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REVIEW ARTICLE

Breast cancer in young women: an overview

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Abstract Despite dramatic advances in cancer research setting, breast cancer remains a major health problem and represents currently a top biomedical research priority. Worldwide, breast cancer is the most common cancer affecting women, and its incidence and mortality rates are expected to increase significantly the next years. Recently the researchers' interest has been attracted by breast cancer arising in young women. Current evidence suggests that in women aged <45 years, breast cancer is unquestionably the leading cause of cancer-related deaths. This type of cancer seems to be highly heterogeneous and has potentially aggressive and complex biological features. However, management strategies, recommendations and options are not age based and the 'complex' biology of this type of cancer remains uncertain and unexplored. In this review, we summarize the latest scientific information on breast cancer arising in young women highlighting the heterogeneity and the complex nature of this type of cancer.

Keywords Breast cancer · Guidelines · Young woman · Tumor heterogeneity · Next-generation sequencing analyses · Personalized cancer medicine

Introduction

Despite important advances in research, breast cancer remains a major health problem and represents a top biomedical research priority. The incidence of this aggressive disease with approximately 1,7000,000 new cases each year remains alarmingly high; these rates are suggestive of slow progress made in the prevention setting [1, 2]. Nevertheless, for women with already established diagnosis mortality rates have been improved, but unfortunately the median survival in the metastatic setting is dramatically low (~24 months). Worldwide, breast cancer is the most common cancer affecting women, and its incidence and mortality rates are expected to increase significantly the next 5–10 years [3]. These cancer rates are expected to be disproportionately high in developing countries and are estimated to reach 55% increased incidence and 58% greater mortality in 20 years [4].

Unquestionably, with the standardization of systemic chemotherapy as the gold-standard approach for most cancer types and the modest improvement in both survival rates and toxicity reduction, most interest by the scientific community and funding by the pharmaceutical industry have been attracted by targeted therapy [5, 6]. Nevertheless, the resistance to therapy represents the 'big' problem and the substantial improvement in survival rates still remains a researchers' dream. It has to be highlighted that great efforts have been made in breast cancer field over the past decade. However, the 'battle' against this enigmatic and aggressive type of cancer continues [7].

Recently, the researchers' interest has been attracted by breast cancer arising in young women. Robust evidence suggests that in women aged <45 years, breast cancer is undoubtedly the leading cause of cancer-related deaths. Moreover, available data to date suggest that breast cancer

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in young women represents a significant burden in developing countries contrarily to developed countries and that a disproportionate number of young women lost their life every year because of this type of cancer. The exact definition of a young woman in breast oncology setting varies, with most articles referring to women <35, 40, or 45 years as young [8]. Nevertheless, several studies support that, among women with premenopausal breast cancer, further subdivision into those with very early disease (<40 years) and relatively early disease (<40–49 years) could be meaningful [9].

In this article, we deal with breast cancer arising in young women and we try to provide the latest scientific information on this issue highlighting the heterogeneity, the complexity and the 'aggressive' nature of this type of cancer. A view toward the future is also provided.

Breast cancer

It is now established knowledge that women with breast cancer are treated with combinations of surgery, chemotherapy and radiotherapy. Continued research efforts are making treatments more personalized with the hope to minimize side effects and to improve overall survival rates [10].

Despite recent progress on cancer therapy, current evidence-based medicine shows that progress against breast cancer over the past decade is slow. This is translated into few months of survival prolongation in the metastatic field. This is not surprising if we consider important limitations of currently available targeted therapies. The reasons for high intrinsic and acquired resistance rates to available targeted drugs include their temporary antitumor activity and the lack of consideration of interpatient and intratumor heterogeneity. The understanding of this extremely complex heterogeneity is crucial in the 'war' against breast tumorigenesis and metastasis [11].

It has to be highlighted that important progress has been made for HER2-positive breast cancer, which accounts for 20% of all breast cancer patients. The identification of the HER2 pathway and its dysfunction when the *HER2* gene is amplified has led to the development of the famous anti-HER2 monoclonal antibody (mAb), trastuzumab [12]. Phase III randomized controlled trials reported that trastuzumab in addition to chemotherapy in HER2-positive breast cancer significantly improves overall survival in metastatic and adjuvant settings. For these reasons, trastuzumab has been the standard first line of treatment for these patients [12, 13]. However, recurrence and disease progression rates still remain dramatically high. The single agent trastuzumab emtansine (T-DM1) provides a potentially improved clinical outcome. The safety and efficacy of this novel agent in breast cancer field as well as its limitation in the treatment of metastatic HER2-positive breast cancer has been assessed recently [12–14]. Phase III trials are currently underway, comparing both this single agent with various regimens and an important variety of novel combinations of mAbs with TKIs. The major hope for the future in the fight against this aggressive and enigmatic type of cancer is the discovery of novel 'druggable' agents [12, 13].

Breast cancer biology in young women

General considerations

It has to be highlighted that in USA each year, approximately 10,000 women aged <40 years are diagnosed with invasive breast cancer, accounting for 4–5% of all women diagnosed with breast cancer. In the West, it is reported that <4% of women diagnosed with breast cancer are aged <35 years. As for the East, the Asian breast cancer Society reports that 13% of women diagnosed with breast cancer are aged <40 years, while 5% are aged <35 years. This dramatic increase of breast cancer cases in young women is very important because the behavior of these tumors is in the majority of cases more aggressive in comparison with older women. This leads unfortunately to a disproportionate number of lost lives because of cancer each year [14, 15].

Notably, the usual presentation of advanced stages at diagnosis, more aggressive pathological characteristics, a greater rate of triple-negative and HER2-overexpressing tumors, and higher rates of recurrence at any clinical stage in comparison with older women represent the main causes of the 'aggressive' nature of breast cancer in young women [16]. To date, it is supported that the increased risk of loco-regional recurrence in young women with breast cancer, methods for fertility preservation in these women, psychological interventions and potential, challenges and perspectives associated with longer survival rates remain highly uncertain, unexplored and controversial [17].

Recent evidence suggests that young age at diagnosis of breast cancer represent an independent prognostic factor of survival [18]. Several large-scale studies report that young age at diagnosis is highly associated with huge risk of recurrence and death [19, 20]. In addition, endocrine receptors, HER2 and proliferation markers, appear to be different in young women. Recent studies support that more aggressive and invasive subtypes of breast cancer are more frequent in young women [21]. Moreover, the researchers believe that hormonal therapy efficacy is significantly lower in young women [9]. Tamoxifen role and its relationship with endometrium cancer in young women are also controversial. More frequently in young women occur type I endometrial cancers. These cancers are

developing in an environment of unopposed estrogen and often arise out of endometrial hyperplasia, characterized by mutations in the PTEN gene, K-ras, and microsatellite instability inception [22]. In this way, it has to be highlighted that 'high' connection of genetic mutations for breast and endometrium cancers is reported in the literature [23]. These findings underline that tumors presenting in young women are more aggressive and this is maybe due to biological differences. In addition, great skepticism exists about the intratumor heterogeneity status of the disease that arises in young women [24].

Breast cancer heterogeneity, mutational background and current evidences

Recent studies have made an important effort to assess the mutational landscape of breast cancer using powerful next-generation sequencing (NGS) analyses [25]. Point mutations have been observed in TP53 and PIK3CA genes, accounting for ~25% of cases. However, there is a lack of evidence regarding the landscape of somatic mutations in young women [26, 27].

It has to be highlighted that Stephens et al. [28] performed a powerful whole-genome sequencing (WGS) analyses of 100 breast tumors. No association between total number of somatic base substitution and age at diagnosis in both ER-positive and ER-negative tumors was observed. Recently, the pattern of somatic mutations was evaluated in 167 young breast cancer women, of whom 54 were diagnosed during pregnancy. An amount of 84 mutations in 19 genes were assessed, including 29 different mutations of PIK3CA and 7 and 6 mutations for ERBB2 and TP53, respectively [29]. The researchers report that no differences were observed between the pregnant and non-pregnant groups of women. Only 5% of patients had a TP53 mutation, although it should be noted that only 12% of known P53 mutations were explored in this study. No ERBB2 mutations were observed in this study. Regarding germline mutations, BRCA1/2 mutations were the most common, accounting for up to 40% of familial breast cancer [30].

The largest analysis on this issue enrolled 3.340 women with age ≤50 years at diagnosis time. The most important finding was that 7% of breast cancer women had a BRCA1 mutation. BRCA1 carriers were significantly younger (mean age 41.9 versus 44.1, $P < 0.001$) and had more ER-negative (84.1 versus 38.1%, $P < 0.001$) and HER2- negative (93 versus 79%, $P < 0.001$) tumors [31]. It has to be emphasized that CHEK21100delC represents another mutation that occurs more frequently in younger patients. Notably, recent evidence assessing 25.600 women reported that ~2% were CHEK2*1100delC heterozygous [32]. These patients were younger, and most of them were at a premenopausal status and have ER-positive disease. The more interesting aspect is that women with familial breast cancer develop this aggressive disease frequently at an earlier age. This fact adds undoubtedly further complexity and heterogeneity to the genetic landscape of breast cancer in young women. It is obvious that more extensive research is clearly needed in order to clarify the 'biological background' for the development of this enigmatic disease [33].

Recently, results of the largest prospective study to date evaluating women who were aged <40 years at diagnosis with breast cancer were published [34]. This important study enrolled ~3000 young women diagnosed with breast cancer between 2000 and 2008. The median age at diagnosis of the disease was 36 years, and the majority of women had ductal histology (86.5%) and grade III (58.9%) disease. Approximately 50% of women had node-positive disease, and 27% had multifocal tumors. One-third of tumors were ER-negative, while one-quarter were HER2-positive. Similar results were reported among 400 women assessed in the Young Women's Breast Cancer Study [35], which started in 2006 including women aged <40 years at diagnosis. It has to be highlighted that this study on young women with breast cancer reported high rates of lymphovascular invasion and lymphocytic infiltration. Other retrospective studies have assessed important differences in breast cancer women according to age. The largest analysis up to date was conducted by Gnerlich et al. [36] including >200.000 women. Approximately 15,000 breast cancer women were aged <40 years at diagnosis. The most important finding was that young women were more frequently diagnosed with large tumors ($P < 0.0001$), lymph-node involvement ($P < 0.0001$), poorly differentiated tumors ($P < 0.0001$), and ER-negative tumors ($P < 0.0001$). These findings highlight the aggressive nature of the disease in young patients. In addition, a California Cancer Registry study [37] including 5600 women aged <40 years at diagnosis reported a statistically significant HER2-higher expression in the younger women. It is more than clear from the results of these studies that tumors diagnosed in young women have more aggressive pathological characteristics [36].

We have also to highlight that important issues about the biology of breast cancer in young women have been arisen by Azim et al. [38]. The researchers suggested that the high BRCA1 mutation signature expression is consistent with the reported high prevalence of BRCA1 mutations in young patients that are commonly diagnosed with basal-like tumors; The high expression of the BRCA1 mutation rate and luminal progenitors in younger patients may explain why young women develop more frequently basal-like tumors. Moreover, it is reported that RANKL (receptor activator of nuclear factor kappa-B ligand) stimulates osteoclastogenesis and therefore targeting RANKL can reduce the risk of osteoporosis and skeletal events secondary to bone metastases [38]. It is also known that in young women the breast is

enriched with an immature mammary cell population, which increases during pregnancy and breastfeeding, an effect that has been shown to be mainly regulated by RANKL. The researchers report that in preclinical breast cancer models RANKL inhibition arrested progestin-induced cancer. Therefore, RANKL appears to be a potentially robust breast cancer target, beyond its already known and established role in bone metastases [39].

Another important issue is that nowadays several genomic tests are available to improve prognosis and help at the decision-making process in the adjuvant setting. These tests include Oncotype Dx®, Mammaprint®, Endopredict, Breast Cancer Index and others. The critical point is that they add important prognostic information in patients with ER-positive breast tumors and represent a reliable tool to distinguish women at low and high risk of recurrence. These tests are integrated in standard clinical practice with great success, but there is yet great skepticism whether they have the same prognostic role in young women with breast cancer because they were initially developed using postmenopausal women. In the future, the role of genomic tests in young women with breast cancer remains to be clarified [40, 41].

Moreover, it has to be highlighted that *BRCA1* and *BRCA2* are involved in breast and ovarian cancer, increasing the risk of both in women with mutations of these genes. Dealing with young women, recent evidence suggests that laparoscopic surgery and robot-assisted laparoscopic approach seem to be adequate for the treatment of early-stage ovarian cancer [42]. Medical and surgical treatment in different types of cancers in women can be very challenging [43].

Conclusions–future perspectives

There is clear evidence that breast cancer arising at young women is more aggressive and has potentially unique, aggressive and complex biological features [44–46]. Nevertheless, to date, management strategies and options are not age based. Unquestionably, there is a crucial need to adapt a biology-based strategy to plan the treatment for younger breast cancer women. The major hope is that the characterization of somatic mutations occurring in breast cancer arising in young women using NGS technologies could identify important key driver mutations, significantly mutated genes and key-tumorigenic pathways that can be effectively targeted in the near future [47]. Protein-coding and non-coding mapping of the genome using powerful NGS technologies for whole-genome sequencing/whole-exome sequencing can improve our understanding of cancer. Novel drugs could be used in the future versus novel pathways and targets that could be identified by the application of these new technologies. But the most crucial point is the effort that should be made to try to understand the inter-individual genetic heterogeneity as a cause of diversity in phenotypes [48]. Notably, interpatient tumor genetic mutational complexity and heterogeneity, or both coding and non-coding DNA and RNA, are essential for understanding, preventing and treating cancer. The major challenge for the scientific community today is how to predict therapeutic resistance and how to select the ideal therapeutic agent combination for each patient in order to improve survival. In this effort to reach pragmatic personalized cancer treatment, the crucial point is to understand how this diversity–heterogeneity affects genome function and gene expression regulation in young women with breast cancer [48–50]. Unquestionably, extensive scientific work is still necessary in order to understand the complex biology of this disease. Then, the multidisciplinary management and the attempt to improve the outcomes of young women with breast cancer must represent the top biomedical priority in this field.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Research involving human participants and/or animals This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent For this type of study formal consent is not required.

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