GLANDULAR CELL progesterone receptors (PR) were significantly increased and stromal cell oestrogen receptors (ER) were significantly decreased in tamoxifen-treated versus atrophic endometria. PR staining was not significantly different in tamoxifen-treated versus control polyps, although staining was high in both groups.

Stromal cell ER staining was significantly reduced in tamoxifen-treated versus control polyps. The immunohistochemistry (IH) scores of the two adenocarcinomas in tamoxifen-treated patients were high for PR and low for ER in glands. The pattern of reduced stromal cell ER IH scores and increased glandular cell PR IH scores was consistently found in all tamoxifen-treated patients regardless of endometrial diagnosis.

There were no significant differences between the subgroups of tamoxifen-treated patients with benign versus malignant or premalignant endometrial pathologies in either the mean number of years of tamoxifen use (4.3 ± 0.8 versus 3.8 ± 1.4, respectively, $P = 0.71$) or endometrial steroid receptor status. There was no significant difference in the mean number of years of tamoxifen use in the women with postmenopausal (PMP) bleeding (3.5 ± 1.1) versus those without bleeding (4.6 ± 0.9) ($P = 0.42$).

There were no significant differences in the histological features of polyps from tamoxifen-treated versus non-hormonally treated patients, including the mean number ($P = 0.87$) and thickness ($P = 0.87$) of blood vessels and the mean stromal cellularity ($P = 0.39$). Every polyp in both the tamoxifen-treated and untreated groups contained dilated, cystic glands, and secretions within the glands. The polyps in each group exhibited other similar typical histological features including variations of glands and spindled-shaped stroma. The tamoxifen-associated polyps did not display any unusual histological features, except for one polyp that contained adenocarcinoma in which there was focal adipose cells within the stroma.

The tamoxifen-associated changes in endometrial steroid receptors and their persistent distinct pattern when compared to all the other study groups supports an oestrogenic uterine effect. This effect is independent of the type of endometrial pathological diagnosis, and the duration of tamoxifen use. This oestrogen-like action of tamoxifen at the endometrial steroid receptor level may contribute to the pathogenesis or growth of endometrial polyps and carcinomas in these patients.

Acknowledgements—Supported by the 1995–1996 North American Menopause Society (Bristol-Myers Squibb Company Research Fellowship Award and the Helena Rubenstein Foundation.

European Journal of Cancer, Vol. 34, Suppl. 4, pp. S24–S25, 1998

Printed in Great Britain
0959-8049/98$—see front matter

PII: S0959-8049(98)00096-3

II.7 The Progestin-like Activity of Tamoxifen on the Endometrium

G. Dallenbach-Hellweg and D. Schmidt

Institut für Pathologie, A 2,2,D-68159 Mannheim, Germany

We examined 17 carcinomas, one adenosarcoma, one malignant mesenchymal mixed tumour and 100 endometrial biopsies with non-neoplastic lesions from patients under tamoxifen therapy. Of the 17 carcinomas 12 were mucinous, four were of clear-cell type and one was a serous-papillary carcinoma. All carcinomas arose within atrophic endometrium from endocervical type mucinous, clear cell or serous-papillary metaplasias. Fifty-seven of the non-neoplastic specimens showed simple or cystic atrophy, 44 contained atrophic polyps with stromal fibrosis, 28 had moderately proliferating endometria, 32 had endocervical type metaplasias. Our histological studies support the assumption that tamoxifen has an anti-oestrogenic progestin-like action on the endometrium. Adjuvant gestagen therapy given to patients with endometrial carcinoma therefore appears contra-indicated in patients with tamoxifen-induced carcinomas. © **1998 Elsevier Science Ltd. All rights reserved.**

IN RECENT years tamoxifen therapy for breast carcinoma has been associated with endometrial carcinoma. In the literature more than 350 endometrial carcinomas have been reported developing in breast cancer patients during or after tamoxifen therapy [1]. Most of these reports, however, do not provide histological descriptions or microphotographs of the endometrial cancer. This lack of information has led to the false assumption that the tamoxifen-related carcinomas are of the oestrogen-stimulated endometrioid type. Furthermore, sonographic thickening of the endometrium and the detection of

Correspondence to G. Dallenbach-Hellweg.

polyps in tamoxifen-treated patients has been interpreted as additional evidence of an oestrogenic effect of the anti-oestrogen tamoxifen.

From operative specimens at the Mannheim Institute, we have re-evaluated 19 malignant endometrial tumours: 17 carcinomas, one adenosarcoma and one malignant mesenchymal mixed tumour and 100 endometrial biopsies with non-neoplastic lesions collected between July 1996 and July 1997 from patients on tamoxifen therapy or after its cessation.

None of our 17 carcinomas was of the endometrioid type: 12 were mucinous, 4 were of clear-cell type and one was a serous-papillary carcinoma. All mucinous adenocarcinomas gave a positive reaction with carcino-embryonic antigen (CEA) and were negative with antivimentin. These immunohistochemical reactions help to distinguish the mucinous from the endometrioid type adenocarcinomas, which initially may resemble one another under low power of the microscope. Clear-cell and serous-papillary carcinomas, in contrast, are structurally quite different from endometrioid carcinomas. All of our tamoxifen-related endometrial carcinomas developed from endocervical type mucinous, clear-cell or serous-papillary metaplasias that arose within an otherwise atrophic or polypoid cystic atrophic endometrium. Foci of preceding metaplasias could still be found in most of our carcinomas.

Fifty-seven of our 100 non-neoplastic endometrial specimens after tamoxifen therapy showed simple or cystic atrophy, some with stromal decidualisation. Forty-four contained cystic atrophic polyps with extensive stromal fibrosis. Only 28 had polyps with moderately proliferating glands or areas of basal hyperplasia. Thirty-two had benign or atypical endocervical type metaplasia.

From our review of the literature those authors who provided microphotographs and/or histological descriptions made observations that were almost identical to ours: cystic atrophy of the endometrium with or without cystic polyps with a dense fibrous stroma, as well as multiple foci of epithelial, mainly mucinous, clear cell, serous-papillary and apocrine metaplasias [2–4]. In a large study of the Yale New Haven Tumour Registry 67% of the carcinomas after therapy with tamoxifen were poorly differentiated serous-papillary or clear cell carcinomas as compared to only 24% in the non-treated group. The authors concluded that tamoxifen-associated carcinomas may have a different origin from those associated with oestrogen therapy [5].

As has been known for quite some time, there are at least two histogenetically different types of endometrial carcinomas: the endometrioid type, stimulated by high oestrogen levels, and the non-endometrioid type, which is independent of oestrogen levels and usually associated with endometrial atrophy. The distinction between these two types of carcinoma is clinically important, since their prognosis and their therapeutic requirements differ greatly.

Oestrogens and anti-oestrogens differ less in their mode than in their site of action: whereas oestrogens stimulate endometrial growth, anti-oestrogens like synthetic gestagens and tamoxifen induce endometrial atrophy. They stimulate, however, proliferation of the endocervical glands and reserve cells and may induce endocervical-type metaplasias in the resting or atrophic endometrium as potential precursors of endocervical type atypical hyperplasias or carcinomas. Consequently, when we consider the histological structure of carcinomas developing during therapy with tamoxifen, it is not necessary to postulate a causative agonistic oestrogen effect of tamoxifen on these tumours. Sonographic measurements of endometrial thickness provide little information about the histologic change of the endometrium. Biochemical measurements of serum hormone levels are vague and dependent upon circadian and pulsatile rhythms.

The anti-oestrogenic effect of tamoxifen is therefore most likely responsible for the development of mucinous metaplasias and corresponding endocervical type carcinomas within an atrophic endometrium. Since tamoxifen occupies oestrogen receptor sites and inhibits their replenishment in the cytoplasm, an oestrogenic action of tamoxifen, if any, must be weak and of short duration, but might be responsible for the high concentration of progesterone receptors in tamoxifen-associated mucinous adenocarcinomas of the endometrium. Since oestrogen induces the formation of progesterone receptors, it is understandable why oestrogen receptor-negative endometria fail to respond to tamoxifen or progestin when used alone. By increasing progesterone receptor concentrations tamoxifen may well augment its own gestagen-like anti-oestrogenic effect, which is also occasionally seen in stromal decidualisation of endometrial polyps [6].

The series of tamoxifen-associated endometrial carcinomas reported in the literature, as well as our own study, allow the conclusion that the frequency of endometrial carcinoma developing under tamoxifen increases with the dose as well as with the length of duration of therapy, whereby a possible cumulative effect of the drug has been discussed [4, 7–9]. In a series of 70 such carcinomas, 15% of the patients received 20 mg, 17.2% 30 mg and 59.4% 40 mg of tamoxifen [10].

We believe that adjuvant gestagen therapy given to patients with endometrioid type carcinoma is contra-indicated in patients with tamoxifen-induced carcinomas. The distinction between the two types may occasionally be obscure in routine histology but is readily made immunohistochemically.

1. Assikis VJ, Neven P, Jordan VC, *et al.* A realistic clinical perspective of tamoxifen and endometrial carcinogenesis. *Eur J Cancer* 1996, **32A**, 1464–1476.
2. Nuovo MA, Nuovo GJ, McCaffrey RM, Levine RU, Winkler B. Endometrial polyps in postmenopausal patients receiving tamoxifen. *Int J Gynecol Pathol* 1989, **8**, 125–131.
3. Segna RA, Dottino PR, Deligdisch L, Cohen CJ. Tamoxifen and endometrial cancer. *Mt Sinai J Med* 1992, **59**, 416–418.
4. Ismail SM. Pathology of endometrium treated with tamoxifen. *J Clin Pathol* 1994, **47**, 827–833.
5. Magriples U, Naftolin F, Schwartz PE, Carcangiu ML. High grade endometrial carcinoma in tamoxifen-treated breast cancer patients. *J Clin Oncol* 1993, **11**, 485–490.
6. Corley D, Rowe J, Curtis MT, *et al.* Postmenopausal bleeding from unusual endometrial polyps in women on chronic tamoxifen therapy. *Obstet Gynecol* 1992, **79**, 111–116.
7. De Muylder X, Neven P, Sesomer M, van Belle Y, Vanderick G, De Muylder E. Endometrial lesions in patients undergoing tamoxifen therapy. *Int J Gynecol Obstet* 1991, **36**, 127–130.
8. Rutqvist LE, Johansson H, Signomklao T, *et al.* Adjuvant tamoxifen therapy for early stage breast cancer and second primary malignancies. Stockholm Breast Cancer Study Group. *J Natl Cancer Inst* 1995, **87**, 645–651.
9. van Leeuwen FE, Benraadt J, Coebergh JW, *et al.* Risk of endometrial cancer after tamoxifen treatment of breast cancer. *Lancet* 1994, **343**, 448–452.
10. Seoud MA, Johnson J, Weed Jr. JC. Gynecologic tumours in tamoxifen-treated women with breast cancer. *Obstet Gynecol* 1993, **82**, 165–169.