Fatal myocardial infarction in the Scottish adjuvant tamoxifen trial

C C McDonald, H J Stewart for the Scottish Breast Cancer Committee

Abstract

Objective—**To investigate the incidence of fatal myocardial infarction in women in the two randomised arms of the Scottish adjuvant tamoxifen trial.**

Design—**Retrospective review of hospital notes to determine with the greatest possible certainty women who had died of an acute myocardial infarction.**

Setting—**Scottish Cancer Trials Office, the University of Edinburgh.**

Patients—**1070 postmenopausal women with operable breast cancer who were randomised to receive either adjuvant tamoxifen for five years or until relapse (539 patients) or tamoxifen for at least six weeks on the confirmation of first recurrence (531 patients).**

Main outcome measures—**Incidence of fatal myocardial infarction in women with no known or suspected systemic cancer.**

Results—**Of the 200 women who died in the adjuvant tamoxifen arm of the trial, 44 were free of cancer at death and 10 of these died of myocardial infarction. In the observation arm 251 women died, of whom 61 showed no evidence of systemic cancer and 25 had a fatal myocardial infarction. The incidence of fatal myocardial infarction in the two groups was significantly different (χ^2=6·88, p=0·0087).**

Conclusion—**Tamoxifen given for at least five years as adjuvant therapy for breast cancer seems to have a cardioprotective oestrogen-like effect in postmenopausal women.**

Introduction

Tamoxifen is a non-steroidal antioestrogen and is considered to be the front line endocrine treatment for breast cancer. It is widely used in postmenopausal women both as treatment for advanced disease[1,2] and as adjuvant treatment in early disease, when it has been shown to delay recurrence and increase survival.[3] Increasing numbers of premenopausal women are also now receiving tamoxifen as adjuvant treatment.[4]

Although tamoxifen was given for up to two years in most early clinical trials, evidence is growing that better results may be obtained with longer treatment.[5] Studies in animals have shown that the effect of tamoxifen on breast carcinoma cells is tumorostatic rather than tumoricidal. The growth of MCF-7 tumour cells can be reactivated by supplementation with oestrogen after up to six months' treatment with tamoxifen,[6,7] suggesting that long term or indefinite treatment should be advised. A trial has been proposed to investigate whether five years' treatment with tamoxifen has any preventive effect on the development of breast cancer in women considered to be at increased risk.

Increased length of exposure to tamoxifen raises the question what are the long term effects of the treatment. Acute toxicity is known to be low,[8] but the possibility that prolonged exposure may result in premature osteoporosis and cardiovascular disease as a result of antioestrogenic action must be considered, oestrogens being essential for maintaining bone density and a favourable lipid profile. Various oestrogen-like actions of tamoxifen have been shown, including effects on the liver resulting in increased concentrations of sex hormone binding globulin and thyroxine binding globulin.[9] Laboratory studies have shown that tamoxifen has a favourable effect on bone density,[10] and clinical results have been encouraging.[11,12]

The Scottish adjuvant tamoxifen trial was set up to compare the effect on survival of adjuvant tamoxifen for five years with that of tamoxifen for recurrent breast cancer. We compared the incidence of fatal myocardial infarction in postmenopausal women randomised within this trial.

Patients and methods

Between 1978 and 1984, 1323 women with operable breast cancer were entered into four randomised controlled trials of adjuvant tamoxifen. Patients were randomised to receive tamoxifen either immediately after mastectomy (20 mg/day for five years or until confirmed relapse) or for a minimum of six weeks on confirmation of first recurrence. Eleven women were withdrawn from the trial within the first month because of major protocol violations, leaving 1312 evaluable cases. Fatal myocardial infarction was not recorded in any premenopausal woman, and this analysis is confined to the 1070 women who had not had a menstrual period for more than one year at entry to the study. Of these women, 539 were randomised to receive adjuvant tamoxifen and 531 to receive tamoxifen at first relapse.

Those patients who had not had a recurrence and were still taking tamoxifen after five years were considered eligible for rerandomisation to stop tamoxifen or to continue until relapse or death. As a result 176 patients continued treatment beyond five years, either after rerandomisation or electively.

Information on disease state, possible new primary tumours, and details of tamoxifen and other treatments was collected annually and at death. After a woman died the records were carefully checked, with particular importance being placed on establishing, with the greatest possible certainty, the cause of death. Any doubt about the presence or source (from breast or other confirmed or suspected primary tumour) of metastatic disease was recorded (table I).

We analysed the results using Pearson's χ^2 test and a survival analysis in which women who had died of myocardial infarction were treated as events and women who had died of other causes or who were still alive were censored. The hazard ratio and 95% confidence interval were calculated with Cox's proportional hazards regression model.

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Results

Table I shows the cause of death in the 451 women who died (200 from the adjuvant arm and 251 from the observation arm). Evidence from postmortem examination was available for 38 women. We restricted the analysis to those who had a fatal myocardial infarction in the absence of known or suspected systemic cancer.

Ten women in the adjuvant tamoxifen arm of the trial were recorded as having died of acute myocardial infarction. The median age of these women was 71 (range 65-77) years and the median duration of exposure to tamoxifen was 29 (9-93) months. Nine of the women were still receiving tamoxifen at the time of death and one had stopped treatment two months before her death.

TABLE I—*Cause of death in 451 postmenopausal women in trials of adjuvant tamoxifen*

Cause of death	Adjuvant arm (n=200)	Observation arm (n=251)
Breast cancer present at death:		
Breast cancer	137	163
Breast cancer and myocardial infarction	2	7
Breast cancer and vascular disease*	6	10
No breast cancer present at death:		
Myocardial infarction	10	25
Vascular disease*	14	13
Second primary cancer	12	15
Other causes	8	8
Disease state at death uncertain:		
Unproved systemic spread	6	7
Cancer but source uncertain	5	3

*Includes cerebrovascular accident, congestive cardiac failure, chronic ischaemic heart disease, and mitral valve disease.

In the observation arm 25 women died of acute myocardial infarction at a median age of 73 (59-80) years. Twenty one of these women had had no known exposure to tamoxifen. The four other women were all receiving tamoxifen when they died: one had received adjuvant tamoxifen for four months in error, two women had been successfully treated for local or regional recurrence with local therapy and tamoxifen for 12 and 13 months, and one woman had received tamoxifen for 14 months after excision of a contralateral primary breast tumour. Table II shows the distribution of duration of treatment of women in the adjuvant and observation arms.

TABLE II—*Duration of treatment with tamoxifen in women who died of myocardial infarction in adjuvant and observation arms of trials*

Duration of treatment (years)	Adjuvant arm (n=10)	Observation arm (n=25)
No treatment		21
<2	4	4
2-4	2	
>4	4	

Women in the adjuvant arm were significantly less likely to die of myocardial infarction than were women in the observation arm ($\chi^2=6{\cdot}88$, p=0·0087). Women receiving adjuvant tamoxifen have a significantly increased survival[13] and hence a longer time at risk of dying from a cause other than breast cancer. Thus, the beneficial effect of tamoxifen on myocardial infarction could be greater than is apparent from these data. Survival analysis using death from myocardial infarction as the end point confirms the significance of this result (p=0·0054, Mantel-Cox); the hazard ratio was 0·37 (95% confidence interval 0·18 to 0·77).

Twenty seven women died of vascular diseases, which included cerebrovascular accident, congestive cardiac failure, chronic ischaemic heart disease, and mitral valve disease. We found no difference in the distribution of these various causes within the adjuvant and observation arms of the trials.

Discussion

Tamoxifen exhibits a range of complex pharmacological properties, and may behave as an oestrogen or an antioestrogen depending on the target site.[14]

Studies in which the serum concentrations of lipids and lipoproteins in patients receiving tamoxifen have been monitored have shown an oestrogenic effect, with decreases in total and low density lipoprotein cholesterol concentrations and an increase in high density lipoprotein cholesterol concentration.[9,15-17] Cholesterol and lipoproteins are implicated as risk factors for cardiovascular disease, and the authors of these studies conclude that tamoxifen exerts a favourable effect on the lipid profile over 12 months' treatment. Additional studies are needed to determine if the effect is maintained beyond 12 months' treatment and the effect of stopping tamoxifen.

We found a significant reduction in the incidence of fatal myocardial infarction in women receiving adjuvant tamoxifen, which provides clinical evidence to support the above biochemical findings. A similar reduction in deaths from myocardial infarction in postmenopausal women receiving oestrogen replacement therapy was observed in a study in southern California.[18] Among 8841 women aged 44-101 years followed up for six years, 55 women who were receiving oestrogen therapy died of myocardial infarction compared with 94 women who were not given oestrogens (relative risk=0·59, p=0·002).[18]

Bourne *et al* have shown that administering transdermal oestradiol to postmenopausal women reduces arterial impedance and decreases vascular tone, which would be an alternative explanation for the effect of tamoxifen on myocardial infarction.[19] Other mechanisms, such as effects on insulin metabolism, should not be overlooked.[20]

Reduced concentrations of antithrombin III have been reported during treatment with tamoxifen,[15] and Dahan *et al* have suggested that tamoxifen could increase the risk of thromboembolism.[21] We found no such increased risk, and a recent study has shown that the decrease in antithrombin III concentration is paralleled by a greater decrease in fibrinogen concentration[8]; the ratio of fibrinogen to antithrombin III concentration is thus decreased and the risk of thrombosis reduced.

Further follow up may provide information on whether the reduced incidence of fatal myocardial infarction in the adjuvant arm reverts to that found in the observation arm in those women who stopped treatment at five years. We are currently investigating whether adjuvant tamoxifen has a similar effect on the incidence of non-fatal myocardial infarction.

The members of the Scottish Breast Cancer Committee are W D George (chairman), K Bartlett, U Chetty, J A Dewar, D Everington, O Eremin, Patrick Forrest, T Habeshaw, R A Hawkins, A Hutcheon, D Kerr, R E Leake, R C F Leonard, C S McArdle, M McCallum, C McDonald, P Preece, R Prescott, A Rodger, D C Smith, H J Stewart, and P V Walsh.

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Survival with bladder cancer, evaluation of delay in treatment, type of surgeon, and modality of treatment

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Abstract

***Objective*—To determine whether length of delay before treatment; specialty and grade of the surgeon; and use made of surgery, radiotherapy, and chemotherapy influenced the survival of patients with cancer of the bladder, after adjusting for case severity.**

***Design*—Retrospective cohort study.**

***Setting*—South East and South West Thames health regions.**

***Patients*—609 men aged under 75 resident in the South Thames regions who had been registered as new cases of bladder cancer in 1982, 35 of whom were excluded, leaving 574 eligible patients. Analysis was based on 75% retrieval rate for case notes.**

***Main outcome measures*—Duration of survival from date of diagnosis of the bladder tumour.**

***Results*—10 prognostic variables were used to adjust for case severity. The median delay from referral to first treatment was 48 (interquartile range 27-84) days. Treatment after a short delay was associated with shorter survival because of the early treatment of more severe cases. Consultants treated 68% of patients, trainee surgeons treated less severe cases. Initial treatment was by a urologist in 67% of cases, but the specialty of the surgeon was not associated with prognosis. The associations of radiotherapy, cystectomy, and systemic chemotherapy with survival were interpreted in terms of selection bias as well as therapeutic effect.**

***Conclusions*—Case severity was the most important influence on survival and influenced length of delay before treatment, grade and specialty of the surgeon, and main treatment allocation. After adjusting for case severity variations in these processes of care were not strongly associated with variations in survival.**

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Introduction

In England and Wales there are substantial variations in mortality from conditions which should be amenable to medical treatment[1,2]; variations in survival with cancer have also been reported.[3,4] Cancer of the bladder is one of the most common cancers,[5] and health care is thought to influence the prognosis.[6] An analysis of cancer registry data for the South Thames regions showed systematic variation in the survival of patients with bladder cancer according to district health authority of residence (A Walker *et al*, unpublished data). One explanation for this observation could be that the quality of health care varied sufficiently to influence survival of these patients.[7] The outcome of treatment for cancer of the bladder might be influenced by several characteristics of health care, including the length of delay before treatment[6]; the grade and specialty of the surgeon[8,9]; and the use made of surgery, radiotherapy, and chemotherapy.[10] These were relevant factors to investigate, given current problems with long waiting times,[11] staffing and surgical specialties,[12] and organisation of cancer treatment services.[13] This study aimed at determining whether, after allowing for the severity of the underlying disease, survival of patients with cancer of the bladder in the South Thames regions was influenced by these processes of care.

Patients and methods

The patients in the study were men aged below 75, resident in the South Thames regions, and registered with cancer of the bladder at the Thames Cancer Registry in 1982. The registry supplied a list of 609 names believed to fulfil the entry criteria. We excluded 35 men after examining their hospital records: seven in whom a diagnosis of bladder cancer had not been confirmed, four who were not resident in the South Thames regions at the time of diagnosis, and 24 whose disease was not first diagnosed in 1982. Thus 574 patients were eligible for further investigation. After consultants' approval had been obtained we abstracted data from the patients' hospital notes and radiotherapy records at 71 hospitals and 11 radiotherapy centres with standard data collection forms.

The patient's age was calculated as 1982 minus the year of birth and was included as a continuous variable. The presence of associated disease was noted from the record of the first hospital admission. The categories none, cardiac, respiratory, renal, and other (specify) were reduced for analysis to "comorbidity present" and "comorbidity absent." The histological extent of tumour invasion was classed according to the Inter-