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Breast cancer in young women

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ABSTRACT

Breast cancer (BC) in young women is rare, affecting only 4–6% of women under the age of 40. Regardless, BC remains the most common malignancy among younger patients. Recently, a significant increase in BC rates has been observed among pre-menopausal subjects. Breast cancer in young women requires special attention due to its specific morphologic and prognostic characteristics and unique aspects, including fertility preservation and psychosocial issues (e.g. its impact on family life and career). Young women are more likely to have tumors with higher incidence of negative clinicopathologic features (higher histological grade, more lymph node positivity, lower estrogen receptor (ER) positivity, higher rates of *Her2/neu* overexpression). Also, they tend to be diagnosed at more advanced stages of the disease. That, in turn, contributes to less favorable prognosis as compared to older women. Young women are generally treated similarly to older patients. Surgical management includes mastectomy or breast-conserving surgery, followed by radiation therapy (younger women have higher local recurrence rates than older women, especially after breast-conserving therapy). Although the basics of chemotherapy are the same for patients of all ages, younger women have some special considerations. It is important to consider options for fertility preservation before starting systemic treatment. Patients should have access to genetic testing as their results may affect the choice of therapy. Younger women and their families should receive adequate psychological support and counselling.

Key words: breast cancer, treatment, fertility

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INTRODUCTION

Attempts have been made to define 'young age' but the definitions are frequently ambiguous and open to interpretation. In case of breast cancer (BC), 'young patients' are women diagnosed with cancer before the age of 40, although such occurrence is rare as BC typically affects older women, over the age of 50. Identification of young patients is clinically valid as BC in that age group presents with certain biological differences and often requires special management. Typically, BC in young women has a more aggressive course, less favorable prognosis, and worse survival rates as compared to older subjects [1]. Also, treatment of young patients is associated with numerous additional challenges, i.e. preservation of fertility, possibility of continuing the pregnancy despite the diagnosis, or problems with breast feeding. BC in young women is also a social issue since the disease often appears during the time of the highest family and career activity.

EPIDEMIOLOGY

BC is the most common malignancy in women in Poland — in 2012 its incidence reached 17000 [2]. The risk increases with age but women between 50–69 years of age are the most frequently affected, and only 2–7% of all cases are diagnosed in the age group under 40 [3]. Despite the risk for BC in the third decade of life being only 0.04% per year, it remains the most common malignancy in women under 35 years of age [4]. In Poland, a growing number of cases are registered every year. Even if morbidity rates in women under 40 years of age have not been statistically significantly different since the 70s of the previous century, (e.g. in the United States), due to a steadily increasing number of cases in that age group, the absolute number of young women with BC continues to grow [5]. Some sources also report increased BC incidence in young women. The GRELL study analyzed epidemiological data from 7 European countries

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and found the mean rate to be increasing by 1.2% annually between 1990-2008. The rate was the highest in the age group between 15–34 years as compared to older women (34–39 years of age), especially in France and Portugal [6]. The fact that a growing number of patients are diagnosed in more advanced stages, which is the direct consequence of lack of screening and preventive measures in that age group and more aggressive disease course in young women, has become a cause for concern. Delayed diagnosis may also result from lack of oncological vigilance among practitioners who encounter young women with breast changes (during pregnancy, puerperium or lactation).

BC incidence varies greatly, depending on race and ethnicity, which is especially visible in a multi-ethnic American society. In the age group of > 45 years, the disease is more frequently detected in Caucasian women as compared to African-Americans, whereas in the age group of ≤ 35 years the morbidity and mortality rates in the latter group are 2- and 3-fold higher, respectively as compared to the former [5, 7]. Also, genetic background and family history are more often detected in women under 40.

DIAGNOSTIC TESTING

Young women with suspicion of BC ought to be diagnosed by an experienced team of doctors and even despite relatively low risk for BC in patients < 40 each abnormality detected on palpation requires speedy and careful diagnostic testing using the approach known as the 'triple test' — physical breast examination, imaging test, and cyto- or histopathologic verification. It allows to confirm the initial diagnosis in 95% of the cases and avoid surgical removal of benign lesions. The use of oral contraceptives has no effect on the possibility of performing the imaging test. Ultrasound tests may be performed at any phase of the menstrual cycle, mammogram in the first two weeks and MRI in the second week of the menstrual cycle, although in case of a dynamic pattern of the lesions it is vital to conduct the tests as soon as possible [4, 8]. The literature offers no data on the benefits of regular preventive screening in women < 40 [9], as dense structure of the breasts in that age group often hinders proper interpretation of mammogram results. Due to low specificity of mammogram imaging in young women, its application in screening programs might increase the number of false-positive results and become the source of unnecessary stress and anxiety.

Although the use of breast implants has no correlation with the risk for BC, their presence lowers the effectiveness of mammogram testing, thus contributing to delayed diagnosis [10, 11]. Therefore, women who consider breast implants ought to be informed about that risk.

The most valuable imaging techniques in young women include ultrasound and MRI, although they both have their limitations and are not recommended for screening in women < 40. Ultrasound is a valuable screening tool, complementary to a mammogram in case of significant density of the breast, but the sensitivity of the test itself is low and its value depends largely on the skills and expertise of the sonographer. In turn, MRI has high sensitivity but its insufficient specificity results in a significant number of false-positive findings. Regardless, the method is currently being considered as a screening tool for young women at high risk for BC [4]. Perhaps medical advances will soon propagate new imaging techniques, e.g. contrast-enhanced mammogram, ultrasound elastography, or MRI spectroscopy.

The test itself is the cheapest and the most available diagnostic method. Young women should be advised to perform breast self-exam and undergo breast exam during the doctor's appointment on regular basis, even if clinical data on the correlation between such management and survival are limited. Regardless, these methods detect one-third of BC malignancies in the entire population, with 80% in women < 35 years of age who undergo no screening tests (mean tumor size is 2 cm) [12].

TUMOR BIOLOGY

Unfavorable prognostic factors are more often observed in young women as compared to their older peers. At diagnosis, the lesions are larger, less mature, less often contain estrogen receptors (ER) and progesterone receptors (PR), with more cases of HER2 overexpression and vascular invasion [1]. Anders et al., in their retrospective study of 700 tumors, found a higher rate of grade 3 tumors and lower number of lesions with expression of estrogen receptor in women < 45 years of age [13].

A retrospective observational study, which included histopathological characteristics of breast cancer in women < 40, has recently been published. In that large group of cases (2956) invasive ductal carcinomas were dominant — 86.5%, including 58.9% G3 tumors. Approximately 50% of the affected women were diagnosed with metastases to axillary lymph nodes, and 27% had multifocal lesions. HER2 overexpression was observed in 24% of the tumors and estrogen receptors were found in 66% of the cases. Triple-negative (lack of ER, PR expression, and HER2 overexpression) tumors were detected in 19.9% of the patients [14]. In another study, triple-negative cancers were found in 26% of the affected women and HER2 overexpression in 34% of women aged ≤ 40 [15]. A recent molecular classification of breast cancers, based on DNA-microarray analysis, distinguishes between 5 subtypes: luminal A, luminal B, HER2 overexpression, basal-like, and normal-like subtype with expression of genes typical for normal breast cells [16].

Molecular studies have confirmed that BC subtypes with worse prognosis are more often found in young women.

One study found basal cancers with the worst prognosis (typically, with the phenotype of triple-negative cancers) in 34% of young patients, with only 17% in older women. Luminal A cancer, with better prognosis, was detected in 35% of the older and 17% of the younger women [17]. However, it seems that worse tumor biology in patients with BC is not only connected with less beneficial distribution of particular molecular subtypes of cancer. Analysis of the expression of various genes revealed that increased gene expression connected with poor prognosis is often found in young women [13].

Recently introduced genetic tests (*Oncotype DX*, *MammaPrint*) are useful for the evaluation of the risk for recurrence in patients with early-stage disease, without metastases to the lymph nodes, with tumor showing ER expression and without HER2 overexpression. Such criteria are most often met by postmenopausal women and so the tests are commonly performed in older patients. Reports about young patients, rare as they are, have revealed high risk indices in that age group more often than in older women. The risk for disease recurrence was 56% and 82% (52/63) in the *Oncotype DX*, and *MammaPrint* tests, respectively [18].

SURGICAL MANAGEMENT

The rules of surgical management in young and older women are essentially the same. Radical breast amputation or conservative, breast-conserving management followed by radiotherapy remain the standard approach in early-stage breast cancer, regardless of patient age [19]. Despite the fact that conservative treatment is associated with higher rate of local recurrence, both methods allow to achieve comparable survival rate [20]. Young age is an independent risk factor for local recurrence after conservative management (patients aged < 35 are at a 9-fold higher risk than older women), but the OS remains unaffected [21]. Due to the specific expectations of that particular age group (the need to preserve sexuality, cosmetic result), conservative treatment ought to be offered to young patients as the first choice. Skin- and/or nipple-sparing mastectomy with immediate reconstruction also meets patient expectations [22]. There are no special recommendations for young women as far as surgical management of the axillary lymph nodes is concerned.

Prophylactic bilateral mastectomy remains the topic of much heated debate and considerable controversy. There is no evidence that such management benefits young non-carriers of the BRCA1 gene mutation diagnosed with breast cancer. Such approach may be taken into consideration if the affected woman is determined to proceed, after providing detailed information about the risk for complications and enough time to avoid hasty decisions, fear, and anxiety.

ADJUVANT RADIOTHERAPY

Recommendations for adjuvant therapy are the same as in older women. Radiotherapy is always used after breast-conserving surgery, after mastectomy in case of large tumors (≥ 5 cm), or metastases to at least 4 lymph nodes. According to recommendations, radiotherapy is also advised in case of metastases to 1–3 lymph nodes in BC patients with unfavorable phenotype [24]. It is important to bear in mind that young women are at higher risk for local recurrence not only after breast-conserving surgery but also after mastectomy, so they benefit more from radiotherapy than their older peers [23, 24].

SYSTEMIC THERAPY

Chemotherapy

In Europe, adjuvant therapy is carried out in accordance with the regularly held bi-annual St. Gallen Conference (hence the St. Gallen Consensus). Earlier recommendations considered young age to be an independent, unfavorable prognostic factor so all patients < 35 years of age received adjuvant chemotherapy. According to the 2013 and 2015 recommendations, patient age is no longer the decisive factor for adjuvant chemotherapy. Tumor biology has a decisive influence and young patients receive the same kind of therapy as their older peers. Adjuvant chemotherapy is recommended in the following cases:

- cancers with the so-called triple-negative tumor phenotype (without ER and PR expression and without HER2 overexpression);
- cancers with HER2 overexpression — recommendations include chemotherapy with anthracyclines and taxanes, plus annual therapy with trastuzumab, a monoclonal antibody against HER2;
- cancers with ER expression (the so-called luminal cancers, treated predominantly with HT) — chemotherapy is used in case of additional risk factors which include high-grade (G3) tumors, metastases to at least 4 lymph nodes, high Ki-67 proliferation index, low steroid receptor expression, and extensive infiltration of lymph and blood vessels [23].

Treatment of extensive disease in young patients resembles therapy in older women. Young age should not be an indication for more aggressive forms of treatment [24].

Hormonal therapy

Hormonal therapy (HT) has a strong position in both, adjuvant treatment of early-stage BC and palliative therapy of the extensive disease in young women with BC which shows steroid receptor expression. However, it is not recommended for neoadjuvant therapy in young women due to lack of evidence for its benefits. Tamoxifen, possibly with

ovarian function suppression (OFS), remains the gold standard in hormonal therapy. For many years, researchers have believed the 5-year period to be optimal for tamoxifen use. The ATLAS study revealed that a 10-year period lowers the mortality rate by one-third during the first 10 years since the initial diagnosis and by half in later years. However, at the same time, the study found an approximately 2-fold higher risk for cervical cancer in the group of patients receiving tamoxifen for 10 years [25]. Similar results were reported by the ATOM study. At present, prolonged adjuvant therapy with tamoxifen is believed to be possible in selected patients (both, pre- and postmenopausal) after careful analysis of their prognostic factors, the risk for late recurrence, estimated disease-free survival, and possible complications. In hormone-dependent cancers, late recurrence after primary radical treatment poses a serious problem as the survival curves practically never reach a plateau, and the annual risk for recurrence, even after several years, is 2–3%.

For a long time, there has been no proof for any benefits of using adjuvant therapy with aromatase inhibitors in premenopausal patients. Two large randomized studies — SOFT and TEXT — compared exemestane with OFS versus tamoxifen, also with hormonal suppression. After an over 5-year observation, aromatase inhibitors combined with suppression were found to slightly although significantly (4% of relative difference) prolong median disease-free survival, although median overall survival (OS) was unaffected [26].

The SOFT study was designed to determine the role of ovarian suppression as well. In this three-arm study (tamoxifen vs. tamoxifen with ovarian suppression vs exemestane with OFS), combination therapy lowered the risk for disease recurrence in high-risk patients (after previous chemotherapy), especially > 35 years of age, as compared to tamoxifen. The benefit was even greater in case of exemestane with OFS than tamoxifen with OFS [27]. Regardless, it is important to bear in mind that combination therapy is associated with a number of adverse symptoms due to premature menopause, which significantly negatively impacts the quality of life of the young women.

In case of palliative treatment in young women, HT ought to be considered in all patients who do not require an aggressive course of action due to intensified clinical symptoms. In practice, HT in young women is typically used after patients achieved maximum response to chemotherapy but the literature offers no reliable data on methods of combining different forms of HT with chemotherapy or biological therapy in that age group.

Management in BRCA carriers

The risk for breast cancer in the carriers of the *BRCA1* or *BRCA2* gene mutation has been estimated at even 70% [28]. Healthy carriers ought to undergo screening tests, which allow for early BC detection. They should perform breast self-exam every month since the age of 18, and report for physical evaluation since the age of 25. Noteworthy, ultrasound test in that age group is characterized by high specificity but relatively low sensitivity, whereas regular mammogram at such young age remains the source of much controversy due to cyclic exposure to ionizing radiation, so MRI is an especially useful tool in that population.

Local disease recurrence or cancer spread to the other breast are significantly more often found in BRCA carriers patients than in women with sporadic BC.

The risk for local recurrence is obviously greater if conservative treatment rather than radical management was applied, although type of surgery in the latter approach has no correlation with the overall survival [29]. Current data indicate that radiation as an element of conservative management does not elevate the risk for carcinogenesis in BRCA carriers as compared to other BC patients. The risk for cancer in the other breast among BRCA carriers has been estimated at 3–4% annually. Therefore, preventive mastectomy of the other breast should be offered to these patients as such management greatly improves the OS [30]. Nipple-areola complex sparing mastectomy allows to maintain oncologic safety and achieve good effects after the subsequent reconstructive surgery.

Systemic adjuvant therapy in BRCA carriers is consistent with the general recommendations. Although BRCA gene damage seems to be a predictive factor for disease sensitivity to drugs which damage DNA strands (cisplatin, carboplatin), we lack conclusive evidence to recommend other protocols of adjuvant therapy [23]. Platinum derivatives are sometimes used in advanced disease.

FERTILITY PRESERVATION AND MATERNITY AFTER CANCER THERAPY

Patients < 40 years of age are in fact women in the reproductive age. Recent years have revealed a steady trend for delayed motherhood so doctors will continue to treat women with diagnosed breast cancer who are either nulliparous or wish to have more children. Thus, fertility preservation has become an important aspect of breast cancer therapy. Chemotherapy is administered to the majority of young cancer patients, which may damage the ovaries. The extent of the damage depends predominantly on patient age, type and dose of the drug. Observational studies reported cessation of menstruation after standard chemotherapy in about 25% of BC patients < 30 years of age, 30–70% aged 30–40 years, and 80% aged > 40 [31]. However, post-therapy amenorrhea does not unequivocally signify infertility, while menstruation does not equal the procreative potential. As for the evaluation of fertility, measurement of the anti-Müllerian hormone (AMH) is a use-

ful indicator of the ovarian reserve. Therefore, AMH levels should be checked not only after treatment completion but also before therapy. Estradiol, FSH, or inhibin levels will not give conclusive results as far as fertility is concerned. HT also affects fertility and although toxicity of tamoxifen is infinitely smaller than chemotherapy, duration of the treatment presents a problem. Until recently, a 5-year tamoxifen therapy was the standard management but after the results of ATLAS and ATOM studies have been published, a 10-year-long treatment has been recommended for patients from high-risk groups. The latest St. Gallen recommendations allow for a break in the adjuvant HT to conceive and treatment recommencement after delivery. During chemotherapy, gonadoliberin analogues may be used in patients with ER-negative cancers to preserve fertility. However, those medicines have not been approved in such indications and their effectiveness is limited.

Pregnancy after breast cancer treatment does not increase the risk for disease recurrence and for congenital fetal malformations. Also, the newborns may be breastfed.

PROGNOSIS

Breast cancer in young women presents a number of different biological features, resulting in shorter progression-free and overall survival as compared to other age groups. Therefore, the St. Gallen Expert Panel (2005) found age to be an unfavorable prognostic factor. The experts stated that young patients are never actually in the low-risk group and, as such, should always undergo systemic treatment. Currently, it is believed that the decision about systemic treatment of young women should be based — as in other age groups — on the evaluation of the biological features of the tumor, tumor stage, and concomitant diseases.

Palliative care of young women with BC presents a particular challenge as these patients are usually young mothers and the whole family requires complex care.

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