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Over-treatment in metastatic breast cancer

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ABSTRACT

Metastatic breast cancer is an incurable disease and the main goals of treatment are prolongation of survival and preservation/improvement of quality of life. Thus the main philosophy of treatment should be to use the least toxic methods, as long as they provide sufficient disease control. In ER-positive tumours this can be in many cases achieved by endocrine therapy; in HER2-positive cancers efficacy of backbone therapy can be enhanced by an anti-HER2 agent. In patients requiring chemotherapy, consecutive single agent regimen provide disease control of a duration at least comparable to multidrug regimen, at a cost of significantly lower toxicity and are a preferred strategy in the majority of cases. Available data demonstrate, however, that aggressive chemotherapy is still overused in many metastatic breast cancer patients. The objective of this manuscript is to critically review available data on treatment choices and sequence in metastatic breast cancer across all breast cancer subtypes in relation to possible overtreatment, including therapies which are not recommended by current guidelines or not even approved. Our aim is to provide guidance on applying these data to clinical practice, but also to describe various, often non-scientific factors influencing therapeutic decisions in an aim to identify areas requiring educational and possibly political actions.

Metastatic breast cancer (MBC) is an incurable disease. That means that realistic therapy goals do not include cure, no matter how aggressive is the treatment. What can be achieved in most of cases is the prolongation of life and improvement or preservation of its quality. This last objective means symptomatic improvement at the cost of minimal toxicity. These principles are simple and clear, but unfortunately seem to be often forgotten by oncologists. Another wording of this general rule of cancer treatment states that toxicity should not outweigh the efficacy. In incurable diseases, the efficacy by definition is limited and gives no justification for aggressive therapies with high toxic death rate (an extreme example being high dose chemotherapy (ChT) with bone marrow/stem cell support).

Although in the vast majority of cases MBC is fatal, many patients, in particular those with luminal or human epidermal growth factor receptor 2 (HER2)-positive (HER2+) tumors, may live for years [1] – continuously or intermittently receiving antineoplastic treatment and experiencing its toxicities. Therefore at some points of the disease course majority of MBC patients may be exposed to overtreatment and oncologists need to know more about how to do less. Any treatment benefit needs to be weighed against its side-effects and realistic therapy goals together with patient' preferences must be always kept in mind. The treatment decision-making is additionally hurdled by the paucity of quality of life (QoL) data for particular compounds and treatments and over-time risk-benefit ratio fluctuations [2]. In symptomatic patients initial response to therapy results in symptomatic relief and improvement of QoL. With prolonged treatment, however, toxicities may accumulate and symptoms of disease may be replaced by those caused by therapy.

In view of limited data on comparative efficacy of available strategies, major role in treatment choices is unfortunately played by prejudices demonstrated both by patients and often – their physicians. Patients frequently expect to get "strong" treatment for their "deadly" disease and being treated less aggressively often becomes a source of anxiety related to fear of receiving suboptimal therapy. Similar attitude is unfortunately also frequently represented by oncologists, particularly in non-academic setting and in developing countries. On the other hand, physicians, even reluctant to choose more aggressive and toxic therapy are sometimes under pressure to do so because of patient preferences. Many patients accept much lower chance of benefit than the healthy individuals

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and health professionals, and are willing to undergo even serious toxicity of therapy for a relatively small objective gain [3].

Another important issue is the overuse and misuse of new therapies. Unfortunately, only a handful of recently approved agents substantially impact the course of disease. The consequence of accelerated approval of new agents is not only poor recruitment to confirmatory trials, but also possible overuse of expensive treatments without sufficient evidence on their efficacy and toxicity. Additionally, many drugs are easily used off-label based on the early results of clinical trials. It is important to remember that promising activity seen in early studies does not necessarily translate into survival benefit, and signals about significant toxicity may arise late. Geographical differences in the management of MBC are partially caused by availability and access to new agents and differences in reimbursement policy in particular countries. Overuse of new drugs is typical for high per capita income countries.

As shown in multiple surveys and market research studies, clinical practice often differs from evidence based data and existing guidelines [4–7]. The objective of this manuscript is to critically review available data on treatment choices and sequence in MBC across all breast cancer (BC) subtypes in relation to possible overtreatment, including therapies which are not recommended by current guidelines or not even approved. Our aim is to provide some guidance on applying these data to current clinical practice, but also to describe various, often non-scientific factors influencing therapeutic decisions in an aim to identify areas requiring educational and possibly political actions.

Luminal HER-2 negative breast cancer

Luminal HER2-negative (HR+/HER2-) BC in 2010 in the US made up for 61.2% of primary stage IV BC and, as it constitutes almost three quarters of all newly diagnosed BC, remains also the most prevalent subtype among patients who relapse following treatment for early disease [8]. The most important issues regarding treatment of luminal HER-2 negative MBC is: (i) the binary choice between ET and ChT as initial therapy; (ii) the optimal sequence of ET; and (iii) combining ET with molecularly targeted agent to enhance efficacy and prolong ChT free interval.

The main decision point for metastatic patients from this subgroup is the choice between endocrine therapy (ET) and ChT. These decisions are difficult and there are limited data directly supporting that choice. The few available randomized trials directly addressing this question were conducted in the 1970's and 1980's, and compared tamoxifen, progestins or androgens against ChT combinations which today are largely abandoned or considered suboptimal [9]. In a Cochrane review of these studies higher tumor response rate was observed in those treated with ChT, but this did not translate into any difference in overall survival (OS) [9]. No studies in MBC are available for comparisons between aromatase inhibitors or fulvestrant and modern chemotherapeutic agents, such as taxanes, capecitabine, vinorelbine or eribulin. Lack of high level of evidence data supporting treatment choices in metastatic luminal BCs forces oncologists to rely on indirect evidence from retrospective studies or prospective non-comparative data. Although comparisons of patients treated with ChT and ET outside studies randomizing subjects between these options are impossible, in general those treated with first line ET achieve longer PFS and OS. Obviously, populations selected for ChT and ET are different, but these differences are smaller than could be expected: in general the percentage of ER/PgR-positive patients in ChT studies ranges between 70 and 80%, whereas visceral involvement is present in about 50–80% of patients undergoing ChT and in about 50% of those treated with ET.

In spite of clear recommendations ET continues to be underused in MBC. A retrospective German study of patients treated between 2002 and 2004 showed that less than half of women with hormone-receptor positive MBC (48%) received ET in any line of treatment [4] – Table 1. Combination ChT was preferred in first-line treatment of MBC irrespective of the number of organs involved and hardly any patient received ET only [5]. In a large MarketScan based American study of almost 20 thousand post-menopausal patients with ER+/HER2- MBC on first line therapy, ET was used first in 60%, but the average number of ET lines was only 1.36 [5]. In a Dutch study of metastatic luminal HER2- BC patients treated in eight mostly non-academic institutions, 24% received initial ChT: these patients tended to be younger, have less comorbidities, were more often exposed to adjuvant ChT and ET, and were more likely to have visceral metastases. Not surprisingly, long term outcomes were significantly better in those selected for ET; this effect, however, remained also after adjusting for known prognostic factors [6]. In another study of "real life" data from 5 European countries (France, Germany, The Netherlands, Belgium, and Sweden), among 355 patients with HR+/HER2- advanced BC who progressed on ≥1 line of ET (adjuvant or advanced) and completed ≥1 line of ChT (advanced), 69% received ET in first line setting, whereas only 7% continued with 2nd line ET. The most frequent explanations for the choice of ChT were rapid disease progression and heavy tumor burden, irrespective of the line of treatment [7]. Although there are no such pattern of care studies available for other parts of the world, informal sources and personal communications suggest that the percentage of metastatic luminal BC patients beginning their treatment with ChT, at least in some parts of the world, is remarkably high.

One of major misunderstandings among many, mostly community oncologists is confounding visceral metastases and visceral crisis as an indication for ChT, resulting in not even considering ET in any case of visceral involvement. Indeed, as demonstrated in data from 1396 patients from 4 phase III studies of 1st line ET, the response rate is higher in non-visceral metastases, but if disease control is achieved, its duration is equal in patient with and without visceral involvement [10]. In view of lack of good evidence of the superior efficacy of either of the two treatment choices, therapeutic decisions need to rely rather on toxicity profiles and patient preferences. In a cross-sectional survey of 360 post-menopausal women from the US and Europe, with HR+/HER2– MBC, currently using ET or ChT, ET users reported better health-related quality of life, greater satisfaction with treatment, better feelings about side-effects, less bother with treatment side-effects and less activity impairment than ChT users [11].

Importantly, among luminal MBC patients on ET response is not a surrogate for long term benefit and similar OS is observed in those achieving an objective tumour regression or long term disease stabilization [12]. It thus needs to be kept in mind that, as most patients undergoing early lines of treatment for MBC are

Table 1
"Real life" patterns of treatment of metastatic luminal HER2- breast cancer.

Study	Number of patients	% ET-treated	
		1st line	≥2nd line
United States MarketScan databases 2002–2012 [5]	19,120	60	26
Southeast Netherlands Breast Cancer Consortium [6]	482	76	–
European (5 countries) [7]	355	–	69
German (Organgruppe Mamma der Arbeitsgemeinschaft Gynaekologische Onkologie) [4]	703	48% (any line)	

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