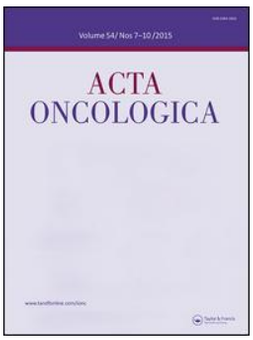

Acta Oncologica

ISSN: 0284-186X (Print) 1651-226X (Online) Journal homepage: https://www.tandfonline.com/loi/ionc20

Thymic malignancy in a breast cancer patient Is there an association with anti-estrogenic effects of tamoxifen?

Başak Oyan, Sercan Aksoy, Ozlem Yavas, Ayse Kars, Alev Turker & Ibrahim Barista

To cite this article: Başak Oyan, Sercan Aksoy, Ozlem Yavas, Ayse Kars, Alev Turker & Ibrahim Barista (2004) Thymic malignancy in a breast cancer patient Is there an association with anti-estrogenic effects of tamoxifen?, Acta Oncologica, 43:1, 115-116, DOI: 10.1080/02841860310017649

To link to this article: https://doi.org/10.1080/02841860310017649

Published online: 08 Jul 2009.

Taylor&Francis
healthsciences

Thymic Malignancy in a Breast Cancer Patient

Is there an Association with Anti-estrogenic Effects of Tamoxifen?

Başak Oyan, Sercan Aksoy, Ozlem Yavas, Ayse Kars, Alev Turker and Ibrahim Barista

From the Department of Medical Oncology, Hacettepe University, Institute of Oncology, Ankara, Turkey

Correspondence to: Başak Oyan, Hacettepe University, Institute of Oncology, Department of Medical Oncology, TR-06100 Sihhiye, Ankara, Turkey. Tel: +90 312 3052 937. Fax: +90 312 3242 009. E-mail: basakou@yahoo.com

Acta Oncologica Vol. 43, No. 1, pp. 115–116, 2004

Received 12 June 2003
Accepted 18 August 2003

With the increasing success of modern therapies in achieving long-term remissions in many cancer patients, the incidence of second primary tumors is rapidly increasing. Second tumors are closely related to the treatment of primary malignancy and to the effect of the curative therapy on pre-existing genetic susceptibility, predisposing the patient to a secondary malignancy.

Adjuvant chemotherapy, hormonal therapy and radiation therapy have been shown to be effective in reducing cancer recurrence and death in women with early-stage breast cancer (1). However, as patients with breast cancer receive intensive treatment and survive longer, the risk of therapy-induced secondary malignancies is more than a clinical problem (2, 3). Specific risk factors cited include use of multiple alkylating agents and their cumulative dose, duration of treatment, use of combinations of radiotherapy and chemotherapy (4). Besides chemo- and radiotherapy, tamoxifen is being increasingly blamed for increasing the incidence of new primary tumors (5).

We present the case of a female patient who developed thymic cancer following successful treatment of breast cancer with adjuvant chemo- and radiotherapy and who was currently receiving adjuvant tamoxifen therapy, and discuss the possible mechanisms underlying the development of secondary thymic cancer in breast cancer patients. It is a known fact that thymoma is associated with an increased risk of second malignancy (6), but to our knowledge this is the first published case of thymic cancer following the treatment of breast cancer.

Case report. A 51-year-old premenopausal woman who underwent right modified radical mastectomy due to breast cancer in September 1999 was referred to our department in the post-operative period. The histopathological diagnosis was invasive lobular carcinoma. The patient had stage IIIA (T3N1M0) disease but there was no evidence of metastatic disease. She received six cycles of adjuvant cyclophosphamide (500 mg/m^2 i.v. day 1), doxorubicin (50 mg/m^2 i.v. day 1), 5-fluorouracil (500 mg/m^2 i.v. day 1) combination chemotherapy (CAF) regimen and received radiotherapy after the third cycle of the CAF regimen (chest wall 2 Gy/day, total 46 Gy, and internal mammary chain 50 Gy). Adjuvant tamoxifen 10 mg twice daily was started in November 2001, as the patient's tumor was shown to be progesterone receptor positive, although estrogen receptor negative. In routine follow-ups, a widening of the upper mediastinum was detected on a chest x-ray in the 8th month of tamoxifen treatment. Computed tomography of the thorax revealed multinodular goiter with retrosternal extension and a retrosternal lobulated mass, 3 × 2 cm in diameter. Laboratory examinations including complete blood count, electrolyte count, liver function tests, thyroid function tests, tumor markers and bone scintigraphy were all within normal ranges. The patient complained of mild shortness of breath probably caused by multinodular goiter. She underwent left near total, right subtotal thyroidectomy and mediastinal tumor excision in September 2002. The pathology was consistent with nodular hyperplastic thyroid and well-differentiated thymic carcinoma according to the Müller-Hermelink classification (7) with capsular and vascular invasion (WHO Grade B 3). The thymic region was not treated with radiotherapy as the patient had already received the maximum dose of radiation to this area.

Discussion. Adjuvant chemotherapy, hormonal therapy and radiotherapy, and a combination of these modalities are being administered to a growing proportion of breast cancer patients. In view of the proven therapeutic benefit of these treatments and the prolonged life expectancy of those treated, it has been important to evaluate the carcinogenic potential of adjuvant treatment (8). There is evidence that second primary malignancies may be associated with potentially carcinogenic treatment of the initial cancer, such as radiation therapy or chemotherapy (9). A combination of radiotherapy and chemotherapy may further increase the risk of these cancers.

In any discussion of treatment-related second malignancies, it is of important to remember that not all second cancers are due to previous therapies. The occurrence of second primary malignancies may be a chance occurrence, and may result from host susceptibility factors such as genetic predisposition or immune deficiency, or may be linked to common carcinogenic influences, e.g. environmental factors or a clustering of different risk factors in the same individual.

In relation to the general population, women with breast cancer have a significant, excess incidence for some cancers. However, thymoma is not included among them. In our case, the association between thymoma and breast cancer can be fully or partly explained by a common etiology such as genetic predisposition and hormonal risk factors. Sex hormones strongly influence the development of thymus tumors in spontaneous thymoma BUF/Mna rats through their receptor within the tumor cells (10, 11). Thymic epithelial cells have cytoplasmic estrogen receptors and estrogen regulates a normal cellular differentiation process indirectly via its receptor in the thymus (12). Estrogens depress thymosin release from the thymus, leading to involution of the thymus. So, in

 ISSN 0284-186X
DOI: 10.1080/02841860310017649

contrast to breast cancer, estrogen is a negative risk factor for thymoma development. Thymoma and breast cancer apparently cannot be linked to the same risk factors.

Decreasing levels of estrogen may facilitate thymosin release and then increase the size of the thymus (13). Once thymomagenesis is induced, the tumor cells lose their sensitivity to estrogen as neoplastic changes start in the thymic epithelial cells with the impairment of estrogen-receptor function (because of decreased estrogen receptors), resulting in automatic differentiation and/or proliferation. It has been demonstrated that some phenotypic changes in thymic epithelial cells are important in the development of thymomas. In particular, the enhanced expression of epidermal growth factor (EGF) and thymosins may play an important role in the proliferation of epithelial cells and lymphocytes, respectively (14). The regulation of EGF receptor by estrogen in rat uterus has been reported (15). As tamoxifen results in a decrease in the availability of estrogen, in our case this could have led to the increase in thymus size, owing to increased thymosin release. This could have resulted in some phenotypic changes in thymic epithelial cells, leading to the development of thymoma. Thus, thymoma development may be due to the anti-estrogenic effect of tamoxifen.

Tamoxifen increases the incidence of endometrial cancer. The joint analyses of Scandinavian tamoxifen trials showed an increased risk of colorectal and stomach cancer after tamoxifen use (5). To date, no increased risk of thymoma in tamoxifen-treated patients has been demonstrated. However, thymoma is a rare disease and existing studies have not had sufficient power to exclude a risk increase.

Another risk factor in this case is radiotherapy. In animal studies, SCID mice have been reported to be radiation sensitive (16) and prone to developing thymic tumors as a result of low-level ionizing radiation (17). However, these tumors are lymphomas, and not of epithelial origin. No association between radiation and thymoma has been demonstrated in humans, but there is insufficient data to rule out radiation as the etiological factor in the development of thymoma. Radiotherapy, possibly combined with chemotherapy, may be a contributor to the excess risk of thymoma.

In conclusion, thymoma secondary to breast cancer may be related to the anti-estrogenic effects of tamoxifen and possibly to the mutagenic effects of radiation on the epithelial cells of the thymus. A chance association is also possible, but the combination lends further support to the suggestion that thymic malignant lesions be added to the list of diseases already accepted as being associated with breast cancer and tamoxifen. However, unless similar reports appear in the literature, this association will remain as a postulation.

REFERENCES

1. Early Breast Cancer Trialists' Collaborative Group. Polychemotherapy for early breast cancer: an overview of the randomized trials. Lancet 1998; 352: 930–42.
2. Dong C, Hemminki K. Second primary neoplasms in 633 964 cancer patients in Sweden, 1958–1996. Int J Cancer 2001; 93: 155–61.
3. Thirman M, Larson RA. Therapy-related myeloid leukemia. Hematol Oncol Clin North Am 1996; 10: 293–320.
4. Curtis RE, Boice JO Jr, Stovall M, et al. Risk of leukemia after chemotherapy and radiation treatment for breast cancer. N Engl J Med 1992; 326: 1745–51.
5. Rutqvist LE, Johansson H, Signomklao T, et al. Adjuvant tamoxifen therapy for early stage breast cancer and second primary malignancies. J Natl Cancer Inst 1995; 87: 645–51.
6. Pan CC, Chen PC, Wang LS, Chi KH, Chiang H. Thymoma is associated with an increased risk of second malignancy. Cancer 2001; 92: 2406–11.
7. Kirchner T, Muller-Hermelink H. New approaches to the diagnosis of thymic epithelial tumors. Prog Surg Pathol 1989; 10: 167–71.
8. Early Breast Cancer Trialists' Collaborative Group. Systemic treatment of early breast cancer by hormonal, cytotoxic, or immune therapy: 133 randomized trials involving 31 000 recurrences and 24 000 deaths among 75 000 women. Lancet 1992; 339: 1–14.
9. Kaldor J. Second cancer following chemotherapy and radiotherapy. An epidemiological perspective. Acta Oncol 1990; 29: 647–55.
10. Sakabe K, Seiki K, Kowashima I, et al. Effect of sex hormones on development of thymus tumor in spontaneous thymoma BUN/Mna rats, with special reference to sex hormone receptors and thymulin (FTS). Pathophysiology 1994; 1: 117–25.
11. Ezaki T, Fujii H, Matsuna KC, Kawatsu R, Kotani M. Oestrogen retards the development of spontaneous thymomas in BUF/Mna rats. Virchows Arch [A] 1992; 421: 505–11.
12. Grossman CJ. Possible underlying mechanisms of sexual dimorphism in the immune response, fact and hypothesis. J Steroid Biochem 1989; 34: 241–51.
13. Savino W, Bartoccioni E, Homo-Delarche F, et al. Thymic hormone containing cells. IX. Steroids in vitro modulate thymulin secretion by human and murine thymic epithelial cells. J Steroid Biochem 1988; 30: 479–84.
14. Hirokawa K, Utsuyama M, Kasai M, et al. Age-related hyperplasia of the thymus and T-cell system in the Buffalo rat. Virchows Arch [B] 1990; 59: 38–47.
15. Mukku VR, Stancel GM. Regulation of epidermal growth factor receptor by estrogen. J Biol Chem 1985; 260: 9820–4.
16. Fulop GM, Philips RA. The scid mutation in mice causes a general defect in DNA repair. Nature 1990; 347: 479–82.
17. Lieberman M, Hansteen GA, Waller EK, Weissnman IL, Sen-Majumdar A. Unexpected effects of the severe combined immunodeficiency mutation on murine lymphomagenesis. J Exp Med 1992; 176: 399–405.