Pergamon

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I.1 Tamoxifen and the Breast

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WITHOUT DOUBT tamoxifen has been one of the great success stories in the pharmacological management of cancer of all time. Its value in the management of breast cancer was discovered almost by serendipity approximately 30 years ago. In the early 1970s it soon established its place as the treatment of choice in the management of advanced breast cancer in postmenopausal women, replacing the then conventional management with the non-steroidal oestrogen Oestradiol. It has an excellent toxicity profile and serious adverse side-effects are extremely rare. Using conventional UICC criteria, tamoxifen will produce about a 30% objective remission rate in unselected cases, but if one accepts stable disease as a useful endpoint and is more selective in the choice of patients, i.e. those without visceral disease, or those with positive oestrogen receptors, then useful response rates go up to the order of 60%. The median duration of response in these cases is about 2 years, but ultimately all patients will relapse and die [1–3].

Perhaps of much greater importance is the benefit of tamoxifen as adjuvant therapy following the surgical treatment of early breast cancer. The first trials for adjuvant therapy were started in the late 1970s and reported in the early 1980s. Originally the control groups received no adjuvant therapy and the treated groups received either 1 or 2 years of tamoxifen. The first trial to demonstrate a survival advantage with adjuvant tamoxifen was the NATO study published in the *Lancet* in 1983 [4]. Within a short time other studies demonstrated a survival advantage with tamoxifen prescribed for 2–5 years after surgery and the meta analysis of adjuvant tamoxifen trials took place in 1990 and demonstrated unequivocally that adjuvant tamoxifen was associated with a relative risk reduction for relapse and death of about 25% over a 10-year period [5]. In the last decade we have refined our knowledge on adjuvant tamoxifen and know that the groups most likely to benefit are the postmenopausal women with oestrogen receptor positive (ER+) tumours, where in absolute terms ~12% improvement in 10 years survival can be expected, but even postmenopausal women with oestrogen receptor negative (ER−) tumours and premenopausal women with ER+ tumours can also demonstrate a benefit [5].

We have also moved closer to understanding the optimum duration of the adjuvant therapy and it is clear that 2 years is insufficient and that the optimum duration might be anything between 5 or 10 years [6–8]. Much uncertainty remains and large-scale pragmatic trials (ATLAS, and ATTOM) have been designed to address this problem [9]. There is now increasing evidence that some degree of synergy may be achieved between tamoxifen and chemotherapy in selected cases, producing a summation of benefit [10]. Last but not least, tamoxifen is of proven value in reducing the risk of contralateral breast cancer with the latest overview, suggesting that 5 years of tamoxifen may reduce the relative risk of a contralateral disease by up to 50% [5]. Based on these observations large-scale trials are in progress in the U.K., the U.S.A. and Europe, for preventing breast cancer in women judged to be at high risk.

Much biological research is throwing light on the mechanisms of response and the mechanisms of resistance to tamoxifen which can no longer be considered simply as an anti-oestrogen. In fact its agonistic properties may also be responsible for some of its unanticipated benefits and potential harm. As an attenuated oestrogen, tamoxifen appears to protect the myocardium and reduce the incidence of ischaemic heart disease [11, 12], reduce the loss of anticipated bone mineral density amongst postmenopausal women [13, 14] and has even been used in the treatment of mastalgia. At the same time its agonistic properties are thought in part to limit its usefulness as an anti-oestrogen and there is some experimental evidence that experimental clones of breast cancer cells can develop a dependence on tamoxifen, so in theory the late failure or *de novo* resistance of adjuvant tamoxifen might be related to these observations [15, 16].

Finally, tamoxifen has been implicated in the excess of endometrial cancers that have been observed in some of the clinical trials and reported in the meta-analysis [17, 18]. I am personally sceptical about these observations as we cannot exclude an ascertainment bias with patients receiving tamoxifen being more intensively screened for uterine abnormalities than control groups. Furthermore, the one published study of screening asymptomatic women for endometrial cancer showed a prevalence not dissimilar to that observed in the tamoxifen-treated group [19]. (See Table 1).

Table 1. *Screening causes endometrial cancer*

	NSABP-B14*		Normal screened U.S. population†
	Tamoxifen	Nil	
No. of women	1439	1435	2586
Women years in 1000s	10.41	9.4	10.5
Number of endometrial cancers	17	1	18
Incidence per 1000 women years	1.65	0.1	1.71

*Fisher B, and colleagues. Endometrial cancer in tamoxifen-treated breast cancer patients: findings from the (NSABP) B-14. *J Natl Cancer Inst* 1994, **86**(7), 527–537. †Koss LG and colleagues [19].

Since 1985 we have witnessed an overall reduction in breast cancer mortality in the U.K. which in large part must be attributed to the widespread adoption of adjuvant tamoxifen, but it is essential not to be complacent and it is likely that we are close to recognising the limitations of this useful and relatively non-toxic agent [20, 21].

The theme of this international conference is tamoxifen and the uterus. It would be irresponsible of us all if by exaggerating the risk of endometrial cancer, which in any case might be an artefactual adverse side-effect, we frightened women into refusing or abandoning their treatment. Indirectly this could lead to thousands of unnecessary deaths world-wide in any one year.

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I.2 From the Breast to the Uterus. The Past and the Present

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Discussing whether or not tamoxifen is truly responsible for endometrial side-effects can only be done if we also consider some historical events. Long before the introduction of tamoxifen, women with breast cancer were known to be at risk for endometrial cancer. Non-steroidal hormones to treat breast cancer and active detection bias added up to this increased risk. Presently, history seems to repeat