Which patients with metastatic breast cancer benefit from subsequent lines of treatment? An update for clinicians

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Abstract: The outcome of patients with metastatic breast cancer (MBC) has clearly improved over the past decades and the proportion of women living with their disease for several years is increasing. However, the usefulness of multiple lines of treatment is still debated and under evaluation. The available data from both randomized trials and large retrospective series are reviewed and discussed in order to analyze management practices, with emphasis on potential prognostic and predictive factors for clinical outcome. At present, evidence-based medicine provides some support for the use of second-line and to a lesser degree and in selected cases, third-line chemotherapy in human epidermal growth factor receptor 2 (HER2) negative MBC. Beyond third-line treatment, messages from recently reported retrospective studies also suggest a clear potential gain for women receiving further therapies after disease progression, since each line can contribute to a longer survival. In HER2-positive disease, the data from observational and retrospective studies support a clinical benefit from the use of trastuzumab beyond disease progression and emerging evidences from randomized controlled trials are leading to the introduction of newer HER2-targeted therapies in multiple lines. The question 'How many lines of treatment should we give patients?' clearly needs further research through prospective, high-quality clinical trials, aiming for a better definition of factors with prognostic and predictive role. In the meantime, the 'optimal' treatment strategy should probably be to use as many therapeutic options as possible, either in sequence or combination, to keep the best efficacy/toxicity balance, considering MBC as a chronic disease.

Keywords: chemotherapy, metastatic breast cancer, HER2-targeted therapies, subsequent lines, survival benefit

Introduction

Although many advances have been achieved over the past two decades in terms of both efficacy and tolerability of treatments, the prognosis of women with metastatic breast cancer (MBC) remains poor and therapeutic goals are palliative in nature [Chung and Carlson, 2003; Jones, 2008]. Data from population-based studies and analysis of clinical trials show that the outcome of MBC women is slowly but steadily improving, as risk of death is decreasing by 1–2% each year [Andre *et al*. 2004; Giordano *et al*. 2004] and median overall survival (OS) has increased from 18 to 24 months in recent years [Dawood *et al*. 2008; Mauri *et al*. 2008; Gennari *et al*. 2011]. It is possibly the greatest improvement to be related to the development and widespread availability of modern systemic therapies, with increased response rate, progression-free-survival (PFS) and/or OS [O'Shaughnessy, 2005; Gennari *et al*. 2005; Chia *et al*. 2007; Dawood *et al*. 2010].

Once first-line treatment of MBC has failed, management becomes even more challenging, and there is a general consensus that the benefit of second and subsequent lines of chemotherapy is uniformly poor [Cardoso *et al*. 2002; Jones, 2008; Roché and Vahdat, 2011]. However, MBC is a heterogeneous disease that exhibits a variety of different clinical scenarios, ranging from

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solitary metastatic lesions to diffuse multiple organ involvement. The ideal therapeutic approach to MBC should be highly individualized, and several disease- and patient-related factors must be taken into account in the selection of treatment [Pagani *et al.* 2010]. Classically, oncologists rely on the results of clinical trials when deciding which therapy is most likely to be beneficial for their patients following first-line strategy failure. However, nearly all trials focus on the comparison of specific drugs in preselected groups of patients, in certain situations and at certain point of time; the benefits of treatment have been evaluated by the response to first and second-line therapy, not directly on the different factors compounding all median OS [Fossati *et al.* 1998; Cardoso *et al.* 2002]. Finally, most of them have a relatively short follow up, so little is known about the impact on outcome and the exact proportion of long-term survivors. The truth, beyond the clinical trials, is that many MBC women do not fit the profile of clinical studies participants; they live with their disease for several years and receive a variety of therapies until death. In routine clinical practice, an increasing proportion of MBC patients ask for further treatment at disease progression. The most challenging question for clinicians remains 'which therapy to which patients for which benefit?'

Aiming to bring our contribution to such a debated issue, in this paper the available data supporting the benefit of subsequent treatment lines in MBC are presented and discussed in order to analyze management practices, with emphasis on potential prognostic and predictive factors for clinical outcome.

Chemotherapy beyond first line

The evidence-based lesson: an update from randomized phase III trials

Compared with the hundreds of randomized phase III studies investigating first-line treatment strategy in MBC, only 22 published trials specifically addressed the role of multiple chemotherapy lines. A total of 9423 women with human epidermal growth factor receptor 2 (HER2) negative disease were included: 5771 of them received a second-line treatment, 1567 a third-line, 308 a fourth-line and 178 ≥5 lines (Table 1).

It is not so easy to underline the common features of the available studies: they have a 20-year history, and during this period deep changes took place in the fields of molecular and genetic characterization, pharmacology and study endpoints, and also in the expectations of clinicians and patients. Despite this, their lessons remain crucial because they define the best standard of care in this setting on the basis of (almost) strong evidence. Some key points can be underlined.

There are drugs, as single agents or in combinations, which are able to prolong survival in women with advanced/metastatic disease when treated beyond the second-line. An improved OS with experimental treatment can be observed in 7 out of 22 studies [Jones *et al.* 1995, 2005; Nabholtz *et al.* 1999; O' Shaughnessy *et al.* 2002; Icli *et al.* 2005; Gradishar *et al.* 2005; Jones *et al.* 2005; Cortes *et al.* 2011]. Interestingly, when significant, survival gain is similar among the agents in study, ranging from 2 to 5 months. Since many patients receive further lines of therapy beyond the one in study, we could argue that the advantage in survival gained from a successful line is not always diluted by subsequent treatments.

None of the five randomized studies comparing anthracyclines (doxorubicin, epirubicin, pegylated liposomal doxorubicin) *versus* other drugs reached the statistical significance for the end points of response rate (RR), time to progression (TTP) and OS, suggesting a minor role for anthracycline in the therapeutic strategy of pretreated MBC patients [Henderson *et al.* 1989; Bontenbal *et al.* 1998; Joensuu *et al.* 1998; Norris *et al.* 2000; Keller *et al.* 2004].

Among the newer classes of antineoplastic agents, the epothilones were the most extensively investigated through two recently reported large phase III studies involving 1973 women with MBC. The addition of ixabepilone to capecitabine improved PFS and RR compared with capecitabine alone in second, third and fourth-line of treatment, but no significant benefit in OS was reached [Thomas *et al.* 2007; Hortobagyi *et al.* 2010; Sparano *et al.* 2010]. A recently reported Q-TWiST analysis of the first trial showed a positive risk–benefit ratio for the combination compared with the single agent arm, with quality-adjusted survival values of 42.2 *versus* 38.4 weeks, respectively, despite the potential for added toxicities [Corey-Lisle *et al.* 2012].

The role of anti-vascular endothelial growth factor (VEGF) drugs in lines of treatment beyond

Table 1. Randomized phase III studies: second and subsequent treatment lines in metastatic breast cancer (MBC).

Reference	Number of patients	Therapeutic setting	CT regimen	RR	TTP	OS	Toxicity	QoL
Henderson *et al.* [1989]*	Total: 325 Eligible: 272	Second line	NVT *versus* Doxo	20.6% *versus* 29.3% n.s.	104 *versus* 70 days n.s.	10.4 *versus* 11.1 months n.s.	Significantly higher in Doxo arm	n.r.
Jones *et al.* [1995]	Total: 183 Eligible: 179	Anthra-refractory disease	VNR *versus* melphalan	46% *versus* 28% $p = 0.06$	12 *versus* 8 weeks $p < 0.001$	35 *versus* 31 weeks $p = 0.034$	Similar in both arms	Similar in both arms
Joensuu *et al.* [1998]	Total: 303 Eligible; 294	Second line = 162 patients	EPI->MitoC *versus* CEF ->MitoC + VBL	14% *versus* 6% n.s.	n.r.	10 *versus* 8 months n.s.	Lower in single agent arm	Better in single agent arm
Bontenbal *et al.* [1998]	Total: 259 Eligible: 232	Second line = 225 patients	Doxo *versus* EPI	36% *versus* 28% n.s.	23 *versus* 19 weeks n.s.	47 *versus* 44 weeks n.s.	Significantly higher in Doxo arm	n.r.
Nabholtz *et al.* [1999]	Total: 392 Eligible: 387	PD after anthra-based CT Second line: 194 patients Third line: 124 patients	DOC *versus* MitoC+VBL	30% *versus* 11.6% $p < 0.0001$	19 *versus* 11 weeks $p = 0.001$	11.4 *versus* 8.7 months $p = 0.0097$	Significantly worse in DOC arm	Similar in both arms
Sjöström *et al.* [1999]	Total: 283 Eligible: 267	PD after anthra-based CT Second line = 236 patients	DOC *versus* MTX->5FU	41% *versus* 21% $p < 0.001$	6.3 *versus* 3 months $p < 0.001$	10.4 *versus* 11.1 months n.s.	Significantly worse in DOC arm	Similar in both arms
Chan *et al.* [1999]	Total: 326 Eligible: 322	Prior alkylating agents as first line or adjuvant CT Second line = 174 patients	DOC *versus* Doxo	47.8% *versus* 33.3% $p = 0.008$	26 *versus* 21 weeks n.s.	15 *versus* 14 months n.s.	Severe neutropenic complications higher in Doxo arm $p = 0.02$	Similar in both arms
Norris *et al.* [2000]	Total: 303 Eligible: 300	Not previous vinca alkaloid, anthra, or NVT Second line = 75 patients	Doxo + VNR *versus* Doxo	38% *versus* 30% n.s.	6.2 *versus* 6.1 months n.s.	13.8 *versus* 14.4 months n.s.	More frequent gr.3-4 neurotoxicty in the Doxo/NVT arm	Similar in both arms
O'Shaughnessy *et al.* [2002]	Total: 511 Eligible: 511	Anthra-resistant patients Second line: 257 patients Third line: 76 patients	Cape + DOC *versus* DOC	41.6% *versus* 29.7% $p = 0.006$	6.1 *versus* 4.2 months $p = 0.0001$	14.5 *versus* 11.5 months $p = 0.0126$	Worse in the combination arm	Trend for better QoL GHS in the Cape + DOC arm overtime

(Continued)

Table 1. (Continued)

Reference	Number of patients	Therapeutic setting	CT regimen	RR	TTP	OS	Toxicity	QoL
Bonneterre *et al.* [2002]	Total: 178 Eligible: 176	Anthra-resistant disease Second line: 116 patients	DOC *versus* 5FU + VNR	43% *versus* 38.8% n.s.	6.5 *versus* 5.1 months n.s.	16 *versus* 15 months n.s.	Worse hematological toxicity in DOC arm	Better in DOC arm
Keller *et al.* [2004]	Total:301 Eligible: 301	PD after taxane-based CT Second line: 163 patients Third line. 270 patients Third line: 16 patients	PLD *versus* VNR or MitoC+VBL	10% *versus* 12% n.s.	2.9 *versus* 2.5 months n.s.	11 *versus* 9 months n.s.	More frequent gr.3-4 stomatitis and erythrodysesthesia in PLD group	Better global QoL domain in PLD arm 20% *versus* 14.6%
Icli *et al.* [2005]	Total: 201 Eligible: 193	Second line = 117 patients Third line = 38 patients	CDDP+ VP16 *versus* Paclitaxel	36.3% *versus* 22.2% p= 0.038 3 CR in each group	5.5 *versus* 3.9 months p= 0.003	14 *versus* 9.5 months p= 0.039	More frequent hematological toxicity in experimental arm	n.r.
Gradishar *et al.* [2005]	Total: 460 Eligible: 454	MBC patients eligible for taxane-based CT Second line = 190 patients Third line = 58 patients ≥fourth line = 20 patients	Nab-Paclitaxel *versus* paclitaxel	27% *versus* 13% p= 0.006	20.9 *versus* 16.1 weeks p= 0.02	Similar in both arms in first line; ≥Second line: 56.4 *versus* 46.7 weeks p= 0.024	Higher gr.3 sensory neuropathy (10% *versus* 2%; p< 0.001) and lower gr. 4 neutropenia (9% *versus* 22%; p< 0.001)in the experimental arm	Similar in both arms
Jones *et al.* [2005]	Total: 449 Eligible: 425	PD after anthra-based CT Second line = 249 patients	DOC *versus* paclitaxel	32% *versus* 25% n.s.	5.7 *versus* 3.6 months p< 0.0001	15.4 *versus* 12.7 months p= 0.03	Globally worse in DOC arm	Global FACT-B scores similar in both arms p≥ 0.68
Miller *et al.* [2005]	Total: 462 Eligible: 462	Second line: 205 patients Third line: 166 patients Fourth line: 19 patients	Cape+ Beva *versus* Cape	19.8% *versus* 9.1% p= 0.001	PFS: 4.8 *versus* 4.17 months n.s.	15.1 *versus* 14.5 months n.s.	Drug specific side effects in Beva arm	Similar in both arms
Geyer *et al.* [2006]	Total: 324 Eligible: 300	HER2 + MBC PD after anthra/ taxane/trastuzumab Second line = 296 patients	Lapatinib + Cape *versus* Cape	22% *versus* 14% p= 0.09	8.4 *versus* 4.4 months p< 0.001	n.r.	Similar in both arms	n.r.

(Continued)

Table 1. (Continued)

Reference	Number of patients	Therapeutic setting	CT regimen	RR	TTP	OS	Toxicity	QoL
Harvey *et al.* [2006]	Total: 527 Eligible: 524	Second line	DOC 60 mg/m2 *versus* DOC75 mg/m2 *versus* DOC100 mg/m2	22.1% *versus* 23.3% *versus* 36% p= 0.007	13.7 weeks *versus* 13.9 weeks *versus* 18.6 weeks p= 0.014	Up to 12.3 months Similar across the 3 groups	Dose-related adverse events	n.r.
Martin *et al.* [2007]	Total: 252 Eligible: 251	PD after anthra/ taxane-based CT Second line = 133 patients Third line = 73 patients	VNR *versus* VNR + GEM	26% *versus* 36% n.s.	4 *versus* 6 months p= 0.0028	15.9 *versus* 16.4 months n.s.	More frequent gr.3-4 neutropenia in the VNR/GEM arm p= 0.0074	n.r.
Thomas *et al.* [2007]	Total: 752 Eligible: 752	PD after anthrax/ taxane-based CT Second line= 363 patients Third line= 290 patients Fourth line= 39 patients	Ixabepilone + Cape *versus* Cape	35% *versus* 14% p< 0.0001	5.8 *versus* 4.2 months p= 0.0003	12.9 *versus* 11.1 months n.s.	More frequent gr.3-4 neuropathy, fatigue and neutropenia in the experimental arm	Similar in both arms (75% data missing)
von Minckwitz *et al.* [2009]	Total: 156 Eligible: 156	HER2 + MBC PD on trastuzumab therapy Second line	Trastuzumab + Cape *versus* Cape	48.1% *versus* 27% p= 0.0115	8.2 *versus* 5.6 months p= 0.034	25.5 *versus* 20.4months n.s.	Similar in both arms	n.r.
Barrios *et al.* [2010]	Total: 482 Eligible: 482	PD after anthra/ taxane–based CT Second line = 405 patients	Sunitinib *versus* Cape	11% *versus* 16% n.s.	2.8 *versus* 4.2 months p= 0.002	15.3 *versus* 24.6 months n.s.	More frequent gr.3-4 toxicity in the sunitinib arm	n.r.
Sparano *et al.* [2010]	Total: 1221 Eligible: 1198	Second line: 757 patients Third line: 213 patients ≥ fourth line: 5 patients	Ixabepilone + Cape *versus* Cape	43.3% *versus* 28.8% p= 0.0001	6.2 *versus* 4.4 months p= 0.0005	16.4 *versus* 15.6 months n.s.	Cumulative sensory neuropathy in the combination arm	n.r
Cortes *et al.* [2011]	Total: 762 Eligible: 762	Second line = 96 patients Third line = 259 patients Fourth line = 245 patients Fifth line = 136 patients > sixth line = 22 patients	Eribulin *versus* TPC (randomization 2:1)	12% *versus* 5% p= 0.002	3.7 *versus* 2.2 months p= 0.002	13.1 *versus* 10.6 months p= 0.041	Peripheral neuropathy in the experimental arm	n.r.

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Table 1. (Continued)

Reference	Number of patients	Therapeutic setting	CT regimen	RR	TTP	OS	Toxicity	QoL
Brufsky *et al.* [2011]	Total: 684 Eligible: 679	Second line	TPC *versus* Beva + TPC (randomization 2:1)	29.6% *versus* 39.5% $p = 0.0193$	5.1 *versus* 7.2 months $p = 0.0072$	16.4 *versus* 18 months (interim analysis) n.s.	More frequent gr. 3-4 toxicities in Beva arm	n.r.
Verma *et al.* [2012]	Total: 991 Eligible: 991	HER2-positive MBC Second line	TDM-1 *versus* Capecitabine + Lapatinib	43.6% *versus* 30.8% $p = 0.0193$	9.6 *versus* 6.4 months $p < 0.001$	30.9 *versus* 25.1 months $p < 0.001$	More frequent gr. 3-4 toxicities in control arm	n.r.
Blackwell *et al.* [2012]	Total: 296 Eligible: 291	HER2-positive MBC PD after anthra/taxane-trastuzumab	Lapatinib + Trastuzumab *versus* trastuzumab	10.3% *versus* 6.9% n.s.	11.1 *versus* 8.1 weeks $p = 0.011$	14 *versus* 9.5 months $p = 0.021$	Similar in both arms	Similar in both arms

*phase II–III study.
anthra, anthracycline; Beva, bevacizumab; Cape, capecitabine; CEF, cyclophoshamide/epiribicin/5-fluorouracil; CR, complete response; CT, chemotherapy; DOC, docetaxel; Doxo, doxorubicin; Epi, epirubicin; GHS, global health score; MBC, metastatic breast cancer; MitoC, mitomycin C; n.r., not reported; n.s., not statistically significant; NAB, nanoparticle albumin bound; NVT, mitoxantrone; OS, overall survival; PLD, pegylated liposomal doxorubicin; QoL, quality of life; RR, response rate; TPC, treatment on physician choice; TTP, time to progression; VNL, vinblastine; VNR, vinorelbine; VP-16, etoposide, GEM, gemcitabine.

the first remains unclear, since contrasting results have been reported with the addition of bevacizumab to different chemotherapy agents [Miller *et al.* 2005; Brufsky *et al.* 2011].

All reviewed trials compared one chemotherapy regimen to another in different treatment lines; no study has compared the OS of continuing chemotherapy *versus* giving no anticancer treatment in the refractory setting. The only trial that got close to assess this concept was EMBRACE, a phase III open-label trial in which, in Author's opinion, is denied the common place that improvement of OS would be an unrealistic expectation during evaluation of new anticancer therapies in the 'refractory' setting. The study compared eribulin mesilate to treatment of physician's choice, thus allowing patients to receive 'best supportive care' which could include palliative care alone. Unfortunately, no woman in that trial received only palliative care, virtually all of them receiving chemotherapy [Cortes *et al.* 2011].

When provided, multivariate analysis of factors independently associated with a more favorable outcome in terms of PFS or OS were found to be a Karnofsky index ≥80%, positive hormone receptor (HR) status and nonvisceral metastases [Icli *et al.* 2005; Jones *et al.* 2005; Hortobagyi *et al.* 2010].

The study endpoints did not significantly change over the time: PFS remains the most frequently chosen primary endpoint in randomized trials in the scenario of pretreated MBC, and in 15 out of 19 studies this objective was met. Only one of the three studies in which OS was used as primary endpoint showed a clinically meaningful and statistically significant survival benefit [Cortes *et al.* 2011]. However, it is well known that first-line PFS and/or TTP have not been convincingly shown to be good surrogates for OS; since multiple lines of therapy play a major role in determining OS in the advanced disease, the actual role of PFS/TTP *versus* postprogression survival (PPS) needs further investigation [Burzykowski *et al.* 2008; Saad *et al.* 2010].

Finally, we might wonder if the survival benefit is considered clinically worthy when obtained with serious toxicities in women given multiple chemotherapy lines. In the discussed trials, despite an increased toxicity reported with the experimental arms compared with control arms, the toxic deaths were referred to as absolutely anecdotal

and the treatment-related side effects appeared globally manageable. The data on quality of life (QoL), available in 13 trials, showed no detrimental effects in women receiving the experimental treatments.

Retrospective studies: the message from routine clinical practice

The lack of data from randomized trials led investigators to perform studies retrospectively, aiming to analyze management practice and to look for predictive and/or prognostic factors of outcome in patients with MBC given multiple chemotherapy lines (Table 2).

A first signal of rising interest in the field is witnessed by a retrospective cohort study published in 1994. The authors sought to analyze all salvage therapies given over patients' lifetime in a well-defined cohort of 140 MBC women formerly randomized to receive FEC, either monthly or weekly, as first-line chemotherapy for the metastatic disease. Only one complete response (CR) during second-line and 18 partial responses (PRs) were observed, for a total RR of 11%. After third-line chemotherapy, virtually no responses were found, and after the sixth line all patients progressed regardless of therapy. For unknown causes, patients who received second-line hormonal therapy fared better than those who received other forms of treatment. Median time-to-treatment failure (TTF) decreased from 3.4 to 0.5 months as therapy lines increased from first to eighth. These results led the authors to underline the little benefit of giving more than two salvage regimens, especially when focusing exclusively on cytotoxic treatment [Porkka *et al*. 1994].

More than 10 years later, the experience of the Royal Marsden Hospital in London on 149 patients with MBC who had received third-line chemotherapy over a 7-year period was reported. The 18 different regimens used were classified into seven subgroups, including single agents or drug combinations. No statistically significant differences between subgroups in RR, TTP or OS were found. Multivariate analysis of factors influencing the outcome of patients receiving third-line chemotherapy showed that only response to previous treatment independently predicted RR, TTP and OS ($p = 0.025$, 0.04 and 0.004, respectively). Patients responding to the first two lines of treatment (31/149, 21%) had a better outcome compared with those who had responded to one but not to both the first two lines (69/149, 46%); patients who did not respond to either first or second line (49/149, 33%) had the worse outcome. Overall, the results of this audit suggested patients failing to respond to either of two prior lines should be considered for treatment in clinical trials or supportive care [Banerji *et al*. 2007].

Some additional arguments concerning the impact of chemotherapy beyond the first-line derive from a large retrospective analysis on 934 MBC women treated at four French centers between 1992 and 2002. In this trial the evaluation of treatment benefit was based on a stringent criterion named 'time of disease control' (TDC), defined by the interval between time of treatment beginning and date of progressive disease or death. A threshold of 8 months for TDC duration was arbitrary selected to consider the treatment as beneficial in the 772 women eligible for the analysis. Although the significant decrease of median TDC in the successive lines of treatment, 50% of patients in the second-line, 40% in the third-line, 33% in the fourth-line and 25% in the fifth-line had a clinical benefit according to the criterion of TDC duration longer than 6 months. Interestingly, in all but the fifth line of treatment, the achievement of an objective response to chemotherapy was favorably linked to a longer disease control. In multivariate analysis the only prognostic factor identified to significantly influence the duration of TDC in each chemotherapy line was its duration in the previous line [Dufresne *et al*. 2008].

A similar retrospective analysis was performed at the Eugène Marquis Anticancer Center between 2000 and 2004 on 162 women who had received at least three chemotherapy lines (CT3) focusing on factors affecting survival from CT3 and predictive factors of nonprogressive disease (NPD). Median OS from CT3 was 13 months, with a statistically significant difference between the NPD group and PD group (15 months *versus* 5 months, respectively, $p < 0.001$); 34% of the women survived more than 2 years after CT3. Multivariate analysis identified seven factors that had a positive influence on OS from CT3, but only two variables resulted significantly predictive of NPD after CT3: histology (ductal *versus* lobular carcinoma, $p = 0.004$) and administered drug group (anthracycline/taxanes *versus* others, $p = 0.002$). In this series, 110 and 71 patients, respectively, received a fourth- and fifth-line, and 21 had up to 8–10 subsequent lines [Vauléon *et al*. 2009].

Table 2. Retrospective studies evaluating the benefit of chemotherapy beyond the second line in metastatic breast cancer (MBC).

Reference	Total/ evaluable patients Median age (range)	Study period	Line of treatment	RR	Median TTP (months)	Median OS (months)	Significant PFs for OS	*p* value (multivariate analysis)
Porkka *et al.* [1994]	140/115 53 years [24-70]	1986–1991	Second line: 63 patients Third line: 41 patients Fourth line: 24 patients Fifth line: 22 patients Sixth line: 13 patients Seventh line: 6 patients Eighth line: 5 patients Ninth line: 1 patient	11% (19/175 assessable courses) 1 CR during second line 23% for first line	2.6 for first line 2.6 for second line 1.8 for third line 1.3 for fourth line	17.2	n.r.	n.r.
Banerji *et al.* [2007]	149/149 52 (25–80)	1998–2005	Third line	45% in responders to two prior lines 30% in responders to one prior line 26% in non-responder to prior two lines	4 in responders to two prior lines 4 in responders to one prior line 3 in non–responders to two prior lines	8 in responders to two prior lines 8 in responders to one prior line i6 in non-responders to prior two lines	Response to first–second line CT	0.004
Dufresne *et al.* [2008]	934/772 51.5 years for second line (23.4–92.6) 49.7 years for third line (26.9–92.6) 47.3 years for fourth line (29–75.9) 42.6 years for fifth line (29–75.9)	1992–2002	Second line: 505 patients Third line 283 patients Fourth line: 127 patients Fifth line: 55 patients	42% for second line 28% for third line 12% for fourth line 21% for fifth line	9.3 TDC1 (range 0–120) 5.9 TDC2 (range 0–83.6) 4.63 TDC3 (range 0–37.23) 4.13 TDC4 (range 0–36.7) 3.23 TDC5 (range 0–15)	24.9 (range 0.3-210.9)	For TDC2*: no liver mts DFI ≥2 years TDC1 ≥9 months For TDC3: no liver mts TDC2 ≥6 months OR to prior CT For TDC4: TDC3 ≥6 months OR to prior CT For TDC5: TDC4 ≥6 months OR to prior CT	 0.0133 0.0142 0.0243 0.0036 0.0024 <0.0001 0.016 0.0011 0.0043 0.0029
Vauléon *et al.* [2010]	468/162 53 years (26–72)	2000–2004	Third line	65% NPD 1 CR	8	13 from third line (range 5–15)	SBR grade I No adjuvant HT DFI ≥2 years No cerebral mts Unique mts PoliCT as second line CR to first–second line	0.0047 0.0006 0.0008 0.036 0.0089 0.0227 0.0124

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Table 2. (Continued)

Reference	Total/ evaluable patients Median age (range)	Study period	Line of treatment	RR	Median TTP (months)	Median OS (months)	Significant PFs for OS	*p* value (multivariate analysis)
Tacca *et al.* [2009]	578/487 n.r.	1973–2006	Second line: 331 patients Third line: 225 patients Fourth line: 141 patients Fifth line: 77 patients Sixth line: 40 patients Seventh line: 25 patients ≥Eighth line: 11 patients	16% for fourth line 10% for fifth line 17% for sixth line 12% for seventh line	4.7 for second line 4.9 for third line 3.9 for fourth line 4.3 for fifth line 3.1 for sixth line 5.4 for seventh line 3.6 for ≥eighth line	30.8 for second line 34.2 for third line 37.2 for fourth line 43 for fifth line 49.7 for sixth line 60.1 for seventh line 60.3 for ≥eighth line	n.r.	n.r.
Bernardo *et al.* [2010]	992/980 54 years (37–78)	1998–2006	Second line: 838 patients Third line: 684 patients Fourth line: 302 patients Fifth line: 88 patients ≥Sixth line: 40 patients	72% for second line 48% for third line 32% for fourth line 20% for fifth line 18% for ≥sixth line	7.8 for second line 6.4 for third line 6.2 for fourth line 5.2 for fifth line 4.8 for ≥sixth line	22.6 months for second line 14.6 months for third line 12.4 months for fourth line 9.4 months for fifth line 8.2 months for ≥sixth line	OR to first–second line TTF duration	0.002 0.038
Planchat *et al.* [2011]	590/529 n.r.	1994–2010	Second line: 401 patients Third line: 304 patients Fourth line: 226 patients Fifth line: 149 patients Sixth line: 99 patients ≥Seventh line: 65 patients	72% for second line 48% for third line 32% for fourth line 20% for fifth line 18% for sixth line 11% for ≥seventh line	7.8 for second line 6.4 for third line 6.2 months for fourth line 5.2 months for fifth line 4.8 months for sixth line 4.6 months for seventh line	20.8 months for second line 15.6 months for third line 12.6 months for fourth line 43 months for fifth line 49.7 months for sixth line 60.1 months for seventh line	CR to first–second line TTF duration	0.0247 0.008

*PFs for TDC in each CT line.
CR: complete response; CT: chemotherapy; HT: hormone therapy; MBC: metastatic breast cancer; mts: metastasis; n.r.: not reported; NPD: non-progressive disease; OR: objective response; OS: overall survival: PFs: prognostic factors; RR: response rate; TDC: time of disease control; TTF: time to treatment failure; TTP: time to progression.

In the same year an additional retrospective study focusing on the potential gain after the third-line of chemotherapy on 578 MBC patients treated at the Centre Jean Perrin, France, between 1973 and 2006 was published. In the 487 analyzed patients OS (evaluated from day 1 of every line) decreased with each line given, from 22.5 months of the first-line to 17 months of the second-line and 12.3 months of the third-line, with rather stable values around 8 months for the subsequent lines. When survival was evaluated as function of total number of lines, the median OS increased with each supplementary line given, reaching values of 60 months for the 36 patients given 7 or more regimens. Interestingly, in this study the median TTF, defined as the interval from start of treatment until progressive disease or death, stabilized around 4 months regardless the chemotherapy line examined. The evaluation of tumor response showed that about 10–17% of patients obtained a partial response after the third line and clinical benefit (stable disease plus partial remission) was observed in around 50% of women between the fourth and seventh chemotherapy salvage regimen [Tacca *et al.* 2009].

The database used by Tacca and coworkers has been recently updated and enriched with new patients treated after the advent of the 'taxane-anti-aromatase era'. A total of 529 women receiving a median of three chemotherapy lines for MBC were analyzed, with survival data updated in March 2010, for a median follow up of 163 months (range 72–651). In this work the previously reported results were confirmed, with a stable OS gain of around 11 months for each considered line; the TTF was stable at approximately 3 months and related to OS, and at least one third of women obtained a clinical benefit. Overall, significantly more patients continued treatment after the third-line in the updated analysis (43% in 2010 *versus* 30% in 2007). Interestingly, the median duration of chemotherapy was 11.7 months and patients survived a median of 20.6 months without therapy. Thus, patients were treated by chemotherapy during only 36% of OS duration, suggesting the possibility of better QoL. However, toxicities of given treatments and QoL were not systematically evaluated; approximately 5% of patients stopped chemotherapy due to toxicity [Planchat *et al.* 2011].

Similar findings have been reported by our group in a retrospective analysis including 992 women treated with chemotherapy for MBC at our institution over a 8-year period. The study aimed to determine which benefit could be brought by successive treatment lines in patients with advanced disease and to identify factors affecting outcome and survival. With OS data updated at December 2008, the median follow up of the 980 evaluable women was 125 months (range 48–192). Median OS evaluated from day 1 of each treatment decreased with the line number from 34.8 months in the 980 patients receiving first-line to 8.2 months in the 45 patients given 7 or more lines. Median TTF ranged from 9.2 months to 7.8 and 6.4 months for the first, second and third-line, respectively, with no significant decrease observed beyond the third-line (median 5.2 months, range 4.8–6.2). In univariate analysis, factors positively linked to a longer TTF for each line were positive HR status, absence of liver metastasis, adjuvant chemotherapy exposure, response to chemotherapy for the metastatic disease; in the multivariate analysis, the duration of TTF for each chemotherapy line and the achievement of an objective response to the first and second-line were the only factors with significant impact on OS for subsequent treatments p = 0.002 and 0.038, respectively) [Bernardo *et al.* 2010]. An updated analysis further confirmed the benefit of multiple lines of treatment in a significant subset of MBC women, suggesting that each chemotherapy line could contribute to a longer OS. Of interest, such a benefit was also observed for patients with HR-positive disease, although the number of received hormone therapy lines did not influence the outcome [Palumbo *et al.* 2012].

HER2-targeted therapies: which evidence for multiple lines?

The advent of HER2-targeted therapies has significantly changed the clinical outcome of patients with HER2-overexpressing MBC, a tumor subtype known to be associated with an aggressive biological behavior and with a shorter disease-free interval and OS [Slamon *et al.* 1987; Gonzales-Angulo *et al.* 2009]. Trastuzumab, the first humanized monoclonal antibody specifically developed to block HER2 pathway, has not only positively altered the natural history of women with HER2-positive tumors, but has also improved their prognostic outcomes beyond those of women with HER2-negative disease [Slamon *et al.* 2001; Dawood *et al.* 2010; Gradishar, 2013]. Owing to its innovative biological target and its possible mechanisms of actions, this agent has become a 'backbone' of treatment

across multiple lines of chemotherapy, although the benefits of continuing trastuzumab beyond disease progression have not clearly established. Actually its use in clinical practice was adopted on the basis of retrospective and phase II studies, in the absence of evidence-based data from randomized trials.

A large body of retrospective and observational series have been published in the last 10 years, including >1400 women receiving trastuzumab-based chemotherapy for their MBC. All but two of them suggest a clinical benefit when trastuzumab is used beyond disease progression, as summarized in two recently reported comprehensive reviews [Mannocci *et al.* 2010; Pegram and Liao, 2012]. Despite the heterogeneity and often limited sample size of the analyzed populations, some indications useful for the clinicians can be derived from such experiences.

- Patients who received second-line trastuzumab-based chemotherapy for metastatic disease achieved a median OS significantly better than whose discontinuing trastuzumab at disease progression [Fountzilas *et al*. 2003; Gelmon *et al*. 2004; Stemmler *et al*. 2005; Fabi *et al*. 2008; Extra *et al*. 2010; Campiglio *et al*. 2011; Waddell *et al*. 2011].
- Improved objective response and clinical benefit rates were observed in women given multiple lines of trastuzumab therapy, from two to seven [Bartsch *et al*. 2006; Cancello *et al*. 2008].
- Time to first tumor progression might be able to predict longer TTP at subsequent lines and longer PPS [Metro *et al*. 2010; Hayashi *et al*. 2011; Esposito *et al*. 2012]; in addition, response to the first-line trastuzumab-based therapy was significantly associated with response to subsequent lines [Garcìa-Sàenz *et al*. 2005].

Several prospective, nonrandomized trials further support the clinical benefit of trastuzumab in combination with different chemotherapeutic agents in pretreated HER2-positive MBC [Mannocci *et al*. 2010; Pegram and Liao, 2012].

The first attempt to prospectively assess the benefit of continuing trastuzumab beyond progression was performed by von Minckwitz in a phase III randomized study comparing capecitabine *versus* capecitabine plus trastuzumab in patients progressing after first-line trastuzumab-based therapy. The trial, prematurely closed because of slow accrual, met the primary endpoint, with TTP significantly higher in the experimental arm (8.2 *versus* 5.6 months, $p = 0.0338$), while no significant difference in OS was observed [von Minckwitz *et al*. 2009]. In a post hoc analysis of the study, however, patients who received third-line anti-HER2 therapy experienced longer median OS than those who did not (18.8 months *versus* 13.3 months, respectively; $p = 0.02$) [von Minckwitz *et al*. 2011].

The identification of the mechanisms of *de novo* and acquired resistance to trastuzumab has led to the development of novel target agents for the treatment of HER2-positive disease. Lapatinib, a dual inhibitor of the tyrosine kinase activity of epidermal growth factor, received US Food and Drug Administration (FDA) approval on the basis of a phase III, open-label trial comparing lapatinib plus capecitabine *versus* capecitabine monotherapy in 324 patient with HER2-positive MBC refractory to treatment with anthracyclines, taxanes and trastuzumab. The addition of lapatinib to capecitabine resulted in improved TTP (8.4 months *versus* 4.4 months, respectively; $p < 0.001$) with a reduced risk of progression by 51% (HR 0.49, $p < 0.001$) [Geyer *et al*. 2006]. The subsequent logical step in the development of HER2-targeted therapies was the evaluation of the double HER2 blockade with lapatinib and trastuzumab, based on preclinical data supporting the hypothesis of a more effective inhibition of the HER2 pathway [Konecny *et al*. 2006]. A statistically significant improvement in PFS for patients receiving lapatinib/trastuzumab combination compared with lapatinib alone has been shown in a recently reported phase III study on heavily pretreated patients who had progressed after trastuzumab-based therapy (12 weeks *versus* 8.1 weeks, $p = 0.008$). A greater clinical benefit rate in the combination arm was also observed (25% *versus* 12%, $p = 0.01$), associated with a significant 4.5 month median OS gain (14 *versus* 9.5 months, HR = 0.74, $p = 0.026$). In the subgroup exploratory analysis, the greatest clinical benefit was observed for the 128 patients with estrogen receptor (ER) negative disease (median 16.5 *versus* 8.9 months, $p = 0.012$); conversely, patients with ER-positive disease did not derive OS gain from the combination compared with the monotherapy (12 *versus* 11.2 months, $p = 0.404$) [Blackwell *et al*. 2012].

The therapeutic armamentarium for HER2-positive disease was later expanded by pertuzumab, another HER2 inhibitor that targets the HER2 extracellular domain at a different epitope, resulting in inhibited dimerization of HER2 with other HER family receptors. The addition of pertuzumab to trastuzumab has shown activity in two phase II trials of patients who progressed on previous treatment with trastuzumab [Portera *et al*. 2008; Baselga *et al*. 2010]. The better performance of the anti-HER2 drugs in combination over a monotherapy has recently been replied by a phase III trial of trastuzumab/docetaxel ± pertuzumab in the first-line setting [Swain *et al*. 2013]; in the second-line setting such an approach is still investigational, and the PHEREXA trial, an open-label phase II study of trastuzumab/capecitabine ± pertuzumab in patients progressing on first-line trastuzumab-based chemotherapy, is currently addressing this issue. Two further randomized studies focusing on the clinical utility of trastuzumab in multiple lines of therapy (THOR and PANDORA) are ongoing and their data are awaited.

The possibility of reaching a significant survival gain in pretreated HER2-positive MBC has recently been confirmed in a large phase III study on 991 women refractory to trastuzumab/taxane therapy, comparing lapatinib/capecitabine with TDM-1, an antibody–cytotoxic conjugate drug in which trastuzumab is conjugated to an antimicrotubule agent (emtansine). A consistent OS and PFS advantage for TDM1 has been shown (30.9 *versus* 25.1 months, HR 0.68, $p < 0.001$; 9.6 *versus* 6.4 months, HR 0.65, $p < 0.001$, respectively). The results for all the additional secondary endpoints including RR (43.6% *versus* 30.8%, $p < 0.001$) favored the experimental arm too [Verma *et al*. 2012].

The data discussed above have substantially changed treatment guidelines in recent years and have opened up new options for patients with HER2-positive MBC in first-line setting and beyond [Cardoso *et al*. 2011; Cardoso *et al.* 2012; Theriault *et al*. 2013]. The preliminary results of BOLERO-3 trial presented at the 2013 meeting of the American Society of Clinical Oncology (ASCO) add further insights in the field of HER2-targeted therapies in multiple lines. In this phase III randomized, double-blind, placebo-controlled study, 569 trastuzumab-resistant patients were randomly assigned to receive the mechanistic target of rapamycin (mTOR) inhibitor everolimus plus vinorelbine/trastuzumab weekly, or placebo plus the same vinorelbine/trastuzumab combination. A statistically significant longer PFS was reached in the experimental arm (7.00 months *versus* 5.78 months; $p = 0.0067$) and an interesting more consistent benefit was observed in the HR-negative subgroup [HR 0.65, 95% confidence interval (CI) 0.48–0.87%], supporting the biological hypothesis that the blockade of PI3K/AKT/mTOR pathway could be overcome by ER pathway activation [O'Regan *et al.* 2013].

Globally, the results from the available trials suggest that optimally exploiting the biology of the HER2 pathway results in the best clinical outcome for patients with HER2-positive disease and a number of rationally designed clinical trials are evaluating a 'dual targeting' approach (investigational HER2-targeted agents with trastuzumab or lapatinib) in an effort to overcome treatment resistance in the setting of trastuzumab-progressive disease.

Discussion

Despite more than 40 years of clinical research, the true impact of multiple lines of treatment on the outcome of MBC is still debated. The lack of a single standard of care for patients with metastatic disease makes such evaluation difficult. In addition, until recently data in the literature failed to provide any insight for third-line treatment, since the majority of published trials devoted to second-line chemotherapy were very small, non-comparative and limited.

In an attempt to answer the question 'How many lines of treatment should we give patients?', clinicians should be primarily refer to the results of prospective, randomized phase III trials. At present, the available data provide some support for the use of second-line and, to a lesser degree and in selected cases, third-line chemotherapy in HER2-negative MBC (Table 1). Unfortunately, none of the reviewed trials has compared the OS of continuing chemotherapy *versus* no anti-cancer treatment in the refractory disease, so we do not have any evidence that chemotherapy in third, fourth and further line settings improves survival compared with palliative care. Since evidence-based medicine often does not make clinical practice, but people do, we must also consider more favorable messages coming from the recently published retrospective series. These globally suggest that chemotherapy beyond the

second line can obtain a prolonged disease control and OS improvement in a substantial subset of MBC patients. An interesting indication for the routine clinical practice is the potential prognostic role of response to first and second-line chemotherapy, which can be observed in five out of seven trials (Table 2). Nevertheless, we should be aware of several weaknesses, in addition to the well-known limitations of retrospective analysis: the women in study were not treated with chemotherapy alone and thus the observed impact on survival was the result of an alternation of chemotherapy- and hormone-based strategies during the disease course; no conclusion can be derived about the contribution of each agent to the survival gain in the studied populations, mainly because of the small number of patients in each subgroup; and no information is available about the impact of subsequent lines of chemotherapy on the patient's QoL.

Finally, the lesson coming from HER2-targeted therapies appears even more intriguing and quickly evolving, since the introduction of these agents has markedly changed a classical paradigm in oncology, that is to switch to a noncross-resisting treatment when the disease progresses. Data from retrospective and prospective studies provide an indication that the use of trastuzumab in multiple lines of therapy allows us to obtain objective responses and delay disease progression. An open question is whether trastuzumab should remain the HER2-suppressing agent throughout multiple lines of treatment or whether clinical benefit would be increased if different HER2-targeted agents were used. No currently available data answer the question. However, emerging evidences from phase III randomized studies support the latest guidelines changes, with the incorporation of lapatinib + trastuzumab combination or TDM1 among the treatment options for HER2-positive disease. Future studies addressing the underlying mechanisms of sensitivity to and progression on trastuzumab will be useful in predicting response to subsequent treatment lines with the different available HER2-targeted agents.

The challenge for clinicians remains the prospective selection of MBC women who could benefit from multiple treatments. Nevertheless, based on current data, we can make an attempt to draw the profile of the 'ideal' woman eligible to such an approach; she would be the one who responded to her very first lines of treatment, who maintained an adequate performance status during the disease course, and who benefited from the therapeutic choice with the highest response rate and efficacy parameters. The adequate number of lines to be administered would be the one that she could tolerate and benefit. The choice of drugs, their timing and optimal treatment duration, route of administration and side effects will be considered individually, also taking into account treatment acceptability and adherence and patients' preferences. The 'optimal' treatment strategy for such a woman will probably be to use as many therapeutic options as possible, either in sequence or combination, to keep the best efficacy/toxicity balance, considering her as affected with a chronic disease.

Conclusion

The scenario of global therapeutic strategy in MBC is changing and treatment's goals are moving from improved survival to stabilization of metastatic disease and potential cure in selected patient populations. In this dynamic process, the question of survival benefit from subsequent therapies clearly needs further research.

From a clinical viewpoint, the data reviewed in this article globally support some benefit associated with the administration of multiple treatment lines in MBC, both in HER2-negative and HER-2-positive settings. Such an approach may be justified on the basis of an appreciable survival gain for some patients and it is also consistent with the increasing population of women who ask for subsequent therapies at disease progression.

From a scientific viewpoint, these findings clearly suggest the need of further investigation in an attempt to increase the observed survival benefit. To this aim, the identification of new predictive markers of sensitivity to select therapies, as well as innovative evaluation criteria to assess long-term treatment efficacy, appear to be essential requisites to address the potential benefit of subsequent therapies within the biological complexity and heterogeneity of MBC.

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