Metastatic Breast Cancer: Is There a Differential Therapy Efficacy between Visceral and Non-Visceral Metastatic Breast Cancer?

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Keywords

Metastatic breast cancer · Therapy efficacy · Visceral metastasis · Non-visceral metastasis

Abstract

Purpose: Differential efficacy of newly registered therapies in subgroups of metastatic breast cancer (MBC) is an important consideration for subsequent use in clinical practice. Unfortunately, such subgroup analyses often are exploratory and rarely statistically adequately powered and may thus be misleading. This analysis aimed to explore a potentially different treatment response to i.v. therapies between visceral and non-visceral MBC. **Methods:** In a systematic literature analysis (PubMed) comprising phase III registration studies for MBC from 1994 to 2014, differences in outcome were evaluated regarding progression-free survival, time to progression, overall survival (OS), and visceral versus non-visceral disease. The impact of HER2 and hormone receptor status was also considered. A total of 16 studies comprising 13,083 patients were selected by considering the information given in the medical product's professional information and the decision of the US Food and Drug Administration or the European Medicine Agency for approval of the respective therapeutic agents now used in the treatment of MBC. **Results:** No statistically significant differences regarding treatment response and therapy benefit were found in MBC patients with visceral versus non-visceral metastases based on reported hazard ratios and confidence intervals in registration trials. Interesting but nonsignificant differences were found regarding a distinct therapy benefit regarding differ-

ent metastasis locations in 4 studies. **Conclusion:** For targeted i.v. therapies based on biomarker selection, there is a trend – although not significant – toward a benefit (OS) from combination therapies favoring visceral disease. However, at the present time, metastasis localization should not be used as a predictive marker for choice of systemic therapy in MBC.

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Introduction

Primary metastatic breast cancer (MBC) amounts to about 5–10% of all breast cancer patients [1]; about 20–30% of breast cancer patients will experience metastatic disease during the course of their disease. Median survival is 2–3 years, and long-term survival >5 years is still rare with only about 25% [2].

In the treatment of MBC, there is a great variety of different therapeutic agents from the field of endocrine therapy, targeted therapy, or chemotherapy. The decision for a specific therapy regimen mainly depends on the pattern of metastasis, the intrinsic subtype, and the clinical presentation and on whether a rapid remission is required. Tumor biology and prior treatments but also the patient's general condition and preferences are additional criteria for treatment choice.

Clinically, it is a very relevant question whether there is an efficacy difference of certain therapies according to site of metastasis. Unfortunately, given the diversity of the available study data for MBC and their inhomogeneous in- and exclusion criteria, the therapy effect in visceral

Table 1. Overview of the results of the analyzed trials differentiated according to site of metastases (visceral vs. non-visceral)

Therapy regimen	End-point	HR total	CI	<i>p</i> value	Visceral metastases	CI	Non-visceral metastases	CI
<i>HER2 positive</i>								
[3] L+Tr vs. L	OS	0.74	0.57–0.97	na	<0.8	<1.00	<0.8	>1.00
[4] L+Tr vs. L	PFS	0.73	0.57–0.93	0.008	0.6–0.8	<1.00	0.8–1.00	>1.4
[5] T-D vs. L+C	PFS	0.65	0.55–0.77	<0.001	0.55	0.45–0.67	0.96	0.71–1.30
[6] P+Tr+D vs. Tr+D	PFS	0.69	0.58–0.81	na	0.63	0.53–0.76	0.89	0.61–1.31
	OS	0.66	0.52–0.84	0.0008	0.57	0.44–0.74	1.42	0.71–2.84
[7] L+Le vs. Le	PFS	0.71	0.53–0.96	na	0.6–0.8	<1.00	0.8–1.00	>1.20
<i>HER2 unknown</i>								
[8] Le vs. T	TTP	0.70	0.6–0.82	na	0.69	0.55–0.87	0.73	0.53–1.00
[9] T vs. A	TTP	1.13	≥1.00	na	>1.00	crossing 1.00	>1.00	crossing 1.00
[10] Dox vs. PLD	PFS	1.00	0.82–1.22	na	1.00–1.20	<1.00	0.8–1.00	crossing 1.00
[11] A vs. megestrol acetate	TTP	0.97	0.75–1.24	na	no differences, no numbers available			
[12] F 500 mg vs. F 250 mg	PFS	0.8	0.68–0.94	0.006	0.8–1.00	≤1.00	<0.8	<1.00
<i>HER2 negative</i>								
[13] C+BV vs. C+PL	PFS	0.69	0.56–0.84	na	0.72	0.57–0.9	0.58	0.4–0.83
Ta+An+BV vs. Ta+An+PL	PFS	0.64	0.52–0.8	na	0.68	0.54–0.86	0.63	0.42–0.94
[14] Pa+BV vs. Pa	PFS	0.6	0.51–0.7	na	0.59	0.49–0.79	0.63	0.4–0.97
[15] Pa+BV vs. Pa	PFS	0.48	0.385–0.607	<0.0001	0.58	0.46–0.72	0.28	0.1–0.79
[16] CT+BV vs. CT PL	PFS	0.78	0.64–0.93	na	0.77	0.62–0.96	0.74	0.5–1.07
[17] BV vs. non-BV	PFS	0.64	0.57–0.71	na	0.66	0.59–0.75	0.6	0.49–0.74
	OS	0.97	0.86–1.08	na	0.96	0.85–1.09	1.07	0.85–1.35
[18] Ev+Ex vs. Ex	PFS	0.45	0.38–0.54	na	0.47	<0.7	0.41	<0.7

A, anastrozole; BV, bevacizumab; C, capecitabine; CI, confidence interval; D, docetaxel; Dox, doxorubicin; Ev, everolimus; Ex, exemestane; F, fulvestrant; HR, hazard ratio; L, lapatinib; Le, letrozole; na, not available; OS, overall survival; P, pertuzumab; Pa, paclitaxel; PL, placebo; PFS, progression-free survival; PLD, pegylated liposomal doxorubicin; T, tamoxifen; Ta+An, taxane + anthracycline; T-D, T-DM1; Tr, trastuzumab; TTP, time to progression.

versus non-visceral disease has mostly been addressed by subgroup analyses within individual trials. Moreover, visceral and non-visceral disease was defined differently in individual studies with different organ systems being included into the individual definition (see below). This made classification and correlation with clinical outcome difficult. We sought to detect differences in therapy benefit in MBC patients with visceral versus non-visceral metastasis using outcome (e.g., progression-free survival [PFS], time to progression [TTP], and overall survival [OS]) as a surrogate. Per definition, PFS includes all deaths, while deaths before progression are censored with TTP. If available, tumor biology as indicated by HER2 and hormone receptor (HR) status was also considered.

Material and Search Methods

A systematic literature search ($n = 6,362$ hits) in the meta-database PubMed of the US National Library of Medicine was performed, reviewing the publishing period from 1994 to 2014 for registration trials in MBC with appropriate search terms such as “metastatic breast cancer,” “clinical trial,” “phase III study,” and “visceral metastasis.”

We included 257 studies ($n = 126,291$ patients) into our analysis. Among those 257 studies, we identified 69 studies which had published separate data for visceral (defined as the presence of

visceral metastases independent of the presence of other metastatic sites) versus non-visceral (defined as non-visceral metastases in the absence of visceral involvement) disease. These included phase III trials plus the respective subsequent secondary publications.

Visceral metastases were defined by the following locations: liver, lung, ascites, pleural effusion, and metastases in the central nervous system. Non-visceral metastases were defined as bone, skin, and lymph node metastases. Out of these 69 studies, we selected 16 studies ($n = 13,083$ patients) by considering (a) the information given in the SmPC (Summary of Product Characteristics) and (b) the decision of the US Food and Drug Administration (FDA) or the European Medicine Agency (EMA) for approval of the respective therapeutic agents for MBC. The selected 17 studies all reported the outcome endpoints mentioned above [3–19]. In order to achieve comparability, we extracted the information for metastasis pattern, hazard ratios, and confidence intervals as well as times in weeks (if available) for PFS, TTP, and OS of the entire study population divided into three main groups according to HER2 status: HER2-positive, HER2-negative, and unknown HER2 status. These main groups then were stratified by HR status of the study population into subgroups. HR-positive and HR-all (i.e., independent of HR status) subgroups were found. No studies reported on “visceral versus non-visceral in the subgroups”: HR-negative and HR-unknown (i.e., HR status not reported). Regarding the group of HR-all, where available, the respective study results are additionally shown for HR-positive and -negative groups. The information whether therapy response was different or similar in visceral versus non-visceral was taken from the respective hazard ratios and confidence intervals.

Fig. 1. Overview and analysis of trials including a HER2-positive study population; stratification by hormone receptor status (HR+ vs. HR-) and metastasis localization (visceral vs. non-visceral). ER, estrogen receptor; HR +/-all, hormone receptor status positive/negative/all (i.e., independent of HR status); L, lapatinib; Le, letrozole; OS, overall survival; PR/PgR, progesterone receptor; PFS,

Fig. 2. Differences in therapy response in the HER2-positive study population. DTR, different therapy response; HR +/-/all, hormone receptor status positive/negative/all (i.e., independent of HR status); L, lapatinib; NV, non-visceral disease; OS, overall survival; P, pertuzumab; Tr, trastuzumab; V, visceral disease; nS, statisti-

Regimes with a differential therapy benefit were defined by a hazard ratio distinct from 1.00 and a confidence interval not overlapping 1.00. Trends toward better, worse, or similar response to therapy (i.e., hazard ratio distinct from 1.00 but confidence interval overlapping with 1.00) were also reported.

Trials were first looked at on an individual trial basis, then results were also summarized. We were not able to perform a formal meta-analysis as there were only 16 trials in the final set which differed rather substantially regarding lines of therapy, drugs used, etc.

Fig. 3. Overview and analysis of trials including a study population with unknown HER2 status; stratification by hormone receptor status (HR+ vs. HR-) and metastasis localization (visceral vs. non-visceral). A, anastrozole; F, fulvestrant; HR +/-/all, hormone receptor status positive/negative/all (i.e., independent of HR status); Le, letrozole; PFS, progression-free survival; T,

tamoxifen; Ta+An, taxane + anthracycline; TTP, time to progression. The therapeutic regimes with an increased benefit (smaller hazard ratio) are shown on the left side (for example: Y+Z vs. Z). Red numerals = hazard ratio. Blue numerals = confidence intervals (95%); ×1 = crossing 1. Green numerals = time in weeks (we).

Fig. 4. Differences in therapy response in the HER2-unknown study population. Dox, doxorubicin; DTR, different therapy response; HR +/-/all, hormone receptor status positive/negative/all (i.e., independent of HR status); NV, non-visceral disease; PFS, progression-free survival; PLD, pegylated liposomal doxorubicin;

V, visceral disease; nS, statistically not significant. The therapeutic regimes with an increased benefit (smaller hazard ratio) are shown on the left side (for example: Y+Z vs. Z). Red numerals = hazard ratio. Blue numerals = confidence intervals (95%); ×1 = crossing 1. Green numerals = time in weeks (we).

Results

No statistically significant difference in treatment response and therapy benefit was found in MBC patients with visceral versus non-visceral metastases based on reported hazard ratios and confidence intervals in breast cancer registration trials. Interesting but not statistically

significant differences were found regarding a distinct therapy benefit of different metastases locations in four studies. Confidence intervals and *p* values were taken directly from the publications. Table 1 gives an overview of the results of the analyzed trials including the differentiated presentation of the treatment effects in visceral compared to non-visceral metastasized patients.

Fig. 5. Overview and analysis of trials including a HER2-negative study population; stratification by hormone receptor status (HR+ vs. HR-) and metastasis localization (visceral vs. non-visceral). BV, bevacizumab; BV vs. non-BV, therapy with bevacizumab/without bevacizumab; C, capecitabine; CT, chemotherapy; Ev, everolimus; Ex, exemestane; HR +/-/all, hormone receptor status positive/negative/all (i.e., independent of HR status); OS, overall

survival; Pa, paclitaxel; PL, placebo; PR/PgR, progesterone receptor; PFS, progression-free survival; Ta+An, taxane + anthracycline. The therapeutic regimes with an increased benefit (smaller hazard ratio) are shown on the left side (for example: Y+Z vs. Z). Red numerals = hazard ratio. Blue numerals = confidence intervals (95%); x1 = crossing 1. Green numerals = time in weeks (we).

Fig. 6. Differences in therapy response in the HER2-negative study population. BV, bevacizumab; BV vs. non-BV, therapy with bevacizumab/without bevacizumab; DTR, different therapy response; HR +/-/all, hormone receptor status positive/negative/all (i.e., independent of HR status); NV, non-visceral disease; V, visceral dis-

ease; nS, statistically not significant. The therapeutic regimes with an increased benefit (smaller hazard ratio) are shown on the left side (for example: Y+Z vs. Z). Red numerals = hazard ratio. Blue numerals = confidence intervals (95%); x1 = crossing 1. Green numerals = time in weeks (we).

HER2-Positive Tumors

The collected data for the HER2-positive group are shown in Figure 1 and the differences found in this group are shown in an overview in Figure 2. Interesting but statistically nonsignificant differences were found in the HER2-positive group. There was an enhanced

benefit regarding OS for patients with visceral metastases receiving modern combination therapies, i.e., lapatinib in combination with trastuzumab [3] or trastuzumab and docetaxel in combination with pertuzumab [6].

HER2-Unknown Tumors

The collected data for the HER2-unknown group are shown in Figure 3 and the differences found in this group are shown in an overview in Figure 4. For the group with unknown HER2 status, there was a numerical but not statistically significant difference in therapy response (PFS): patients with non-visceral disease seem to derive more therapy benefit from pegylated liposomal doxorubicin and patients with visceral disease from doxorubicin therapy [10]. Yet, it can be assumed that there is no clinically relevant difference as the respective hazard ratio and confidence interval of the total study population was 1.00 (0.82–1.22), with an only minor deviation in visceral versus non-visceral disease.

HER2-Negative Tumors

The collected data of the HER2-negative group are shown in Figure 5 and the differences found in this group are shown in an overview in Figure 6. Within the HER2-negative group, there was again a numerical but not statistically significant difference detected regarding therapy response (OS). Patients with non-visceral disease seem to derive more benefit from chemotherapy plus bevacizumab compared to patients with visceral disease and to the total population [17]. However, it can be assumed that there are no clinically relevant differences given a hazard ratio of 0.97 for the total study population (confidence interval: 0.86–1.08), with only minor deviations for visceral versus non-visceral disease.

Discussion

There is a perception among many clinicians that visceral metastases respond less to certain therapies such as endocrine therapy and better to chemotherapy than non-visceral metastases. Moreover, explorative, often retrospective analyses of small subgroups from large randomized trials also suggest differential therapy benefit according to metastasis localization. As such clinical perceptions may interfere with guideline-oriented therapy decisions, we undertook this systematic analysis of the literature in order to substantiate or dismiss these preconceived notions.

MBC has a median survival of about 24 months, with local relapses and lymph node metastases being associated with more favorable survival times than visceral disease [20]. OS after progression does not just differ according to relapse site (local relapse, lymph node relapse, distant metastasis) but also according to HR and HER2 status. In particular, OS after progression is very poor in triple negative disease [20]. Different breast cancer subtypes are correlated with different metastasis patterns [21].

In summary, we did not find a significant difference of therapy efficacy according to metastasis location in our

analysis of breast cancer registration trials until 2014. It has to be noted that given the inhomogeneous nature of the published trials, we were only able to stratify according to HR and HER2 status.

In the future, it may well be that by subdividing MBC not just by HR and HER2 status but rather by molecular subtypes, there may be distinct therapeutic efficacy of certain agents according to metastatic site. Using rather simple stratification criteria such as HER2 or HR status, we were not able to detect such a difference in recent registration trials. Our observed lack of site-specific efficacy is in accordance with a review of 4 phase III randomized trials of first-line endocrine therapy. Overall, visceral metastases appeared to be as sensitive to endocrine therapy as non-visceral metastases [22].

Epidemiological data have not demonstrated differential survival according to treatment period and tumor biology [20]. It was thus reasonable to combine the registrations trials over 20 years from 1994 to 2014. Nevertheless, there are certainly limitations to our analyses: the vast majority of trials was not powered to show therapeutic efficacy by clinical subgroups such as by metastatic site. Moreover, terminology differed substantially between trials. Thus, our project demonstrates the difficulty to look at clinically relevant questions across several phase III trials. Besides in- and exclusion criteria or the definition of HR positivity versus negativity, also definitions of visceral and non-visceral metastases differ substantially between trials. For example, in some trials, central nervous system metastases are included with visceral metastases, in other trials they are considered a separate metastatic entity. Thus, it would be desirable to have unified definitions for future cross-trial comparisons as it was suggested for several items such as “endocrine resistance” or “visceral crisis” by the ABC2 consensus [23]. Furthermore, the impact of modern targeted therapies (i.e., CDK4/6 inhibitors, PD1 and PDL1 inhibitors) was not considered since our analysis only included studies published before 2014.

Conclusions

We evaluated and stratified the registration trials in MBC until 2014 according to HER2 status and HR status and pattern of metastasis. In the published subgroup analyses, we did not find any significant differences in response rates for visceral versus non-visceral metastases. For targeted i.v. therapies based on biomarker selection, there is a numerical trend – although statistically not significant – toward a beneficial effect of combination therapies favoring visceral disease regarding OS. Therefore, at the present time, there is no evidence for a predictive value of metastasis localization regarding response to systemic therapy in the published registration trials in MBC.

Patients should therefore receive guideline-recommended evidence-based therapies based on tumor biology (ER, PgR, HER2, PD-L1, gBRCA), response and toxicities to prior therapies, recurrence-free interval, general health, and life expectancy, as well as patients' preferences [24] but irrespective of their metastasis localization unless disease dynamics demand specific interventions.

Statement of Ethics

This article does not contain any studies with human participants performed by any of the authors.

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Disclosure Statement

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