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Tumour Review

Time for more optimism in metastatic breast cancer?

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ABSTRACT

Treatment of metastatic breast cancer has substantially changed in the last decades. Availability of new cytotoxics and targeted therapies as well as changes in treatment philosophy and strategy have all contributed to a significant improvement in both survival and patients' quality of life. The multidisciplinary approach, personalised treatments based on tumour characteristics, patient's and disease history, as well as re-definition of treatment goals, aiming at the lowest possible impact on patients' life by replacing aggressive multidrug chemotherapy with single-agent cytotoxic treatment or endocrine ± targeted therapies, have all been the bases of the new treatment paradigm. More recently the development of the international advanced breast cancer (ABC) consensus guidelines have further contributed to this improvement. This review will focus on the major achievements and challenges in the different tumour subtypes and sites, with a focus on future research topics and trends.

Introduction

Breast cancer (BC) is the most prevalent female malignancy and the second most common cause of death in developed countries. In 2013 in the United States, an estimated 234,580 women will be diagnosed with invasive BC and 40,030 will die from it [1]. In 2008, in Europe there were 424,800 new BC cases and 128,700 BC-related deaths [2]. Every year almost half a million women lose their lives to breast cancer [2]. Recent years have faced remarkable changes both in the treatment philosophy of metastatic breast cancer (MBC) and in the available therapies, contributing to improvements in survival rates and quality of life.

BC is a heterogeneous disease, characterised by deregulation of multiple cellular pathways, different morphology and sensitivity to various treatments. Better understanding of BC biology has led to targeted treatments against specific molecular subsets, resulting in improved outcomes. In a large single-institution retrospective study of 2091 women, after adjusting for patient and tumour characteristics, women with HER2+/ER+(luminal HER2+) disease treated with trastuzumab had 5 years' survival similar to those with HER2-/ER+(luminal HER2−) tumours (29.7% vs. 31.3%, respectively), while the 5 years' survival of women with luminal HER2+ disease who did not receive trastuzumab was significantly worse (14.5%) and similar to trastuzumab-treated women with HER2+/ER− disease (17.7%). Finally, women with HER2+/ER− disease who did not receive trastuzumab had only 8.9% 5 years' survival, similar to that of triple negative (TN) patients (7.9%) [3].

Breast cancer subtypes also differ by the pattern of metastatic disease. In a large series of 3726 early BC patients from British Columbia bone was the most common metastatic site in all subtypes except basal-like tumours. Compared with luminal HER2−, luminal HER2+ and HER2+/ER− tumours were associated with significantly more brain, liver, and lung metastases, whereas basal-like tumours had higher rate of brain, lung, and distant nodal metastases but significantly less liver and bone metastases [4]. A strikingly high tendency of TN cancers to metastasize to brain was also seen in other series [5,6], whereas luminal B tumours seem to be related to higher risk of bone metastases [7]. Median survival was dependent on the tumour subtype and ranged from 0.5 years for basal-like to 2.2 years for luminal HER2− tumours ($p < 0.001$) [4]. Several studies have also demonstrated significant differences in the timing of distant recurrence: oestrogen receptor negative (ER−) tumours tend to be associated with early relapse whereas ER+ tumours show a persistent late risk beyond 5 years [8–10]. In the British Columbia population, although at the 5-year time point HER2+/ER− patients had significantly higher relapse rate than luminal HER2+ tumours, this difference was lost at 15 years as a result of more late relapses in the latter group [4].

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Selecting therapies in MBC requires therefore consideration not only of patient status and disease extent but also of the tumour molecular characteristics, defined by either genomic testing [11] or immunohistochemistry [12–14]. When considering survival improvements and potential areas of progress in MBC it is hence crucial to analyse each disease subtype separately.

Her2 negative breast cancer

Endocrine responsive (luminal) breast cancer

Luminal HER2-negative BC represents 60–65% of all newly diagnosed patients. Although prognosis in this subtype is generally good, still many women will relapse and luminal HER2-negative BC remains the most common subtype among MBC patients.

What are the available options in luminal MBC?

The choice of endocrine treatment (ET) in luminal BC is substantiated by its targeted mechanism of action, low toxicity profile, which allows prolonged treatment in responding patients, and lower sensitivity of these tumours to chemotherapy.

Overall, in patients with luminal MBC, ET achieves a response rate (ORR) of 20–40% and a clinical benefit ratio (CBR) of 40–80%, according to the type of therapy and prior drug exposure. The median response duration is about 8–14 months, although responses can last several years [15].

The progress in ET predominantly lies not in the new agents being "better", but in creating additional treatment options, resulting in widening the range of active and not generally cross-resistant agents, enabling sequential treatments and long-term disease control.

In postmenopausal women. The cochrane review of 25 studies of aromatase inhibitor (AI) versus any other treatment (9416 women) demonstrated a significant overall survival (OS) benefit for AI over other ET (HR 0.89), with a consistent effect across all subgroups [16].

An additional drug enriching the armamentarium of ET is fulvestrant, used as 2nd-line therapy after failure of tamoxifen and as 3rd-line after failure of tamoxifen and AIs [17]. At currently recommended dose of 500 mg, fulvestrant showed a significant PFS prolongation in comparison to 250 mg and to anastrozole [18,19]. The combination of fulvestrant and AIs as 1st-line therapy provided discordant results and has still to be considered an exploratory approach, deserving additional evaluation in well-designed trials [20–22].

In patients with acquired resistance to ET, the mTOR inhibitor everolimus has led to important improvements in treatment outcomes. In the phase II TAMRAD study the addition of everolimus to tamoxifen resulted in improvements in CBR (61% vs. 42%) and TTP (8.6 months vs. 4.5 months, HR 0.54). The observed 55% reduction in the risk of death awaits confirmation by the phase III trial [23]. The phase III BOLERO-2 study demonstrated substantial prolongation of median PFS (10.6 months vs. 4.1 months, HR 0.36; $p < 0.001$) in patients administered exemestane + everolimus vs. exemestane alone [24]. On the contrary, no benefit in terms of PFS was seen in a Phase III trial in AI-naive, ER+ advanced disease from the addition of temsirolimus to letrozole in 1st-line therapy [25]. The explanation of these conflicting results is not known – the most plausible include suboptimal temsirolimus schedule (intermittent inhibition of mTOR likely to be less effective) and the different patient population in the temsirolimus study (1st-line ER+ patients have high tumour control rates on ET alone, leaving less place for improvement, and are also less likely to have acquired resistance mechanisms).

In premenopausal women. The combination of a gonadotropin-releasing hormone (GnRH) agonist and tamoxifen is an established option [26]. Clinical data with ovarian suppression plus AIs, despite encouraging results as 1st- and 2nd-line therapy, are still limited [27–29]. The combination can be considered in case of adjuvant tamoxifen discontinued by <12 months or relapse while on tamoxifen. Fulvestrant used alone or with GnRH agonist demonstrated promising activity in small phase II studies; these results warrant confirmation in larger trials [30,31].

What are the challenges and future directions?

As about 25–50% of luminal BCs are de novo resistant to ET and most if not all MBCs develop acquired resistance, better knowledge of the resistance mechanisms may help developing new targeted drugs blocking resistance pathways. Downregulation of ER expression, ER mutations, activation of downstream molecules in other growth factor signalling pathways, alterations in the balance of co-regulators and co-activators or modifications in epigenetic regulation, angiogenesis, and other tumour and host-related factors are all recognized resistance mechanisms and focus of extensive research programs [32]. The molecular cross-talk between ER and growth factor signalling pathways (i.e. EGFR, HER2, IGF-1R) is one of the most critical contributors to endocrine resistance, involving two major cascades (RAS-MEK-MAPK and PI3K-PTEN-AKT-mTOR). Some of the combinations of ET with drugs targeting these downstream signalling pathways, such as everolimus, have demonstrated activity and entered clinical practice, other are under evaluation in preoperative and advanced disease setting [33].

Interesting hypothesis-generating data come from the phase III trial of 1286 patients with ER+ MBC randomized to receive letrozole ± lapatinib, where a non-significant trend toward prolonged PFS for the combination was seen in patients relapsing within 6 months after tamoxifen discontinuation, i.e. those with presumed secondary ET resistance (HR 0.78; $p = 0.117$) [34].

New classes of drugs hold promise for improvement in luminal BC: in a phase II study of letrozole ± an oral cyclin-dependent kinase (CDK) 4/6 inhibitor PD-0332991, an impressive prolongation of median PFS from 5.7 to 18.2 months (HR 0.38; $p = 0.015$) was observed and a phase III study is currently ongoing [35].

Triple negative breast cancer

TNBC accounts for 15% of all BCs. It shows substantial overlap with basal-type and *BRCA*1-related BCs, but this overlap is not complete and TNBC is a heterogeneous subgroup [36,37]. Generally, TNMBC is characterized by aggressive clinical course with median survival around 12 months, much shorter than in other subtypes of MBC [6,38].

What are the available options in TNMBC?

In contrast to other BC subtypes, there is no specific systemic regimen for TNBC, and little data to support treatment selection [39,40]. Notably, TNMBC can have higher ORR to a variety of standard chemotherapy agents, although the duration of response is usually short (median of 12 weeks to 1st-line, 9 weeks to 2nd, and 4 weeks to 3rd-line) [6,41].

Platinum agents are facing a renewed interest in TNBC and *BRCA1/2* related BC, based on preclinical and clinical data and several studies to confirm their efficacy are underway. However there are yet no randomized data supporting platinum-based chemotherapy as the optimal regimen [42]. Several trials suggest a lack of specific benefit for taxanes for TNBC; the efficacy of anthracycline-based regimens also remains controversial [42,43].

What are the challenges and future directions?

BRCA-associated BCs have a defect in homologous DNA repair and as alternative DNA repair mechanism use base excision repair,

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