Treatment Modification in Young Breast Cancer Patients

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Introduction

There is no clear definition of whom the term ‘young patient’ exactly refers to. For this paper we focus on women not older than 35–40 years. Breast cancer in these patients tends to show a more aggressive biological behaviour. There is no doubt that these women benefit from chemo-, endocrine and anti-HER2 therapy to a similar degree as older women. Surgery and radiation therapy also follow the same recommendations as those for women aged 40 years or older [1–4]. However, the life expectancy of young women is longer, thereby extending the time in which the breast cancer may recur. Treatment decisions, especially omission of treatment modalities, must therefore be contemplated very thoroughly. In addition, the following 3 topics need special consideration in young women and are, therefore, addressed in this manuscript: (1) endocrine therapy and ovarian suppression; (2) fertility protection and family planning; and (3) genetic counselling.

Endocrine Therapy and Ovarian Suppression

Adjuvant therapy with tamoxifen (TAM) improves the prognosis of women with hormone receptor-positive breast cancer. The 2011 Early Breast Cancer Trialists’ Collaborative Group (EBCTCG) meta-analysis of randomized trials showed that a 5-year-TAM treatment reduced relapse rates by 47% in the years 1–4 and by 32% in the years 5–9. Only after 10 years was no further gain noted. Breast cancer mortality was reduced over the entire 15-year observation period by about one third (29% in the years 1–4, 34% in the years 5–9 and by 32% in the years 10–14). The benefits were independent of age, nodal status, tumour size or additional chemotherapy, and were found both for post- and premenopausal patients. The incidence of contralateral breast cancer was halved [5].
Prolonging TAM therapy to 10 years did not increase the benefit of endocrine treatment during the first 10 years after diagnosis (compared to 5 years of TAM therapy). However, thereafter, relapse rate were lower by 25%, and mortality by 29%. The 10-year therapy reduced mortality in the first decade by a third and in the second decade by half. Both the incidence of endometrial cancer and pulmonary embolism were significantly increased through 10 years of therapy; in contrast, contralateral breast cancer rates and risk of ischemic heart disease were significantly reduced. These statistics describe the improvements in relative terms. In absolute numbers, 10 instead of 5 years TAM reduces breast cancer mortality by 3%, while breast cancer-unrelated mortality rises by 0.2% [6].

Whereas relative improvements apply to a group of patients, only the absolute advantage is relevant for the individual patient. This is calculated from the mortality or relapse risk and the relative benefit. The lower the risk for recurrence of a tumour, the lower is the individual benefit from treatment [7].

Only 10% of all patients in the ATLAS trial were premenopausal [6]. Therefore, it is possible that due to small sample size the effects of 10 versus 5 years TAM were not significant in this patient group. However, because no age-dependent differences in the efficiency of TAM were detected in the meta-analyses, it sounds reasonable to assume that these effects also hold true for young women under the age of 35–40 years [5, 6].

Aromatase inhibitors (AIs) are not a valid anti-cancer treatment in women with ovarian oestrogen production. Rather, AIs are known to stimulate ovarian function in pre- and perimenopausal women. To be effective in premenopausal patients, AIs would be required to suppress ovarian function.

Suppression of ovarian function (OFS) in premenopausal women is an effective treatment for hormone-sensitive tumours. However, the effect of OFS in addition to TAM has long been controversial. Overall, chemotherapy-induced amenorrhoea seems to be a good prognostic factor [8, 9]. Nevertheless, so far there have been no data showing any benefit for administering gonadotropin-releasing hormone (GnRH) analogues after menses recur following chemotherapy [2, 10, 11].

The randomized SOFT and TEXT phase III trials examined the effect of a 5-year endocrine therapy with the combination of TAM or the AI exemestane with OFS in premenopausal patients [12, 13]. OFS was achieved by the GnRH agonist triptorelin, by oophorectomy or ovarian irradiation. In the TEXT study, 2,672 patients received OFS and either TAM or exemestane no later than 12 weeks after surgery. The SOFT study recruited 3,066 women, who were stratified according to whether adjuvant chemotherapy was performed. The study included patients receiving no chemotherapy (46.7% of the patients) or those who remained premenopausal within 8 months after completion of chemotherapy (53.3%). Randomization was performed in 3 groups: TAM alone; TAM plus OFS; and exemestane plus OFS. In both the TEXT and the SOFT studies the 5-year overall survival rate was very good and exceeded 95% in all groups. For a valid statistical statement on possible differences in overall survival the observation period is still too short. In summary, these studies found advantages for OFS only in disease-free survival (DFS: no recurrence and no second invasive carcinoma of the breast or other organ) and cancer-free survival (BFS: no breast cancer event) and only in patients in whom chemotherapy was indicated because of their high risk status. In this context, in combination with OFS, exemestane was superior to TAM.

In a joint analysis of the TEXT and SOFT trials after a median observation time of 68 months including 4,690 patients [13] who had received OFS, the 5-year DFS and BFS were significantly better in the exemestane group than in the TAM group (DFS 91.1% vs. 87.3%; hazard ratio (HR) 0.72; 95% confidence interval (CI) 0.60–0.85; p < 0.001; BFS 92.8% vs. 88.8%; HR 0.66; CI 0.55–0.80; p < 0.001).

After 67 months median observation time in the SOFT trial [12], there was no significant advantage for OFS in addition to TAM versus TAM alone with respect to the 5-year DFS, either in the patients without or with chemotherapy (overall population: TAM 84.7%; TAM plus OFS 86.6%; HR 0.83, CI 0.66–1.04; p = 0.10; patients with chemotherapy: TAM 78.0%, TAM plus OFS 82.5%; HR 0.78, CI 0.60–1.02). After adjusting for prognostic factors, a greater treatment effect with TAM plus OFS than with TAM alone was suggested (HR 0.78; 95% CI 0.62–0.98). A significant difference was also found between TAM monotherapy and exemestane plus OFS in the group of patients who had received chemotherapy because of an increased risk: 5-year BFS was 85.7% with OFS plus exemestane and 78.0% with TAM monotherapy (HR 0.65, CI 0.49–0.87). Overall survival at 5 years in the chemotherapy cohort was high in all subgroups. There was a statistically significant better overall survival among patients assigned to TAM plus OFS (94.5%; 95% CI 92.0–96.2) compared to patients with TAM only (90.9%; 95% CI 87.9–93.2) (HR for death 0.64; 95% CI 0.42–0.96). However, the SOFT trial is currently underpowered, and the overall survival analysis is premature after ‘only’ 5% of patients have died. The most obvious advantage of OFS was found in the group of women aged 35 years or less, of whom 94% had received chemotherapy. The BFS after 5 years was 67.7% for TAM alone, 78.9% for TAM plus OFS and 83.4% for exemestane plus OFS. However, the sample size of 233 patients included in the analysis was too small for a valid statistical significance.

The TEXT and SOFT trials found significant differences in the rate of side effects [12, 13]. Side effects included typical menopausal symptoms (hot flushes, sweating, decreased libido, vaginal dryness, insomnia, depression, musculoskeletal pain), hypertension, impaired glucose tolerance and osteoporosis. Grade 3 and 4 toxicity was specified with TAM only (SOFT trial) in 23.7%, in the groups with OFS (SOFT and TEXT) in 30.5% for exemestane and 29.4% for TAM. Osteoporosis (T score < -2.5) was found in TAM 78.0% for TAM plus OFS and 83.4% for exemestane plus OFS. However, the patients without or with chemotherapy (overall population: BFS after 5 years was 85.7% with OFS plus exemestane and 78.0% with TAM monotherapy (HR 0.65, CI 0.49–0.87)). Overall survival at 5 years in the chemotherapy cohort was high in all subgroups. There was a statistically significant better overall survival among patients assigned to TAM plus OFS (94.5%; 95% CI 92.0–96.2) compared to patients with TAM only (90.9%; 95% CI 87.9–93.2) (HR for death 0.64; 95% CI 0.42–0.96). However, the SOFT trial is currently underpowered, and the overall survival analysis is premature after ‘only’ 5% of patients have died. The most obvious advantage of OFS was found in the group of women aged 35 years or less, of whom 94% had received chemotherapy. The BFS after 5 years was 67.7% for TAM alone, 78.9% for TAM plus OFS and 83.4% for exemestane plus OFS. However, the sample size of 233 patients included in the analysis was too small for a valid statistical significance.

The advantage of AI versus TAM in premenopausal patients suggested by the SOFT/TEXT trials, however, should be viewed with caution, given that they contradict (in part) the results of the ABCSG12 study. In this trial, 1,803 premenopausal patients with hormone-sensitive breast cancer and less than 10 involved lymph nodes were treated for 3 years with a combination of GnRH ana-
logues and the AI anastrozole or TAM. After a median of 94.4 months follow-up there was no DFS benefit of anastrozole over TAM; on the contrary, the AI group had a significantly higher risk of death (HR 1.63, 95% CI 1.05–2.54; p = 0.030) [14]. The cause for this discrepancy in results between ABCSG12 and TEXT/ SOFT trials is unclear. Endocrine therapy in the ABCSG12 study lasted only 3 years instead of 5 years in the SOFT and TEXT studies. Despite the shorter duration of therapy and the relatively high risk potential – about one third of patients had nodal positive disease with up to 9 lymph nodes affected and only 5.8% had received chemotherapy – the DFS after 5 years in ABCSG12 was also very high at 94%. A difference in the effectiveness of the different AIs used as the cause for the different results is unlikely because the MA.27 study showed no difference between anastrozole and exemestane [15] in postmenopausal women.

Side effects are frequent epiphenomena of endocrine therapy, especially in the form of menopausal symptoms. The extent of the side effects can be very different individually and independent from the oncological benefit of therapy.

The oncological benefits of endocrine treatment, however, are only realized with high adherence, i.e. the regular intake of the recommended dose and schedule. The more the actual duration of therapy or dose density deviate from the recommendations, the lower the therapeutic effect. With an adherence of less than 60% mortality increases by a factor of 3.6 when compared to complete treatment [16].

The adherence found in clinical studies is unfortunately not transferred to everyday therapy. In studies of endocrine treatment, a relatively high compliance is achieved. In the fifth year of a study in the order of two-thirds of participants are compliant, as demonstrated, for example, in the IBIS II prevention study in which healthy female volunteers were recruited to examine the benefit from administering an AI in preventing the development of breast cancer [17]. In everyday therapy this compliance is not achieved as is evidenced by numerous studies. These reports come to the conclusion that, in the fifth year, only about half of the patients carried on with endocrine treatment [16, 18]. In addition to inadequate knowledge about the value of treatment and decreasing motivation, side effects play a major role in non-compliance. Even though muscle and joint pain and menopausal symptoms are indeed a typical sequence of endocrine therapy, they are also typical symptoms of aging. Patients tend to view complaints that emerge during therapy as a result of this therapy, even if there is no causal link. This holds true especially if such complaints are listed as possible side effects in the package insert. A recent study showed that patients who had several typical complaints before starting treatment (e.g. insomnia, fatigue, mood swings, anxiety and difficulty concentrating) were more likely to not adhere to endocrine therapy. Patients who already had 3–5 of these symptoms at baseline were more than twice as likely to abandon an AI intake compared to women with no more than 2 such symptoms [19].

Unfortunately, the complaints that occur during hormonal therapy are obviously given too little space in the doctor-patient communication. Comparative studies show that patients suffer from side effects far more frequently and more strongly than perceived by the doctors [20]. Thus, they are not addressed in the doctor-patient interaction, let alone treated.

Even the best therapy is only effective if it is carried out. Therefore, optimal compliance is of crucial importance. It may be more appropriate to carry out a limited range of treatment modalities with optimal compliance, than several measures half-heartedly [7]. The higher rate of side effects with OFS carries the risk of reduced compliance. In everyday therapy, if the higher rate of side effects with the combination of TAM or exemestane with OFS results in impaired compliance, the advantage of a possibly better treatment can be lost quickly. A decreased treatment adherence leads to increased mortality, while the additional OFS does not improve overall survival – at least according to the data available to date, but ‘only’ reduces recurrence rates.

While TAM is an effective treatment even when OFS is omitted, the omission of OFS terminates the effectiveness of exemestane. Therefore, the suggested advantage of OFS plus exemestane in women receiving chemotherapy, which as of now is limited to recurrence rates, should be weighed against the higher rate of side effects with the risk of decreased adherence to therapy. A combination therapy of OFS plus TAM, especially of OFS plus AI should therefore only be initiated if a very good and long-term care and high reliability of the patient is absolutely guaranteed. Otherwise the opposite of the intended prognosis improvement may be achieved.

For these reasons, the breast commission of the AGO (Arbeitsgemeinschaft gynäkologische Onkologie, Working Group for Gynaecological Oncology) advises restraint in the use of OFS in combination with TAM or exemestane in premenopausal women and rates this treatment as an option for individual cases rather than a general recommendation. TAM remains the backbone of endocrine treatment in young women [21].

**Fertility Protection and Family Planning**

Improvements in oncology in recent decades has led to increased chances of cure, especially in relatively young patients. An increasing number of young long-term survivors have the prospect of a ‘normal’ life after being diagnosed with and treated for cancer. Whereas earlier curing cancer was by far the most outstanding task, today oncology is increasingly confronted with issues concerning the life after cancer (‘survivorship’) and the quality of life [1, 3, 22–24].

Increasingly this includes fertility and parenthood. Over the past few decades, the phase of family formation shifted ever further into the 4th decade of life. In 1970, the average age at first birth was 24.3 years in West and 21.9 years in East Germany. In 2013, it almost reached 31 years in the unified Germany [25, 26]. More and more women are now faced with a diagnosis of cancer before they have completed their family planning. Since many cancer treatments can impair fertility, an increasing number of women face the problem of infertility after cancer treatment [24]. According to re-
cent studies, up to 50% of these patients consider the ability to fulfil the desire to have children very important [27, 28]. However, only a fraction of these women indeed achieve pregnancy [29]. Preserving fertility through preventive action seems to positively influence the quality of life of those affected [30]. Therefore, the AGO recommends that all patients who have not yet completed their family planning should be advised on ways of preserving fertility before oncological therapy [1, 3]. Unfortunately, the aspect of fertility preservation is not taken into account sufficiently when planning oncological therapy. There are many reasons: insufficient knowledge about the possibilities, too little time to talk, concern about a delay in the treatment and its consequences, or the assumption that there is no need for consultation if the patients do not raise the issue on their own [31].

In many cases doctors have the misleading assumption that pregnancy and childbirth compromise the chances of recovery, and that the oncological therapies would constitute undue risk for the children; even abortions are recommended [28]. However, pregnancy and childbirth following cancer treatment usually do not have adverse effects on the oncological prognosis. This is especially true for breast cancer, even if it is receptor positive [24, 27–29, 32]. There is no significantly increased risk for pregnancy complications following cancer treatment. Despite chemotherapy or radiotherapy neither the teratogen risk nor the risk for cancers of the children appear to be increased. However, there is a small increased risk of abortions after chemotherapy. Overall, the wish of cancer survivors for childbearing can be supported given adequate care during pregnancy and birth [24, 32]. According to the data currently available, assisted reproduction techniques do not seem to increase the risk of cancer significantly, at least not for breast cancer; the risk of borderline tumours of the ovary and endometrial could in contrast be slightly increased [29].

Chemotherapy involves a risk for premature ovarian failure. The risk is related to the agents used, the total dose delivered and the patient’s age. Combination regimens used as adjuvant treatment have different rates of premature menopause. High cumulative doses of alkylating agents after the age of 35 years are associated with a high probability of premature menopause [1–3, 24, 29, 33]. Strategies against premature ovarian failure have been researched extensively over the last decade. The ‘silver bullet’ has not yet been found. Recently, several studies have examined the extent to which ovarian function can be protected by GnRH analogues. These protocols start with an ovarian suppression by GnRH not later than 2 weeks prior to chemotherapy. Observational studies have reported a protective effect associated with chemotherapy regimens as cyclophosphamide, methotrexate and 5-fluorouracil (CMF), anthracycline-based therapies, or even high-dose protocols. The results of randomized trials, however, are inconsistent. The German ZORO study, which used appropriate, modern chemotherapy regimens including taxanes [34], is one of those that have seen no benefit. In contrast, a meta-analysis of 9 randomized trials with 765 patients reported that GnRH resulted in a significant reduction of premature ovarian insufficiency. However, there was significant heterogeneity between the studies [2, 35]. An advantage was also recently presented by the POEMS study with 218 patients. The rate of ovarian insufficiency 2 years after chemotherapy was significantly reduced from 22% without to 8% with GnRH. The oncological safety did not seem to be affected; the GnRH group even had a significantly lower recurrence rate. The validity of the study, however, suffers from the fact that no data for evaluation were available for 38% of the study participants [36]. Therefore, the AGO evaluates the application of GnRH to achieve ovarian protection with restraint and as an option for individual cases only [1, 3].

Techniques of assisted reproduction with oocyte harvesting, in vitro fertilization and cryopreservation of ova and embryos are established medical measures, which have been used successfully and safely worldwide in infertile couples. These techniques are also available for oncological patients before the start of oncological treatment [2]. One drawback is that they require a period of a few weeks to perform, thereby delaying the start of therapy. In most cases, however, such a delay of treatment does not impair the success of the treatment. So far there is no evidence that ovarian stimulation applied for oocyte harvesting adversely affects prognosis even in hormone-dependent tumours [2, 37]. Loss of time and ovarian hyperstimulation are avoided by utilisation of the unstimulated in vitro maturation. Here immature oocytes are obtained in the spontaneous cycle and matured in vitro [38]. Methods of assisted reproduction are fully recommended by the AGO as measures for fertility preservation [1, 3].

Cryopreservation of ovarian cortical tissue is another method that has been successfully used to preserve fertility. Ovarian tissue is harvested laparoscopically, cryopreserved and reimplanted into the pelvis when needed. The reimplemented ovarian tissue resumes ovarian function. The first healthy children have already been born to mothers who had used this technique to treat chemotherapy-induced ovarian failure [39].

The technique should be chosen to best fit the needs of the individual patient. Specific factors of the patient including attitudes and preferences must be accounted for as well as the experience of the individual reproductive medical centre. An individual counselling by experts is essential for oncological patients who have not yet completed their family planning. A close cooperation between experts for reproductive medicine and oncologists is critical to ensure adequate consultation and planning. A recent analysis from Germany shows that this approach is successful and improves the chance for motherhood in young cancer patients [40].

Another important issue that needs to be addressed in young patients is contraception [2, 41, 42]. Young women are potentially fertile even if they have menstrual irregularities during or after treatment [2, 43]. Amenorrhoea and elevated gonadotropins such as follicular stimulating hormone (FSH) are unreliable markers of infertility in women who have received chemotherapy [2, 43, 44].

Although there is a large body of evidence that current or former application of modern oral contraceptive is not associated with a significantly increased risk of breast cancer [45–47], some studies have reported that distinct groups of recent oral-contraceptives users may experience an increase in risk [48, 49]. This may be accounted for by usage of higher dose contraceptive formulations
However, after breast cancer occurrence has been histologically proven, use of hormonal contraceptives is considered an unacceptable health risk and, according to the United States Medical Eligibility Criteria (US MEC) for Contraceptive Use 2010 [50], should not be utilized. Although at present it is not known whether this also applies to non-endocrine-responsive disease, caution should also be taken in this subset of women [1–3]. Even though a review of studies on progestin-only formulations did not find any indication for an increase of breast cancer risk [51], even local intrauterine progestin application, such as levonorgestrel-releasing systems, should not be used [1, 3, 50]. A small study did not find an overall increased risk of recurrence, but there was concern about an increased hazard of breast cancer recurrence in a subgroup who developed breast cancer while using a levonorgestrel-releasing intrauterine device (IUD) and continued its use [52].

During the evaluation for breast cancer a patient on hormonal contraceptives should continue until she receives appropriate counselling regarding future family planning, and until a new method is initiated [50], because an unplanned pregnancy at a time when breast cancer treatment should be initiated can lead to difficult choices about pregnancy termination or treatment delay.

Reliable and reversible non-hormonal methods such as copper IUDs and barrier methods have no restriction in use in this setting. With barrier methods such as condoms and cervical diaphragms, however, the high failure rate even with perfect use should be taken into account. Women not wishing further fertility may consider female or male (in case of a steady partner) sterilization [1–3, 50].

According to the World Health Organization there is no medical condition for which the risks of emergency contraception outweigh its benefit. A reliable method that does not interfere with breast cancer treatment or impair prognosis is the insertion of a copper IUD [53].

**Genetic Counselling**

Recommendations for genetic testing for mutations in breast cancer susceptibility genes (hereditary breast cancer; e.g. BRCA1 or BRCA2 mutation) are based on algorithms that utilize risk factors such as family history, ethnicity, and age at diagnosis of breast cancer to identify women deemed appropriate for testing. According to the guidelines of the ‘German Consortium for familial breast and ovarian cancer’, being diagnosed with breast cancer at young age of less than 36 years is sufficient to qualify for genetic counselling and testing, even without a family history of breast and ovarian cancer [54].

In addition to these conventional risk factors, the phenotype of the breast cancer can also impact the probability of finding a BRCA mutation. Compared to other subtypes of breast cancers, BRCA mutations are enriched in the population of women with triple-negative breast cancer (TNBC: negative for oestrogen receptor, progesterone receptor, and HER2). TNBC is an entity that has close correlation to mutations of the BRCA1 gene [55]. Sharma et al. tested 207 unselected TNBC patients for BRCA1/2 mutations. Deleterious BRCA1/2 mutations were identified in 15.4% of patients (BRCA1 11.1%, BRCA2 4.3%). Mutation prevalence in patients with and without a significant family history (SFH: defined as ≥ 1 relative with breast cancer at age ≤ 50 or ≥ 1 relative with ovarian cancer) was 31.6% and 6.1%, respectively. In a multivariable model, age at diagnosis and SFH were highly significant predictors of mutation status. The authors provided a diagram displaying the age-dependent probability of a BRCA mutation with respect to SFH. Based on this model, a patient diagnosed with TNBC at the age of 35 years carries a probability of a BRCA mutation of roughly 20% without SFH and of 67% with SFH, respectively. At the age of 40 years these figures are 15% and 55% and at the age of 45 years 10% and 42% [55].

Besides the fact that hereditary breast cancer has a severe impact on other members of the family, especially for siblings and descendants, surgical prevention of secondary malignancies (contralateral mastectomy for prevention of contralateral breast cancer, bilateral adnexectomy for prevention of ovarian cancer) needs to be discussed in mutation carriers as part of the treatment plan [1, 3]. Furthermore, specific systemic treatment options for diseased mutation carriers are already reality in recurrent ovarian cancer [56]. At present several clinical trials are recruiting patients to evaluate the clinical value of new drugs exclusively for BRCA mutation carriers with early or metastasized breast cancer [57, 58]. Therefore, it is crucial that genetic counselling is included in the treatment plan of young breast cancer patients.

**Disclosure Statement**

The authors declare no conflicts of interest.

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