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Adjuvant endocrine treatment with medroxyprogesterone acetate or tamoxifen in stage I and II endometrial cancer—a multicentre, open, controlled, prospectively randomised trial

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Abstract

Endometrial cancer is a hormone-dependent disease and therefore an adjuvant hormonal therapy might improve the outcome in the early stages of the disease. Between 1983 and 1989, we conducted a randomised trial of 388 patients who received either medroxyprogesterone acetate (MPA) ($n=133$) or tamoxifen ($n=121$) orally for 2 years, or were observed only ($n=134$) after surgical therapy. The aim was to evaluate whether an adjuvant treatment can improve disease-free and overall survival rates. After a median follow-up period of 56 months (range 3–199 months), we observed no differences in the disease-free and overall survival rates for the tamoxifen group compared with the control or the MPA group. Side-effects were more frequent and severe in the MPA-group than in the tamoxifen group. In patients with early endometrial cancer, adjuvant endocrine treatment did not significantly improve the outcome. However, tamoxifen did have some beneficial effects on coexisting morbidity.

Keywords: Adjuvant therapy; Endometrial cancer; Medroxyprogesterone acetate; Randomised trial; Tamoxifen

1. Introduction

Endometrial cancer (EC) is the most common malignant disease of the female genital tract [1]. Although 75% of patients with carcinoma of the endometrium are initially diagnosed with early stage disease, the mortality is still significant. The prognosis of EC is excellent in stage Ia and Ib patients, with 5-year survival rates of 91% and 88%, respectively. The 5-year survival rate of EC dropped to 77–67% in stage II patients [2]. Primary treatment, including surgery and radiation, cannot provide sufficient tumour control, especially in high grade, undifferentiated tumours with deep muscle infiltration. Therefore, in 1983, we considered an adjuvant treatment for endometrial cancer to prevent recurrence and death. Based on the analogy with breast cancer, we considered the use of tamoxifen (30 mg for 2 years). In 1983, the German standard dose and duration of medroxyprogesterone acetate (MPA) in endometrial cancer was between 400 and 600 mg for 1–2 years. This was based on incomplete empirical information. Unfortunately, earlier studies using cytotoxic agents such as cisplatin or doxorubicin in recurrent endometrial cancer had not been very promising. The response rates ranged

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from 30 to 40%, but the responses lasted for only approximately 6 months [3]. The dose intensity that could be achieved was low because of the patients' pre-existing multimorbidity. However, a phase II study using carboplatin and paclitaxel in advanced or recurrent endometrial cancer demonstrated a response rate of up to 78%. Nevertheless, the median time to progression lasted for 6 months and the overall survival time was only 15 months [4]. Progestins, by contrast, have produced similar results and are better tolerated. Recurrences of well differentiated, steroid receptor-positive tumours, responded better than those of moderately or poorly differentiated, receptor-negative tumours [5]. Additionally, adjuvant therapy with progestonal agents was starting to be investigated in the late 1970s [6,7]. One trial with only 205 patients, demonstrated a survival benefit for the progestin-treated group. However, 30% of the enrolled patients had stage II-III disease [8].

Jordan and colleagues have shown that tamoxifen can block the binding of oestradiol to the oestrogen receptor of endometrial carcinomas and proposed that anti-oestrogen should be used to treat endometrial cancer [9]. Subsequently, numerous clinical trials in recurrent disease have been carried out that showed an overall response rate of 22% for tamoxifen [10]. However, no trial on the adjuvant use of tamoxifen in endometrial cancer has been reported. Based on this knowledge, we started the first clinical trial of tamoxifen as an adjuvant treatment in endometrial cancer. The following are the results of an open, controlled, multicentre co-operative study. The primary objective of the trial was to evaluate whether endocrine treatment can influence disease-free and overall survival rates in risk-adapted, surgically pretreated patients with early endometrial cancer.

2. Patients and methods

Between April 1983 and October 1989, a total of 468 patients were entered into the study. Of these, 80 patients had to be excluded from further analysis because of protocol violations (51 were older than 75 years; 22 were lost to follow-up; 4 had stage III or IV disease; 3 had previous second primaries). The 388 eligible patients had a median age of 63 years (range 34–75 years) at diagnosis (Table 1). All patients underwent abdominal hysterectomy, bilateral salpingo-oophorectomy, and partial colpectomy. Pelvic lymph node biopsies were taken in 60 patients with node-positive disease on intra-abdominal palpation. To prevent vaginal apex recurrence, vaginal vault radiation with 20 Gy was performed in 247 patients (64%) if the tumour involved the cervix (stage IIA or IIB) or if the vaginal cuff was not removed upon surgery. Patients ($n = 102$) with grade III tumours, with deep muscle infiltration (stage IC), and/or stage II disease received 56 Gy by external-beam pelvic radiation. All tumours were surgically staged and graded according to the International Federation of Gynecology and Obstetrics (FIGO) criteria [11].

The inclusion criteria for entering the study were histologically-confirmed endometrial carcinoma FIGO stage I or II, no residual tumour, initiation of endocrine therapy within 2 weeks after surgery, age < 76 years, Karnofsky Index $> 50\%$, no other concomitant invasive carcinomas, and no contraindications for endocrine treatment.

By a 1:1:1 unblinded randomisation, 133 patients received MPA at a daily dose of 500 mg orally, 121 patients received tamoxifen 30 mg per day and 134 patients were randomised to the control arm. Each participating centre had sealed envelopes that contained the allocated treatment. Endocrine therapy was stopped after 2 years or if disease progression occurred.

The compliance of the patients and the treatment toxicity (according to World Health Organization (WHO) criteria) were evaluated every 3 months, for the first 2 years of the study. After discontinuation of the treatment, follow-up was performed every 6 months. Median duration of follow-up was 56 months (range 3–119 months).

Survival data were plotted according to Kaplan and Meier and analysis was performed using Peto's log rank test. The diagnosis of a second primary was not considered as a recurrence.

Because the analysis was done per protocol only, a retrospective intent-to-treat analysis was not possible.

Typical pre-existing conditions were found with the following frequencies in patients: obesity (Body Mass Index (BMI) > 25 kg/m^2) 50%, high blood pressure ($> 135/85$) 38%, chronic heart failure 24% and diabetes mellitus 21%.

Oestrogen receptor and progesterone receptor contents were measured on shock frozen tumour tissue from 208 patients using the dextran-coated charcoal (DCC)-method. Levels > 60 fmol/mg were considered positive [12]. An overview of clinical and histological parameters is given in Table 2.

3. Results

3.1. Efficacy

During the observation period, 22 local recurrences and 30 distant metastasis were detected. 64 patients died, of which 32 deaths were directly related to cancer progression. Other main causes of death unrelated to malignant disease were heart failure (11), second primary tumours (6) and strokes (3). However, in all of these patients, definitive evidence of death with endometrial cancer remained unclear.

Table 1
Progress of patients throughout the study ($n=468$)

Randomised to control $n=162$	Patients enrolled $n=468$ Randomised to MPA $n=156$	Randomised to Tam $n=150$
Post-randomisation data $n=142$	Post-randomisation data $n=140$	Post-randomisation data $n=128$
Age > 75 years $n=17$	Age > 75 years $n=14$	Age > 75 years $n=20$
Stage III/IV $n=1$	Stage III/IV $n=2$	Stage III/IV $n=1$
Previous 2nd primaries $n=2$	Previous 2nd primaries $n=0$	Previous 2nd primaries $n=1$
Eligible for analysis $n=134$	Eligible for analysis $n=133$	Eligible for analysis $n=121$
Lost to follow-up $n=8$	Lost to follow-up $n=7$	Lost to follow-up $n=7$
Treatment compliance $n=134$	Treatment compliance $n=125$	Treatment compliance $n=101$
	Treatment discontinued $n=20$	Treatment discontinued $n=8$
	Patient's decision $n=5$	Patient's decision $n=6$
	Toxicity $n=15$	Toxicity $n=2$
Survival status	Survival status	Survival status
Survived $n=111$	Survived $n=110$	Survived $n=103$
Survived with recurrence $n=14$	Survived with recurrence $n=12$	Survived with recurrence $n=11$
Survived with 2nd primary $n=8$	Survived with 2nd primary $n=9$	Survived with 2nd primary $n=2$
Cancer-related deaths $n=11$	Cancer-related deaths $n=10$	Cancer-related deaths $n=11$
Non-cancer-related deaths $n=12$	Non-cancer-related deaths $n=13$	Non-cancer-related deaths $n=7$

Tam, tamoxifen; MPA, medroxyprogesterone acetate.

Table 2
Baseline characteristics of 388 patients with stage I or II endometrial cancer

Parameter no. of patients	Total	Control	Treatment tamoxifen	MPA	*P* value
Patients	388	134	121	133	0.7
Age (years)					
⩽60	143	52	39	52	0.3
>60	245	82	82	81	0.9
FIGO stage					
IA	41	15	13	13	0.9
IB	222	76	70	76	0.9
IC	59	19	19	21	0.9
II	66	24	19	23	0.7
Histological grade					
I	173	62	52	59	0.6
II	164	54	57	53	0.9
III	44	16	8	20	0.1
Unknown	7	2	4	1	0.4
Oestrogen receptor (fmol/mg)					
⩽60	65	24	22	19	0.7
>60	126	32	52	42	0.1
Unknown	197	78	47	72	
Progesterone receptor (fmol/mg)					
⩽60	37	11	15	11	0.6
>60	153	43	62	48	0.1
Unknown	198	80	44	74	

FIGO, International Federation of Gynecology and Obstetrics.

The incidence of recurrences and deaths in the three groups were as follows: tamoxifen (recurrences: 8.3%; deaths: 14%); control group (recurrences: 11.2%; deaths: 17.2%) and the MPA-treated group (recurrences: 9.7% deaths: 18%). If tumour-related deaths were assessed alone, the percentages for recurrence and death in all three groups were similar (Table 1). After a median follow-up of 56 months the overall survival rate was 67.8% (control group: 66.5%, tamoxifen group 70.2%; MPA group 66.1%) Kaplan–Meier analysis of

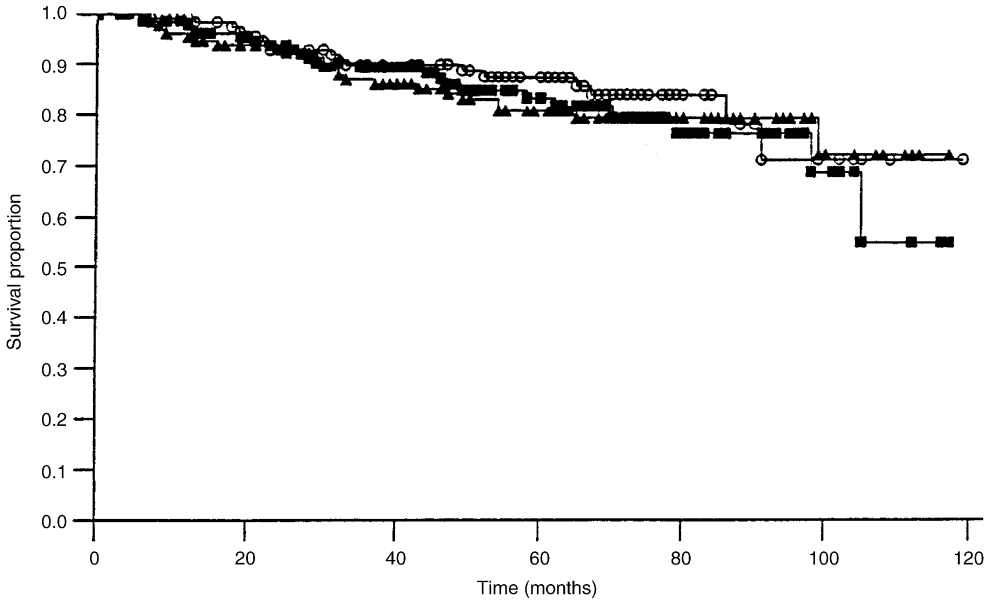

Fig. 1. Acturial analysis of overall survival in 388 patients with surgically pretreated endometrial cancer stages I and II (Kaplan–Meier; log rank; $P=0.7$). (■) Control group (23/134); (○) tamoxifen treatment (18/121); (▲) MPA treatment (23/133).

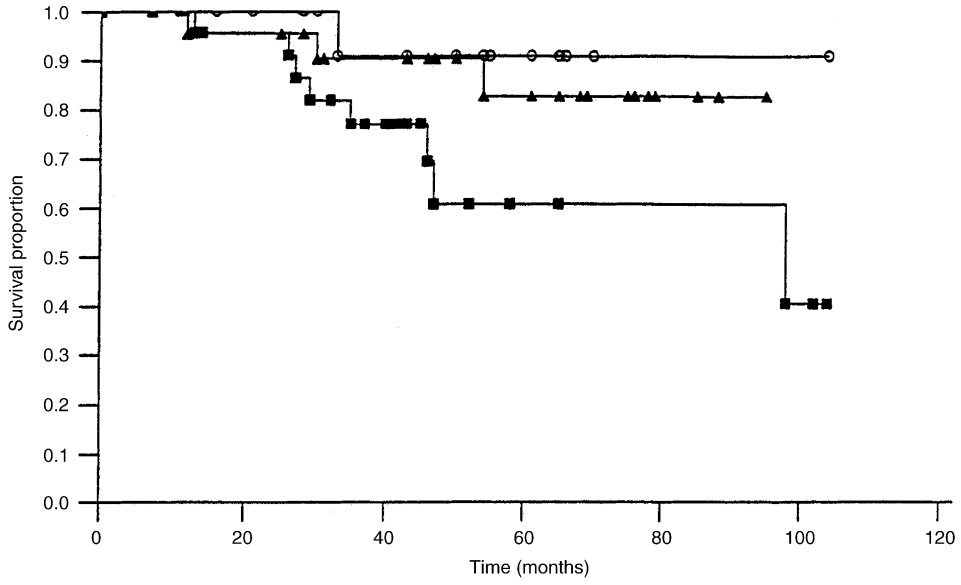

Fig. 2. Acturial analysis of overall survival in 66 patients with surgically pretreated stage II endometrial cancer (Kaplan–Meier; log rank; $P=0.05$). (■) Control group (8/24); (○) tamoxifen treatment (1/19); (▲) MPA treatment (3/23).

recurrence-free ($P=0.8$) and overall survival ($P=0.7$) (Fig. 1) was not significantly different between the groups assessing all of the eligible patients in the study.

Nevertheless, subgroup analysis demonstrated, that in stage II disease ($n=66$) overall survival was prolonged for patients being treated with Tamoxifen (Fig. 2). Tumour grading appeared to be of significant prognostic value in all patients irrespective of treatment. Well and moderately differentiated tumours showed a better survival rate than poorly differentiated tumours (101.7 [97.330–106.1] versus 76.8 [66.0–87.8] months, $P=0.0042$). Patients in the MPA group with grade I tumours had a far worse outcome than the patients in the other two groups (MPA: 89.3 [77.9–100.7] months versus tamoxifen: 100.9 [87.8–114.1] and control: 103.7 [96.8–110.6] months, $P=0.018$). No difference was apparent between the tamoxifen and the control group in patients with grade I tumours. In contrast, patients in the MPA group with GII and GIII tumours ($n=72$) showed a significantly better survival rate than the control group ($n=72$) (89.2 [77.9–100.6] versus 103.2 [96.8–110.6] months, $P=0.0075$); however, this was not observed for the same tamoxifen-treated patient subgroup.

Patients aged more than 60 years of age showed a worse prognosis in comparison to younger patients (survival: 90.7 [84.8–96.5] versus 113.2 [109.8–117.1] months, $P < 0.0001$; recurrence: 105.6 [100.9–110.3] versus 118.2 [116.6–119.8] months, $P = 0.001$); however, no differences for all three treatment groups could be demonstrated. In an additional analysis, 51 non-eligible patients aged 76 years or older also showed no difference in prognosis according to the allocated treatment.

Due to the limited numbers of events, these subgroup analyses have to be interpreted with caution. Finally, hormone receptor content could not be confirmed as a prognostic factor in these endometrial cancer patients. No differences in response to treatment were found for the three groups with respect to the hormone receptor status.

3.2. Toxicity

Preterm discontinuation of treatment was documented in 28 patients. Non-compliant patients were observed with a similar frequency in the tamoxifen group ($n = 6$) and in the MPA group ($n = 5$). However, withdrawal due to toxicity appeared to be far more frequent in the MPA group ($n = 15$) than in the tamoxifen group ($n = 2$). The main causes for withdrawal from the study were deterioration of diabetes mellitus, peripheral oedema and thrombembolic events. A listing of adverse and serious adverse events is given in Table 3. Most of the side-effects occurred in the MPA group (59%), but adverse events were observed in the tamoxifen arm (49%) and also in the control arm (40%). Most importantly, the frequency of deteriorated diabetes or heart failure was reduced in patients being treated with tamoxifen. Nevertheless, hot flushes were observed in 12 patients as a specific side-effect of tamoxifen.

Table 3
Incidence of adverse events in 388 patients with endometrial carcinoma

Event	Control	Tamoxifen	MPA
Total number of events	54	60	79
Adverse events (occurring in more than 5 patients)			
Weight gain	6	10	30
Hot flushes	0	12	8
Deterioration of diabetes mellitus	5	1	11
Deterioration of heart failure	7	2	2
Peripheral oedema	2	2	10
Nausea	0	5	5
Dryness of the skin	0	6	0
Depression	2	3	4
Serious adverse events			
Deep vein thrombosis	2	3	4
Pulmonary embolism	0	1	1
Stroke	1	0	3

Table 4
Second primaries detected after study enrolment

Site	Control	Tamoxifen	MPA
Breast	4	0	4
GI-tract	3	2	2
Leukaemia	0	0	2
Polycythaemia vera	1	0	0
Hypernephroma	0	0	1
Total	8	2	9

GI, gastrointestinal.

Second primary cancers were detected after randomisation in 19 of the 388 evaluable patients. Eight and nine primary tumours occurred in the control and MPA groups, respectively, but only two second primaries (gastrointestinal) were found in the tamoxifen group. Approximately half of the tumours were breast carcinomas; however, none of these appeared in the tamoxifen group (Table 4).

4. Discussion

Earlier studies of adjuvant treatment of endometrial cancer with progestins compared different dose regimens with a control group. In trials recruiting more than 2500 patients, no difference in survival could be demonstrated [6,7,13,14]. Previously, the COSA-NZ-UK Endometrial Cancer Study Group reported on a large trial including 1012 high-risk endometrial cancer patients in a non-placebo controlled trial to evaluate the use of 200 mg twice daily (b.d.) MPA for 3 years [15]. There were significantly fewer relapses in the MPA group, but there were no differences in survival. However, most patients received MPA on relapse, which would explain this discrepancy. The modest improvement of the outcome is probably not enough to substantiate its use if one considers the frequency of adverse events like thrombembolic disease or weight gain which is especially a problem in endometrial cancer patients who are more likely to be obese [16]. A large trial for adjuvant use of MPA showed an increased incidence of cardiovascular diseases in the progestin group compared with the control group [13]. MPA has largely been discontinued.

In contrast, no adjuvant trials using tamoxifen in endometrial cancer have been reported. A recent study by the Gynecological Oncology Group (GOG) demonstrated a modest activity with an overall response rate of 10% [17]. Earlier data on tamoxifen and endometrial cancer in the treatment for recurrent disease demonstrated a response rate of 22%, but are too small to provide reliable estimates [18].

Interestingly, the main benefit for patients with stage I disease treated with tamoxifen was obtained by pre-

venting deterioration of cardiovascular diseases or by preventing second primary cancers. We know from adjuvant tamoxifen trials in primary breast cancer that tamoxifen can protect the contra-lateral breast and lowers cholesterol levels [19–21]. Tamoxifen can decrease the morbidity and mortality in heart disease, but this effect on overall survival is generally modest [22,23]. However, in our study a decreased level of cholesterol and a possible beneficial effect for heart diseases may be of importance in patients with endometrial cancer because of their pre-existing multimorbidity and risk of fatal cardiovascular diseases. Additionally, the patient population is older than that in breast cancer studies, so the risk of heart diseases may be higher.

Currently, the association between tamoxifen and an elevated risk of endometrial cancer is being discussed extensively [24,25], especially with regard to the use of tamoxifen as a preventive drug for breast cancer in healthy high-risk women [26]. Its oestrogen-agonistic effect induces typical oestrogenic changes of the vaginal epithelium in approximately two thirds of postmenopausal breast cancer patients [27]. The partial oestrogenic agonistic effect also causes endometrial polyps and histological changes of the endometrium ranging from proliferation to hyperplasia [28]. The major concern about tamoxifen has been its link with endometrial cancer. Tamoxifen does not cause the endometrial carcinoma, but increases the risk 3–4-fold in postmenopausal women [25]. However, the increase in the detection of endometrial cancer from 1 to 3 per 1000 women per year is consistent with the known rate of occult disease. More importantly, the stage and grade of endometrial cancer in women taking tamoxifen is the same as the general population [29]. The presented study demonstrates that tamoxifen does not promote recurrences of pre-existing endometrial cancer. Our data are supported by the findings of O'Regan and colleagues, that tamoxifen is at least partially anti-oestrogenic on the growth of human endometrial cancer in athymic mice [30]. At the moment, several new anti-oestrogens are being developed with different side-specific oestrogen response modulations. For instance, raloxifene shows no oestrogenic effects on the uterus and ICI 182.780 is completely anti-oestrogenic in all organ systems [31]. The evaluation of these drugs in endometrial cancer may improve the outcome.

The demonstrated trial failed to reveal a survival benefit for adjuvant MPA and tamoxifen in patients with early-stage endometrial carcinoma, which supports the hypothesis that such hormone treatments benefit those with well differentiated, PR-positive tumours [5,32]. However, this is a group which has a survival rate of approximately 90% [2]. At present, there seems to be no benefit from progestin or tamoxifen as an adjuvant therapy after primary surgical treatment. Moreover, it is important to point out that the uncertain effectiveness of tamoxifen in preventing recurrences is at least not impaired by negative side-effects. A modest positive action of tamoxifen on the cardiovascular system and on preventing second primaries may improve clinical outcome.

However, adjuvant endocrine therapy in surgically treated endometrial cancer with modern hormonal agents such as selective oestrogen receptor modulators of the third generation (SERM III), aromatase inhibitors, oestrogen receptor down-regulators or antiprogestins should be considered for further evaluation.

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