Fertility and breast cancer

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ABSTRACT

Breast cancer is the most common cancer among females worldwide. The mean age of breast cancer patients is > 60 yrs old, and it is seldom found in women < 40 yrs old (6.5%) and in very young women < 35 yrs old (0.6%).

In young females, fertility and all its aspects are an additional therapeutic challenge. Before initiating treatment, the oncologist should offer effective contraception to be applied throughout the therapy, bearing in mind that fertility preservation is of utmost importance. When it comes to breast cancer in pregnancy, the attending physician should use a therapy which is safe for both the mother and the foetus.

Chemotherapy, radiotherapy, hormonal therapy and immunotherapy can, to a lesser or greater degree, damage the ovarian function resulting in amenorrhea in women < 50 yrs (33–76%). However, owing to fertility preservation strategies, more and more pregnancies are successful, even in breast cancer survivors.

KEY WORDS: breast cancer in young women, breast cancer during pregnancy, fertility, fertility preservation strategies

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INTRODUCTION

Breast cancer is the most common type of cancer in female patients worldwide. It rarely occurs in women below the age of 40 (approx. 6%) and 35 (less than 1%) [1]. However, there are two biologic subtypes of breast cancer associated with poor prognosis which are more common in this age group: the so-called triple-negative and HER2-positive breast cancer [2]. In addition, mutations in *BRCA1* or *BRCA2* genes are more common, and young age is an independent poor prognostic factor [3].

Young age-onset is also associated with additional considerations that do not come into play with older patients, such as the desire to start a family and have children, maternity, contraception and start of a professional career. On the other hand, a young patient has fewer co-morbidities, is more physically fit and has better chances of a long life, although the latter may be affected by late effects of cancer treatment. This makes particularly important to monitor patients after cancer treatment, because over time increases the risk of late complications. Once breast cancer is diagnosed and the patient is planning on having children, emotions run high and questions arise: Will this be safe and, if so, when? What about further cancer treatment?

When answering the questions and dispelling uncertainty, the oncologist should assure the patient that having children after completion of cancer therapy is and possible and safe, also improves prognosis. A meta-analysis of 14 studies involving 1,244 breast-cancer patients who became pregnant after completion of treatment, and 18,145 patients diagnosed with breast cancer who did not become pregnant showed that mortality risk in the first group was 41% lower than in breast cancer survivors who did not get pregnant. The difference in prognosis was particularly evident among those women in both groups who had a history of node-negative disease [4].

EFFECT OF SYSTEMIC TREATMENT ON THE PREGNANT WOMAN AND THE FOETUS

Procreation plans should, however, be postponed until the cancer treatment is completed. Expectant patients are particularly not advised to undergo chemotherapy based on antimetabolites (methotrexate) and alkylating agents (cyclophosphamide) as these agents increase the risk of miscarriage and foetal malformation while anthracyclines and Vinca alkaloids seem to be a safer alternative. The risk of malignancy in pregnancy increases when multi-drug therapies are used or when chemotherapy is administered in combination with radiotherapy [5, 6].

Use of chemotherapy in the first trimester of pregnancy increases the risk of foetal malformations by 10–20%. However, when chemotherapy is used in the second and third trimester the rate of congenital malformations is not higher than the baseline population risk of approx. 3% [7]. The effect of anthracycline-based chemotherapy on pregnant women and foetuses has been studied most extensively owing to the frequent use of this agent. Case reports of pregnant patients diagnosed with breast cancer who have been treated at cancer centres provide a wealth of information. In 2008, Azim et al. published a paper describing 26 patients who received chemotherapy in the neoadjuvant (35%), adjuvant (61%) and palliative (4%) settings. An average of four courses of chemotherapy (2–5) were administered to the patients in the second trimester. The median gestational age at delivery was 35 weeks (28–40 weeks). In the follow-up period which lasted 27 months on average (0–84 months), only one child was diagnosed with polycystic kidneys while all other children developed normally [8].

In contrast, tamoxifen is associated with a significantly higher risk of pregnancy complications and foetal defects than that of the general population [9]. Apart from modulating oestrogen receptors, the drug may, similarly to clomiphene, induce ovulation in women who are infertile due to ovulation disorders. However, owing to its teratogenic effect it is only recommended for treatment of cancer and for chemoprevention of breast cancer [10]. After tamoxifen is initiated, it takes approx. 4 weeks to achieve a constant concentration in blood, and the half-life is 7 days. The saturation with, and elimination of the active metabolite of tamoxifen (N-desmethyl tamoxifen) takes twice that long, therefore it is recommended to wait approx. 2 months after the end of therapy before attempting to conceive [11]. Information about tamoxifen's safety in pregnancy mostly comes from case reports and the manufacturer's database.

The database of AstraZeneca includes case reports of 44 patients using tamoxifen in pregnancy. Eleven patients gave birth to children with malformations, 6 had an abortion and 2 experienced a miscarriage, which means that one in three pregnancies was complicated to some extent. A significantly more favourable outcome was reported in another study which focused on the use of tamoxifen for chemoprevention of breast cancer in 85 patients who conceived while receiving treatment. None of the children who were born had any developmental abnormalities [12].

The results of both studies are contradictory but papers published worldwide report on many cases of unsuccessful pregnan-

cies or malformations in new-borns. This is why the summary of product characteristics recommends to use contraception over the course of treatment and at least two months after its completion [13].

Carcinoma with HER2 overexpression is associated with poor prognosis and mostly occurs in younger patients. Trastuzumab, a human monoclonal antibody, binds to HER2, inhibits its dimerization with another receptor of the epidermal growth factor receptor (EGFR) family and suppresses signal transduction into the cell. HER2 is found not only of the surface of breast cancer cells but also, among others, on the foetal renal cells. Therefore, exposure to trastuzumab in pregnancy may impair kidney development [14]. Publications around the globe include few cases of patients who used trastuzumab while pregnant. According to the reports, three out of six children died of renal failure or respiratory syndrome, while the other three developed normally [15–19].

For this reason, patients are not recommended to conceive while receiving systemic treatment. The use of contraception is recommended. The most effective birth-control method in breast cancer patients receiving treatment is a copper intrauterine device (IUD) or barrier methods. Patients who receive tamoxifen may be considered for placement of a levonorgestrel-containing IUD [20].

FERTILITY PRESERVATION STRATEGIES

Therapy of most cancer types reduces fertility of female patients and the lowest pregnancy rate is reported among breast cancer survivors. These patients' chances of conceiving are as much as 67% lower than those of the general population [21]. Every young patient who is diagnosed with breast cancer should be able to consult a fertility preservation specialist before starting cancer treatment. The chances of conceiving a child depend on the patient's age, ovarian reserve and amount of time available before cancer treatment starts [22]. An ovarian reserve is determined on the basis of the level of Anti-Müllerian hormone which is produced by ovarian granulosa cells. The level remains constant throughout the different stages of the menstrual cycle. The ovarian reserve may also be assessed by means of an intravaginal ultrasound scan which measures the ovarian volume and the antral follicle count [23].

To preserve fertility in women with cancer, two methods are used that require hormonal stimulation based on, among others, letrozole, as well as cryopreservation of oocytes and embryos. Both hormonal techniques require time (approx. 4 weeks on average) necessary to stimulate the ovaries and retrieve egg cells before cancer therapy is initiated. Regardless of the status of steroid receptors in cancer cells, use of hormonal stimulation is not associated with higher risk of breast cancer recurrence, and the success rate of these methods is quite high and represents ca. 30% in young patients aged around 30 [24].

There are two other methods do not require hormonal stimulation. Cryopreservation of ovarian tissue obtained by laparoscopic procedure is mostly used in young patients treated in paediatric wards as well as patients whose response to hormonal stimulation may be too weak or there is simply no time for hormonal stimulation. The success rate of this method is up to ca. 25% and it is still considered to be experimental. As soon as cancer treatment is completed, the ovarian tissue is thawed and implanted in the pelvis (autotrophic graft) or e.g. in the forearm region (heterotrophic graft). [25].

Another method used when there is no partner available is retrieval of immature oocytes, their *in-vitro* maturation and freezing, or freezing and *in-vitro* maturation after thawing just before insemination [26].

PROTECTION OF OVARIES

Apart from surgical procedures that are designed to preserve fertility, the oncologist may also protect the ovaries by selecting appropriate chemotherapy and hormonal therapy, as well as using gonadoliberin analogues in the course of adjuvant chemotherapy in patients with hormone-independent breast cancer. According to the POEMS study, these measures not only resulted in a greater number of pregnancies and children born (22 vs. 13) but also less frequently led to premature ovarian failure (8% vs. 22%) and achieved a longer progression-free survival and overall survival [27].

The aTTom and ATLAS studies demonstrated that a prolonged hormonal therapy improves prognosis in some patients with hormone-independent breast cancer. However, this treatment may reduce fertility given that the ovarian reserve decreases with age [28].

At present, there is a POSITIVE trial underway which explores the possibility of interrupting tamoxifen therapy after 18–30 months of exposure for a period not longer than 2 years. The patient may use the time off to conceive, give birth and breastfeed. After this break, she should re-start the hormonal treatment [29].

SUMMARY

Breast cancer in young age not only disrupts everyday life but may also cause irreversible changes in patient's body, including menopause. It is natural for patients in reproductive age to desire having children. This desire should be taken into account by the oncologist when planning treatment.

Duration of therapy depends on the biologic subtype of cancer, and may extend over the course of months or years. The patient should use effective contraception and avoid conceiving while receiving systemic treatment. The risk of foetal malformations caused by chemotherapy is several times higher in the first trimester than in the second and third trimester when it decreases to the level of the general population [7]. When used in pregnancy, tamoxifen may result in pregnancy complications or foetal defects in as many as one in three patients [9].

The cancer treatment options offered to the patient should preserve her chances of childbearing to the greatest extent possible.

Occurrence of premature ovarian failure (POF) depends, among other things, on the chemotherapy regimen used, exposure to tamoxifen and patient's age. The risk of POF increases with patient's age and represents < 20% in patients below the age of 30, 40–60% in patients below the age of 40 and approx. 80% in patients over the age of 40 [30].

Young women increasingly often request ovarian protection during systemic treatment and opt for fertility preservation by surgical methods whose success rate is up to 30% [24].

The oncologist should respect the patient's wishes, ensure the cancer therapy is safe and take a number of different measures to preserve the patient's fertility and chances of childbearing.

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