

Use of Adjuvant Endocrine Therapy in Postmenopausal Hormone Receptor-Positive Breast Cancer at German Breast Cancer Centers and University Hospitals – Results of an Enquiry (Adjuvant Endocrine Therapy Enquiry)

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Keywords

Breast cancer · Endocrine therapy · Aromatase inhibitors

Summary

Background: Many studies about the adjuvant endocrine therapy of postmenopausal patients with hormone receptor-positive breast cancer have shown significant superiority of aromatase inhibitors (AIs) compared to tamoxifen only. Within these studies, different AIs (anastrozole, letrozole, exemestane) and treatment strategies (upfront, switch, extended adjuvant) were applied. **Material and Methods:** The intention of our enquiry was to evaluate the implementation of the results of these studies in German breast cancer centers and university hospitals. Questionnaires were sent to 200 breast cancer centers and university hospitals (returns: 108). **Results:** Our enquiry showed that most centers preferred anastrozole as upfront therapy in patients with an intermediate or high risk of relapse. Furthermore, during AI therapy, additional bisphosphonate treatment was applied 'always' in only 9% of cases, and in 78% of cases of proved osteopenia/osteoporosis. Surprisingly, 50% of the participating centers do not exclude AIs in premenopausal women. **Conclusion:** At the time of our enquiry, anastrozole as upfront therapy was consistent with the recommendations of the Arbeitsgemeinschaft Gynäkologische Onkologie (AGO) from 2009. Compared to tamoxifen, AIs increase the risk of osteoporosis, which can, however, be prevented and treated with concomitant bisphosphonate therapy. The rare use of bisphosphonates as well as contraindicated AI therapy in premenopausal patients show amongst others the substantial need for more information.

Schlüsselwörter

Mammakarzinom · Endokrine Therapie · Aromataseinhibitoren

Zusammenfassung

Hintergrund: Viele Studien zur adjuvanten endokrinen Behandlung des postmenopausalen Mammakarzinoms zeigten, dass der Einsatz von Aromataseinhibitoren (AI) gegenüber alleiniger Behandlung mit Tamoxifen die Ergebnisse signifikant verbessert. Im Rahmen der Studien kamen unterschiedliche AI (Anastrozol, Letrozol, Exemestan) und Therapieschemata (Upfront-, Switch-, erweiterte adjuvante Therapie) zum Einsatz. **Material und Methoden:** Ziel unserer Erhebung war es, die Umsetzung der Studienergebnisse hinsichtlich der AI-Therapie in deutschen Brustzentren und Universitätskliniken zu evaluieren. Dazu wurde ein Fragebogen erstellt, der an 200 Brustzentren und Universitätskliniken versendet wurde (Rücklauf: 108). **Ergebnisse:** Unsere Umfrage ergab, dass die meisten Zentren bei mittlerem und hohem Rezidivrisiko den Einsatz von Anastrozol im Rahmen einer Upfront-Therapie favorisieren und dass im Rahmen der AI-Therapie nur in 9% aller Fälle immer und in 78% bei nachgewiesener Osteopenie oder Osteoporose eine Bisphosphonat-Begleittherapie eingesetzt wird. Erstaunlicherweise schlossen 50% der teilnehmenden Zentren bei prämenopausalen Patientinnen eine AI-Therapie nicht aus. **Schlussfolgerung:** Die Art der Anwendung von AI entsprach zum Zeitpunkt der Erhebung weitgehend den Empfehlungen der Arbeitsgemeinschaft Gynäkologische Onkologie (AGO) von 2009. Der eher sporadische Einsatz von Bisphosphonaten begleitend zu den AI, die im Vergleich zu Tamoxifen ein erhöhtes Osteoporoserisiko bewirken, und der prämenopausale AI-Einsatz trotz Kontraindikation zeigen, dass hier erheblicher Informationsbedarf besteht.

Introduction

Breast cancer is the most common cancer entity in women. This disease ranks first in the causes of death related to cancer. Almost 58,000 women suffered from breast cancer in Germany in 2006, and around 17,300 women die every year from the sequelae of the disease [1]. In industrial nations, around 75% of breast cancer occurs in postmenopausal women, 80% present with hormone receptor-positive tumors [2]. For many years, treatment with tamoxifen (20 mg for 5 years) was considered as standard adjuvant endocrine therapy of postmenopausal, hormone receptor-positive breast cancer patients. Peto [3] showed in an analysis of 200,000 such patients that adjuvant antiestrogen therapy for 5 years significantly increases disease-free and overall survival independent of the lymph node status. A 15-year follow-up after 5 years of tamoxifen showed a reduction in the relative risk of relapse of 37% in nodal-positive patients and 43% in nodal-negative patients. A clear improvement of relapse-free survival (absolute 13.4%, relative 33%), as well as a 9% absolute decrease in breast cancer-related mortality, were demonstrated. An increase in mortality rate due to endometrial carcinomas or pulmonary embolisms of about 0.2% per decade was observed after 5 years of tamoxifen. Extended tamoxifen therapy over 10 years versus 5 years resulted in no advantages, as shown in the NSABP-14 study [4].

Several studies have demonstrated that aromatase inhibitors (AIs) are superior to tamoxifen, be it in upfront, sequential, or extended adjuvant therapy [5]. Therefore, the current recommendations for adjuvant therapy of postmenopausal patients with early hormone receptor-positive breast cancer include the use of an AI. Besides the non-steroidal AIs anastrozole and letrozole, the steroidal AI exemestane is used. Both classes of AI reduce the circulating estrogen level to 1–10%. The clinical efficacy of the AIs of the 3rd generation can be explained by the reliable reduction of the peripheral estrogen levels and the thereby diminished availability of estrogen in the tumor tissue. AIs are usually applied in

3 treatment strategies: i) primary adjuvant use of an AI as an alternative to 5 years of tamoxifen immediately after the primary breast cancer therapy (upfront therapy); ii) primary use of an AI subsequent to a shortened tamoxifen therapy of 2–3 years until a total duration of therapy of 5 years is reached (sequential/switch therapy); iii) use of an AI after 5 years of adjuvant tamoxifen therapy in relapse-free patients (extended adjuvant therapy). A list of relevant studies is given in table 1. It is not yet certain which treatment strategy is best and which conditions determine the use of the different AIs.

Material and Methods

Questions

In order to achieve an up-to-date overview of the situation in Germany regarding the adjuvant hormonal therapy in postmenopausal patients with early hormone receptor-positive breast cancer, we conducted the enquiry presented here. The goal of our enquiry was to find out how the results of the studies mentioned above are implemented in German breast cancer centers and university hospitals, and to investigate which AIs and treatment strategies are applied in relation to the risk of relapse (low, moderate, high) according to the St. Gallen-classification (table 2).

Questionnaire

A 2-sided questionnaire was sent to a total of 200 German breast cancer centers and university hospitals for the evaluation of our questions in April 2009. The questionnaire included 6 questions. In addition, a cover letter with instructions and an addressed envelope to preserve the anonymity of the respondent were attached.

Statistical Analysis

An entry mask for data collection and evaluation of the returned questionnaires was created in the program SPSS, version 17 (SPSS Inc., Chicago, IL, USA).

Results

Response

Of the 200 questionnaires sent to German breast cancer centers and university hospitals, 108 (54%) were returned.

| Trial [ref.] | Therapy upfront | sequential/switch | extended adjuvant |
|--------------|--|--|----------------------------|
| | ATAC [23], BIG 1-98 [24], TEAM [25] | IES [14, 26], ARNO-95 [27, 28], ITA [29, 30], ABCSG-8 [31], BIG 1-98 [15], TEAM [32] | MA 17 [13], NSABP-B33 [33] |

Table 1. Adjuvant endocrine therapy of postmenopausal hormone receptor-positive breast cancer – overview of trials

| Relapse risk | | |
|---|---|--|
| low | moderate | high |
| pT ≤ 2 cm, nodal negative, G 1, no vessel invasion, Her-2/ neu-negative, age ≥ 35 years | pT > 2 cm, nodal negative, G 2–3, peritumoral vessel invasion, Her-2/neu-positive or nodal positive (1–3 LN metastases) and Her-2/neu-negative | nodal positive (1–3 LN metastases) and Her-2/neu-positive or nodal positive with ≥ 4 LN |

Table 2. Definitions of risk of relapse

LN = Lymph node.

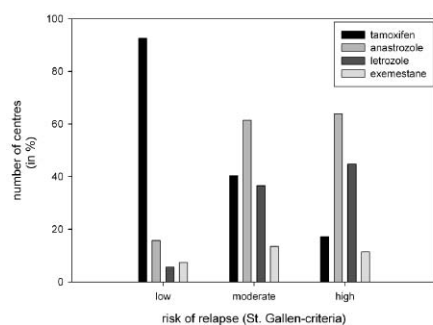


Fig. 1. Frequency of administration of drugs in postmenopausal breast cancer relative to the risk of relapse (multiple answers possible).

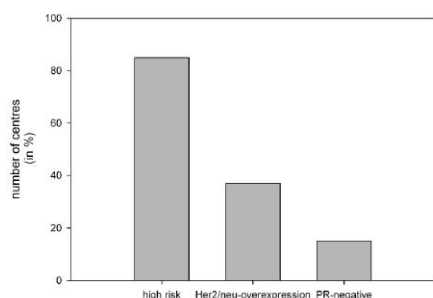


Fig. 3. Criteria for upfront therapy with an aromatase inhibitor (multiple answers possible; PR = progesterone receptor).

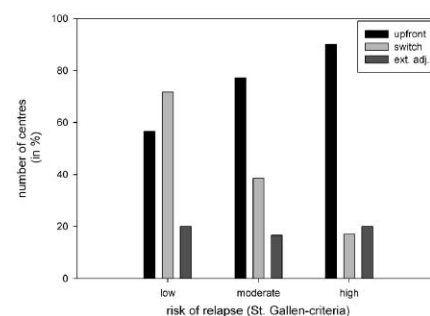


Fig. 2. Strategies of aromatase inhibitor use (upfront, switch, extended adjuvant (ext. adj.)) in postmenopausal breast cancer relative to the risk of relapse (multiple answers possible).

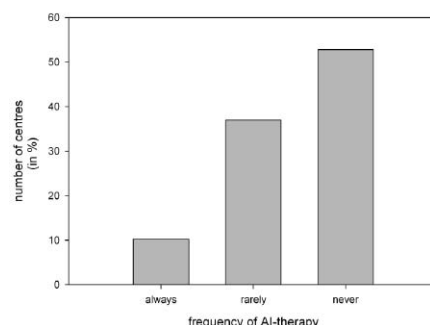


Fig. 4. Frequency of use of aromatase inhibitors (AIs) in the adjuvant therapy of premenopausal breast cancer.

Postmenopausal Breast Cancer with Low Risk of Relapse

In German breast cancer centers, the use of tamoxifen was clearly preferred to AIs in the adjuvant endocrine therapy of postmenopausal breast cancer patients with low risk of relapse (table 2). Tamoxifen was named as the drug of choice in 93%, anastrozole in 16%, letrozole in 6%, and exemestane in 7% (multiple answers possible) (fig. 1). In the case of ongoing tamoxifen therapy, 71% of the centers preferred a change to an AI which 72% of the centers would apply as sequential/switch, 57% as upfront, and 20% as extended adjuvant therapy. Again multiple answers were possible (fig. 2).

Postmenopausal Breast Cancer with Moderate Risk of Relapse

In the therapy of postmenopausal breast cancer with moderate risk of relapse (table 2), German breast cancer centers mostly used AIs: 62% anastrozole, 37% letrozole, and 14% exemestane. Only 40% used tamoxifen. Again multiple answers were possible (fig. 1). In the case of ongoing tamoxifen therapy in patients with moderate risk of relapse, 98% suggested a switch to an AI. The preferred treatment strategy was the upfront therapy (77%), followed by sequential/switch therapy (39%) and extended adjuvant therapy (17%) (fig. 2). The centers frequently named multiple therapy options.

Postmenopausal Breast Cancer with High Risk of Relapse

In the treatment of postmenopausal breast cancer with high risk of relapse (table 2), AIs were also the preferred option

(64% anastrozole, 45% letrozole, 11% exemestane). Only 17% indicated to use tamoxifen in this setting. Multiple answers were possible (fig. 1). In the case of ongoing tamoxifen therapy, 97% of the centers preferred a change to an AI. 90% marked upfront therapy, and 37% marked sequential/switch therapy or alternatively extended adjuvant therapy as the preferred option (fig. 2).

Osteodensitometry and Additional Bisphosphonates in AI Therapy

Before starting AI therapy, 78% of the centers would perform an osteodensitometry, 22% would not. Additionally to AI therapy, 9% of the centers give bisphosphonates 'always', 13% 'never', and 78% 'in the case of manifest osteoporosis, osteopenia, and risk of fractures'.

Criteria for Use of AI

A 'high risk of relapse' is regarded as a criterion for upfront AI therapy in 85%. Her-2/neu overexpression and progesterone receptor negativity represent criteria for upfront AI use in 37 and 15% of cases, respectively (fig. 3).

AI Therapy in Premenopausal Patients

The question whether AIs also is used in the adjuvant therapy of premenopausal patients was answered by 10% of the centers with 'always', by 37% with 'rarely', and by 53% with 'never' (fig. 4).

Discussion

The scale of the questionnaire had to be limited to the most important items regarding AI therapy in order to achieve a sufficient rate of return. In creating this questionnaire, we were aware of the limitations concerning the evaluation of the reasons for the use of different AIs in different settings. In postmenopausal breast cancer, the superiority of AIs compared to tamoxifen concerning the relapse-free and in some studies also the overall survival was clearly verified in the trials listed in table 1. Despite the fact that some authors propose specific AIs for the primary use in adjuvant therapy, no studies dealing with a head-to-head comparison of different AIs have been published to date. Therefore, guidelines on the use of specific AIs are lacking. The head-to-head comparison between letrozole and anastrozole in patients with early breast cancer and a high risk of relapse is currently investigated within the ongoing Femara Anastrozole Clinical Evaluation (FACE) trial. In patients with advanced breast cancer, however, a recent phase II study showed equal effects of exemestane compared to anastrozole [6]. In the neoadjuvant setting, another phase II study showed no differences between exemestane, letrozole, and anastrozole [7]. In our enquiry, the most commonly administered drug for postmenopausal breast cancer patients with low risk of relapse was tamoxifen (93%), while the sequential or upfront use of AIs (particularly anastrozole followed by letrozole) was preferred in patients with moderate and high risk of relapse (62 and 64%, respectively). Besides the missing guidelines for the use of specific AIs, the preferred choice of anastrozole and letrozole for upfront therapy can be explained by the fact that both substances are licensed for upfront use [8, 9]. Exemestane is currently only licensed for sequential/switch therapy [10] (table 3). The most experience exists with anastrozole which the ATAC trial showed to provide the greatest benefit in patients undergoing upfront therapy. Follow-up data of 10 years are now available [11].

According to our enquiry about treatment strategies, a change to an AI was made 'always' in 71, 98, and 97% of patients with low, moderate, or high risk of relapse, respectively, even if a therapy with tamoxifen had already begun. This was remarkable particularly in patients with low risk, since a therapy with tamoxifen alone may have been sufficient in those cases.

In its 2010 guidelines, the Arbeitsgemeinschaft Gynäkologische Onkologie (AGO) placed the sequential/switch therapy for a duration of a total of 5 years at the highest level of recommendation with '++', upfront therapy was classified as '+'. Up to now, a survival benefit could only be confirmed in the sequential/switch studies (IES, ARNO-95, ABCSG-8), while proof of a survival benefit for upfront therapy is still lacking. An argument in favor of the sequential therapy is the potential development of resistance which could occur in the course of 5 years of adjuvant therapy with a single substance

Table 3. Approval for treatment strategies (2009)

| | Therapy | | |
|-------------|---------|-----------------------|----------------------|
| | upfront | sequential/ switch | extended adjuvant |
| Anastrozole | + | + | – |
| Letrozole | + | – | + |
| Exemestane | – | + | – |

and which could affect the therapeutic success. The development of resistance under tamoxifen is examined well and can be avoided or at least postponed by the sequential use of the drug. In our enquiry, the majority of the centers chose a switch, especially in patients with early postmenopausal breast cancer and low risk of relapse (switch 72%, upfront 57%, extended adjuvant 20%). Upfront therapy was favored by the majority of centers in breast cancer patients with a moderate or high risk of relapse (77 and 90%, respectively). At the time of our enquiry, this was consistent with the 2009 AGO guidelines in which the upfront therapy was set at the highest level of recommendation ('++'). In the 2010 guidelines, however, 5-year sequential/switch therapy ranks highest and upfront therapy is classified as '+'.

Our enquiry shows that at the beginning of an AI therapy, an osteodensitometry is carried out in only 78% of cases. At this point it should be mentioned that osteodensitometry in association with AI treatment is not usually covered by the public health insurance in Germany. The use of an AI is named as a reason for a bisphosphonate therapy in 9% of cases. 13% indicated no reason for a bisphosphonate therapy, and 78% used bisphosphonates only if a bone pathology existed (i.e. manifest osteoporosis, osteopenia, or risk of fractures). According to the recommendations from the 2007 St. Gallen conference, an osteodensitometry is to be initiated at the beginning of an AI treatment, and bisphosphonate therapy is to be applied if necessary according to the guidelines [12]. The risk of osteoporosis and bone fractures increases due to the reduction in peripheral estrogen caused by the AIs. The trials show that all AIs cause an increased risk of osteoporosis compared to tamoxifen, with only minor and insignificant differences between the single substances (letrozole 3.6% vs. placebo 2.9% [13], exemestane 3.1% vs. tamoxifen 2.3% [14], anastrozole 7.1% vs. tamoxifen 4.4% [2]). While all fractures have an impact on a patient's quality of life, only some have potentially life-threatening consequences. In the ATAC trial, the number of hip fractures in the anastrozole group was similar to the fracture rate in the tamoxifen group (16 vs. 20) [15]. In a recent study of 343 early breast cancer patients who were to receive AI therapy, Servitua et al. [16] showed that only 59 (17.7%) had normal bone mineral density. In view of these numbers, it seems to be absolutely necessary to promote the use of osteodensitometry in breast cancer patients in Germany. In the 'ASCO Guidelines for Bisphosphonates', patients with early postmenopausal breast

cancer, who receive AIs, are classified as belonging to the high-risk group for osteoporosis. For these patients, an osteodensitometry at the beginning of therapy is recommended as well as the use of bisphosphonates where necessary [5]. In the current AGO guidelines (2010), bisphosphonate treatment for the prevention and therapy of tumor therapy-induced osteoporosis is recommended most strongly ('++'). The recommendation of bisphosphonate therapy for the prevention of bone metastases in the adjuvant therapy of primary breast cancer obtained a '+'. In premenopausal patients receiving goserelin for ovarian suppression, Gnant et al. [17] showed improved disease-free survival in patients treated with anastrozole or tamoxifen by adding zoledronic acid. These results support the general recommendations for the prophylactic use of bisphosphonates in breast cancer patients receiving endocrine therapy. Another possible explanation for the benefit of bisphosphonate therapy is based on its supposed anticancer activity in both the pre- and postmenopausal adjuvant setting [18].

In our enquiry, we asked, in which case an upfront therapy with an AI is carried out routinely. High risk of relapse was named in 85%, positive Her-2/neu status in 37%, and progesterone receptor negativity in 15%. At the 2007 St. Gallen conference, an extended adjuvant therapy with an AI was suggested for all patients with early hormone receptor-positive breast cancer and positive lymphatic nodes after 5 years of tamoxifen. The risk of relapse in patients with breast cancer reaches its maximum during the first 2 years after primary therapy. However, a small risk remains up to 15 years after the primary diagnosis. The average risk of relapse is 4.3% per year between the 5th and the 12th year after primary therapy. The most frequent events of relapse are distant metastases, followed by local relapse and axillary lymph node relapse [19]. The rates of relapse change corresponding to the time since the primary therapy, which should be considered when choosing an endocrine therapy. Patients with a high risk of relapse benefit more from an upfront therapy with an AI. Mauriac et al. [20] showed that letrozole appeared to provide a greater than average reduction in the risk of early relapse in

patients with many involved lymph nodes, large tumors, and vascular invasion. Lin [21], however, is convinced that patients with a hormone receptor-positive tumor have an almost constant risk of relapse during the first 5–10 years after the primary diagnosis, while patients with a hormone receptor-negative tumor only have an increased risk of relapse in the first years after the primary diagnosis. He concludes that an upfront therapy is not compulsory for patients with a hormone receptor-positive tumor [21].

Premenopausal status is still regarded as a contraindication for AI therapy. Another contraindication is chemotherapy-induced amenorrhea because the AI could stimulate the remaining ovarian function. The reduction of the peripheral estrogen levels leads to an increased central release of gonadotropins which could even provoke an ovulation [5]. If necessary, perimenopausal patients may receive a sequential therapy, if they are still amenorrheic after 2–3 years of tamoxifen treatment [22]. Up to now, the use of AIs in premenopausal women has been examined only within clinical trials using gonadotropin-releasing hormone analogues for ovarian suppression [17]. The fact that despite the guidelines and recommendations of the oncologic societies almost half of the participating centers use AIs in the adjuvant therapy of premenopausal breast cancer patients, shows amongst others that there is a substantial demand for more information regarding this aspect.

In summary, the German breast cancer centers perform adjuvant endocrine therapy of early postmenopausal breast cancer patients largely in accordance with current recommendations. However, there is a need for improvement concerning the additional use of bisphosphonates, and especially the surprisingly high use of AIs in premenopausal patients indicates a need for more information.

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