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Therapeutic approaches in young women with advanced or metastatic breast cancer

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Introduction

Advanced breast cancer is a chronic disease with a remarkably heterogeneous clinical picture and a mean survival of 2 to 4 years [1]. Treatment goals are to increase overall survival and disease-free survival, and improve quality of life [2]. The inclusion of novel targeted therapies in recent years has brought renewed hope for the possibility of improving these goals, and has broadened the spectrum of therapeutic choices.

Prognostic and predictive factors for early disease differ from those of advanced disease. In spite of this, many therapeutic decisions in young women with advanced breast cancer are based on predictive characteristics of early breast cancer. There is evidence demonstrating that approximately 20% of metastatic or relapsed tumors undergo changes in the expression of either hormone receptors or human epidermal growth factor receptor-2 (HER-2)/neu in comparison to the primary tumor [3]. Although methodological reasons might be behind some of the discordances in results, true biological changes in the clinical phenotype cannot be completely excluded. At any rate, the discordance in pathology and molecular markers between primary and metastatic tumors seen in breast cancer may have a negative impact on overall survival because of inadequate use of the available therapies [4].

In early beast cancer, young age *per se* at diagnosis is universally considered a negative prognostic factor, but this does not seem to translate to women with advanced breast cancer [5]. However, breast tumors in women under 40 are more likely to be associated with high-risk tumor features and poorer prognosis [6], and therefore, in the setting of metastatic breast cancer, younger age could be considered an additional factor of worse prognosis. Until specific markers of metastatic breast cancer in young women are identified, therapeutic options in this age group remain the same as for older women, i.e. endocrine therapy, chemotherapy, targeted therapy, or a combination of the three.

Endocrine therapy

Endocrine therapy is indicated in young women with luminal-type tumors, low tumor burden, no visceral involvement, slow progression, long disease-free intervals and a history of sensitivity to endocrine treatments.

The vast majority of women under 40 years are premenopausal. Therefore, as in early breast cancer, in advanced breast cancer the abolition or suppression of ovarian function is the primary objective [7]. Currently, the best therapeutic option for this purpose is the use of luteinizing hormone-releasing hormone (LHRH) agonists, either alone or in combination with tamoxifen, although the latter option is significantly better in terms of overall survival and progression-free survival than an LHRH agonist alone [8].

Currently, there is insufficient data to support the use of aromatase inhibitors (AI) in premenopausal women with early breast. Nevertheless, in metastatic breast cancer, preliminary data from Agrawal et al [9] on 36 premenopausal patients (median age 44 years) showed that treatment with goserelin plus anastrozole produced sustained clinical benefit and minimal side effects in premenopausal women with estrogen receptor (ER)-positive advanced breast cancer.

On the other hand, treatment recommendations in young postmenopausal women are as follows:

- In women who have not received prior endocrine therapy, AIs are the treatment of choice [10]. There is evidence suggesting that letrozol may be more active than anastrozole in metastatic breast cancer as second-line therapy [11].
- In women who have received prior treatment with tamoxifen, second-line treatment choices include AIs and the selective estrogen receptor down-regulator fulvestrant. Both therapies have been shown to be equally effective, although fulvestrant is associated with a significantly lower incidence of joint disorders compared

with anastrozole and seems to produce a non-significant increase in time to progression [12, 13].

- In women previously treated with AIs, and who have remained amenorrheic, second-line treatment could involve the use of fulvestrant, or a non-steroidal AI (such as anastrozole) if prior treatment involved a steroidal AI (such as exemestane), and *vice versa*; i.e. a steroidal AI if prior treatment involved a non-steroidal AI [14].

Chemotherapy

Chemotherapy is indicated in young women with triple- and HER-2-negative tumors, luminal-type tumors refractory to endocrine therapy, and in rapidly progressive disease or high tumor burden, regardless of phenotype.

Therapeutic recommendations for young premenopausal women regarding adjuvant chemotherapy are the same as for older women. However, the fact that a larger proportion of young women are HER-2 positive, hormone receptor negative, and tolerate better chemotherapy than their older counterparts may have a bearing on the type of regimen used.

In patients without prior treatment, anthracyclines and taxanes followed by vinorelbine, gemcitabine and capecitabine are currently the most active agents for advanced breast cancer according to the 'Third Consensus on Medical Treatment of Metastatic Breast Cancer' [15]. A large body of evidence has shown that the combination of anthracyclines and taxanes is superior to the use of either drug alone [15].

In patients with recurrent disease and prior anthracycline therapy, gemcitabine in combination with paclitaxel, and capecitabine in combination with docetaxel, were shown to be superior to the use of taxanes alone [16, 17]. However, none of these studies separately analyzed patients younger than 40 years of age; therefore, it is not known whether there are significant differences in terms or efficacy or toxicity in this subgroup of patients.

Triple-negative breast cancer, defined as the absence of endocrine and HER-2 receptor expression, deserves to be mentioned separately, because of its high prevalence in advanced breast cancer and in women under 40 years [18].

At present, no specific recommendations can be made for young premenopausal women, but data collected from trials with neoadjuvant chemotherapy have yielded interesting findings. Importantly, women with triple-negative tumors respond extremely well to chemotherapy, especially to taxanes, platinum-based cytotoxics and anthracyclines, as well as to high-dose regimens [19, 20], however survival rate in non-responders is short.

Targeted therapies

The identification of specific cellular receptors has encouraged the search for molecules aimed at specific molecular targets, such as the intracellular and extracellular domains of HER (trastuzumab, gefitinib or erlotinib) and the vascular endothelial growth factor [21].

To date, the three agents approved for the treatment of advanced breast cancer are trastuzumab, lapatinib and bevacizumab.

Trastuzumab

In combination with paclitaxel, trastuzumab is indicated for the first-line treatment of HER-2 overexpressing metastatic breast cancer or as monotherapy for the treatment of HER-2 overexpressing breast cancer in patients who have received one or more chemotherapy regimens for metastatic disease (http://www.accessdata.fda.gov/drugsatfda_docs/label/2008/022059s004lbl.pdf).

The mechanism of action of trastuzumab is not fully understood, but may involve inhibition of HER-2 cleavage and shedding, induction of HER-2 gene expression, inhibition of the PI3K pathway and/or inhibition of angiogenesis [22].

The pivotal trial by Slamon et al [23] demonstrated that the addition of trastuzumab to chemotherapy was associated with a significantly longer time to progression, higher rates of objective response, longer duration of response, lower mortality at 1 year, longer survival and a 20% reduction in the risk of death in women with metastatic breast cancer overexpressing HER-2. Unfortunately, there are no specific data on women under 40 years, but the fact that younger women tend to have a greater expression of HER-2 than their older counterparts can give us an indication of the benefits this targeted therapy may offer young women with advanced breast cancer.

Lapatinib

In combination with capecitabine, lapatinib is indicated for the treatment of patients with advanced or metastatic breast cancer whose tumors overexpress HER-2 and who have received prior therapy including an anthracycline, a taxane and trastuzumab (http://www.accessdata.fda.gov/drugsatfda_docs/label/2007/022059s002lbl.pdf).

Lapatinib produces a reversible and selective inhibition of HER-1 and HER-2 tyrosine kinases [24]. Lapatinib in combination with capecitabine was superior to capecitabine alone in terms of time to progression in women with HER-2 advanced breast cancer that had progressed after treatment with anthracycline, taxane or trastuzumab-based regimens [25]. Again, there are no specific data for women younger than 40 years.

Bevacizumab

In combination with paclitaxel, bevacizumab is indicated for the treatment of patients who have not received chemotherapy for metastatic HER-2-negative breast cancer (http://www.accessdata.fda.gov/drugsatfda_docs/label/2009/125085s0168lbl.pdf).

Bevacizumab is a humanized monoclonal antibody that recognizes and neutralizes all major isoforms of VEGF, preventing receptor binding and inhibiting endothelial cell proliferation and vessel formation [26].

In a phase III trial, bevacizumab plus paclitaxel significantly prolonged progression-free survival compared with paclitaxel alone and increased the objective response rate. The overall survival rate, however, was similar in the two groups. Importantly, a subgroup analysis showed an additional benefit in patients under 49 years and those with triple negative disease [27].

Conclusions

Advanced breast tumors in young women are more likely to be associated with high risk features, such as hormone receptor negativity, increased HER-2 expression and triple negative disease. Unfortunately, specific data on the epidemiology and treatment of women younger than 40 years is almost nonexistent, and therefore, to date treatment of these women does not differ from the treatment of older women, being endocrine therapy, chemotherapy, targeted therapy, or a combination of the three. Current endocrine treatment on young premenopausal women relies on the administration of LHRH agonists. In relation to chemotherapy, in patients without prior treatment, anthracyclines and taxanes followed by vinorelbine, gemcitabine and capecitabine are currently the most active agents. Regarding targeted therapies, the three agents currently approved for the treatment of advanced breast cancer are trastuzumab, lapatinib and bevacizumab.

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