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ORIGINAL ARTICLE

Usefulness of chemotherapy beyond the second line for metastatic breast cancer: a therapeutic challenge

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Abstract
Purpose Several lines of chemotherapy can be proposed for patients with metastatic breast cancer, but beyond the second line, agreement is lacking concerning the most appropriate therapeutic strategy.
Methods We conducted a retrospective analysis of the files of 162 patients, who had received at least 3 lines of chemotherapy (CT3) for metastatic breast cancer during a 5-year period (2000–2004), in order to analyze management practices and search for factors affecting survival from CT3 and predictive factors of non-progressive disease (NPD) after CT3.
Results Multivariate analysis identified seven factors which had a positive influence on survival from CT3 (SBR grade I, absence of adjuvant hormone therapy, free interval $\geq$2 years, absence of cerebromeningeal metastasis before CT, unique focus at initiation of CT3, use of polychemotherapy for CT2, and complete response to CT1 or CT2) and two predictive factors of NPD (histology and drug group used for CT3).
Conclusions These factors should help determine the appropriate strategy for proposing a third line of chemotherapy.

Keywords Breast cancer · Chemotherapy · Third line · Prognosis factor · Treatment outcome

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Introduction

According to the 2006 figures, breast cancer is the most common tumor in women worldwide, and is the leading cause of death [1, 2]. When the disease reaches the metastatic stage, the primary objectives of treatment are to ensure longer patient survival and good quality-of-life [3, 4]. A large spectrum of drugs, delivered with various chemotherapy protocols, is available to reach these objectives [5, 6]. Nevertheless, because of the lack of a commonly accepted well-defined strategy [7], debate remains open on several points: is it reasonable to propose more than two lines of chemotherapy, and if so, how many, and for what expected benefit? Considering these questions, we conducted a retrospective analysis of our experience with patients presenting metastatic disease given a third line of chemotherapy (CT3), searching for factors with predictive and prognostic value. Our goal was to determine a way to recognize women who could benefit from multiple lines of chemotherapy and, conversely, those for whom more than two lines would be expected to provide little benefit.

Patients and methods

This was a retrospective descriptive study based on the clinical records of patients treated at the Medical Oncology Department of the Eugène Marquis Anticancer Center in Rennes France. The diagnostic and therapeutic summaries of all clinical records in the department database were screened to select women given chemotherapy for metastatic breast cancer between 1 January 2000 and 31 December 2004. The following inclusion criteria were applied: female patient, age 18 years or over, breast cancer, delivery of at least 1 systemic chemotherapy protocol beyond line 2 (CT3 or higher) for metastatic disease. Exclusion criteria were another active cancer or strictly local or contralateral recurrence.

A first set of data collected concerned the primary disease: histological tumor size at diagnosis (pT), histological nodal status (pN), metastasis (M), Scarff Bloom Richardson (SBR) grade, status of hormone receptors. A second set of data concerned the treatment: surgery, adjuvant chemotherapy (CT), locoregional radiotherapy, adjuvant hormone therapy. Disease recurrence was noted with the third set of data: free interval, contralateral and local recurrence, age at diagnosis of metastatic spread, metastases (localization, number). Survival after CT3 being the outcome to be assessed, the following items were also recorded: metastatic focus or foci identified at CT3, therapeutic response to the first two lines of CT, duration of non-progression and quality of response, other treatments delivered before CT3, drug or drugs delivered, protocol, number of cycles delivered, efficacy, tolerance, cause of discontinuation. RECIST criteria were used to assess efficacy, according to the clinician's opinion for measurable lesions, and according to clinical, biological or radiographic findings for non-measurable lesions. Two groups of patients were defined: patients with progressive disease (PD) which led to a change in treatment, and patients with non-progressive disease (NPD). Patients with partial response, complete response and stable disease were assigned to the NPD group.

Six groups of chemotherapy were defined according to the principle agents used: anthracyclines, taxanes, 5-fluorouracil (5FU) and oral prodrug, vinca-alkaloids, gemcitabine, other drugs. So far, the anthracycline has been considered the major drug for the treatment of breast cancer. That is why all combination regimens using anthracyclines were arbitrarily assigned to the anthracycline group, even if it was a combination of taxanes and anthracyclines. Patients included in therapeutic trials were also analyzed according to the chemotherapy delivered.

Non-discrete data were expressed as percentage and discrete data as mean ± standard deviation or median and compared with the Chi-square test or Fisher's exact test as appropriate. The Kaplan–Meier method was used to plot the survival curves which were compared with the log-rank test.

Cox model univariate analysis was used to search for variables influencing survival from CT3 and variables at CT3 predictive of NPD. Multivariate analysis was applied for variables exhibiting significance ($p < 0.05$) or near significance ($p < 0.07$) at univariate analysis. Unless specified otherwise, the survival analysis was calculated starting with the first day of CT3 (t0). Differences were considered significant for $p < 0.05$. Relative risk (RR) >1 corresponded to risk of death and risk of shorter survival. SAS 9.1 software was used for the statistical analysis.

Results

Descriptive analysis

Among the 468 female patients managed in the department for metastatic breast cancer during the 5-year period under study, 162 (35%) fulfilled the defined inclusion criteria. Most of the women included in the study had infiltrating ductal cancer (89%), were graded SBR II (36%), and were hormone receptor positive (71%) (Table 1). Initial disease staging was pT2 (41%), pN1 (62%); 129 patients (80%) were free of metastasis at initial diagnosis (M0). Among the M0 patients, most (95%) were given locoregional radiation therapy, adjuvant chemotherapy was delivered for 69 patients (42.6%), hormone therapy for 44 (34.1%), and both for 23 patients.

Median age at diagnosis of metastatic spread was 53 years. Most patients had one focus, mainly bone and soft tissues; 18.9% of patients had a unique metastasis. Median recurrence-free survival, i.e., free interval from diagnosis to recurrence, was 32 months.

Before CT3, certain patients were given local and/or systemic treatments (Table 2). 126 patients have been treated by palliative endocrine therapy before CT3 for a metastatic breast cancer in our study. Some of the patients received as many as seven lines of hormone therapy. The HER2 status was not systematically checked because some of the patients had developed a metastatic disease before the year 2000. However, 34 patients with HER2 positive status had been treated by Trastuzumab in our series. Among these 34 patients, 17 were treated before CT3.

The chemotherapy lines and their efficacy in terms of non-progression are given in Table 3. Thirty-seven different therapeutic regimens were delivered; all were assigned to the six groups defined in the data collection scheme.

Table 1 Study population: characteristics at initial diagnosis of breast cancer

	n	%
Median age [range]	49 years [26–72]	
Mean age ± standard deviation	48.8 ± 10.5 years	
Hormone status		
Menopause	74	54%
Not menopaused or uncertain	88	46%
pTNM		
pT1	44	27%
pT2	66	41%
pT3	19	12%
pT4	24	15%
pTx	9	5%
pN0	60	37%
pN1	101	62%
1–3 N+	40	24%
>3 N+	61	38%
pNx	1	1%
M0	129	80%
M+	33	20%
Histology		
Infiltrating ductal carcinoma	144	89%
Infiltrating lobular carcinoma	13	8%
Other	5	3%
SBR		
I	12	8%
II	59	36%
III	46	28%
Unknown	45	28%
Hormone receptors: RE and/or PgR		
Negative	35	22%
Positive	122	75%
Not determined	5	3%

n number of patients

Table 2 Treatments which had been given for metastatic disease before the third line of chemotherapy (CT3) was initiated

	n	%
Hormone therapy	126	78%
Radiation therapy	47	29%
Trastuzumab	17	11%
Surgery	34	21%
Prior chemotherapy regimens		
Anthracyclines	65	40%
Taxanes	27	17%
Anthracyclines and taxanes	47	29%
Neither anthracyclines nor taxanes	23	14%
First-line polychemotherapy	93	57%
Second-line polychemotherapy	38	24%
Median time from diagnosis to CT3	59 months [3–302]	
Mean time from diagnosis to CT3	76.9 ± 58.9 months	
Median time from CT1 to CT3	14 months [2–114]	
Mean time from CT1 to CT3	18.5 ± 15.4 months	
CT3 (1st regimen using these drugs)		
Anthracyclines	12 (9)	7%
Taxanes	51 (44)	32%
5 FU	42 (42)	26%
Vinca-alkaloids	27 (22)	29%
Gemcitabine	3 (3)	2%
Others	7 (7)	4%

Patient survival

Median overall survival, from diagnosis of metastasis, was 3 years in patients given at least three lines of chemotherapy.

Median survival from CT3 was 13 months (Fig. 1). It was significantly better ($p < 0.001$) in the NPD group than in the PD group, median 15 versus 5 months, respectively. Counting from the third line of chemotherapy, 47 patients (29%) survived less than 6 months and 39 (24%) more than 2 years. The overall survival rate, from diagnosis of metastasis, was 66% at 2 years, 48% at 3 years and 29% at 5 years in our study.

Univariate and multivariate analyses of factors potentially predictive of survival from CT3 (Tables 4 and 5)

Univariate analysis identified the following variables as having a significantly or nearly significantly favorable influence on survival after CT3: SBR grade I, free interval ≥2 years, NPD early (response or stable disease during first two chemotherapy lines), use of a polychemotherapy regimen for CT1 and CT2, complete response and long interval between the first and third lines (Table 4).

Multivariate analysis identified seven variables with significantly favorable prognostic value: SBR grade I, absence of adjuvant hormone therapy, free interval ≥2 years, absence of cerebromeningeal metastasis before CT, unique focus at initiation of CT3, use of polychemotherapy for CT2, and complete response to CT1 or CT2 (Table 5).

Univariate and multivariate analyses of factors predictive of non-progression after CT3

From the ten variables significant at univariate analysis (histology, no metastasis at diagnosis, no adjuvant hormone

Table 3 Regimens of chemotherapy following lines of utilization: number of patients treated/number of patients who achieved at least stable disease

	Anthracycline *n/n* *n/n* NPD	Taxane *n/n* NPD	5-FU *n/n* NPD	Vinca-alkaloid *n/n* NPD	Gemcitabine *n/n* NPD	Other *n/n* NPD	*e*?	*n*
CT1	94/76	24/22	17/13	23/22	1/1	3/1	0	162
CT2	26/25	45/97	28/15	51/34	3/1	3/2	6	162
CT3	12/10	51/40	42/28	46/27	2/0	7/1	2	162
CT4	9/8	27/22	24/14	35/17	3/0	6/2	6	110
CT5	10/6	18/9	15/7	13/30	10/4	1/0	4	71
CT6	2/1	11/8	3/1	6/3	8/4	4/1	4	38
CT7	2/1	9/8	0/0	6/1	4/2	1/0	2	24
CT8–CT10	3/1	2/2	0/0	3/1	5/2	4/1	4	21

e? number of patients, which efficacy could not be determined, because the treatment stopped before the first evaluation

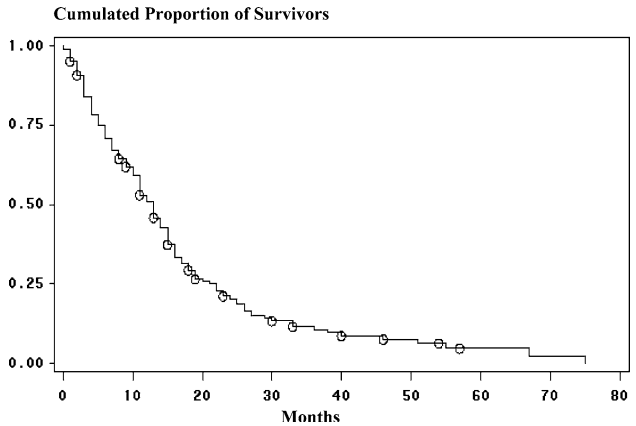

Fig. 1 Overall Survival from the third line. The D0 is the beginning of the third line of chemotherapy

therapy, soft tissue metastasis, non-progression at CT1 and/or CT2, duration of non-progression ≥6 months after CT1 and/or CT2, polychemotherapy for CT2, complete or major partial response at CT1 and/or CT2, duration of response to CT1 and type of CT3), multivariate analysis retained only two variables as significantly predictive of non-progression at CT3: histology ($p = 0.004$) and drug group used for CT3 ($p = 0.002$). Thus, infiltrative ductal carcinoma was more chemosensitive in our series than other histology types (infiltrative lobular carcinoma and others). The subgroups of chemotherapy drugs found to be the most effective, even for CT3, were, in decreasing order of efficacy: anthracyclines, taxanes, and 5-FU. In all, 23 patients achieved complete response. Anthracycline or taxane CT yielded complete response in 14 patients, after CT1 ($n = 9$), CT2 ($n = 2$), CT3 ($n = 1$), CT4 ($n = 1$), and CT6 ($n = 1$). Some patients who achieved complete response with these drug groups had several metastatic foci. 5-FU or vinca-alkaloid CT yielded complete response in nine patients after CT1 ($n = 3$), CT3 ($n = 3$), and CT4 ($n = 3$). All nine of these patients had a unique metastasis. Anthracycline or taxane regimens were more effective with a better rate of non-progression, even beyond CT3, even in patients who had already received two successive lines, and even after early progression.

Table 4 Univariate analysis of factors potentially affecting outcome after CT3

Factors tested/reference	Univariate analysis		
	n	RR [CI 95%]	*p*
Age at diagnosis ≥50/<50ans	162	1.49 [1.06–2.09]	0.0212
N1/N0	162	1.13 [0.99–1.28]	0.066
SBR grade	117	1.49 [1.11–2.00]	0.0085
SBR II and III/I	117	2.43 [1.22–4.85]	0.0123
Type of adjuvant chemotherapy	162	1.21 [1.04–1.41]	0.0151
Adjuvant hormone therapy	161	1.43 [0.99–2.08]	0.060
Recurrence-free survival ≥2/<2 years	162	0.64 [0.46–0.90]	0.0093
Metastasis focus before CT1			
Organ	162	1.44 [1.02–2.02]	0.037
Cerebromeningeal	162	2.60 [0.95–7.07]	0.06
Liver	162	1.47 [1.03–2.10]	0.0318
Metastasis focus before CT3			
Organ	162	1.58 [1.10–2.26]	0.0137
Cerebromeningeal	162	1.93 [1.19–3.15]	0.0082
Liver	162	1.37 [0.98–1.92]	0.0677
Unique metastasis before CT3	162	0.63 [0.42–0.96]	0.0294
Non-progression CT1 CT2	156	0.72 [0.60–0.87]	0.0006
Polychemotherapy	162	0.71 [0.56–0.91]	0.0066
Polychemotherapy CT2	162	0.68 [0.45–1.01]	0.0571
Complete response	162	0.49 [0.29–0.82]	0.0064
Time from CT1 to CT3	162	0.98 [0.97–0.99]	0.0083

Discussion

The purpose of this retrospective analysis was to determine which patients could be expected to benefit from

Table 5 Multivariate analysis of factors potentially affecting survival from CT3

Factors tested/reference	Multivariate analysis	
	RR [CI 95%]	*p*
SBR II and III/I	4.29 [1.56–11.78]	0.0047
Adjuvant hormone therapy	2.87 [1.58–5.22]	0.0006
Recurrence-free survival ≥2/<2 years	0.38 [0.21–0.66]	0.0008
Cerebromeningeal metastasis before CT1	18.6 [1.21–287.7]	0.036
Unique metastasis before CT3	0.42 [0.22–0.80]	0.0089
Polychemotherapy CT2	0.29 [0.10–0.84]	0.0227
Complete response	0.25 [0.09–0.74]	0.0124

chemotherapy beyond the second line. Factors with prognostic power and predictive of response to chemotherapy after the third line and beyond were thus analyzed to obtain objective evidence.

Several biases related to study design must, however, be examined.

First, this single-center study selected patients who had received at least three chemotherapy lines during the 5-year study period (2000–2004). Patients given hormone therapy alone during this period and patients who were given only two lines of chemotherapy could have a poor performance status and/or a chemoresistance. Furthermore, as our study was retrospective, missing data produced an analysis bias. Sample size was also small for some subgroups; e.g., only 4 patients had brain metastases before CT1, 14 before CT2 and 20 before CT3. Standard protocols were not used for CT1 and CT2, so that very heterogeneous regimens were delivered. Similarly, the referring physician often provided the outcome assessment (PD or NPD), leading to another bias since many lesions were non-measurable: bone metastasis or isolated effusion is frequent in breast cancer. Toxicity was not evaluated, precisely because this was a retrospective study.

This was nevertheless a study of real life clinical practices.

Median age of our population was 53 years at diagnosis of metastasis, comparable with other large retrospective studies in the literature [8, 9], or large-scale randomized-controlled trials of first-line metastasis patients. None of our patients were older than 72 years at diagnosis of breast cancer and none were older than 79 years at diagnosis of metastasis. The fact that our series did not include old patients is remarkable and may be an expression of physicians' reluctance to propose chemotherapy for elderly women, particularly a third line.

Recurrence-free survival was longer, 32 months, than the 18–19 months reported in retrospective series and the 20–26 months observed in randomized [10, 11]. Our recruitment bias might have had an effect here; the inclusion of women who had received at least three chemotherapy lines may have selected patients with less progressive disease, or who were at least more sensitive to treatment. The disease would have been more progressive earlier in the other patients who thus were not eligible for third-line chemotherapy. In our series, the median survival from the diagnosis of metastasis was 3 years, comparable with recently published series reporting a median survival in the 1.5–3.5 years range [4, 12]. The median survival, counting from CT3, was 13 months, comparable to the paclitaxel trial after failure of two anthracycline and taxane line [4, 13]. Our analysis also recalled the efficacy of taxane chemotherapy, even in patients who had had prior treatments [14]. Survival rates differed from CT3 between the NPD and PD groups.

The efficacy and safety profiles of chemotherapy protocols used for breast cancer have been described basically for first- and second-line treatments. Therapeutic protocols, especially those using new compounds, generally exclude patients who have already received two lines of chemotherapy. There have nevertheless been a few phase II and III trials which have included CT3 patients [13, 15] in order to assess the efficacy and safety of new drugs. Elsewhere, treatments proposed for patients with metastatic disease are generally grouped together (chemotherapy, hormone therapy, both) with a median of three different lines of treatment [12]. Reviewing the CT lines delivered showed that a large number of different regimens and lines had been delivered. The highest line was CT3 in 52 patients, but 9 patients had reached CT9, and 3 had CT10. The rate of response and non-progression was good beyond CT3, and even after CT5 or CT6 the rate of non-progression remained high.

Multivariate analysis identified the seven following factors as having a positive effect on survival from CT3.

- SBR grade I is a recognized factor predictive of good outcome after [16, 17].
- A long interval, greater than 2 years, between the diagnosis of breast cancer and metastatic relapse also favors good prognosis after CT1 [18, 19].
- The absence of adjuvant hormone therapy in our study, irrespective of the status of hormone receptors, had a positive influence on survival. The metastatic recurrence despite adjuvant hormone therapy might signal more aggressive disease.
- Survival is also known to be mediocre in patients with cerebromeningeal metastasis [17, 20], despite the lack of adequate analysis since most therapeutic trials exclude these patients because of their low life expectancy. We found a similar trend in our series with a small number of patients.

- For metastases to other organs, spread to the liver is known to associated with poor prognosis after [14, 19], similarly for two metastatic foci [16, 19]. From CT3, liver involvement does not appear to affect survival as it was not affected at multivariate analysis, unlike multiple metastatic foci.
- According to the literature [21, 22], survival after CT1 for metastatic disease would be better with a combination regimen, although a sequential protocol can also be proposed for the first two lines [23, 24]. In our series, the positive impact of polychemotherapy regimens on survival from CT3 was only apparent at CT2, probably because the majority of the patients had responded to CT1 using single or multiple drug regimens. But since quality-of-life is a priority for metastasis patients, those for whom a multiple drug CT2 would have been proposed probably had a good general status and could be expected to tolerate a more aggressive treatment; otherwise, it may have proposed for patients with a rapidly progressing disease who needed an aggressive treatment to achieve rapid response.
- Complete response to the first lines of chemotherapy favored longer survival from CT3, as has been demonstrated in series of long survivors after CT1 [21, 22]. Here again, this is probably related to the disease per se: the tumor being more sensitive to chemotherapy, and to the therapeutic attitude, more aggressive treatments would be proposed for relapse if the first line had produced complete response.

Table 6 Factors significantly affecting survival after first-line chemotherapy: multivariate analyses in the literature

Authors	Significant prognostic factors at multivariate analysis
Pierga et al. [16]	Adjuvant chemotherapy
	Recurrence-free survival
	Karnofsky index ≤60
	Number of metastatic foci
	Metastatic foci (liver, lung)
	Blood tests: LDH >1 N
Pierga et al. [17]	Adjuvant chemotherapy
	Recurrence-free survival
	Karnofsky index ≤60
	Number of metastatic foci
	Metastatic foci (liver)
	Quality of response
	Blood tests: LDH >1 N
Insa et al. [18]	Number of positive lymph nodes
	Status of hormone receptors
	Recurrence-free survival
	Soft tissue and bone metastases
Yamamoto et al. [19]	Adjuvant chemotherapy
	Recurrence-free survival
	Metastatic foci (nodes, liver)
	Blood tests: LDH >1 N

Factors in bold were also found in the present study beyond the second-line chemotherapy

Multivariate analyses performed on other series in the literature have retained several factors as having a significant effect on survival after CT1 (Table 6). Data on certain significant factors, such as the Karnofsky index and LDH level, were not collected in our study. Most of the other factors identified elsewhere were also recognized by our multivariate analysis. Beyond the factors related to the disease per se, we also identified factors related to the therapy delivered. In our analysis, the only factor retained by multivariate analysis as significant was complete response after CT1 or CT2.

There are many reports in the literature relating factors of response or resistance to first-line anthracycline chemotherapy for metastatic disease, but data on prognostic factors for CT3 are scarce. In clinical practice, when a patient is considered for CT3, the physician is confronted with two major decisions. First, should chemotherapy be proposed, considering the potential risk of toxicity and the psychological impact of abstention [25, 26]? And if the decision is made to treat, how aggressive should the treatment be? In the present state-of-the-art, it is difficult to choose a treatment on the basis of prognostic factors determined for CT1. Data in the literature fail to provide any insight for CT3 since the majority of the published trials devoted to CT2 were small-scale, non-comparative, and limited, evaluating only the feasibility of monotherapy or a combination of several cytotoxic agents used in a phase II setting in patients with a very good general status [13, 15, 27–29]. Several studies have demonstrated a positive effect of chemotherapy on quality-of-life and symptom relief [30, 31] even for CT3 [32], although the assessment of quality-of-life is difficult [33, 34]. Our results not only confirmed certain well-known prognostic elements such as delay before development of metastasis and SBR grade, but also disclosed certain factors which would argue in favor of proposing CT3, i.e., use of polychemotherapy regimen for CT2 and complete response before CT3. The factors the most predictive of non-progression at CT3 were the histological type (infiltrating ductal carcinoma), and the chemotherapy regimen (anthracycline, taxanes, 5FU).

While awaiting further diagnostic and therapeutic advances, which will certainly have an important impact not only on early treatments, but also on management practices later on in the disease course [35, 36], clinicians should find our data, notably the seven prognostic factors,

useful in better apprehending the appropriateness of proposing chemotherapy beyond the second line for metastatic breast cancer.

Conclusion

Metastatic breast cancer presents a complex therapeutic challenge, particularly after the first two lines of chemotherapy. In our experience with 467 patients given chemotherapy for metastatic breast cancer from 2000 to 2004, 162 received at least one third-line chemotherapy protocol and 71 received at least five chemotherapy lines. It would be reasonable to propose CT3 in a targeted population with a good chance of response or stability. In our series, two factors were predictive of response and seven had a positive influence on survival from CT3. Thus, a patient with infiltrating ductal carcinoma who responded well to prior treatments could be given a third-line chemotherapy regimen using anthracyclines or taxanes. On the contrary, it would be less reasonable to propose a supplementary chemotherapy for patients with cerebromeningeal metastases before the first-line chemotherapy, with multiple metastatic foci before the third-line chemotherapy, or who exhibited resistance to the first two chemotherapy regimens. The final decision will nevertheless be a joint decision made by the patient and the physician, relying heavily on the sound relationship established since the initial contact.

A prospective study devoted to the therapeutic strategy for metastatic breast cancer will be needed to confirm the present findings.

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