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Breast Cancer: Chemotherapy in the Treatment of Advanced Disease

M. Clavel and G. Catimel

Chemotherapy in patients with advanced breast cancer remains palliative. Although the majority of patients will experience an initial response or stabilisation of the disease, the survival is only modestly improved. The search for new drugs and more effective combinations must therefore continue. High-dose chemotherapy with or without autologous bone marrow transplant (ABMT) is an enthusiastic perspective of progress but the available data do not permit conclusions about the effectiveness of high-dose therapy compared with conventional treatment.
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INTRODUCTION

ALTHOUGH METASTATIC breast cancer is considered to be sensitive to chemotherapy, it remains incurable with current therapeutic approaches. Chemotherapy is usually reserved for endocrine-resistant patients, oestrogen receptor-negative patients, or patients who have life-threatening metastases. Various chemotherapeutic agents produce objective tumour responses.

Doxorubicin is the most effective single cytotoxic agent, giving a 40% response rate in previously untreated patients [1]. Combination chemotherapy regimens generally produce higher

Table 1. Doxorubicin single agent chemotherapy in metastatic breast cancer

Treatment	No. of patients	Response rate (%)	Reference
Pre-treated patients			
20 mg/m²/(D1, D8)	60	27	6
12 mg/m²/1 week	81	32	7
60 mg/m²/3 weeks	40	38	8
Non-pre-treated patients			
75 mg/m²/3 weeks	32	38	9
60 mg/m²/3 weeks	20	50	10
60 mg/m²/3 weeks	79	39	11

Table 2. Randomised studies comparing epirubicin and doxorubicin single-drug chemotherapy in metastatic breast cancer

Dose	Response rate (%)	Reference
EPI 75 mg/m²/3 weeks	62	
DOXO 75 mg/m²/3 weeks	52	18
EPI 75 mg/m²/3 weeks	30	
DOXO 90 mg/m²/3 weeks	30	19
EPI 90 mg/m²/3 weeks	27	
DOXO 60 mg/m²/3 weeks	13	20
EPI 85 mg/m²/3 weeks	25	
DOXO 60 mg/m²/3 weeks	25	21
EPI 75 mg/m²/3 weeks	62	
DOXO 75 mg/m²/3 weeks	52	22

EPI = epirubicin, DOXO = doxorubicin.

Table 3. Randomised studies comparing mitozantrone and doxorubicin single drug chemotherapy

Treatment	Response rate (%)	Reference
MTZ 14 mg/m²/3 weeks	25	23
DOXO 75 mg/m²/3 weeks	35	
MTZ 12 mg/m²/3 weeks	23	24
DOXO 60 mg/m²/3 weeks	33	
MTZ 14 mg/m²/3 weeks	14	25
DOXO 60 mg/m²/3 weeks	28	

MTZ = mitozantrone, DOXO = doxorubicin.

response rates, ranging from 50% to 80% [2, 3]. However, results are still disappointing: the fraction of complete responders is less than 20%, the duration of response is less than 1 year, and median survival time of these patients is about 2 years [4, 5].

The main objectives of cytotoxic chemotherapy for metastatic breast cancer are: palliative relief of symptoms, better quality of survival, and prolongation of survival. In this review, we will attempt to provide an overview of the literature on chemotherapy for the treatment of advanced breast cancer.

SINGLE AGENT CHEMOTHERAPY

A wide variety of cytotoxic agents are effective against metastatic breast cancer. The most active well-established single agent is doxorubicin. At a dose ranging from 50 mg/m² to 75 mg/m² given intravenously every 3 weeks, the objective response rate in previously untreated patients ranges from 38% to 50%. In previously treated patients, a 30% response rate can be obtained (Table 1). Because of its toxic effects (cardiac toxicity, nausea and vomiting, hair loss) several analogues of doxorubicin have been developed with fewer associated toxicities. The best studied of these is epirubicin (4'-épi-doxorubicin). A dose of 75 mg/m² to 90 mg/m² is associated with a response rate varying from 16% to 43% [12–17]. Furthermore, five randomised studies have demonstrated that epirubicin is as effective and is better tolerated than doxorubicin (Table 2).

Mitozantrone, an anthracenedione, is a drug with biochemical mechanisms of action similar to that of doxorubicin, but with fewer toxic effects.

This agent has been associated with a 33% response rate in previously untreated patients. In randomised studies, mitozantrone was associated with a lower response rate than doxorubicin (Table 3).

Alkylating agents provide a response rate ranging from 20 to 35% [26]. Cyclophosphamide is the classical drug of this group of agents, which also includes phenylalanine mustard, chlorambucil and thiotepa (Table 4). Ifosfamide is another alkylating agent, evaluated in the recent years, but so far it appears to have no clear advantage over cyclophosphamide.

The most commonly used antimetabolites are 5-fluorouracil and methotrexate. 5-Fluorouracil is associated with a response rate of 26%, while methotrexate provides a 34% response rate [27].

The vinca-alkaloids represent a group of drugs with modest activity: vincristine, vinblastine and vindesine are associated with a mean response rate of about 20% [27]. However, a new vinca-alkaloid, vinorelbine, has been associated with a relatively high response rate (30% in pre-treated patients, and 50% in previously untreated patients) [28, 29].

Several other cytotoxic agents have been evaluated in the past including dacarbazine, cisplatin and nitrosoureas. These agents were usually associated with a low response rate (< 20%).

COMBINATION CHEMOTHERAPY

One of the first combination chemotherapy regimen was presented in 1969 by Cooper [30]. The CMFVP (cyclophosphamide, methotrexate, 5-fluorouracil, vincristine, prednisone) combination gave a 90% response rate in 60 hormone-resistant patients. Several subsequent clinical trials failed

Table 4. Alkylating single-drug chemotherapy in metastatic breast cancer adapted from Carter [26]

Treatment	No. of patients	Response rate (%)
Cyclophosphamide	529	35
Nitrogen mustard	92	35
Melphalan	177	22
Chlorambucil	54	20
Thiotepa	162	30

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to confirm this efficacy, with a mean response rate of about 50% [31, 32].

In randomised trials, the superiority of combination chemotherapy over single alkylating agent regimen was clearly demonstrated. In the trial reported by Mouridsen, the CMFVP combination was superior to cyclophosphamide alone in terms of response rate (63% vs. 25%) and duration of response (400 days vs. 210 days) [33]. Doxorubicin has been widely used in combination chemotherapy regimens. Several randomised clinical studies have compared CMFVP to a doxorubicin-containing regimen (Table 5). About half of these trials were in favour of the superiority of the doxorubicin combinations in terms of response rate and duration of response.

The use of non-cross resistant combination chemotherapeutic regimens in a sequential design has been investigated in the hope to improve complete response rates and survival. The rationale for this approach had been described by Goldie *et al.* [43].

Unfortunately, long term analysis of trials comparing a sequential administration of alternating non-cross-resistant regimens to the administration of a given regimen until disease resistance, has failed to demonstrate a significant advantage of the sequential approach in metastatic breast cancer (Table 6).

COMBINATION OF CHEMOTHERAPY AND HORMONAL TREATMENT

The rationale for the use of a combination of chemotherapy and endocrine treatment is based on the hypothesis that there are distinct populations of tumour cells, some that are chemo-sensitive and hormono-resistant, others that are chemo-resistant and hormono-sensitive. In this situation, each modality acting through a different mechanism might lead to a greater effect.

Many trials have evaluated the concurrent use of both therapies, with conflicting results. While higher response rates could be achieved with chemohormonal treatment compared with chemotherapy alone or hormonotherapy alone, the advantage was generally not translated into an improvement of duration of response or duration of survival [47].

Table 5. Randomised studies of combination chemotherapy with and without doxorubicin in metastatic breast cancer

Treatment	No. of patients	Response rate (%) CR+PR	CR	Response duration (months)	Reference
FAC	59	64	20	7	
CMFVP	54	37	5	5	34
FAC	79	53	17	11	
CMFP	76	53	5	6	35
FAC	38	82	18	10	
CMF	40	62	7	9	36
CMFP	86	63	16	8.4	
CMF	79	57	15	4.5	
AV	166	56	12	7.7	37
CAFVP	76	58	13	13	
CMFVP	72	57	11	15	38
CAF	82	55	9	13	
CMF	99	37	10	6	
CAFVP	79	58	9	9.5	39
CA	47	55	12	9	
CFP	46	57	9	9.5	
CMFVP	48	65	11	11	40
CAFVP	107	71	—	14	
CMFVP	109	50	—	7	41
CAF	163	56	29	11.4	
CMF	181	37	16	6.5	42

A = doxorubicin, C = cyclophosphamide, F = 5-fluorouracil, M = methotrexate, P = prednisone, V = vincristine.

Table 6. Randomised studies comparing conventional chemotherapy and sequential chemotherapy in metastatic breast cancer

Treatment	No. of patients	Response rate (%) CR+PR	CR	Reference
FAC versus	66	44	15	
FAC "CAMELEON"	91	40	10	44
FAC versus	21	63	13	
DAV-CMF	25	70	10	45
AVCMFP versus	61	72	16	
AVCMFP	60	61	8	46

For abbreviations see legend to Table 5.

SURVIVAL OF PATIENTS WITH ADVANCED BREAST CANCER

The issue of whether chemotherapy has improved survival in patients with metastatic disease or not remains a subject of controversy. Several authors have retrospectively evaluated survival.

Kaufman has compared two historical series of patients: 599 patients who were treated from 1947 to 1961, and 328 patients treated from 1967 to 1977 [48]. The 5 year survival rates were similar: 6.3% and 7.9% for the two series, respectively.

Tormey retrospectively compared survival of patients given single agent chemotherapy with survival of patients given combination chemotherapy [49]. While response rate was significantly higher for patients treated with the combination regimen (59% vs. 34%), median survival was similar in either group (15 months vs. 13 months).

The analysis of Patel failed to show any difference of median survival of 500 patients treated between 1942 and 1975. During this period, median survival from first metastasis was not improved, and was approximately 21 months [50].

However, the study conducted by Ross clearly demonstrated that patients treated in the 1970s had significantly better survival compared with patients treated in the earlier two decades (median survivals: 22 months versus 12 months) [51].

However, with conventional approaches, metastatic breast cancer remains an incurable disease.

NEW DRUGS AND NEW COMBINATIONS

New drugs

Many new cytotoxic agents or combinations have been tested in phase II studies during the past years.

Taxol is one of the most interesting and challenging new drugs. Two phase II studies with taxol given as a single agent have been completed in patients with metastatic breast cancer. In the first study, taxol was administered at a dose of 250 mg/m^2 (24 h i.v. infusion) every 3 weeks in 25 patients previously treated with one chemotherapy regimen (14 adjuvant, 11 metastatic). 23 patients had received an antracycline-containing regimen. 14 out of the 25 patients (56%) had objective response (3 complete, 11 partial) [52]. In the second study, 28 patients

with no prior chemotherapy for advanced disease (16 patients had received adjuvant chemotherapy) were treated with taxol 250 mg/m^2 given by 24 h infusion every 3 weeks associated with G-CSF at 5 μg/kg on days 3–10 [53]. 16 out of 26 (62%) evaluable patients have responded. 1 patient had a complete response and 15 patients a partial response. Granulocytopenia was the dose limiting toxicity when taxol was given alone but taxol was well tolerated when given with G-CSF.

According to the results of those studies, taxol has a level of activity approaching that of single agent doxorubicin. It is extracted from the bark of the Pacific yew, and the synthesis of taxol would have major importance in providing sufficient drug. Several years ago, a French group was able to prepare a semisynthetic analogue of taxol using a precursor extracted from the needles of the European yew: taxotere [54]. This analogue has been shown to have superior *in vivo* antitumour activity in B 16 murine melanoma as compared to taxol. Five human phase I trials with taxotere have been conducted. Four partial responses have been observed in heavily pretreated breast cancer patients [55]. A European phase II clinical trial in metastatic breast cancer has now been initiated.

Gemcitabine (2,2 difluorodeoxycytidine) is a deoxycytidine analogue with activity in a number of phase I studies. One phase II clinical trial was conducted in patients with advanced breast cancer, with 4 partial responses among 18 evaluable patients [56].

10-EDAM (edatrexate) is a new antifolate with an improved experimental therapeutic index when compared with methotrexate. In a phase II study including 28 patients 2 complete and 9 partial responses were observed [57].

The activity of these two drugs should now be confirmed in large scale trials.

New combinations

New combinations were recently reported by several groups.

The biochemical modulation of 5-fluorouracil (5-FU) with folinic acid has been evaluated in metastatic breast cancer. The 5-FU–folinic acid combination has shown modest activity when used alone (14% response rate) [58]. However, high response rates have been reported with 5-FU–folinic acid associated with mitozantrone, or cisplatinum, or epirubicin and cyclophosphamide (Table 7).

Clinical phase I trials of combinations of taxol and doxorubicin are currently being performed in order to define the maximum tolerated dose and the best schedule of those two drugs administered concurrently [66, 67]. This combination seems to show promising activity but results are still premature and further investigations are required.

The combination of navelbine and doxorubicin led to interesting results as first line chemotherapy for metastatic breast cancer patients. In a phase II trial including 88 evaluable patients, response was observed in 65 patients (20 CR, 45 PR), response rate = 74% [68].

In the near future, randomised studies comparing these new combinations with standard available regimens will be required.

Table 7. Biochemical modulation of 5-FU with folinic acid in metastatic breast cancer

Reference	Treatment	No. of evaluable patients	Response (%)	
			CR	CR+PR
58	5-FU–folinic acid	56	4 (7)	8 (14)
59	5-FU–folinic acid–mitozantrone	32	7 (22)	21 (65)
60	5-FU–folinic acid–mitozantrone	15	1 (6)	5 (33)
61	5-FU–folinic acid–mitozantrone	25	2 (8)	8 (40)
62	5-FU–folinic acid–mitozantrone	53	0	24 (45)
63	5-FU–folinic acid–mitozantrone	31	2 (6)	20 (65)
64	5-FU–folinic acid–mitozantrone	19	3 (15)	8 (42)
65	5-FU–folinic acid–epirubicin–cyclophosphamide	50	12 (24)	25 (74)

TREATMENT DURATION

In metastatic breast cancer, chemotherapy is usually administered continuously until disease progression. Discontinuation of chemotherapy had been proposed as a means to improve survival and quality of life.

Coates and colleagues have compared a continuous treatment with its discontinuation after three cycles in patients without progression of disease [69]. They concluded that intermittent therapy was associated with lower response rate and lower quality of life. Furthermore, the median time to treatment failure was higher in the continuous therapy group (6 months vs. 4 months). Although statistically significant, this difference was not associated with a survival benefit. More recently, Harris *et al.* reported the results of a trial of mitozantrone single agent chemotherapy [70]. Patients were randomised to stop or to continue treatment after 3 months, provided objective response or stabilisation had occurred. Among the 43 patients entered into this study, there was no difference in time to disease progression, or survival between the two groups.

The Danish Breast Cancer Cooperative Group has compared continuous CEF (cyclophosphamide, epirubicin, 5-FU) chemotherapy every 3 weeks for 18 months or until progression of disease, against similar CEF for 6 months or until progression and resumption of CEF for 12 months in case of progression occurring after 6 months [71]. Out of the 319 evaluable patients, progression-free survival was significantly longer in the group of patients continuing CEF beyond 6 months than in the group that stopped CEF at 6 months (71 weeks vs. 41 weeks). Median survival time was also significantly longer in the former group (93 weeks vs. 77 weeks).

In 1986, the French ERASME group initiated a multicentric prospective randomised study to compare continuous and intermittent chemotherapy in patients with non-hormono-dependent metastatic breast cancer [72]. After 3 monthly courses of FEC, (5-FU, epirubicin, cyclophosphamide) patients with either complete, partial response or stable disease were randomised to receive either continuous [12 monthly courses of FEC followed by monthly CMF (cyclophosphamide, methotrexate, 5-FU) until progression] or intermittent therapy (3 months rest alternating with 3 months of FEC treatment). Between 1986 and 1991, 309 patients entered the study, 63% of them having two or more metastatic sites. 181 of the 291 evaluable patients had non-progressive disease after the induction phase, and 176 were randomised: 86 to the continuous arm and 90 to the intermittent arm. The final analysis of the study has shown no statistically significant difference between the two groups in terms of time to disease progression (median 7 months for the continuous arm vs. 9 months for the intermittent arm) and survival (median 17 months vs. 15 months). However, patients in the discontinuous group received an average of 6.4 chemotherapy courses (range 3–14) whereas those in the continuous group received an average of 9.5 courses (range 3–24).

Discontinuous chemotherapy may represent a real alternative to conventional continuous treatment. This important subject should be further analysed in future trials.

THE DOSE INTENSITY DILEMMA

The importance of dose intensity in breast cancer has been extensively debated but still remains controversial. Different studies have evaluated the value of increasing chemotherapy dose by using different kinds of escalation. The high dose schedules were associated with higher objective tumour response rates, the difference being significant in about half of the trials (Table 8). However, this difference was not associated with a survival benefit.

More recently, the use of very high dose chemotherapy supported by autologous bone marrow transplantation (ABMT) has been investigated in phase I and II clinical trials by several groups. Major controversy arises over the interpretation of the results of these trials. In fact, it is very difficult to make comparisons across studies because of the differences in treatment regimens, in patient-selection criteria, and the small size of the samples. In these trials, response rates are considerably higher than response rates usually observed in series of conventional-dose chemotherapy (70% compared with 39%). Moreover, the complete response rates of about 35% obtained in series of high-dose chemotherapy with ABMT are higher than the 10–20% reported with standard-dose therapy [5, 77].

Some investigators have reported that high-dose therapy led to prolonged disease-free survival [78], while cases of long-term disease-free survival have also been reported with conventional dose therapy.

However to date, there are no trials to provide a definite answer to the question whether high-dose chemotherapy with ABMT improved survival compared with conventional-dose chemotherapy.

High-dose therapy may provide a survival benefit, but it may be at an untenable economic cost [79], or associated with high toxicity and mortality rates. Furthermore, the limited number of units where ABMT is possible makes this technique a very selective one.

The use of high-dose chemotherapy supported by haematopoietic growth-factors without ABMT represents an interesting alternative approach currently under evaluation [80].

Table 8. Randomised studies of high-dose versus low-dose chemotherapy (without bone marrow support) in metastatic breast cancer

Reference	Treatment	No. of patients	Response rate (%) Low dose	Response rate (%) High dose	Median survival (months) Low dose	Median survival (months) High dose
37	LD CMF vs. HD CMF	165	57	63	14	16
73	LD FAC vs. HD FAC	60	39	70	22	19
74	FEC 50 vs. FEC 75	259	42	43	—	—
75	LD LEP vs. HD LEP	209	23	41	11.5	11
76	LDCMF vs. HD CMF	133	11	30	12.8	15.6
10	LD CMFVP vs. HD CMFVP	283	40	59	14	14

LD = low dose, HD = high dose. For drug abbreviations see legend to Table 5.

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Cost Effectiveness in the Treatment of Advanced Solid Tumours

R.D. Rubens

When the treatment of advanced cancer is palliative in intent, evaluation of quality of life is of paramount importance in judging the effectiveness of treatment. The balance between adverse effects (costs) and benefits has been particularly difficult to determine with cytotoxic drugs. An approach to this problem using medical audit is described. It has been found to be a reliable method which has demonstrated a highly significant correlation between achievement of objective regression and acquisition of benefit. The method is now undergoing corroboration by a prospective study.
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INTRODUCTION

IN THE treatment of advanced solid tumours, it is rarely, if ever, realistic for its intention to be curative. The aim of palliation is to control the disease in order to make life as active and symptomless as possible with the least adverse effects from treatment. It is, therefore, understood that the patient's life expectancy will almost certainly be severely shortened by the illness and so evaluation of the effectiveness of treatment must pay special attention to the quality of remaining life.

Methods for the palliative treatment of cancer include direct antitumour treatments such as surgery, radiotherapy, endocrine treatment and cytotoxic chemotherapy in addition to purely symptomatic treatment such as with analgesics and antiemetics. A further useful approach in the palliation of metastatic bone disease is the use of bisphosphonates to inhibit the osteoclastic destruction of bone stimulated by paracrine factors from tumour cells.

The most contentious treatment in palliative care is the use of cytotoxic chemotherapy because of the potentially severe side-effects which may impair quality of life. While high toxicity can readily be accepted when cure is achievable, such as in acute lymphoblastic leukaemia or testicular teratoma, these effects can outweigh any therapeutic value when response frequencies are low and of short duration. For the present, most cancers for which chemotherapy is used can only be considered palliative in intent. These include carcinomas of the breast (except adjuvant use), lung, alimentary tract, ovary, uterine cervix, endometrium, head and neck, kidney and bladder, soft tissue sarcomas, brain tumours, melanoma and low-grade lymphomas.

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INTENTION OF TREATMENT

The intention of palliative chemotherapy will normally be to effect symptomatic relief through the achievement of tumour regression. Prolongation of life is not normally a primary objective, although this may be achieved in certain circumstances, for example, through the regression of lymphangitis carcinoma or liver metastases. A further intention of treatment may, on occasion, be to prevent or delay certain expected complications, an example being the reversal of early signs of brachial plexopathy in advanced breast cancer.

Sometimes there is a strong temptation to give cytotoxic treatment even when there is no realistic chance of a response to treatment. This may be initiated by the oncologist in an attempt to engender hope or to avoid giving bad news. Pressure to give