−239.3	1447.1	15 ± 2 (p<0.00001)	4.0

From the 1995 overview, EBCTCG, 1998 (2).

given for the latest 20 years (see the chapter about Hodgkin's disease).

In conclusion, standard CMF will only marginally increase the risk for secondary leukaemias. The use of anthracyclines will result in a slightly higher risk when standard doses are used. The combination of radio- and chemotherapy seems to be a real risk factor. When higher doses of anthracycline-based chemotherapy are used the risk seems to be even higher and the addition of G-CSF could be speculated to further enhance the risk. Thus, the use of dose-intensive combinations should be reserved for clinical studies and for high-risk patients.

The literature shows that:

- There is solid scientific support from randomised studies that adjuvant polychemotherapy at 10 years will result in an absolute mortality reduction for patients younger than 50 years with 12% for node positive (34% relative mortality reduction year 5, later corresponding to an estimated median survival prolongation of several years) and 6% for node negative patients. For women 50 to 69 years, the corresponding figures for node positive and node negative patients are 6% and 2%, respectively (approximately 10% relative mortality reduction).
- Anthracycline-containing combinations result in a further absolute survival benefit at five years of 3% compared with non-anthracycline based polychemotherapy.
- There were indications that the taxane paclitaxel may further improve the survival compared with anthracyclines. However, an update and the limited data preclude conclusions for routine care.
- The addition of tamoxifen to chemotherapy further enhances the survival benefit for certain subgroups.
- The roles of more dose-intensive regimens, including high-dose therapy with bone marrow stem cell support, are presently studied in randomised investigations. The data presented so far are conflicting but they do not support high-dose therapy.
- Quality of life, based on analyses of randomised studies, demonstrate that adjuvant polychemotherapy has an initial detrimental effect, but long-term follow-up of treated patients demonstrates both improved quantity and quality of life compared with untreated patients.
- Polychemotherapy in standard doses should be offered to premenopausal node positive patients, and the corresponding postmenopausal group with a receptor-negative breast cancer and to node negative patients with high risk factors. Polychemotherapy should be combined with tamoxifen to all patients with receptor-positive tumours. Due to a need of more knowledge in this field, patients should be included in investigational protocols.

Adjuvant treatment of breast cancer

	Scientific evidence*			
	1 = High	2 = Moderate	3 = Low	Total
	Number of studies/number of patients			
M	1/29 769	–	–	1/29 769
C	1/710	2/4 290	–	3/5 000
R	3/5 052	–	–	3/5 052
Total	5/35 531	2/4 290	–	7/39 821

* The weight of scientific evidence for each study was graded as described (Acta Oncol 2001; 40: 155–65). M = meta-analysis, C = controlled clinical trial, P = prospective trial, R = retrospective study, L = literature review and O = other studies. The classification of each study is given in the reference list.

LOCALLY ADVANCED BREAST CANCER

In the era of mammography only around 5% of the Swedish breast cancer patients will present with locally advanced disease. The corresponding international figures vary from 10% to 29% (29, 30). It was recognized already in 1905 that patients with locally advanced disease had no benefit from surgery alone (31). Locally advanced disease is frequently defined as T 3-4 primary cancers or N2-3 lymph node metastases, i.e. large or ulcerated cancers with only microscopic axillary metastases to minute breast cancers with bulky axillary metastases.

Table 8

Polychemotherapy vs control in relation to receptor status

ER status, age	Deaths/patients		Polychemo deaths		Relative mortality reduction (% ± SD)	Absolute mortality reduction (%)
	Allocated polychemo (%)	Adjusted control (%)	Obs-Exp.	Variance of O–E		
ER poor <50	172/710 (24.2)	227/688 (33.0)	−36.9	86.9	35 ± 9	8.8
ER + <50	169/565 (29.9)	202/550 (36.7)	−17.6	78.1	20 ± 10	6.8
ER poor 50–69	584/1 647 (35.5)	638/1 593 (40.1)	−42.5	221.7	17 ± 6	4.6
ER + 50–69	955/3 359 (28.4)	1 053/3 434 (30.7)	−38.6	423.5	9 ± 5	2.3
Total	1 880/6 281 (29.9)	2 120/6265 (33.8)	−135.6	810.2		

From the 1995 overview, EBCTCG, 1998 (2). ER: oestrogen receptor.

The use of preoperative (neo-adjuvant) chemotherapy is more attractive than adjuvant therapy since the response to therapy could clinically be followed; the adjuvant therapy is given 'blindly' based on statistical risk calculations. Studies using primary surgery for the LABC entity followed by systemic therapy with or without loco-regional radiotherapy should more correctly be analysed in the context of the adjuvant studies and will accordingly not be discussed under this heading.

Without systemic therapy the five-year survival has been reported to be between 3.5% and 15% (32–34), the median survival and mean survival for loco-regional therapy only (surgery and/or radiotherapy) has been reported to be 16 to 26 months and four to 23 months, respectively (33, 35, 36). With multimodal therapy, around 70% of the patients will experience local control. Five- and ten-year survival figures around 30% to 40% have been reported (37).

Tumour response rates and effects on operability

Of 113 patients with LABC treated by anthracycline containing polychemotherapy, 91 (81%) became operable and were randomised between radiotherapy or surgery, and in both arms they received two more chemotherapy courses (38).

In another study, patients in both arms received three courses of induction chemotherapy with Doxo combined with Vincr followed by either surgery or radiotherapy followed by seven additional chemotherapy cycles (39). The response rate after completion of the multimodal therapy was 75% in both arms.

In a small randomised study of 60 patients with LABC, primary Mito containing polychemotherapy was compared with endocrine therapy (40). Sixteen (53%) of 30 patients with chemotherapy demonstrated an objective remission at 12 weeks while only three (10%) of 30 endocrine-treated patients did so ($p = 0.001$). This altered further therapy, 13 had to be operated with radical mastectomy in the endocrine group vs seven in the chemotherapy group. In a small three-armed study of 76 patients (41) the use of intra-arterial chemotherapy improved the response rate (68% vs 36%, $p < 0.05$). The question of pre- vs postoperative chemotherapy has been addressed in four randomised trials, however, not strictly restricted to patients with LABC but also including patients with smaller tumours. The four studies revealed that the use of preoperative Mito (212 randomised patients; (42), Doxo (414 randomised patients; (43) and 1523 randomised patients; (44) or Epi (272 randomised patients; (45) containing polychemotherapy regimens induced a clinical tumour response in 65% to 85% of the treated patients. In two of the studies, there was a statistically significantly increase in the possibility to perform breast-conserving surgery ($p < 0.005$ and $p = 0.007$), especially in the NSABP B-18 study for patients with breast cancers larger than or 5 cm before start of chemotherapy compared with no polychemotherapy (42, 44).

Effects on disease-free and overall survival

The addition of even modest, with respect to number of courses and used drugs, preoperative polychemotherapy to radiotherapy only followed by radical mastectomy in both arms statistically significantly improved disease-free survival ($p < 0.05$), and there was a non-significant trend for better overall survival (46). One further trial aiming at evaluating the effect of chemotherapy with or without postoperative radiotherapy was not analyzed in detail due to 78 of 184 randomised patients being 'disqualified' (47).

The disease-free median survival tended to be longer for the surgery group, 29.2 months vs 24.4 months for radiotherapy, but the median overall survival was 39 months for both groups in a study in which both groups received anthracycline-based polychemotherapy (38). The median follow-up was 37 months. In a study with similar design with the chemotherapy consisting of Doxo/Vincr the survival at four years in the surgery arm was 49% and 52% in the radiotherapy arm (39). In the small study comparing Mito-based polychemotherapy with endocrine therapy followed by surgery, the follow-up was only 65 weeks and there were no differences with respect to disease-free and overall survival (40). In a small study by Takatsuka et al.,

Table 9

Combined chemohormonal therapy vs tamoxifen or chemotherapy alone or vs no therapy. Relevance of age. Mortality

ER status	Deaths/patients		Polychemo deaths		Relative mortality reduction (% ± SD)	Absolute mortality reduction (%)
	Allocated polychemo (%)	Adjusted control (%)	Obs.-Exp.	Variance of O-E		
<50 C+tam vs. tam	94/340 (27.6)	97/300 (32.3)	−10.7	37.9	25 ± 14	4.7
<50 C only vs. nil	659/1 992 (33.1)	772/1 908 (40.5)	−102.7	318.0	28 ± 5	7.4
50–69 C+tam vs. tam	1 353/4 582 (29.5)	1 490/4 610 (32.3)	−67.0	567.8	11 ± 4	2.8
50–69 C only vs. nil	1 043/2 205 (47.3)	1 125/2 243 (50.2)	−59.4	485.2	12 ± 4	2.9
Total	3 149/9 119 (34.5)	3 484/9 061 (38.4)	−239.8	1408.9		

From the 1995 overview, EBCTCG, 1998 (2). C = chemotherapy.

the use of intra-arterial chemotherapy did not influence disease-free or overall survival despite improved response rate (41).

A very small study of only 49 patients revealed a non-significant trend ($p = 0.38$) of a better relapse-free survival for the CMF group vs the CMF plus Tam group in addition to surgery (48). The Kaplan-Meier survival curves indicated borderline significance ($p = 0.05$, median survival 80 vs 42 months) in favour of the CMF only group, which has to be interpreted with caution due to the size of the study, but it may of course represent a major and significant difference, not detected with such a low patient number (48).

In a small study on 52 patients, Doxo containing polychemotherapy only did not improve disease-free or overall survival compared with radiation only (49).

Chemotherapy or Tam or their combination with radiotherapy have been compared with radiotherapy only. The combination of chemotherapy and Tam resulted in a statistically significantly improved disease-free period compared with radiotherapy only, in a study of 410 patients randomised into four arms (50). Interestingly, the effect by systemic therapy was most marked on the loco-regional disease control and as expected receptor positive patients responded best to Tam therapy and receptor negative patients had best use of CMF. Furthermore, in an update of this study, the combination of radiotherapy, hormonal therapy and CMF chemotherapy resulted in a statistically significant survival improvement ($p = 0.02$), corresponding to a 35% reduction in death hazard ratio (51). Similar non-significant trends were seen in a smaller study (52).

In the pre- vs postoperative chemotherapy trials, the NSABP study could not reveal any difference in disease-free and overall survival between the two therapy options (44). In the English study, the follow-up was too short to allow these analyses (42). The French study (43) had a partly different design with an initial randomisation between neo-adjuvant chemotherapy + radiotherapy vs primary radiotherapy. Surgery was only used in both arms if a persistent tumour was present after radiotherapy or after the combination of chemotherapy and radiation. There was a non-significant trend of improved disease-free survival ($p = 0.09$) and a statistically significant improved survival ($p = 0.04$) in the group receiving chemotherapy.

The literature review shows that:

- Patients with locally advanced breast cancer should be given neo-adjuvant/preoperative chemotherapy, in order to offer the patients a higher probability of breast-conserving surgery and perhaps also a survival benefit.

Locally advanced breast cancer and neo-adjuvant vs adjuvant therapy

	Scientific evidence*			
	1 = High	2 = Moderate	3 = Low	Total
	Number of studies/number of patients			
C	2/1933	7/1532	5/421	14/3886
Total	2/1933	7/1532	5/421	14/3886

*For abbreviations, see above.

FIRST LINE THERAPY FOR METASTATIC BREAST CANCER

General role of chemotherapy

No prospective, controlled and randomised study comparing chemotherapy with no therapy in metastatic breast cancer has been identified in the databases. Single-agent chemotherapy was introduced in the treatment of metastatic breast cancer in the 1960s. Marked objective

Table 10

Non-breast cancer deaths

	Polychemo (%)	Control (%)
<50	28/1 978 (1.4)	30/1 872 (1.6)
50+	243/6 756 (3.6)	253/6 777 (3.7)
Any	271/8 734 (3.1)	283/8 649 (3.3)

From the 1995 overview, EBCTCG 1998 (2).

tumour responses were immediately observed and several of the patients improved in their well-being, both being plausible reasons why the effects have not been documented in randomised trials. Therefore, indirect evidence, detailed below, is provided.

In a retrospective study, patients treated in the 1970s survived statistically significantly longer ($p < 0.02$), with exceptions for patients with poor performance status at the time of recurrence, compared with patients from the 1950s and 60s (53). In another retrospective study the median survival times steadily improved in patients with metastatic breast cancer from the 1920s until the 1970s, from 21 months to 43 months (54). This was a retrospective study based on a hospital register. However, other reasons than chemotherapy may, of course, affect the survival, e.g. diagnostic methods, staging and better supportive care.

Several studies have addressed the question whether chemotherapy improves survival in metastatic breast cancer (55–57). In these studies it is interesting to note that the authors could not find any survival prolongation in patients treated from late 1960s and during the 1970s in spite of the more extensive use of multiple drug regimens during this time period (56, 57). Selection bias might have affected the outcome of these analyses since they were retrospective and based on hospital registers.

Two studies of special interest are a meta-analysis of randomised trials and a report based on a population-based cohort. If chemotherapy improved survival in advanced breast cancer there should be a tendency for the arm demonstrating the higher response rate to also demonstrate a longer survival. This was analysed on 6056 patients from 50 trials (58). A statistically significant relationship was demonstrated between the relative response rate and median survival ($p < 0.001$). It was claimed that effective chemotherapy might prolong the median survival time by around six months.

The cohort study from Denmark compared the therapy results from the same geographical region during three consecutive decades (59). All patients with subsequent metastatic disease had their therapy at one single oncological centre. Three cohorts of patients ($n = 769$) in 1959, 1969 and 1979 were compared. The assumption was that they were comparable, which was supported by a careful analysis of different factors which may influence the outcome. No significant differences were proven. Patients with recurrent breast cancer were identified ($n = 196$) and divided in two groups, one ($n = 69$) treated by chemotherapy and another ($n = 127$) without cytostatics.

Overall survival from time of diagnosis in all patients was similar in the 1959 and 1969 cohorts, but significantly better in the 1979 cohort when chemotherapy was used. The median survival in the chemotherapy group was 9.5 months longer than in the non-chemotherapy group.

To summarise, following the introduction of chemotherapy as a treatment of advanced breast cancer during the sixties, it soon became established that marked objective remissions were observed and accordingly no controlled clinical trials comparing chemotherapy vs no chemotherapy have been performed. When analysing hospital-based register studies, retrospective reviews, meta-analyses of clinical trials, and a population-based cohort study, there appears to be a survival gain for patients with metastatic breast cancer when treated by chemotherapy. The median survival gain has been estimated to be in the order of six to nine months for non-anthracycline regimens and using conventional doses of chemotherapy.

Since the initial completion of this chapter an overview of randomised chemotherapy and hormonal studies on metastatic breast cancer has been published (60). Based on this, some further information has been added to this final version.

Hormonal therapy vs chemo-/chemohormonal therapy

Six studies with different designs have compared different hormonal therapies with chemotherapy. The studies were small and the CMF chemotherapy was of low dose intensity in one study. Furthermore, at that time, receptor analyses were not made or sometimes were also of less optimal quality. In a British study on 100 randomised patients, statistically significantly more responses ($p < 0.02$) were seen in the chemotherapy group (61). The overall survival at 150 weeks was 23% in the group receiving Doxo containing polychemotherapy and 15% for the endocrine group. The corresponding survival figures at 150 weeks for the premenopausal subgroup was 50% for the chemotherapy group and 20% for the endocrine group (61). The patient number was low and these results did not reach statistical significance.

In a US study, 101 postmenopausal patients were studied comparing low dose CMF and Tam vs Tam alone. Patients with known oestrogen receptor negative tumours were not included (62). No statistically significant difference in survival could be detected. Finally, time to treatment failure was statistically significantly longer (median duration 17.5 vs 6.1 months, $p = 0.01$) in a small study of 34 premenopausal patients receiving CMF vs observation after oophorectomy to both groups (63). However, no survival difference could be detected.

Oestrogen receptor-rich breast cancers in postmenopausal patients seem to have borderline statistical significance survival benefit (72 vs 29 months, $p = 0.05$) from chemohormonal therapy vs oestrogen therapy alone in a subanalysis of only 40 patients, from a study with 122 randomised patients (64). Patients with oestrogen receptor positive cancers had no benefit in a small trial of 52 randomised patients by adding CMF to Tam in a cross-over design with reference to response rate and median survival (65).

In a more recent study on sixty patients, failing on first line hormonal therapy with Tam, randomised to second-

line hormonal therapy with Mpa or four courses of Mito (66), no survival difference could be detected. The duration of the single-agent chemotherapy with moderate activity was short.

Oophorectomy + chemotherapy vs only chemotherapy

Ten-year follow-up data have been presented in a study of 89 premenopausal receptor positive/unknown patients randomised to surgical oophorectomy + FAC vs FAC alone. The median survival for the combined arm was 42 months (confidence interval 26 to 60 months) and 30 months (confidence interval 26 to 55 months) for FAC alone, which was not statistically significant (67). The response rate for the combined arm was 84% and 76% for FAC ($p = 0.42$) (68). These figures were recorded from the initial report also containing non-randomised 58 patients with oestrogen receptor negative cancers which were directly allocated to only FAC therapy (68).

Chemotherapy alone vs chemotherapy combined with hormones

In a large randomised study of 464 patients with advanced breast cancer the postmenopausal group received Tam and the premenopausal group were treated with oophorectomy either concurrently or sequentially in relation to chemotherapy (69). There was a non-significant trend ($p = 0.29$) of improved survival for the premenopausal group of 109 patients receiving concurrent therapy. For the postmenopausal group of 297 patients, there was a non-significant trend ($p = 0.17$) of improved survival for the group receiving sequential therapy. In a subanalysis of a low-risk group this difference became highly significant ($p = 0.003$) in favour of sequential therapy (69), not unlikely due to the tumours being receptor-positive in higher frequency.

Three hundred and thirty-nine postmenopausal patients were randomly investigated as to whether therapy should start directly with Tam alone or in combination with AC or with AC alone (70). Patients progressing on Tam alone received AC and vice-versa. The Tam arm had a statistically significantly worse response rate ($p < 0.0005$). Time to progression in the Tam arm was three months, AC 11 months and AC + Tam nine months ($p = 0.01$). No major difference in median survival could be detected with this cross-over design, 21 to 23 months. The use of Mpa concurrently with VAC polychemotherapy or sequentially was studied on 155 randomised patients (71). The response rates, duration of response and survival, 22 months for the combined arm and 24 months for the alternating arm, were similar for both groups (71). No survival benefits were seen by adding Tam or Mpa to CMF in a three-armed study of 117 patients. However, more responses ($p < 0.05$) were seen in the combined arms (72).

In accordance with this, a higher response rate was reported using CMF + Tam vs only CMF in a study of 153 patients with no report on survival (73). Similarly, the concurrent addition of Tam to FAC with reference to response duration, time to treatment failure and survival in 474 patients added no benefit (74). Response rate was 56% for both oestrogen receptor positive and negative patients, but the survival was statistically significantly ($p = 0.006$) longer for the receptor positive group, median 15 months vs eight months for the receptor negative.

No difference in response was described in a preliminary report on 246 patients receiving FAC + Tam with no survival data included (75). A trend of detrimental effects was seen by adding Tam to CVP with reference to time to treatment failure (287 vs 158 days; $p = 0.07$) and a median survival (544 vs 394 days), respectively, in a study of 131 randomised patients (160).

In second line chemotherapy, the addition of Tam to Doxo and dibromodulcitol resulted in statistically significantly improved response rate ($p = 0.004$), time to treatment failure ($p = 0.001$, 170 vs 110 days) but not statistically confirmed for survival ($p = 0.18$, 340 vs 270 days) for the 135 randomised patients (76). A similar result confirmed no survival benefit by adding either Mpa or prednisolone to second line Mit C and Meth in 108 patients failing on first line Doxo therapy (77). A detrimental effect on survival (13 months vs nine months, $p < 0.05$) was seen in a randomised study of 142 patients by adding Mpa to FuMi or VAC (78). No conclusive data were obtained in a minute study of 40 patients comparing vindesine vs Mit C with the addition of Mpa to both arms (79). An opposite trend, 7.8 months vs 9.7 months ($p = 0.31$), in median survival was described in a randomised study comparing Mit C vs the same drug plus Mpa on 76 randomised patients (80). The addition of Mpa to weekly Doxo resulted in a trend of more responses, 38% vs 26% ($p = 0.08$), but had no impact on the median survival, which was 11 months in both arms in this study of 218 randomised patients (81).

The lack of survival benefit by adding a simultaneous progesterone therapy was demonstrated already in 1978 in a small, but placebo-controlled trial of 77 entered patients (82). In contrast, in three studies that had included 263, 145, and 81 patients, respectively, the addition of Tam to CMF and CMFV resulted in statistically significantly improved response rates ($p = 0.0001$, $p < 0.01$, and $p < 0.0025$, respectively) and trends in survival improvement (34 vs 20 months, p = non-significant; 24 vs 19 months; $p = 0.12$) for the concurrent therapy (83, 84) and vice versa (78 weeks vs 111 weeks; $p = 0.25$) (85). A trend for improved survival from concurrent hormonal therapy was claimed in a pilot study of 34 randomised patients comparing FAC vs mitomycin plus Mpa, (16.7 vs 22.5 months; $p = 0.35$) (86).

In conclusion, the addition of hormonal therapy to chemotherapy adds no survival benefit to chemotherapy alone and cannot be recommended for patients with metastatic breast cancer. In standard care, each treatment

should be used separately. This conclusion is also supported by the recent overview (60).

Early or delayed chemotherapy in addition to hormonal manipulation

In a small randomised study of 75 premenopausal patients the effect by CFP given either early or at progression after oophorectomy was studied. The progression-free interval was 77 weeks for the immediate chemotherapy group compared with 33 weeks for the delayed chemotherapy group ($p < 0.05$) (87).

Thirty-one patients were treated with adrenalectomy-oophorectomy followed by no therapy until relapse or immediate or delayed chemotherapy during three months, the median survivals for the arms were 19 to 20 months, respectively, in this too-small study (88).

To summarise, in studies comparing hormonal therapy with chemotherapy, methodological errors preclude firm conclusions.

Single agent chemotherapy

Randomised studies comparing different single agents are relatively few (89–98). In these studies, the investigators have mainly evaluated the response rate and time to progression. However, weekly Doxo at 20 mg resulted in a similar survival of 13 to 14 months and less toxicity compared with the bi-weekly schedule with Epi given at 50 mg (99).

Non-anthracycline chemotherapy: single-agents vs polychemotherapy

In the earlier studies, response rate was frequently used as the primary end-point. Four randomised studies were identified, three including survival analysis (100–103). The studies compared Cyclo vs CMF-Vinbl (103); Melph vs CMF (100); Cyclo vs MFVP (102) and 5-FU vs CMFVP (101). The objective response rate was statistically significantly better in three (100–102) of the four studies for the combined regimens ($p < 0.01$ to $p < 0.001$).

In the two largest studies, the median survival for CMFVP was 16 months vs five months for 5-FU ($p < 0.001$) (101) and 12 months for CMF vs nine months for Melph (100). In the latter study, subanalysis revealed that the combination arm resulted in statistically significantly improved survival, for patients with liver metastases ($p < 0.05$) and better performance status ($p < 0.01$). In the British study (103) in 99 randomised patients no survival difference could be detected and it was not analysed in the Danish study (102).

In the overview, polychemotherapy was statistically significantly superior compared with the monotherapy regimens (60). The relative hazard ratio for survival was 0.70 (95% confidence interval 0.59–0.84).

Anthracycline chemotherapy: single-agents vs anthracycline containing polychemotherapy

Eleven of these studies included either Doxo or Epi as single-agent compared with polychemotherapy (104–114). In a randomised study of 128 patients, weekly Doxo at 20 mg was demonstrated to be significantly less toxic, but with a similar and relatively modest survival (11 vs 12 months) compared with VAC given every third week (108). The relatively short median survival compared with other studies may be due to patients with more advanced stages being treated.

In the overview, the polychemotherapy regimens compared with single-agent anthracyclines, resulted in a statistically significant survival gain (relative hazard ratio 0.87 (95% confidence interval 0.78–0.97) (60).

Comparisons between non-anthracycline containing polychemotherapy

The CMFVP combination was introduced in 1969 and was used as the standard regimen for many years (115). In prospective randomised studies Vincr and Predn have been found to be poorly active (116, 117). The conclusion has been that CMF is the standard combination chemotherapy from those early years. A higher response rate of borderline significance ($p = 0.06$) for CMFP vs CFP was observed in a randomised study of 345 patients but survival was similar, 15.2 and 14.9 months, respectively (118). CMF was randomly compared with PMF on 153 randomised patients with no difference in response and survival (119). One hundred and forty patients were randomised between the oral CMF schedule vs PE as first line therapy (120). The response rates tended to be higher for PE, 48% vs 63% ($p = 0.08$) but survival was similar, 75 and 76 weeks, respectively (120).

Classical CMF is given with a four-weekly schedule with cyclophosphamide orally. This regimen has been compared with a three-weekly schedule using only intravenous administration at lower dose intensity in a prospective and randomised study. The study was motivated by the frequent use of the intravenous three-week CMF schedule and by the claimed problems with nausea using classical CMF. Both survival (17 vs 12 months) ($p = 0.016$) and response (48% vs 29%) ($p = 0.003$) were statistically significantly better for the classical schedule (121). Similar trends were also observed in a smaller study with a complicated design using the CMFP combination (122). The question of dose-intensity will be discussed under a separate heading.

Comparisons between combinations with anthracyclines vs CMF-like and Mito combinations

Doxo has been the most frequently used anthracycline in these studies (123–141), while in three trials the anthracendion Mito was used (142–144). In three studies, Epi replaced Doxo (145–147).

The effort has been focused on finding if regimens containing Doxo do better than those based on the drugs in the original non-anthracycline 'Cooper' regimen. These studies were mostly of first line chemotherapy type. Anthracycline-containing combinations will, in general, result in a higher response rate.

In the overview, 2790 patients were analysed for survival when treated with different anthracycline-containing combinations vs CMF, CMF-based combination regimens and Mito-like combinations. The anthracycline combinations had a statistically significantly superior survival, relative hazard ratio 0.89 (95% confidence interval 0.82–0.97) (60).

Some of the studies have also been analysed in a meta-analysis on only 1088 patients, demonstrating statistically significant improvements for response, failure-free survival ($p < 0.001$) and overall survival ($p < 0.001$) for the anthracycline-containing regimens (148). In four studies, the non-anthracycline containing CMF-like combination with prednisone/prednisolone resulted in a better median survival compared with the anthracycline combinations (133, 149–151). In the randomised comparisons between VAC or AV, respectively, vs CMFP, in the larger study the median survival was 13.7 months for AV and 16.4 months for CMFP ($p = 0.03$) (149, 151). Furthermore, a non-significant median survival benefit for CFP (15.8 months) and CFPMV (17.2 months), respectively, vs a suboptimal AC regimen (12.3 months, $p = 0.17$) was described in a study with a cross-over design (150). However, an opposite finding in favour of the anthracycline-containing combination was demonstrated in one study with 362 randomised patients (140).

In a randomised phase II study, a Mito combination vs CMF resulted in a higher response rate ($p = 0.027$), but a similar median survival, 19 months compared with 16 months ($p = 0.48$) (142).

Thus, when some anthracycline combinations were compared with CMF + prednisone/prednisolone, the latter had a statistically significant superior survival, with a relative hazard ratio of 1.16 (1.02–1.32) (60). One may speculate that this result may be due to suboptimal anthracycline doses and/or to the use of prednisone/prednisolone, which may have some antitumoural effects by themselves (149, 150, 152).

Comparisons between anthracycline single drugs and anthracycline or Mito based combinations

The original anthracycline was Doxo. Epi, a Doxo analogue, was later released, being claimed to induce less cardiac-, platelet- and mucositis toxicity (153). When anthracyclines are used repeatedly there is a cumulative risk of cardiotoxicity. The recommended maximum cumulative doses are 550 mg/m^2 for Doxo and 1000 mg/m^2 for Epi (17). Possible advantages for Epi are the fewer side-effects with the possibility to be able to give more courses (154). The different anthracyclines have been compared in randomised studies with special reference to the toxicity profile and anti-tumoural activity (97, 99, 155–161).

One hundred and forty-one patients were randomised to Doxo at 60 mg/m^2 or Epi at 90 mg/m^2 as first line therapy for metastatic breast cancer (97). The response rates were similar, 47% (Doxo) and 49% (Epi), as were response duration and median survival, 10 and 12 months ($p = 0.48$) vs eight and ten months ($p = 0.47$), respectively (97). No differences in the toxicity profiles were reported (97). Opposite findings were reported in a small study of only 54 patients who had failed a previous non-anthracycline regimen (92). When Epi was used instead of Doxo together with 5-FU and Cyclo (FEC/FAC) the results indicated that the FEC regimen was similar in efficacy compared with FAC, but with significantly less toxicity (156, 162, 163).

In the overview based on six randomised studies containing 1097 patients, comparing single agent Doxo or Epi or the corresponding polychemotherapy combinations, Doxo/Doxo combinations were statistically significantly superior, relative hazard ratio 1.13 (95% confidence interval 1.00–1.27) (60). In those comparisons Epi demonstrated less toxicity, e.g. leukopenia and cardiac toxicity (60). To obtain equivalence in the anti-tumoural effects of a 60 mg/m^2 Doxo dose, Epi has to be given in a dose of 75 mg/m^2 to 120 mg/m^2 according to the latest calculations (153, 164).

The oral anthracycline Ida was compared with Doxo in a randomised study of 76 patients, Ida was demonstrated to have a worse response ($p = 0.02$) and a trend of shorter survival, 14 vs 20 months ($p = 0.09$) for Doxo (165). However, equivalance with reference to survival ($p = 0.9$) was claimed in another study of 63 patients (166).

In trials comparing Doxo- or Epi combinations with the anthracendione Mito combinations, in the majority of the studies, no significant difference in survival could be demonstrated (90, 126, 134, 145, 147, 161, 167–171). The toxicity was claimed to be lower or with a different profile for Mito, but a slightly better antitumoural effect was noticed for Doxo (126, 155, 158, 161, 168, 172). However, a trend in the opposite direction was noticed in a study of 217 randomised patients, although suboptimal doses of Doxo or Epi were used (147). On the other hand, in a recent study, FAC was compared with FNC in a randomised study of 249 evaluable patients (173). Forty-eight% and 60% responded to the FNC and FAC regimens, respectively. The median survival was statistically significantly ($p = 0.003$) longer for FAC (15.2 months) than for FNC (10.9 months) (173).

Single anthracycline-containing regimen vs alternating regimens

A five-drug combination containing Doxo was studied in a randomised study in 262 patients compared with an alter-

nating Doxo combination (174). The response rates were almost identical, 63% and 64% for the single combination compared with the alternating combination, respectively. The median survival was slightly over one year and no significant difference was seen between the treatment arms. Four hundred and ninety-seven patients were randomised between FAC vs VATH followed by CMFVP upon progression vs an alternation between VATH and CMFVP (175). The objective response tended to be higher in the VATH arm, 57%, vs 50% and 51%, respectively. Time to treatment failure was statistically significantly longer ($p = 0.03$), nine months vs eight months, for the alternating VATH scheme compared with FAC. The alternating arm had statistically significantly ($p = 0.02$) more toxicity and the median survival was 15 months for FAC, 17 months for the other two arms ($p = 0.2$) (175).

Sequential vs alternating polychemotherapy

Two hundred and fifty patients were randomised in a three-armed study comparing EC therapy followed by CMF (Arm A) vs AC alternating with CMF every second course (Arm B) vs EC alternating with CMF (Arm C) (176). A non-significant trend of better response was noticed in arm A and for survival in arm C (176).

Sequential single agent vs combination chemotherapy

The use of sequential single agent therapy vs combination chemotherapy was studied in two randomised trials containing a total of 237 evaluable patients (177). No differences were demonstrated between these two approaches except that patients with liver metastases had statistically significantly better ($p < 0.05$) survival when receiving upfront polychemotherapy compared with sequential single agent therapy.

Single agent Epi at 20 mg/m^2 followed by Mit C has been compared with FEC followed by MV (178). The median survival was 18 months (95% confidence interval, 16–22) for the combination arm and 16 months (95% confidence interval, 14–19) for the single agent arm. The response ($p = 0.21$) and time to progression ($p = 0.07$) tended to be higher for FEC than for Epi, but the toxicity was significantly lower in the single agent arm in some dimensions, described in the life-quality section (178).

Reversal of cytotoxic drug resistance and biomodulation

Two hundred and twenty-three evaluable patients were studied in a placebo-controlled trial using quinidine as a potential resistance modulator of Epi in patients with advanced breast cancer (179). The response rates were similar and a non-significant trend with a median survival of 59 weeks (95% confidence interval 42 to 72 weeks) was noticed for Epi alone vs 47 weeks (95% confidence interval 42 to 72 weeks) for the combined arm (179). The effect by lonidamine, a compound claimed to selectively inhibit aerobic glycolysis and oxidative phosphorylation, was studied in addition to FAC in a randomised study on 265 patients with a statistically significantly prolonged time to progression for the FAC plus lonidamine arm (9 vs 6 months; $p < 0.0001$) (180). No survival data were given in that study. No effect on time to progression and survival was later reported in a randomised study of 207 patients receiving Epi with or without lonidamine, thus not supporting further interest in the drug (181).

Estrogenic recruitment before chemotherapy

Based on the principle of estrogenic recruitment of tumour cells into the cell cycle, five randomised studies have been identified testing the concept. The chemotherapy regimens were CMF, CAMF, FAC and CEF. The patients received either diethylstilbestrol (182, 183), ethinylestradiol (184), or premarin (185) in different schedules in relation to the chemotherapy, with a highly variable proportion (100% to 15%) of the patients being receptor-positive. In a pilot study, 39 postmenopausal patients received aminoglutethimide + 17 β-estradiol before FAC therapy without outcome differences (186). None of the other studies disclosed any statistically significant differences in progression-free survival or total survival. The reason for the negative results may be due to tumour heterogeneity combined with the lack of individually based synchronizing related to each tumour's unique property.

In conclusion, this type of therapy remains experimental and should be tried only within the context of a controlled study.

Scheduling of chemotherapy

The optimal route, schedule, and dose have so far not been identified for most regimens. Traditionally, cytotoxic agents are delivered during a few minutes bolus injection up to a few days of continuous infusion every third to fourth week to allow the patients to recover after each course. This is especially evident for the bone marrow and gastrointestinal tract toxicity.

In two relatively small randomised substudies, CMF-like regimens were studied comparing one or two-day courses vs a five-day course, respectively (187). Significantly more responses were claimed at 6, 9, 12 and 15 months ($p = 0.05$ to $p = 0.01$) for the five-day schedule vs the one-day schedule, but no difference was demonstrated in the comparison between one and two days.

Oral therapy vs intravenous 5-FU therapy has been studied in one small but randomised study (188). The response rate for the intravenous route was 29% vs 24% for the oral route. The corresponding statistically non-significant values for median survival were 9.8 months (intravenous) and 12.1 months (oral), respectively.

Different scheduling of Mit C has been tested in a randomised study on 67 patients. The low dose concept was similar with reference to survival compared with the standard alternative (189).

One hundred and seventy-three patients were randomised to receive standard FEC every fourth week or to receive 1/4 of the dose every week. The median survival was statistically significantly ($p = 0.01$) longer for the monthly schedule vs the weekly schedule, 21.2 months vs 11.8 months for the weekly schedule (190). The median survival for the weekly schedule of 1/4 FEC is almost identical to the previously reported results using single agent Doxo weekly, the so-called low dose concept (108). The median survival time for the low dose concept has recently been confirmed in a randomised Swedish study (191).

The use of six months of continuous 5-FU infusions combined with Epi and Cis has been studied in a phase II study on 52 patients with metastatic disease and LABC (192). The response rate was 81%, 17% clinical complete responders in metastatic disease and 56% in LABC. The median survival for patients with metastatic disease was 14 months. This approach is presently being explored in a phase III study.

Duration of therapy

Six randomised studies have addressed the issue of therapy length (131, 154, 193–196). Time to progression was statistically significantly better in 4 studies using continuous therapy/increased number of courses (154, 193, 194, 196). Furthermore, in the Italian study, intensification therapy and immediate switch to an anthracycline – CMF rotating regimen for six more courses (46 evaluable patients) was not significantly better than continuous CMF (49 evaluable patients) therapy followed by an anthracycline as second line therapy, as regards time to progression ($p = 0.47$) and survival ($p = 0.55$) (131). In the small British study of only 43 patients no difference could be detected (195). This may be due to the low statistical power in the study combined with the fact that the authors used the moderately active drug Mito for only four courses (195). A statistically significant survival benefit in favour of prolonged therapy was demonstrated in two of the studies (154, 194).

In conclusion, continued therapy until disease progression seems superior to limited therapy. Further support for continuous therapy is the improved QoL for the continuous strategy (193).

The literature review shows that:

- The median survival for patients with metastatic disease treated with conventional chemotherapy doses and regimens is 12 to 24 months.
- Retrospective cohort studies indicate that the use of non-anthracycline containing chemotherapy compared with no chemotherapy might add a survival gain of six to nine months. However, this estimation is based on equivocal data.
- Based on overview data, polychemotherapy results in a statistically significant survival gain compared with single-agent therapy.
- Based on repeated randomised studies, the addition of anthracyclines increases the response rate and statistically significantly improves the survival compared with non-anthracycline containing chemotherapy, except for CMF combined with prednisone/prednisolone.

First line therapy for metastatic breast cancer

	Scientific evidence*			
	1 = High	2 = Moderate	3 = Low	Total
	Number of studies/number of patients			
M	4/42 436	1/6 056	–	5/48 492
C	45/11 187	51/7 888	36/2 820	132/21 886
R	5/2 420	–	1/60	6/2 480
Total	54/56 043	52/13 944	37/2 880	143/72 867

*For abbreviations, see above.

SECOND LINE THERAPY FOR METASTATIC BREAST CANCER

Seventeen randomised second line chemotherapy studies have been identified. These studies refer to patients who had failed on primary chemotherapy for advanced breast cancer. The later studies have included patients failing on anthracyclines. None of the studies have, however, included a non-treated supportive care group only. Response rates to second line or further lines of chemotherapy are lower compared with first line therapy.

Second line therapy after first line therapy without anthracylines

Three hundred and twenty-five women previously treated for metastatic disease were randomised between Doxo and Mito (158). The response rate was slightly higher for Doxo (29% vs 21%, $p = 0.07$) while the median survival was similar, 268 days for Doxo and 273 days for Mito ($p = 0.40$) (158). Similar results were described in another randomised study on 158 patients resulting in median survival times from 225 to 232 days (110). In ninety patients randomised to Doxo or Mito after failing on CMF, the response tended to be higher for Doxo while the non-haematological toxicity was less for Mito (96). No survival data were reported. One hundred and twenty-two patients failing on CMFVP were randomised between Doxo or Doxo plus Vp16 (114). Time to progression was statistically significantly longer for Vp16 plus Doxo, 5.1 months vs 4.2 months ($p = 0.02$). The median survival was 9.8 months for Doxo + Vp16 and 8.5 months for Doxo ($p = 0.53$). In a small study of only 54 patients Epi was com-

pared with Doxo. Both treatment options resulted in a 25% response rate and median time to progression was 3.9 months for the former and 5.1 months for the latter ($p = 0.9$), while the median duration of response was 11.9 months for Epi and 7.1 months for Doxo (92). No survival data were reported. In a randomised study of only 49 patients, weekly Doxo and Epi were compared in patients failing on CMF (157). The median survival times were 11 and 12 months for Doxo and Epi, respectively.

One hundred and thirty patients were randomised to Mit C and Tam or Doxo, mitolactol and Tam, and 76 patients previously exposed to Doxo were randomly allocated between Mit C and Tam or these two compounds plus fluoxymesterone (197). The median survivals for the latter groups were 4.6 and 5.9 months ($p = 0.78$), while the Doxo containing group had a survival of 9.7 months vs 7.6 months ($p = 0.25$) for Mit C plus Tam.

Fifty-six previously treated patients were randomised between a polypeptide complex of Melph (peptichemio) and Melph (89). Twenty-five% responded in the peptichemio group and none in the Melph group, no survival data were presented.

Second line therapy after first line therapy with anthracyclines

The effects by the vinca alkaloids Vincr, Vinbl and Vinde were studied in a four-armed randomised study in 131 patients who all had failed on Doxo therapy (98). The median duration of disease control was 13 to 20 weeks, with a marked range of eight to 140 + weeks. The effect of different schedules of Vinde was investigated in a randomised study on 60 patients with Doxo-resistant disease, resulting in 7% to 28% response rates and a response duration from two to nine + months (198). Patients receiving the continuous infusion had the best response.

The effects of taxanes and Vino after failure on anthracyclines have been studied (93). One hundred and eighty-three patients with anthracycline resistant breast cancer were randomised in a 2:1 design comparing Vino with Melph. Median time to treatment failure was significantly longer in the Vino group, 12 weeks vs eight weeks for Melph ($p < 0.001$). The median and one-year survivals for Vino were 35 weeks and 35.7%, respectively. The corresponding values for Melph were 31 weeks and 21.7%, respectively; the median survival being statistically significantly longer ($p = 0.03$) for Vino.

In a randomised multicentre phase II study, 471 patients with advanced breast cancer were randomly allocated to two dose-levels of Pacl, 135 mg/m^2 and 175 mg/m^2, respectively. One hundred and forty-one patients had only received adjuvant therapy before inclusion in the study, 2/3 of the patients had received prior anthracycline therapy either for metastatic disease or in the adjuvant setting (200). However, in the presentation of the data it was not possible to subanalyse the patient failing on anthracycline-based therapy for metastatic disease. This should be known when analysing the results, especially with reference to survival. There was a trend for better response for the 175 mg/m^2 arm, a statistically significantly ($p = 0.03$) longer median time to disease progression (4.2 months vs 3.0 months) and a non-significant trend ($p = 0.3$) of improved survival, 11.7 months vs 10.5 months. Pacl was compared with Mit C in a randomised phase II study in 81 patients failing primary chemotherapy for advanced disease (91). Median time to progression was statistically significantly ($p = 0.03$) longer in the Pacl group compared with the Mit C arm, 3.5 vs 1.6 months, respectively.

Two randomised and controlled studies have recently been analysed comparing single agent Doce vs Meth/5-FU or Doce vs VM in patients failing on anthracycline containing regimens. Three hundred and ninety-two patients were randomised between Doce vs VM, with a statistically significantly improved response ($p < 0.0001$), time to progression (19 weeks vs 11 weeks, $p = 0.001$) and median survival (11.4 months vs 8.7 months, $p = 0.0097$) in advantage for Doce (201). In a randomised study with 283 patients comparing Doce with the Meth/5-FU, results were similar (time to progression; 6.3 months vs three months, $p < 0.00005$), but no survival effect could be demonstrated, most likely due to a cross-over design (202).

The literature shows that:

- Response rates to second line chemotherapy are lower compared with first line therapy.
- Second line therapy, notably with Doce or Vino after first line anthracyline based chemotherapy, might provide a benefit in time to progression and survival of up to three months compared with other regimens. There are no data on the effect of chemotherapy relative to supportive care only.

Second line therapy

	Scientific evidence*			
	1 = High	2 = Moderate	3 = Low	Total
	Number of studies/number of patients			
C	7/1 893	4/467	4/301	15/2 661
Total	7/1 893	4/467	4/301	15/2 661

*For abbreviations, see above.

THIRD LINE THERAPY FOR METASTATIC BREAST CANCER

P, at two different dose levels, and Vp16 were studied in a randomised study as third line therapy (203). The response rates were low and the median survival was 36 and 35 weeks, respectively (203).

The literature shows that:

The role, if any, of third line chemotherapy is yet to be demonstrated.

Third line therapy

	Scientific evidence*			
	1 = High	2 = Moderate	3 = Low	Total
	Number of studies/number of patients			
C	–	1/95	–	1/95
Total	–	1/95	–	1/95

*For abbreviations, see above.

DOSE INTENSITY

The concept of dose-intensity is complex. When correctly used it should include information on amount of drug delivered per time period, e.g. mg/m^2/week. Total dose or cumulative dose, i.e. the dose per time multiplied by the number of courses, may also be important in the context of dose discussions. The marked interindividual tolerance and pharmacokinetic variations make the issue even more complex and other strategies for dose intensification may be considered (204, 205).

The configuration of the clinical dose-response curve for breast cancer is not known, either for adjuvant therapy or for metastatic breast cancer. However, high-dose therapy data with marrow support further endorse the concept of a dose-response curve, i.e. patients failing on conventional doses may experience short-lived marked objective responses when given high-dose therapy (206, 207). This part of the dose-response concept will be discussed under separate headings below, accordingly the other sections will focus on doses in the 'conventional dose range'.

In a new approach, two groups have identified, in retrospective analyses, that those patients who had most benefit of adjuvant therapy were those who experienced acute bone marrow or non-haematological toxicity, respectively, most likely a reflexion of the well-known pharmacokinetic variability (205, 208–211). This indicates the need for tailoring of chemotherapy on an individual basis (26). A positive correlation between leukocyte nadir and outcome both in the metastatic situation and for adjuvant therapy has previously been published (208, 210, 212, 213).

Three review articles have analysed the possibility of a potential dose-response relationship in the adjuvant setting and for metastatic disease (164, 214, 215). The review on dose-response in metastatic disease evaluated Cooper (CMF)-like regimens and focused on response rates and not survival, but it was concluded that an increasing dose was associated with an improved response (214). A statistically significantly ($p < 0.00001$, $r = 0.78$) positive and apparently linear relationship between dose intensity and three-year disease-free survival was disclosed for the adjuvant studies with reference to CMF-like regimens, which also contained single-agent Melph or Cyclo and the combination of MF (215). Conversion formulas were introduced to convert the single agent compounds and MF combination to the CMF dose intensity standard.

In the most recent overview, on patients with metastatic breast cancer, the median survival time was statistically significantly prolonged ($p = 0.007$) for polychemotherapy regimens given with a higher dose intensity compared with a lower dose-intensity. This dose-response effect could not be demonstrated for single agent therapy (164). Those authors introduced the term summation dose-intensity. By increasing the summation dose-intensity by one unit the median survival was claimed to increase by 3.75 months (164).

Dose-response in the adjuvant setting

In a prospective and randomised phase III study on 1529 patients treated in the adjuvant setting, high or moderate ('standard') doses of FAC polychemotherapy in the adjuvant setting were associated with statistically significantly longer disease-free ($p < 0.001$) and overall survival ($p = 0.004$) compared with the low dose-intensity group (199). No difference could be revealed between the high and median dose level. Partly contradictory results have been presented from a three-armed study on 2305 randomised patients comparing a fixed and standard Doxo dose of 60 mg/m^2 for four courses with different doses of Cyclo (216). Cyclo was given either in a standard dose (600 mg/m^2) or twice (1200 mg/m^2) this dose for four cycles, while the third arm received 1200 mg/m^2 two times (216). No difference in relapse-free or overall survival could be demonstrated. Based on this, the escalation of Cyclo may be of less value, at least when a total dose of less than 5 g/m^2 is used.

Escalation of Epi from 50 mg/m^2 to 100 mg/m^2 in the FEC regimen resulted in a randomised study of 565 node positive patients in an absolute survival gain of 12%, 77% vs 65% ($p = 0.007$) at the five-year follow-up. The higher dose level was associated with more toxicity (217).

High-dose therapy with bone marrow support/peripheral stem cell support in the adjuvant setting

The use of very high-doses requiring marrow stem cell and/or cytokine support has been investigated in phase II studies indicating the possibility of up to 100% increase in relapse-free survival, from 30% to 60% – 70% at five years (206, 207, 218). Thirteen international randomised studies are presently testing different facets of high-dose therapy including cytokine-supported therapy with or without bone marrow support (246). So far, only a few of these studies have presented their first data.

In a Dutch study 81 patients with locally advanced/high risk breast cancers were randomised between high-dose

FEC therapy, with Epi at 120 mg/m^2, vs marrow supported CTCb with no difference in outcome (219). Similarly, 78 patients at MD Anderson were randomised between marrow-supported high-dose therapy vs FAC for eight cycles, without any proven difference in outcome (220).

Three randomised high-dose studies were presented at ASCO in 1999. The only study comparing conventional adjuvant therapy, FA(E)C for six courses compared with marrow-supported Mito based high-dose therapy, demonstrated statistically significant improvements in relapse-free survival and overall survival for the latter arm in a study of 154 randomised patients (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, Abstr 4, 35th Annual meeting, 1999). An on-site review of the study has later found evidence for scientific misconduct (Weiss et al, The Lancet 2000; 355: 999–1003), and the results from the study have not been used in the present conclusions. Two other studies, with 874 and 525 randomised patients, respectively, failed to demonstrate any statistically significant survival benefits by the use of stem cell supported high-dose therapy compared with an intermediate G-CSF supported dose level and an individually adapated FEC regimen with G-CSF support, respectively (222). One of the studies, the SBG 9401 study, has later been reported in full (222). For the SBG 9401 study 81 relapses were recorded in the tailored, close-intensive FEC arm and 113 ($p = 0.04$) in the stem cell-supported high-dose arm, at a median follow-up of 34 months.

In conclusion, the potential of high-dose therapy with bone marrow stem cell support, is presently studied in randomised investigations. The data presented so far do not support stem cell-supported high-dose therapy in the adjuvant setting.

Dose-response in metastatic disease

Altogether 19 studies were found where different doses were used (121, 146, 189–191, 200, 203, 223–234), but only in nine was the dose intensity concept evident (121, 190, 191, 223, 224, 227, 230, 232, 234). The evaluated drug combinations were CMF, FAC and FEC and the single-agents were either Doxo or Epi.

A higher dose intensity in the metastatic setting is almost always associated with an increased response rate. In some studies this increased response is translated to a statistically significantly improved survival for Doxo and 'CMF' combinations (121, 191, 225, 234). The dose-response concept was further supported in the randomised study comparing a higher dose-intensity oral CMF with the intravenous regimen, disclosing a statistically significantly survival benefit for the former (121). A dose response relationship has also been demonstrated for Epi (223). This was further confirmed in a randomised study of 174 patients demonstrating a statistically significantly improved median survival (438 days vs 340 days, $p = 0.04$) for patients receiving Epi at 25 mg/m^2 vs 12.5 mg/m^2 on a weekly basis (191).

In conclusion, the application of an increased dose intensity above moderate doses in the conventional dose-range has not convincingly been demonstrated to translate into survival benefit. However, it must be emphasised that cytostatics should be administered in adequate doses when used, otherwise potential benefits might be lost.

High-dose therapy with bone marrow support/peripheral blood stem cell support in the metastatic setting

In one randomised study in 90 patients, primary high-dose therapy with autologous marrow support was compared with conventional chemotherapy for six to eight courses. Responding patients in each group received Tam (235). An update of the study demonstrated a sustained long-term survival for the high-dose arm, even after further years of follow-up (236). (See above concerning scientific misconduct in another high-dose trial by the same group. This study has also recently been subject to an audit).

In 199 randomised patients, recruited from 553 patients starting induction chemotherapy with FAC or CMF for four to six cycles, high-dose therapy with CTCb in patients responding to the induction chemotherapy was compared with maintenance CMF. No survival benefit could be demonstrated (237).

Five thousand eight hundred and eighty-six patients were reported between January 1 1989 to June 30, 1995 to the Autologous Blood and Marrow Transplant Registry of North America, which was estimated by the authors to represent 50% of the patients who had received high-dose therapy with autologous stem cell support (238). Forty-nine percent of the patients with metastatic disease in the registry had visceral involvement and 27% had bone/bone marrow metastases supporting an advanced and serious disease stage. The reported four-year survival for all patients in the registry with metastatic disease was around 20% (238). The 680 patients with complete response on conventional chemotherapy had a statistically significantly higher survival compared with the 1145 patients with a partial response on induction chemotherapy ($p < 0.0001$). Data from Sweden on 94 patients with metastatic disease and selected for their initial chemotherapy sensitivity reveal a survival at five years of 30% to 40% (239).

These results should be seen in the context that the five-year disease-free survival for patients with metastatic breast cancer is in the order of 2% to 35% (depending

on site and receptor status) using conventional therapy (59, 64, 230, 240–244). This indicates that selection procedures may be part of the explanation of the favourable five-year survival figures using high-dose therapy (245).

With reference to the divergent results, there is an urgent need to perform further controlled and randomised studies with high-dose therapy with stem cell support in one arm (246).

The literature shows that:

- Based on numerous randomised studies, breast cancer demonstrates a positive dose-response relationship both in the adjuvant situation and for metastatic disease. However, in the conventional dose-range there seems to be a plateau in the dose-response curve, with no further survival gains for higher doses.
- High-dose therapy with bone marrow support might result in further increased antitumour effects with the potential of significantly increasing survival, but additional phase III studies are required before this can be recommended for routine care.

Dose-intensity

	Scientific evidence*			
	1 = High	2 = Moderate	3 = Low	Total
	Number of studies/number of patients			
C	20/9 769	9/858	9/650	38/11 277
R	4/8 251	–	–	4/8 251
L	1/1 581	3/6 836	–	4/8 417
Total	25/19 601	12/7 694	9/650	46/27 945

*For abbreviations, see above.

CHEMOTHERAPY SUPPORTED BY CYTOKINES

A randomised and placebo-controlled study on 120 patients with inflammatory breast cancer has so far disclosed that the use of G-CSF will statistically significantly reduce neutrophil nadir value ($p = 0.01$ to < 0.001), duration ($p < 0.001$), microbiologically documented infection during neutropenia ($p = 0.042$), hospitalisation due to infection ($p = 0.003$) and number of days with IV antibiotics ($p = 0.018$) (247). The side-effects were up to six times as common (injection site pain 39% of the patients, bone pain 49%) in the G-CSF group compared with the placebo-vehicle group (247). The response rates were 90% and 93% in the placebo and G-CSF groups, respectively, and there was no survival difference at three years, with 62% (G-CSF) and 67% (placebo), respectively. In a small randomised study of only 36 patients the use of prechemotherapy G-CSF was associated with statistically significantly more grade three and four platelet toxicity ($p < 0.001$) compared with conventional administration (248).

In a small randomised study on 54 patients with advanced breast cancer receiving high-dose Mito the addition of thymostimulin together with G-CSF was demonstrated, compared with G-CSF alone, to be statistically significantly better for the combined therapy with reference to neutrophil recovery ($p < 0.0005$) and neutropenic toxicity grade 4 ($p < 0.01$ to < 0.0001 for days six to 12) (249).

The potential positive effect on survival is only reported from a small Finnish study of 32 patients demonstrating a statistically significantly ($p = 0.02$) improved median survival, 10.7 vs 6.5 months using Mito-based second line polychemotherapy (250).

The use of G-CSF or GM-CSF allows increase of the dose intensity of Epi-based polychemotherapy (222, 251, 252). In uncontrolled studies, very high response figures have been recorded in the order of 74% to 100% (253–257).

The literature shows that:

- Cytokines (G-CSF or GM-CSF) stimulate the myelopoesis and thus reduces hematological toxicity, which may enable dose-escalation above the conventional dose-range. However, so far there is no proven effect on survival.

G-CSF or GM-CSF supported chemotherapy

	Scientific evidence*			
	1 = High	2 = Moderate	3 = Low	Total
	Number of studies/number of patients			
C	–	1/120	3/122	4/242
Total	–	1/120	3/122	4/242

*For abbreviations, see above.

IMMUNOTHERAPY IN ADDITION TO POLYCHEMOTHERAPY AND HORMONAL THERAPY

One hundred and one patients were randomised between VAC with or without levamisole in a double blind design (258). There was a borderline statistical significance ($p = 0.05$) in advantage in survival for the combined arm, which was coupled with a statistically significantly improved response ($p = 0.03$). The same principal results were obtained in a study of FAC with or without levamisole in a placebo controlled trial of only 60 randomised patients (259). On the other hand, no differences in response or survival were reported in a placebo controlled trial of FAC with or without levamisole on 105 patients (260). Immunotherapy with a pseudomonas vaccine neither increased the response nor the survival in addition to FAC with or without Tam in a study of 146 patients (261).

Recently, two studies have tested the use of a huminised c-erbB-2 monoclonal antibody (262, 263). In the randomised study the addition of this monoclonal antibody increased the response rate. Chemotherapy alone resulted in a response rate of 32%, while the combined arm demonstrated a response of 62% ($p < 0.001$). Time to progression was 4.6 and 7.4 months ($p < 0.001$), respectively (263). Median survival was 20.3 and 25.1 months ($p = 0.046$), respectively.

The literature shows that:

- There is no support for unspecific immunomodulation to improve outcome. Recent studies using a c-erbB-2 specific monoclonal antibody in combination with chemotherapy indicate the possibility for new immunomodulatory strategies that have to be confirmed in further studies.

Immunotherapy in addition to polychemotherapy with or without hormonal therapy

	Scientific evidence*			
	1 = High	2 = Moderate	3 = Low	Total
	Number of studies/number of patients			
C	–	4/821	1/60	5/881
Total	–	4/821	1/60	5/881

*For abbreviations, see above.

QUALITY OF LIFE

Adjuvant setting

The use of systemic adjuvant therapy for early breast cancer statistically significantly improves the relapse-free and overall survival as detailed above. However, this type of therapy is associated with side-effects. The critical issue is whether the survival benefits counterbalance the side-effects on QoL (264). One thousand four hundred and seventy-five peri- and premenopausal patients were randomised to different schedules of oral CMF and 1212 postmenopausal patients were randomised to Tam or chemoendocrine therapy. The patients were analyzed with single-item linear analogue self-assessment scales (PACIS) and with the Befindlichkeits-Skala, a psychometrically characterised 28-item adjective checklist for emotional well-being (264). At the time of diagnosis, patients with breast cancer with less favourable prognostic factors had statistically significantly worse QoL scores. All treatment groups demonstrated stable improvements in QoL scores at different times, related to the scheduling of therapy, but all different regimens ended at 18 months with markedly improved QoL. Patients with six months of initial oral CMF have no improvement in life quality until the therapy was stopped.

QoL has also been analysed by IBCSG for some of their studies using their quality adjusted (Q) analysis of TWIST. They demonstrated that six or seven months of adjuvant chemotherapy or chemoendocrine therapy improved both quality and quantity of life compared with a short peri-operative course of polychemotherapy in patients with node-positive breast cancer (265). In a small study of 47 patients, side-effects and QoL were claimed to be impaired for patients receiving a five-drug combination vs single agent chlorambucil (266).

Observational studies after adjuvant chemotherapy have generally reported that women free of recurrence do not seem to have any permanent or long-term impairment of QoL indices (267, 268). Some studies have reported that women treated with adjuvant chemotherapy, usually CMF, may have persistent fatigue, disturbed sleep, cognitive dysfunction, slightly more sexual problems or impaired global QoL (269–271). Studies have, however, also shown that women who have completed systemic adjuvant therapy accept six months of chemotherapy for remarkably small benefits (about two-thirds accept treatment for an absolute gain of 5%) (267, 272). One of the studies also found that women treated generally overestimate the value of their therapy (272).

Metastatic setting

In a randomised study, the Australian-New Zealand Breast Cancer Trials Groups investigated the effect of QoL comparing continuous chemotherapy (DC/CMFP) vs three courses of intermittent chemotherapy (DC/CMFP), to be repeated upon progression (193). A self-assessment scale measured physical well-being, mood, pain, nausea, vomiting and appetite and global QoL. The study disclosed a significant improvement in physical well-being, pain, mood and appetite, but not for nausea and vomiting (before the era of effective anti-emetics) for the first three cycles compared with base-line. This study thus confirms the clinical experience that patients often improve in overall well-being during treatment in spite of the toxicity. Thereafter, QoL deteriorated continuously and more rapidly for patients in the intermittent group (193) than for those who continued therapy. The intermittent group was associated with statistically significantly worse response ($p = 0.02$) and time to progression (relative risk 1.8, 95% confidence interval 1.4 to 2.4), and a trend of impaired survival ($p = 0.19$, relative risk 1.3, confidence interval 0.99 to 1.6).

In a small study of 59 patients randomised between Doxo at 75 mg/m^2 q three weeks and 25 mg/m^2 q one week as first line chemotherapy, survival and QoL parameters were studied (232). Response rates and median survival (eight months) were similar in both arms. The group receiving Doxo every third week had a statistically significant improvement in psychological score ($p = 0.01$) vs the weekly schedule.

In a small study of only 40 patients, oral CMF was compared with low dose Epi 20 mg at a weekly interval. QoL was analyzed both with the Nottingham health profile and linear-analogue self-assessment. The more aggressive CMF regimen gave better responses, but similar survival without impairing the overall QoL (106).

In contrast, in a large study with 303 randomised patients, single agent weekly Epi (20 mg/m^2) therapy resulted in a statistically significantly improved QoL in some physical dimensions, but only non-significant trends in the psychologic dimensions, compared with FEC given every third week (178).

In an uncontrolled study of 160 patients, thus not classified, it was demonstrated that those responding to the chemotherapy had significant improvements in pain ($p = 0.01$), lack of energy ($p = 0.02$), tiredness ($p = 0.02$) and psychological distress ($p < 0.0001$). The authors conclude that chemotherapy 'confers benefit on a substantial proportion of patients' (273).

The literature shows that:

- In the adjuvant setting, chemotherapy improves survival without any clear deterioration of long-term QoL, despite initial toxicity from the treatment. In metastatic disease, the very few studies that have included QoL measurements seem to indicate that treatment can improve the QoL of patients. One study indicated that prolonged treatment is superior, whereas the studies testing different dose intensities give an unclear picture.

Quality of life

	Scientific evidence*			
	1 = High	2 = Moderate	3 = Low	Total
	Number of studies/number of patients			
C	4/3 761	2/99	1/47	7/3 907
Total	4/3 761	2/99	1/47	7/3 907

*For abbreviations, see above.

LITERATURE

The articles included in the reference list were classified and graded as follows

	Scientific evidence*			
	1 = High	2 = Moderate	3 = Low	Total
	Number of studies/number of patients			
M	8/72 205	1/6 056	–	9/78 261
C	86/32 798	86/17 100	61/4 597	233/54 495
R	12/15 723	1/483	1/60	14/16 266
L	1/1 581	3/6 836	–	4/8 417
Total	107/122 307	91/30 475	62/4 657	260/157 439

Some studies appear in several sections of the text due specific designs of the studies – and studies and patients may thus have been counted more than once.

*For abbreviations, see above.

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