



HAL
open science

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

Elodie Vauléon, Habiba Mesbah, Brigitte Laguerre, Daniel Gédouin, Claudia Lefeuvre-Plesse, Jean Levêque, Odile Audrain, Pierre Kerbrat

► To cite this version:

Elodie Vauléon, Habiba Mesbah, Brigitte Laguerre, Daniel Gédouin, Claudia Lefeuvre-Plesse, et al.. Usefulness of chemotherapy beyond the second line for metastatic breast cancer: a therapeutic challenge. *Cancer Chemotherapy and Pharmacology*, 2009, 66 (1), pp.113-120. 10.1007/s00280-009-1141-3. hal-00568272

HAL Id: hal-00568272

<https://hal.science/hal-00568272>

Submitted on 23 Feb 2011

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

Usefulness of chemotherapy beyond the second line for metastatic breast cancer

A therapeutic challenge

Elodie Vauléon^{1,2}, Habiba Mesbah³, Brigitte Laguerre¹, Daniel Gédouin¹, Claudia Lefeuvre-Plesse¹, Jean Levêque^{2,4}, Odile Audrain³, Pierre Kerbrat^{1,2}

¹ Département of Medical Oncology, Comprehensive Cancer Center, E Marquis, CS 44229, 35042 Rennes cedex France

² European University in Brittany, Rennes

³ Département of Medical Information, Comprehensive Cancer Center, E Marquis, CS 44229, 35042 Rennes cedex France

⁴ Département of Surgery, Comprehensive Cancer Center, E Marquis, CS 44229, 35042 Rennes cedex France

Corresponding author: Elodie Vauléon, Département d'Oncologie, Centre Eugène Marquis, Avenue de la Bataille Flandres Dunquerque, 35042 Rennes Cedex, France - tel. 33-2-99-25-30-00 ; e.vauleon@rennes.fnclcc.fr

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 three lines of chemotherapy (CT3) for metastatic breast cancer during a 5-year period (2000 to 2004), in order to analyze management practices and search for factors affecting survival from CT3 and predictive factors of non-progressive disease 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 ≥ 2 years, absence of cerebrospinal 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 non-progressive disease (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

Introduction

According to the 2006 figures, breast cancer is the most common tumor in women worldwide, and the leading cause of death by cancer [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, are 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 January 1, 2000 and December 31, 2004. The following inclusion criteria were applied: female patient, age 18 years or over, breast cancer, delivery of at least one systemic chemotherapy protocol beyond line two (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's 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 \pm 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 (t_0). 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 7 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.

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 analysis 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, non progressive disease 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 line (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 analysis of factors predictive of non-progression after CT3

From the ten variables significant at univariate analysis (histology, no metastasis at diagnosis, no adjuvant hormone 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 9 patients after CT1 ($n=3$), CT3 ($n=3$), and CT4 ($n=3$). All 9 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.

Discussion

The purpose of this retrospective analysis was to determine which patients could be expected to benefit from 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 five-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; for example only four 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 are 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 [8,16], 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 [17,19]. 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 to 3.5 years range [20-21]. The median survival, counting from CT3 was 13 months, comparable to the paclitaxel trial after failure of two anthracycline and taxane line [22-23]. Our analysis also recalled the efficacy of taxane chemotherapy, even in patients who had had prior treatments [24]. 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 [25,32] 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 3 different lines of treatment [33]. 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 7 following factors as having a positive effect on survival from CT3.

-SBR grade I is a recognized factor predictive of good outcome after [34-35].

-A long interval, greater than 2 years, between the diagnosis of breast cancer and metastatic relapse also favors good prognosis after CT1[36-37].

-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 cerebro meningeal metastasis [38-39], 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 [40,43], similarly for two metastatic foci [44-45]. 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 [46-47] 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 [48,50]. 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 [51-52]. 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.

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 [53-54] ? 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 [55,58, 59, 60,61]. Several studies have demonstrated a positive effect of chemotherapy on quality-of-life and symptom relief [62-63] even for CT3 [64], although the assessment of quality-of-life is difficult [65-66]. Our results 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 [67-68] 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 7 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.

Fig 1. Overall Survival from the third line.

The D0 is the beginning of the 3rd line of chemotherapy.

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

	n	%
Median age [range]	49 yrs [26-72]	
Mean age \pm standard deviation	48.8 \pm 10.5 yrs	
Hormone status		
Menopause	74	54%
Not menopausal 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 months ± 58.9	
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%

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 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 to 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

Table 4. Univariate analysis of factors potentially affecting outcome after CT3.

Factors tested / reference	Univariate analysis		
	n	RR [IC 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 / <2ys	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

Table 5. Multivariate analysis of factors potentially affecting survival from CT3.

Factors tested / reference	Multivariate analysis	
	RR [IC 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 / <2yrs	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

Table 6. Factors significantly affecting survival after first line chemotherapy: multivariate analyses in the literature. Factors in bold print were also found in the present study beyond the second line chemotherapy.

Authors	Significant prognostic factors at multivariate analysis
Pierga. JY and al (14)	<ul style="list-style-type: none"> -adjuvant chemotherapy -recurrence-free survival -Karnofsky index \leq 60 -number of metastatic foci -metastatic foci (liver. lung) -blood tests: LDH > 1N
Pierga. JY and al (15)	<ul style="list-style-type: none"> - adjuvant chemotherapy - recurrence-free survival - Karnofsky index \leq 60 - number of metastatic foci - metastatic foci (liver) -quality of response - blood tests: LDH > 1N
Insa. A. and al (13)	<ul style="list-style-type: none"> -number of positive lymph nodes -status of hormone receptors - recurrence-free survival - soft tissue and bone metastases
Yamamoto. N. and al (30)	<ul style="list-style-type: none"> - adjuvant chemotherapy - recurrence-free survival -metastatic foci (nodes. liver) - blood tests: LDH > 1N

References

1. Parkin DM, Bray F, Ferlay J et al (2001) Estimating the world cancer burden: Globocan 2000. *Int J Cancer* 94:153-6.
2. Parkin DM(2001) Global cancer statistics in the year 2000. *Lancet Oncol* 2:533-43.
3. Kerbrat P, Botton E (2007) Soins palliatifs : peut-on parler de qualité de vie en phase métastatique ? In: Serin D, de Rauglaudre G, eds. *Cancer du sein avancé : 29es Journées de la Société Française de Sénologie et Pathologie Mammaire (SFSPM) Avignon, 14–16 novembre 2007*. Paris: pp. 181-189.
4. Tacca O, LeHeurteur M, Durando X et al (2009) Metastatic breast cancer: overall survival related to successive chemotherapies. What do we gain after the third line ? *Cancer Invest* 27:81-5.
5. Bergh J, Jonsson PE, Glimelius B et al (2001) A systematic overview of chemotherapy effects in breast cancer. *Acta Oncol* 40:253-81.
6. Carrick S, Parker S, Wilcken N et al (2005) Single agent versus combination chemotherapy for metastatic breast cancer. *Cochrane Database Syst Rev* CD003372.
7. Anonymous (2007) Recommandations pour la pratique clinique : Cancers du Sein, Saint-Paul de Vence 2007. Available from URL.<http://cours-saint-paul.fr/10/recommandations.html>
8. A'Hern RP, Smith IE, Ebbs SR(1993) Chemotherapy and survival in advanced breast cancer: the inclusion of doxorubicin in Cooper type regimens. *Br J Cancer* 67:801-5.
9. Andre F, Slimane K, Bachelot T et al (2004) Breast cancer with synchronous metastases: trends in survival during a 14-year period. *J Clin Oncol* 22:3302-8.
10. Clark GM, Sledge GW, Jr., Osborne CK et al (1987) Survival from first recurrence: relative importance of prognostic factors in 1,015 breast cancer patients. *J Clin Oncol* 5:55-61.
11. Greenberg PA, Hortobagyi GN, Smith TL et al (1996) Long-term follow-up of patients with complete remission following combination chemotherapy for metastatic breast cancer. *J Clin Oncol* 14:2197-205.
12. Hortobagyi GN, Smith TL, Legha SS et al (1983) Multivariate analysis of prognostic factors in metastatic breast cancer. *J Clin Oncol* 1:776-86.
13. Insa A, Lluch A, Prosper F et al (1999) Prognostic factors predicting survival from first recurrence in patients with metastatic breast cancer: analysis of 439 patients. *Breast Cancer Res Treat* 56:67-78.
14. Pierga JY, Robain M, Jouve M et al (2001) Response to chemotherapy is a major parameter-influencing long-term survival of metastatic breast cancer patients. *Ann Oncol* 12:231-7.
15. Pierga JY, Asselain B, Jouve M et al (2001) Effect of adjuvant chemotherapy on outcome in patients with metastatic breast carcinoma treated with first-line doxorubicin-containing chemotherapy. *Cancer* 91:1079-89.
16. Pivot X, Asmar L, Buzdar AU et al (2000) A unified definition of clinical anthracycline resistance breast cancer. *Br J Cancer* 82:529-34.
17. Crown J, O'Leary M, Ooi WS(2004) Docetaxel and paclitaxel in the treatment of breast cancer: a review of clinical experience. *Oncologist* 9 Suppl 2:24-32.

18. Martin M, Pienkowski T, Mackey J et al (2003) TAC improves disease free survival and overall survival over FAC in node positive early breast cancer patients, BCIRG 001: 55 months follow-up. *Breast Cancer Res Treat* 82:Abstract 43.
19. Nabholz JM, Falkson C, Campos D et al (2003) Docetaxel and doxorubicin compared with doxorubicin and cyclophosphamide as first-line chemotherapy for metastatic breast cancer: results of a randomized, multicenter, phase III trial. *J Clin Oncol* 21:968-75.
20. Porkka K, Blomqvist C, Rissanen P et al (1994) Salvage therapies in women who fail to respond to first-line treatment with fluorouracil, epirubicin, and cyclophosphamide for advanced breast cancer. *J Clin Oncol* 12:1639-47.
21. Tacca O, LeHeurteur M, Durando X et al (2009) Metastatic breast cancer: overall survival related to successive chemotherapies. What do we gain after the third line ? *Cancer Invest* 27:81-5.
22. Perez EA, Vogel CL, Irwin DH et al (2001) Multicenter phase II trial of weekly paclitaxel in women with metastatic breast cancer. *J Clin Oncol* 19:4216-23.
23. Tacca O, LeHeurteur M, Durando X et al (2009) Metastatic breast cancer: overall survival related to successive chemotherapies. What do we gain after the third line ? *Cancer Invest* 27:81-5.
24. Atalay G, Biganzoli L, Renard F et al (2003) Clinical outcome of breast cancer patients with liver metastases alone in the anthracycline-taxane era: a retrospective analysis of two prospective, randomised metastatic breast cancer trials. *Eur J Cancer* 39:2439-49.
25. Al-Batran SE, Bischoff J, von MG et al (2006) The clinical benefit of pegylated liposomal doxorubicin in patients with metastatic breast cancer previously treated with conventional anthracyclines: a multicentre phase II trial. *Br J Cancer* 94:1615-20.
26. Blum JL, Jones SE, Buzdar AU et al (1999) Multicenter phase II study of capecitabine in paclitaxel-refractory metastatic breast cancer. *J Clin Oncol* 17:485-93.
27. Fumoleau P, Delgado FM, Delozier T et al (1993) Phase II trial of weekly intravenous vinorelbine in first-line advanced breast cancer chemotherapy. *J Clin Oncol* 11:1245-52.
28. Fumoleau P, Chevallier B, Kerbrat P et al (1996) A multicentre phase II study of the efficacy and safety of docetaxel as first-line treatment of advanced breast cancer: report of the Clinical Screening Group of the EORTC. *Ann Oncol* 7:165-71.
29. Jones SE, Erban J, Overmoyer B et al (2005) Randomized phase III study of docetaxel compared with paclitaxel in metastatic breast cancer. *J Clin Oncol* 23:5542-51.
30. Keller AM, Mennel RG, Georgoulas VA et al (2004) Randomized phase III trial of pegylated liposomal doxorubicin versus vinorelbine or mitomycin C plus vinblastine in women with taxane-refractory advanced breast cancer. *J Clin Oncol* 22:3893-901.
31. O'Shaughnessy J, Miles D, Vukelja S et al (2002) Superior survival with capecitabine plus docetaxel combination therapy in anthracycline-pretreated patients with advanced breast cancer: phase III trial results. *J Clin Oncol* 20:2812-23.
32. Perez EA, Vogel CL, Irwin DH et al (2001) Multicenter phase II trial of weekly paclitaxel in women with metastatic breast cancer. *J Clin Oncol* 19:4216-23.
33. Porkka K, Blomqvist C, Rissanen P et al (1994) Salvage therapies in women who fail to respond to first-line treatment with fluorouracil, epirubicin, and cyclophosphamide for advanced breast cancer. *J Clin Oncol* 12:1639-47.
34. Pierga JY, Robain M, Jouve M et al (2001) Response to chemotherapy is a major parameter-influencing long-term survival of metastatic breast cancer patients. *Ann Oncol* 12:231-7.

35. Pierga JY, Asselain B, Jouve M et al (2001) Effect of adjuvant chemotherapy on outcome in patients with metastatic breast carcinoma treated with first-line doxorubicin-containing chemotherapy. *Cancer* 91:1079-89.
36. Insa A, Lluch A, Prosper F et al (1999) Prognostic factors predicting survival from first recurrence in patients with metastatic breast cancer: analysis of 439 patients. *Breast Cancer Res Treat* 56:67-78.
37. Yamamoto N, Watanabe T, Katsumata N et al (1998) Construction and validation of a practical prognostic index for patients with metastatic breast cancer. *J Clin Oncol* 16:2401-8.
38. Ahmann FR, Jones SE, Moon TE (1988) The effect of prior adjuvant chemotherapy on survival in metastatic breast cancer. *J Surg Oncol* 37:116-22.
39. Pierga JY, Asselain B, Jouve M et al (2001) Effect of adjuvant chemotherapy on outcome in patients with metastatic breast carcinoma treated with first-line doxorubicin-containing chemotherapy. *Cancer* 91:1079-89.
40. Atalay G, Biganzoli L, Renard F et al (2003) Clinical outcome of breast cancer patients with liver metastases alone in the anthracycline-taxane era: a retrospective analysis of two prospective, randomised metastatic breast cancer trials. *Eur J Cancer* 39:2439-49.
41. Greenberg PA, Hortobagyi GN, Smith TL et al (1996) Long-term follow-up of patients with complete remission following combination chemotherapy for metastatic breast cancer. *J Clin Oncol* 14:2197-205.
42. Perez EA, Vogel CL, Irwin DH et al (2001) Multicenter phase II trial of weekly paclitaxel in women with metastatic breast cancer. *J Clin Oncol* 19:4216-23.
43. Yamamoto N, Watanabe T, Katsumata N et al (1998) Construction and validation of a practical prognostic index for patients with metastatic breast cancer. *J Clin Oncol* 16:2401-8.
44. Pierga JY, Robain M, Jouve M et al (2001) Response to chemotherapy is a major parameter-influencing long-term survival of metastatic breast cancer patients. *Ann Oncol* 12:231-7.
45. Yamamoto N, Watanabe T, Katsumata N et al (1998) Construction and validation of a practical prognostic index for patients with metastatic breast cancer. *J Clin Oncol* 16:2401-8.
46. Gennari A, Conte P, Rosso R et al (2005) Survival of metastatic breast carcinoma patients over a 20-year period: a retrospective analysis based on individual patient data from six consecutive studies. *Cancer* 104:1742-50.
47. Greenberg PA, Hortobagyi GN, Smith TL et al (1996) Long-term follow-up of patients with complete remission following combination chemotherapy for metastatic breast cancer. *J Clin Oncol* 14:2197-205.
48. Conte PF, Guarneri V, Bruzzi P et al (2004) Concomitant versus sequential administration of epirubicin and paclitaxel as first-line therapy in metastatic breast carcinoma: results for the Gruppo Oncologico Nord Ovest randomized trial. *Cancer* 101:704-12.
49. Joensuu H, Holli K, Heikkinen M et al (1998) Combination chemotherapy versus single-agent therapy as first- and second-line treatment in metastatic breast cancer: a prospective randomized trial. *J Clin Oncol* 16:3720-30.
50. Miles D, von MG, Seidman AD (2002) Combination versus sequential single-agent therapy in metastatic breast cancer. *Oncologist* 7 Suppl 6:13-9.
51. Gennari A, Conte P, Rosso R et al (2005) Survival of metastatic breast carcinoma patients over a 20-year period: a retrospective analysis based on individual patient data from six consecutive studies. *Cancer* 104:1742-50.
52. Greenberg PA, Hortobagyi GN, Smith TL et al (1996) Long-term follow-up of patients with complete remission following combination chemotherapy for metastatic breast cancer. *J Clin Oncol* 14:2197-205.

53. McQuellon RP, Muss HB, Hoffman SL et al (1995) Patient preferences for treatment of metastatic breast cancer: a study of women with early-stage breast cancer. *J Clin Oncol* 13:858-68.
54. Slevin ML, Plant H, Lynch D et al (1988) Who should measure quality of life, the doctor or the patient? *Br J Cancer* 57:109-12.
55. Al-Batran SE, Bischoff J, von MG et al (2006) The clinical benefit of pegylated liposomal doxorubicin in patients with metastatic breast cancer previously treated with conventional anthracyclines: a multicentre phase II trial. *Br J Cancer* 94:1615-20.
56. Blum JL, Jones SE, Buzdar AU et al (1999) Multicenter phase II study of capecitabine in paclitaxel-refractory metastatic breast cancer. *J Clin Oncol* 17:485-93.
57. Fumoleau P, Delgado FM, DeLozier T et al (1993) Phase II trial of weekly intravenous vinorelbine in first-line advanced breast cancer chemotherapy. *J Clin Oncol* 11:1245-52.
58. Perez EA, Vogel CL, Irwin DH et al (2001) Multicenter phase II trial of weekly paclitaxel in women with metastatic breast cancer. *J Clin Oncol* 19:4216-23.
59. Jones S, Winer E, Vogel C et al (1995) Randomized comparison of vinorelbine and melphalan in anthracycline-refractory advanced breast cancer. *J Clin Oncol* 13:2567-74.
60. Keller AM, Mennel RG, Georgoulas VA et al (2004) Randomized phase III trial of pegylated liposomal doxorubicin versus vinorelbine or mitomycin C plus vinblastine in women with taxane-refractory advanced breast cancer. *J Clin Oncol* 22:3893-901.
61. O'Shaughnessy JA, Blum J, Moiseyenko V et al (2001) Randomized, open-label, phase II trial of oral capecitabine (Xeloda) vs. a reference arm of intravenous CMF (cyclophosphamide, methotrexate and 5-fluorouracil) as first-line therapy for advanced/metastatic breast cancer. *Ann Oncol* 12:1247-54.
62. Coates AS, Humy C, Peterson HF et al (2000) Quality-of-life scores predict outcome in metastatic but not early breast cancer. International Breast Cancer Study Group. *J Clin Oncol* 18:3768-74.
63. Geels P, Eisenhauer E, Bezjak A et al (2000) Palliative effect of chemotherapy: objective tumor response is associated with symptom improvement in patients with metastatic breast cancer. *J Clin Oncol* 18:2395-405.
64. McLachlan SA, Pintilie M, Tannock IF (1999) Third line chemotherapy in patients with metastatic breast cancer: an evaluation of quality of life and cost. *Breast Cancer Res Treat* 54:213-23.
65. Carlson RW (1998) Quality of life issues in the treatment of metastatic breast cancer. pp. 27-31.
66. Waldron D, O'Boyle CA, Kearney M et al (1999) Quality-of-life measurement in advanced cancer: assessing the individual. *J Clin Oncol* 17:3603-11.
67. Rouzier R, Wagner P, Morandi P et al (2005) Gene expression profiling of primary breast cancer. *Curr Oncol Rep* 7:38-44.
68. Rouzier R, Perou CM, Symmans WF et al (2005) Breast cancer molecular subtypes respond differently to preoperative chemotherapy. *Clin Cancer Res* 11:5678-85.

Cumulated Proportion of Survivors