ClinicSearch

Clinical Reviews and Case Reports

JM Wenderlein *

Open Access

Short communication

More Frequent Tamoxifen Adjuvant Therapy Results in Sustained Lower Breast Cancer and Overall Mortality Than Aromatase Inhibitors

JM Wenderlein

JM Wenderlein University of Ulm Germany.

***Correspondence Author:** JM Wenderlein, JM Wenderlein University of Ulm Germany.

Received Date: December 10, 2024 | Accepted Date: December 26, 2024 | Published Date: January 03, 2025

Citation: JM Wenderlein, (2024), More frequent tamoxifen adjuvant therapy results in sustained lower breast cancer and overall mortality than aromatase inhibitors, *Clinical Reviews and Case Reports*, *4*(1); **DOI:**10.31579/2835-7957/102

Abstract

The 45% higher mortality rate among women aged 70 and over with a history of breast cancer than in the USA urgently needs an explanation. This is hardly explainable by different mammography screening. Endocrine therapy needs to be reviewed, i.e. tamoxifen versus aromatase inhibitors. The latter can provide a biologically plausible explanation for higher mortality due to induced severe estrogen deficiency.

Keywords: estrogen effects; osteoporosis; Tamoxifen

Introduction

German researchers in Heidelberg have evaluated central cancer registry data regarding breast cancer prognosis (1975-2015) and compared it with data from the USAThe incidence of breast cancer was higher in the USA than in Germany. Mortality fell in the USA after 1989 and in Germany after 1996, but was 30% higher in Germany. For women aged 70 and over with a history of breast cancer, the mortality rate in Germany was 45% higher than in the USA. The study authors attributed this to differences in mammography screening.In addition, Swedish study data on around a third of women who took part in the local mammography screening over an observation period of 16-25 years. These participants had a 41% lower risk of dying from breast cancer in the 10 years after diagnosis. According to another estimate of the same data, the risk was 34% lower compared to those without screening.The 30% and 45% higher death rates from breast cancer in Germany than in the USA must therefore have other causes. A comparison was made between two countries with slightly different mammography screening start dates but similar participation rates.

Tamoxifen use in the USA much more common

Tamoxifen is a competitive inhibitor of the binding of estrogen to its receptor in the cytoplasm. This reduces cell division in estrogen-dependent tissues, including in estrogen receptor-positive breast cancer. At the same time, tamoxifen has various partial estrogen effects, including on bones with protection against osteoporosis and a better lipid profile for a lower risk of coronary heart disease.

The hormonal alternatives are aromatase inhibitors (AH), which block the conversion of testosterone from the adrenal glands and ovaries into estrogen. This causes a massive estrogen deficiency throughout the body. The result is a fourfold higher risk of osteoporosis fractures and even more frequent osteoporosis problems, which hinder an active, health-conscious lifestyle, especially physical activities for social contacts. It is therefore not surprising that one in three women suffers from depression after breast cancer treatment (1), even when the prognosis is good. Estrogen deficiency after the menopause also causes one in three women to experience prolonged depression for the first time. The latter can shorten life. AH are classified as risky for the brain (2). In addition, taking AH can cause dyslipidemia and thus an additional risk of coronary heart disease, which damages cerebral blood flow.The biological logic is therefore obvious: in old age or from the age of 70 onwards, there is a higher mortality rate when using AA, depending on its duration.Does this explain our 45% higher mortality rate among women aged 70 and over with a history of breast cancer than in the United States?

How often are tamoxifen and AH prescribed?

Tamoxifen was the gold standard in preventive and adjuvant hormonal breast cancer therapy (3) for decades, until 15 years ago. Then this recommendation was relativized by ASCO, AH was also listed and their use slowly began in the USA.

It should be noted that the comparative study USA versus Germany collected data from 1975 to 2015 and that most women there aged 70 and over with a history of breast cancer only received tamoxifen therapy - with significantly lower mortality as a result. Fifteen years ago, the situation in Germany was completely different. The ratio of AH to tamoxifen had been 1:1 for several years, with the number of AH prescriptions continuing to rise. According to the 2020 Drug Prescription Report, there were 45 million DDDs for tamoxifen and 55 million DDDs for AH. The former prescriptions decreased by 1% and the latter increased by 7%. The net DDD costs of tamoxifen were €0.20 and €0.68 for AH (in 2007 they were €5.56, i.e. a factor of 8 higher, or €0.23 for tamoxifen versus AH, a factor of 24 higher). In the last 13 years, AH prescriptions increased from 35 to 55 million DDD, i.e. about a third. The situation is different in the USA. Tamoxifen prescriptions continue to dominate there. In 2020, the NSABPB-42 study on AH, especially letrozole, was evaluated after 10 years (4): no influence on overall survival and a significantly higher risk of VTE events. The latter can be classified as an indication of vascular damage - as a result of permanent estrogen deficiency (5). Tamoxifen is also known to have a VTE risk and can be explained by coagulation activation. This is based on its partial estrogen effects and can be reduced by anticoagulation. This estrogen effect is known from pregnancy, the pill

and HRT. In the case of VTE under AH, vascular damage due to estrogen deficiency can be assumed, especially in the venous system (5).

Better educate people about tamoxifen

The Heidelberg study found that the mortality rate in women aged 70 and over with a history of breast cancer was 45% higher than in the USA. This corresponds to 46 more deaths per 100,000 women. This is much more frequently preceded by morbidity, which is more difficult to determine in studies than mortality. The study authors do not explain the differences by the different quality of cancer care in the two countries. The DKFZ study director is an epidemiologist and aging researcher and may be less familiar with the clinically relevant differences between tamoxifen and AH. The author's simple explanation to patients in the outpatient clinic: Tamoxifen acts directly on the tumor cells and AH on the entire body, including cancer cells. This resulted in almost complete tamoxifen compliance. The following study data (6) illustrates this. Women were prospectively assessed for tamoxifen compliance (n= 1,177). This was objectively measured with tamoxifen levels below 60 ng/ml, 1 year after tamoxifen prescription. Noncompliance was present in 16% and explains tamoxifen failures, according to the study authors in 2020. In comparative studies of tamoxifen to AH, oncological differences of only a few percent were usually observed for only 5-10 years. The side effects of tamoxifen and AH resulting from induced estrogen deficiency are similar, but there are significant differences. Tamoxifen causes subjective symptoms such as those at the onset of menopause. AH also causes serious organ damage, most obviously in the bones. In addition, women develop severe osteoporosis even without menopausal symptoms. This can be avoided by using very low levels of estrogen. The FDA has approved a transdermal estrogen patch for this purpose, with half the dosage of the lowest dose of the estrogen patch available in our country. Both rationally and biologically, it can be assumed that the partial estrogen effects of tamoxifen have a positive preventive effect on many organ systems, particularly the cardiovascular system. This is the most convincing and obvious explanation for the 45% higher mortality rate among women aged 70 years and older with a history of breast cancer in our country, with significantly fewer tamoxifen histories than in the USA.

With 5-year survival rates of 86%, think about senium

Of the 70,000 new cases of breast cancer per year, 80 to 85% have a hormone receptor positive result. These women are suitable for anti-hormonal therapy. In adjuvant indications, the choice should be made in such a way that no higher cancer mortality and overall mortality occurs after the age of 70. Previous studies lasting 5-10 years have failed to recognize this problem. Tamoxifen can be used independently of other systemic therapy. In addition to the oncological effect, the positive estrogen effects on many organ systems should be considered, especially the bones and circulatory system. As early as 2014, the ASCO guideline recommended the use of tamoxifen to reduce the risk of breast cancer for 5 years, 20 mg orally daily. This was confirmed and expanded in an update of this guideline on September 23, 2020 (7). It should be offered to women aged 35 and over with a higher risk of cancer, but also to pre- and postmenopausal women with a higher risk of cancer, with a 1.66% chance of success with 5 years of tamoxifen. This applies to both breast cancer and LCIS findings. This tamoxifen effect persists for at least 10 years after discontinuation. This is a very tamoxifen-oriented statement from the USA and was not made there for AH. This can probably be explained by the fact that internists in the USA are primarily responsible for oncology and pay more attention to estrogen deficiency damage in various organ systems than oncological gynecologists here - with rather marginal internal medicine knowledge. The known contraindications were VTE, stroke, TIA and prolonged immobilization as well as pregnancy and HRT. Anyone who seriously intervenes in hormonal mechanisms, especially in the important control hormone estrogen, should have hormonal competence - not obligatory in oncology. AH use over several years induces organ risks that develop gradually and usually only become clinically manifest when the patient is over 70 years old.

An outpatient clinic experience: Women with a history of AH reported previously unexperienced sleep disorders, particularly less deep sleep. Less REM sleep is known to reduce life expectancy, even by several years. Long-term insomnia worsens the prognosis for cancer. When considering the better survival chances for women after breast cancer in the USA, it should be remembered that life expectancy for women over 2 years is lower there than in Germany. This would lead one to expect worse survival after breast cancer. Does tamoxifen represent a very low level of estrogen substitution with advantages there?

Summary

The 45% higher mortality rate among women aged 70 and over with a history of breast cancer than in the USA urgently needs an explanation. This is hardly explainable by different mammography screening. Endocrine therapy needs to be reviewed, i.e. tamoxifen versus aromatase inhibitors. The latter can provide a biologically plausible explanation for higher mortality due to induced severe estrogen deficiency.

Tamoxifen adjuvant needs no alternative: confirmed with long-term data from Swedish study from 2023

A study from Sweden with 30 years of follow-up confirms 5 years of tamoxifen as the gold standard (7). This country is exemplary in clarifying the benefits of adjuvant tamoxifen. In 1996, a study (8) (n = 3,500) of postmenopausal women (x 63 years) found that in breast cancer stages I-IIIA, 5-year tamoxifen therapy achieved better cancer-specific results and survival times than tamoxifen for 2 years. This was confirmed by a meta-analysis in 2011 (9). This estrogen receptor modulator for 5 years significantly reduces the recurrence rate in the first 10 years after breast cancer surgery - and after that? Now 30-year data (7) confirm that 5 years of tamoxifen is superior to just 2 years, calculated from the time tamoxifen was stopped. Up to 15 years later, mortality was 20% lower than with 2 years of tamoxifen. Breast cancer mortality was reduced by 33% with 5 years of tamoxifen. After a further 15 years, mortality rates were also lower, although less significantly. During the follow-up period after 5 years of tamoxifen, 33% fewer contralateral breast cancers occurred than after 2 years of tamoxifen. The Swedish lead author reported rather "cautiously" that the incidence of lung cancer is halved by 5 years of tamoxifen. This is known from HRT (10). The same can be expected with regard to the risk of colon cancer (11). Tamoxifen is essentially HRT at a fairly low level. More women now die of lung cancer than of breast cancer, thanks to better treatment options. The partial estrogen effects of tamoxifen - without antiproliferative progestogens - can cause endometrial proliferation and even cancer. According to Swedish data, this was the case for 77 of 2019 women after 5 years of tamoxifen and 42 of 21053 after 2 years of tamoxifen, i.e. 3.5% to 2%. The study authors refer to 40 mg of tamoxifen, which is hardly common in Germany, with a tendency towards 20 mg.

comment

Adjuvant tamoxifen therapy for 5 years in hormone receptor positive breast cancer should become standard. The previous "switch" therapy of aromatase inhibitors (AI) for 2 to 3 years and tamoxifen for 2-3 years is now obsolete. This is because complete blockade of estrogen supply from testosterone in the ovaries and adrenal glands is risky in the long term and was overlooked due to short study durations. A comparative study of Germany and the USA by the German Cancer Research Center (12) also shows that in Germany, the mortality rate after breast cancer treatment is about 50% higher than in the USA - for the same tumor stage. In the comparative study, no distinction was made between tamoxifen alone and tamoxifen-AI combination for 2.5 years each. The result is plausible: in the period covered, the vast majority of women after primary breast cancer treatment in the USA were treated with tamoxifen alone, and in the same period in Germany they were treated with tamoxifen-AI combination adjuvantly. The latter is based on underestimating the partial estrogen effects of tamoxifen and overestimating the risk of endometrial cancer. The latter is hardly a problem when vaginal sonography is performed every one to two years. If the smallest tumors are discovered in this way, 100% healing is achieved. The partial effects of tamoxifen and estrogen on the bone system are important. Fewer osteoporosis symptoms make it easier to walk more steps per day. If 7,000 to 13,000 steps are taken per day, the risk of death is halved (13).

Conclusion from Swedish study from 2023

AI therapies should be examined using the same study methodology, i.e. follow-up examinations for 15 years and 30 years. When it comes to the risk of osteoporosis, in addition to fractures, frequent osteoporosis symptoms must be taken into account and less physical activity as a result - detrimental to the heart. Heart failure causes a higher risk of cancer (8).

In men, evolution has set up the metabolism of testosterone to estrogen via the splitting off of 1 carbon atom to provide an essential estrogen supply. In postmenopausal women, this "emergency supply" is blocked with AI.Protection against breast cancer with endogenous and substituted estrogen is biologically plausible: beta-ORs with antiproliferative effects are maintained and apoptosis is promoted. In estrogen deficiency, these regress and alpha-ORs with proliferation effects dominate. Fewer new cases of diabetes under estrogen can act as a "link" to reduce cancer risks (14).All this is clearly proven by a nationwide study in Finland (15): HRT before and during breast cancer reduces mortality by up to two thirds. Tamoxifen does not need an alternative.

References

1. Doege D et al. (2020). Age-specific prevalence and determinants of depression in long-term breast cancer survivors compared to female population controls *Cancer Medicine*, DOI: 10.1002/cam4.3476
2. Wenderlein JM. (2005). Aromatase inhibitors risky for the brain. Obstetrics+Gynecology/Thieme,65;144-148
3. Gerber B et al. (2000). Preventive and adjuvant hormone therapy of breast cancer: just trends or already standard?Dtsch Arztebl 2000; 97(44): A-2947 / B-2516 / C-2335
4. Mamounas P et Al. (2019). Use of letrozole after aromatase inhibitor-based therapy in postmenopausal breast cancer (NRG Oncology/NSABP B-42): a randomized, double-blind, placebo-controlled, phase 3 trial. The Lanct OncologyVolume 20, ISSUE 1, P88-99. DOI:https://doi.org/10.1016/S1470-2045(18)30621-1
5. Wenderlein JM.,G.Rothenbücher. (2004). Ulm Phlebology Study with 711 women: Hormone replacement protects the leg veins of women aged 50 and over.Gyne /2004;213-216
6. Pistilli B et al. (2020). Serum detection of nonadherence to adjuvant tamoxifen and breast cancer recurrence risk.Journal of Clinical Oncology2020Volume 38, Issue 24(presented at the European Oncology Congress Munich 2018)7. Pavani Chalasani et al: Breast Cancer, Guidelines Guidelines SummaryDrugs & Diseases>OncologyUpdated.
7. Nordenskjöld A et al. (2023). Breast cancer survival and incidence of second primary cancers after 30 years in a randomized study of two versus five years of adjuvant tamoxifen therapy. *Breast* https://doi.org/10.1016/j.breast.2023.07.010
8. Early Breast Cancer Trialists' Collaborative Group (EBCTCG): Relevance of breast cancer hormone receptors and other factors to the efficacy of adjuvant tamoxifen: patient-level meta-analysis of randomized trials The LancetVolume 378, ISSUE 9793, P771-784, August 27, 2011
9. Swedish Breast Cancer Cooperative Group:Randomized Trial of Two Versus Five Years of Adjuvant Tamoxifen for Postmenopausal Early Stage Breast Cancer
10. JNCI(1996). Journal of the National Cancer Institute, Volume 88, Issue 21, November 6, 1996, 1543-1549,https://doi.org/10.1093/jnci/88.21.1543/Published.
11. Wenderlein JM.(2023). Hormone replacement therapy (HRT) to protect lung function and prevent lung cancer. gyne 2/1-5
12. Wenderlein JM. (2023). Primary prevention of colorectal cancer by estrogen substitution. Maintaining the microbiome with sufficient lactobacilli. Gynecology+ Obstetrics /Springer 1/ (28):58-59
13. Jansen L et al. (2020). Divergent Patterns and Trends in Breast Cancer Incidence, Mortality and Survival Among Older Women in Germany and the United States. Cancers, 12:2419
14. Banach M et al. (2023). The association between daily step count and all-cause and cardiovascular mortality: a meta-analysis. Eur J Prev Cardiol;https://doi.org/10.1093/eurjpc/zwad229
15. Jaiswal V et al. (2023). Association between Heart failure and incidence of cancer: A Systematic Review and Meta-analysis. *Eur Heart J Open*;https://doi.org/10.1093/ehjopen/oead073
16. Mikkola TS et al. (2016). Reduced risk of breast cancer mortality in women using postmenopausal hormonetherapy: a Finnish nationalwide comparative study.*Menopause*:23(11)1199−1203.