Compliance to adjuvant therapy in breast cancer patients

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Summary

During recent years a continuous reduction of mortality from breast cancer has taken place in the Western countries. We wanted to verify whether the actual therapy for our own cases deviates from our recommendations, although the surgeon, radiotherapist and gynaecological oncologist are on the same premises. We sent out questionnaires to all newly diagnosed breast cancer patients in the last seven years regarding their adjuvant therapy. Comparing these answers to our own recommendation showed a very good compliance regarding chemotherapy and radiation therapy. Adjuvant endocrine therapy showed a very poor compliance with an adherence of 77%. Overall we can conclude that endocrine therapy causes many side-effects that seem to burden the patients. In combination with the duration of the therapy this causes a severe reduction in compliance and length of the therapy.

Key words: Compliance; Breast cancer; Adjuvant therapy; Endocrine therapy.

Introduction

With 55,000 new occurrences per year, breast cancer is the most common cancer of women in Germany; each year breast cancer is responsible for 17,780 deaths, making this the most common cause of death by a malign entity [1]. In Europe, breast cancer is the most common cancer in females and two-thirds occur in postmenopausal women aged 55 years and older [2]. An interesting fact is shown by epidemiologic data evaluated in the EURO-CARE-2: the quality of care in Germany could be better – a survival rate of 72% in the first five years after the diagnosis places us in the European midfield [3].

During recent years a continuous reduction in breast cancer mortality has taken place in Western countries. This is on one hand due to the improvement of early diagnosis and on the other hand to the constant progress of diverse targeted therapies [4]. A large number of patients with chronic diseases do not show a good compliance with the prescribed medication. A study of the University of Marburg has shown that a lot of patients discontinue their antihormonal medication within the first year of therapy [5, 6]. Data provided by German pharmacies stated that three months after the start of the therapy only 66% use their follow-up prescription, 18 months later 50% are remaining [5, 6]. The effects of this lack of compliance in the long run and ways to improve the adherence are currently being evaluated by different studies. They are looking at postmenopausal patients who are taking an aromatase inhibitor to see whether more information on the medication and the disease can improve the compliance.

It has been shown that therapy according to the guidelines improves survival rate [4, 7, 8]. Apart from the correct therapy compliance plays an essential role.

Using our own cases in the last seven years we wanted to verify whether the actual therapy deviates from our recommendations, although the surgeon, radiotherapist and gynecological oncologist are on the same premises.

Materials and Methods

In the context of a retrospective study we evaluated the data of all patients with the first diagnosis of breast cancer between 2000 and 2007 in our clinic, excluding the deceased. Adherence was evaluated via patient self-reports with a detailed questionnaire. Data collected from medical records included, histology, tumour staging and grading, HR status, and primary oncological treatment (surgery, radiation therapy, chemotherapy). We sent questionnaires to 1,621 patients and received 663 back. We did not pursue any other means of getting information since we wanted to rely on the testimony of the women. The answers were compared with our last recommendations for adjuvant therapy.

Our recommendations were fixed when we finished surgery, received the histological results, and the staging results. These recommendations were set up as a letter and sent to the gynaecologist, general practitioner, radiotherapist and gynaecological oncologist if applicable.

The questionnaires contained the following:

Did you receive chemotherapy/radiotherapy/endocrine therapy/antibodies?

If yes, do you know which?

How long did you receive the medication?

Did it come to an early stop of the medication?

In case of yes, do you know why?

Did you receive alternative medicine?

We divided the adjuvant therapy in chemotherapy, radiotherapy and endocrine therapy. Altogether we received feedback from 616 patients; 276 patients were pT1, 183 pT2, 24 pT3 and 14 pT4. Sixteen patients were suffering from a ductal carcinoma in situ (DCIS) and 22 received neoadjuvant chemotherapy. Another ten patients showed bilateral breast cancer. The rest of the patients showed incomplete data and could not be included in the analysis. One hundred and seventy-nine patients were node positive and 353 node negative.

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Results

Chemotherapy

Of 318 patients, to whom we recommended chemotherapy, 277 completed the treatment. This corresponds to a compliance of 87%. Of those who did not follow the recommendations 11 refused chemotherapy, three patients discontinued the therapy due to febrile neutropenia, two patients showed cardiac problems and another three had side-effects. Twenty-two patients did not give reasons for the discontinuation.

Radiotherapy

The greatest compliance was in the field of adjuvant radiotherapy. Five hundred and seventeen patients were advised to undergo radiation; 511 completed the treatment and six refused the treatment. This corresponds to a compliance of 98.8%.

Endocrine therapy

The greatest difference between recommended and received therapy was found regarding endocrine therapy. We divided the patients into four groups: group 1 was recommended five years of tamoxifen (n = 205), group 2 – two years of tamoxifen followed by three years of an aromatose inhibitor (AI) (n = 112), group 3 - five years of AI and group 4 was recommended five years of tamoxifen and two years of GnRH-Analog (n = 28) according to the premenopausal status.

Treatment with tamoxifen

Five years of tamoxifen were completed by 83 of 205 patients, 121 discontinued the therapy early and one patient refused endocrine therapy. Of the 121 patients, 75 were switched to an AI, the time span here was inbetween six weeks and four years. Twenty-six patients discontinued the therapy without giving a reason and 17 patients stopped taking tamoxifen due to side-effects. Ten of these were switched over to an AI. Because of progressive disease the medication was stopped for three patients.

The discontinuation of tamoxifen therapy occurred mainly due to side-effects. Seven patients reported hyperplastic endometrium, one patient postmenopausal bleeding and one patient suffered from endometrial cancer. One patient developed a thrombosis and one a stroke. These patients were switched to an AI. Five patients claimed to have perimenopausal side-effects as a reason for the discontinuation. One patient stopped taking tamoxifen when she developed a benign ovarian tumor.

Group 2: Five years of AI

The upfront therapy with an AI was completed by 70 of the 93 patients; 23 patients discontinued the therapy. The main reasons for discontinuation were rheumatic complaints and arthritis. There were also cases of hair loss and elevation of liver enzymes.

Group 3: Sequential therapy

Of 112 patients 69 completed the recommended therapy and 43 discontinued the therapy or were switched over to a different regime. Five patients received an AI upfront. For three patients tamoxifen therapy was discontinued due to side-effects. One patient was switched over to an AI; she claimed to have had no side-effects. One other patient was operated three months after starting tamoxifen. After the operation the tamoxifen treatment was discontinued and not replaced. One patient was switched over to five years of tamoxifen.

Group 4: Tamoxifen and GnRH-Analog

The combination of tamoxifen and GnRH-Analog was tolerated by 12 of the 28 patients and 16 discontinued therapy. Two patients claimed peripheral edema and menopausal flushing to be the reason for stopping the goserelin. These patients received tamoxifen mono.

Discussion

The data evaluation in this group of patients shows a representative collection regarding compliance with the adjuvant setting of breast cancer patients.

The greatest compliance is shown in the field of radiotherapy. The reason for this could be the relatively short duration and the minor side-effects of the therapy, for example compared to chemotherapy. A positive factor in our setting is that an appointment for the radiotherapy is determined at the dismissal of the patient (at the latest) so that continuous guidance is given.

In second place is chemotherapy, with a compliance of 87%. More than 90% of the women received the chemotherapy in the attached chemotherapy unit of the women's hospital. The first appointment is like the one for the radiotherapy, already set at time of release.

A very poor compliance is shown in the field of endocrine therapy with 77%; 56% actually received the recommended therapy, but those who discontinued due to medical decisions were not taken into account regarding compliance. The highest rate of discontinuation was shown by those women who were supposed to receive five years of tamoxifen with a compliance of 40%. Side-effects like perimenopausal problems were the reason given most often. It should be kept in mind that this group also consisted of those patients that were switched to an AI upfront due to the new findings that were discovered. Five years of AI were completed by 75% of the patients. The main reasons for discontinuation were muscle and bone pain.

The sequential therapy was completed by 62%. Four patients were switched to an AI upfront; three patients were switched over due to the side-effects of the tamoxifen.

Conclusion

Overall we can conclude that endocrine therapy caused many side-effects that seemed to burden patients. In combination with the duration of the therapy this causes a severe reduction in compliance and length of therapy [9]. A recently published study by McCowan *et al*. showed that tamoxifen treatment taken incompletely increases the risk of a disease-associated death [10].

How do we improve compliance? This question has been subject to discussions for several years now. In 2004 Fink *et al*. published a study that showed that patients who did not believe in the effect of endocrine therapy tend to discontinue the medication very soon [11]. This was confirmed by Hadji *et al*. in a publication on improving compliance to adjuvant hormonal therapy in 2010 [12]. Another recently published study concerning compliance to endocrine treatment in the postmenopausal patient showed that compliance can be increased by a close connection to an oncological unit [13].

The limitation of this study is first of all the fact that it is a retrospective study and second that there is no gold standard in measuring adherence. In order to receive a more detailed overview the prescription data has to be collected.

Patient awareness and an understanding of their disease could influence adherence [14, 15]. Studies evaluating influential factors on compliance are the PACT study and the evaluate study. In this setting the collection of data for the management of therapy and compliance in the treatment of postmenopausal primary breast cancer with letrozol is the main goal.

We must not forget that the patients usually don't understand the endocrine therapy to be one of their main oncologic therapies. After completing radiation and/or chemotherapy they perceive themselves as subjectively healthy. The effectiveness and the importance with regard to prevention are not understood by many patients. Due to this a close connection to an oncologic unit also in the field of the endocrine therapy is of great importance.

Aknowledgement

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References

[1] Gesellschaft der epidemiologischen Krebsregister in Deutschland e.V. und das RKI. Krebs in Deutschland. 5. überarbeitete, aktualisierte Ausgabe. Saarbrücken 2006.

[2] Jemal A., Siegel R., Ward E., Hao Y., Xu J., Murray T., Thun M.J. *et al*.: "Cancer Statistics 2008". *CA Cancer J. Clin*., 2008, *58*, 71.

[3] Sant M., Capocaccia R., Verdecchia A., Esteve J., Gatta G., Micheli A. *et al*.: "Survival of women with breast cancer in Europe: variation with age, year of diagnosis and country. The EUROCARE Working Group". *Int. J. Cancer,* 1998, *77,* 679.

[4] Early Breast Cancer Trialists' Collaborative Group (EBCTCG), Clarke M., Coates A.S., Darby S.C., Davies C., Gelber R.D., Godwin J. *et al*.: "Adjuvant chemotherapy in oestrogen-receptor-poor breast cancer: patient-level meta-analysis of randomised trials". *Lancet,* 2008, *5,* 29.

[5] Hadji P., Ziller V., Kalder M., Torode J., Jacklsch C.: "Non-compliance in der adjuvanten endokrinen therapie des mammakarzinoms". *Frauenarzt,* 2007, *27,* 146.

[6] Ziller V., Kalder M., Albert U.S., Holzhauer W., Ziller M., Wagner U., Hadji P.: "Adherence to adjuvant endocrine therapy in postmenopausal women with breast cancer". *Ann. Oncol*., 2009, 20, 431.

[7] Varga D., Wischnewsky M., Atassi Z., Wolters R., Geyer V., Strunz K. *et al*.: "Does guideline-adherent therapy improve the outcome for early-onset breast cancer patients?". *Oncology,* 2010, *78,* 189.

[8] Yood M.U., Owusu C., Buist D.S., Geiger A.M., Field T.S., Thwin S.S. *et al*.: "Mortality impact of less-than-standard therapy in older breast cancer patients". *J. Am. Coll. Surg.,* 2008, *206,* 66.

[9] Cella D., Fallowfield L.J.: "Recognition and management of treatment-related side effects for breast cancer patients receiving adjuvant endocrine therapy". *Breast Cancer Res. Treat.,* 2008, *107,* 167.

[10] McCowan C., Shearer J., Donnan P.T., Dewar J.A., Crilly M., Thompson A.M., Fahey T.P. *et al*.: "Cohort study examining tamoxifen adherence and its relationship to mortality in women with breast cancer". *Br. J. Cancer*, 2008, *99,* 1763.

[11] Fink A.K., Gurwitz J., Rakowski W., Guadagnoli E., Silliman R.A.: "Patient beliefs and tamoxifen discontinuance in older women with estrogen receptor-positive breast cancer". *J. Clin. Oncol.,* 2004, *22,* 3309.

[12] Hadji P.: "Improving compliance and persistence to adjuvant tamoxifen and aromatase inhibitor therapy". *Crit. Rev. Oncol. Hematol*., 2010, *73,* 156.

[13] Güth U., Huang D.J., Schötzau A., Zanetti-Dällenbach R., Holzgreve W., Bitzer J., Wight E.: "Target and reality of adjuvant endocrine therapy in postmenopausal patients with invasive breast cancer." *Br. J. Cancer,* 2008, *99*, 428.

[14] Haynes R.B., McDonald H., Garg A.X., Montague P.: "Interventions for helping patients to follow prescriptions for medications". Cochrane Database Sys. Rev., 2002 CD000011.

[15] WHO. Adherence Project. WHO 2003.

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