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Continuous *versus* intermittent tamoxifen *versus* intermittent/alternated tamoxifen and medroxyprogesterone acetate as first line endocrine treatment in advanced breast cancer: An EORTC phase III study (10863) ☆

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ABSTRACT

Background: Continuous ligand depletion of endocrine responsive tumours may enhance resistance to therapy. Intermittent treatment with tamoxifen (T) was considered to mimic (incomplete) ligand depletion and reintroduction. Furthermore it was postulated that alternating tamoxifen with a non-cross resistant endocrine modality could (further) postpone hormone resistance.

Patients and methods: Postmenopausal patients with advanced breast cancer who did not progress after 4 months of first line T therapy were randomised to continue T (40 mg daily) or to 2 monthly intermittent T or intermittent/alternated T and medroxyprogesterone acetate (MPA, 300 mg daily). At progression during break or during MPA, T should be reintroduced. Endpoints of the study were progression free survival (PFS), time to resistance to tamoxifen and overall survival (OS).

Results: Of 593 registered patients, 276 were randomised. After 8 years follow-up the median PFS for continuous T, intermittent T and intermittent/alternated T and MPA was 11.0 (8.1–15.2), 8.0 (6.2–12.4) and 10.8 (7.1–16.7) months, respectively (NS). Resistance to tamoxifen was established only in 84%, 70% and 55% of patients in the three treatment arms, respectively. The median times from randomisation to resistance to tamoxifen were 12.5 (9.1–21.1), 13.2 (8.8–19.8) and 24.0 (16.9-60.9) months, respectively ($p < 0.001$), without translation in differences in survival times.

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Conclusion: Intermittent T or intermittent/alternated T and MPA had no impact on PFS or OS as compared with classical continuous T in patients with advanced breast cancer.Intermittent/alternated T and MPA resulted in prolonged time to resistance to T, but this might partly be due to bias by omittance of the proof of tamoxifen resistance in a high proportion of the patients in this treatment arm.

1. Introduction

Experimental studies demonstrated that hormone deprivation in hormone dependent tumours, in general by transplantation in a ligand free 'host', might enhance the process of dedifferentiation to autonomy[1–4]. Several experiments reported that dedifferentiation of mammary and prostate tumours from hormone sensitive to hormone independent could be delayed by avoiding total ligand depletion[3,5,6]. In patients with breast cancer who discontinued endocrine therapy during remission, reintroduction at progression could provide repeated clinical benefit[7,8]. However, no data are available about intermittent endocrine therapy during remission or stable disease in advanced breast cancer. This study was designed to assess whether intermittent endocrine therapy with tamoxifen or intermittent treatment with tamoxifen, when alternated with the non-complete cross resistant modality medroxyprogesterone acetate (MPA), could prolong progression-free survival, time to resistance to tamoxifen and overall survival, compared with classical continuous tamoxifen treatment.

2. Patients and methods

Candidates for this study were postmenopausal women with hormone receptor positive or unknown, advanced breast cancer with progressive evaluable disease. Exclusion criteria included prior endocrine therapy for advanced disease or adjuvant endocrine treatment within the previous 12 months; central nervous system or leptomeningeal metastasis; sclerotic bone lesions as the sole manifestation of disease; extensive liver metastasis; other malignant diseases except adequately treated basal/squamous cell skin cancer or in situ cervical cancer or WHO performance status >2. After informed consent, patients were registered to receive tamoxifen 40 mg daily as first line endocrine therapy. If after 4 months an objective remission or stable disease was observed, patients were randomised in one of three arms, continuous tamoxifen, intermittent tamoxifen or intermittent/alternated tamoxifen and MPA (Fig. 1). MPA was administered in a dose of 3×100 mg daily. This dose was based on results of a previous EORTC-study[9].

All periods in the intermittent or intermittent/alternated arm lasted 2 months. This interval was chosen because of the 7–14 days T1/2 of tamoxifen and metabolites[10]. Response evaluation was projected every two months by clinical and radiological examinations. If in any of the 3 arms progression occurred during tamoxifen treatment, patients went off study. If progression occurred during treatment break or MPA, tamoxifen should have been given continuously until further progression. Response was defined according to UICC criteria[11]. For lytic bone lesions recalcification was a requirement for objective remission. Bisphosphonates were allowed only in case of tumour-induced hypercalcemia.

Endpoints of the study were progression free survival (PFS), defined as time from randomisation until progression/relapse or death, whatever occurs first and irrespective of treatment, time to proven resistance to tamoxifen defined as time from randomisation until progression/relapse or death during treatment with tamoxifen and overall survival (OS) defined as time from randomisation to death from any cause.

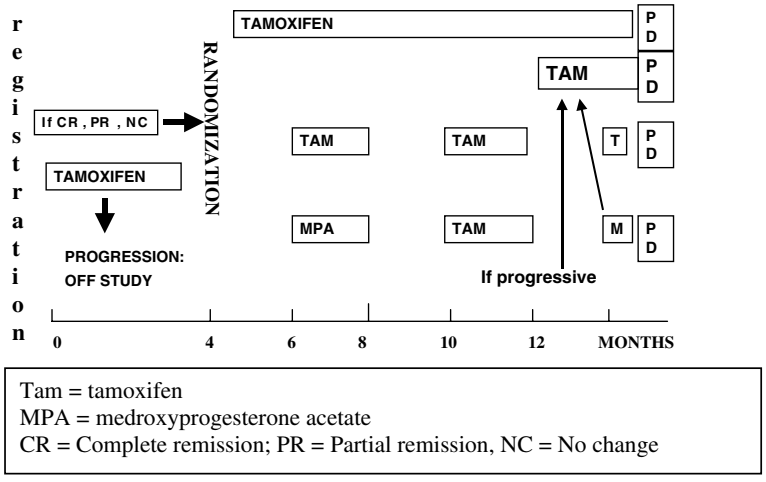

Fig. 1 – Design of the study.

3. Reporting toxicity and side effects

Toxicity and side effects were recorded every 4 months and according to WHO criteria[11]. Flare up was defined as (bone) pain, tumour activation and/or hypercalcemia, related with the onset of treatment with tamoxifen or MPA.

4. Statistical considerations

The number of patients to be randomised was based on the assumption of a 50% increase of median time to progression in one of the experimental arms (for example, from 6 to 9 months). Because virtually all patients will relapse, 85 in each arm (total 255) should be sufficient to observe the required progressions and deaths to approve or reject the hypothesis with $\alpha = 0.05$ and $\beta = 0.20$. Since about 30% of receptor positive or unknown breast cancer can be expected to progress on tamoxifen prior to 4 months, a total of 364 patients should be registered. Analysis of PFS was done with the log rank test. Binary variables were tested for treatment difference by the Chi square test or the Fisher exact test. Ordinal variables were tested for treatment differences by the Wilcoxon rank sum test. The binomial distribution was used to get confidence intervals for the proportions.

5. Results

5.1. *Initial tamoxifen therapy*

The inclusion period started in May 1987 and was extended to March 1997 because of slow accrual and fewer than planned patients subjected for randomisation. Of 593 registered patients, a total of 82 women were ineligible for the study (46 lost for follow-up and 36 not evaluable for first response to tamoxifen). Of the remaining 511 patients, a total of 347 patients (68%, 95% confidence interval (CI) 63.7–71.9%) did not progress during the first four months of initial tamoxifen therapy: 117 (23%, 95% CI 19.3–26.8%) achieved an objective remission and 230 (45%, CI 40.6–49.4%) stable disease. Of those 347 patients, only 276 were randomised. Reasons for not randomising patients with response to induction therapy with tamoxifen are given in Table 1.

The baseline characteristics of the 276 randomised patients at study entry and at the time of randomisation were properly balanced between the treatment groups (Table 2).

Table 1 – Reasons for missing randomisation of patients responding (objective remission and stable disease) to induction treatment with tamoxifen

Reason for no randomisation	Number (%)
Early death	9 (13)
Early progression before 4 months	19 (27)
Refused randomisation	16 (22)
Protocol violation	10 (14)
Lost to follow-up	2 (3)
Unknown	15 (21)
Total	71 (100)

5.2. *Results of therapy after randomisation*

5.2.1. *Progression free survival (PFS)*

At the time of evaluation of this study, almost all patients (268 of 276 patients) had progressed/relapsed or died after randomisation. The median PFS was 11.0 (8.1–15.2) months for continuous-, 8 (6.2–12.4) months for intermittent- (p-log rank = 0.67) and 10.8 (7.1–16.7) months for intermittent alternated treatment (p-log rank = 0.83), respectively (Fig. 2).

5.3. *Time to resistance to tamoxifen*

For patients who relapsed during treatment break (arms 2 and 3) or during treatment with MPA (arm 3), the protocol prescribed reinstitution of tamoxifen continuously until further proven progression. This did not happen consistently in most instances because the investigator judged that this was not in the interest of the patient. During intermittent tamoxifen (arm 2) and intermittent/alternated tamoxifen and MPA (arm 3), 65 of 93 (70%) and 49 of 89 (55%) of the patients, respectively, developed apparent resistance to tamoxifen. Of those, 53 of the 114 (46%) patients in both arms together remained progressive during tamoxifen, whereas in the remaining 61 patients (54%) progression during reinstituted tamoxifen appeared later on: 27 patients in arm 2 and 34 patients in arm 3. For arm 1 (continuous tamoxifen), virtually all patients should be considered resistant to tamoxifen. However, for various reasons, such resistance was established in only 79 of the 94 patients (84%) (Table 3). Apparently the strict adherence to the protocol was more difficult in arm two and three than in arm one.

The median times to resistance to tamoxifen from randomisation were 12.5 (9.1–21.1), 13.2 (8.8–19.8) and 24.0 (16.9–61.0) months for arms 1, 2 and 3, respectively ($p < 0.001$).

5.4. *Overall survival*

At the time of final evaluation of this study, 236 of the 276 randomised patients had died. There were no statistically significant differences in OS between the treatment arms (Fig. 3). The median overall survival was 35.1 (28.2–44.8), 35.2 (23.7–41.3) and 31.4 (25.6–53.9) months in arms 1, 2 and 3, respectively. There was a significant difference in survival times from registration between patients who were or were not randomised (median overall survival are 37.3 (33.1–44.9) and 16.2 (13.6–18.6) months, respectively, $p < 0.001$).

5.5. *Toxicity*

No severe side effects (WHO > 2) have been recorded. Side effects and flare op were mentioned by 64 (23%) and 44 (16%) of randomised patients, respectively. The percentages of side effects in a total of 1793 records were 5.4 in 597, 4.9 in 570 and 13.7 in 626 records for continuous and intermittent tamoxifen and intermittent alternated tamoxifen and MPA, respectively ($p < 0.001$). Four patients in the intermittent tamoxifen/MPA arm went off study because of side effects, in two patients direct by related to MPA therapy. Flare-up phenomena were recorded in 3.5%, 2.8% and 3.5% of all records, respectively.

Table 2 – Clinical characteristics of randomised patients at the time of study entry and at randomisation

	Continuous tamoxifen (n = 94)	Intermittent tamoxifen (n = 93)	Intermittent/ alternated tam/ MPA (n = 89)	Total (n = 276)
Age (median years)	66.9	65.2	66.7	66.3
Range (years)	38.5–86.9	43.6–84.8	41–89.7	38.5–89.7
Years since menopause, median	15	13	14	14
Range (years)	0–36	1–48	0–44	0–48
Disease free interval[a]				
No, *n* (%)	23 (24.5)	20 (21.5)	28 (31.5)	71 (25.7)
Yes	71 (75.5)	71 (76.3)	61 (68.5)	203 (73.6)
Median duration (range) (months)	60 (1–276)	49 (2–282)	57 (6–360)	59 (1–360)
Time since primary, median (years)	4.8	3.8	4.6	4.2
Range (years)	0–23.1	0–24.6	0–29.9	0–29.9
WHO performance status, n (%)				
0	38 (40.4)	35 (37.6)	38 (42.7)	111 (40.2)
1	46 (48.9)	42 (45.2)	37 (41.6)	125 (45.3)
2	10 (10.6)	10 (10.8)	9 (10.1)	29 (10.5)
3	0	1 (1.1)	1 (1.1)	2 (0.7)
Unknown	0	5 (5.4)	4 (4.5)	9 (3.3)
Chemotherapy, prior adjuvant, *n* (%)	16 (17.0)	16 (17.2)	15 (16.9)	47 (17)
Prior adjuvant and/or palliative, *n* (%)	5 (5.3)	9 (9.7)	4 (4.5)	18 (6.5)
Unknown, *n* (%)	1 (1.1)	2 (2.2)	0	3 (1.1)
Endocrine therapy, adjuvant, *n* (%)	10 (10.6)	10 (10.8)	7 (7.9)	27 (9.8)
Endocrine therapy, palliative, *n* (%)	0	1 (1.1)	1 (1.1)	2 (0.7)[b]
Unknown	0	2 (2.2)	0	2 (0.7)
Dominant site of metastasis, n (%)				
Soft tissue	23 (24.5)	32 (34.4)	25 (28.1)	80 (29.0)
Bone	42 (44.7)	25 (26.9)	37 (41.6)	104 (37.7)
Viscera	29 (30.9)	34 (36.6)	27 (30.3)	90 (32.6)
Unknown	0	2 (2.2)	0	2 (0.7)
Receptor status, n (%)				
ER and/or PgR positive	50 (53.2)	51 (54.8)	46 (51.7)	147 (53.3)
ER and PgR negative	2 (2.1)	1 (1.1)	0	3 (1.1)[c]
ER and/or PgR unknown	42 (44.7)	41 (44.1)	39 (43.8)	122 (44.2)
Response to induction tamoxifen, n (%)				
Complete response	5 (5.3)	6 (6.5)	5 (5.6)	16 (5.8)
Partial response	34 (36.2)	36 (38.7)	32 (36.0)	102 (37.0)
No change	55 (58.5)	51 (54.8)	52 (58.4)	158 (57.2)
WHO performance status at randomisation				
0	51 (54.3)	50 (53.8)	46 (51.7)	147 (53.3)
1	40 (42.6)	39 (41.9)	39 (43.8)	118 (42.8)
2	3 (3.2)	3 (3.2)	4 (4.5)	10 (3.6)
3	0	1 (1.1)	0	1 (0.4)[d]

a Disease Free Interval: time from primary to first metastasis.
b Ovariectomy.
c (Not confirmed) receptor negativity.
b–d Included in all analysis.

6. Discussion

The results of induction treatment with tamoxifen for all patients (OR 23% and SD 45%) and PFS of randomised patients (about 16 months from the start of tamoxifen) are within the expected ranges for patients with ER positive or ER unknown advanced breast cancer reported at the time the study was initiated.[12]

PFS after randomisation did not differ significantly between the three treatment arms, indicating that none of the strategies were superior in efficacy.

Time to proven resistance to tamoxifen was found to be equal in the continuous and intermittent treatment arms but longer in the intermittent/alternated tamoxifen and MPA arm. This was not translated into prolonged overall survival. The longer time to resistance to tamoxifen in the

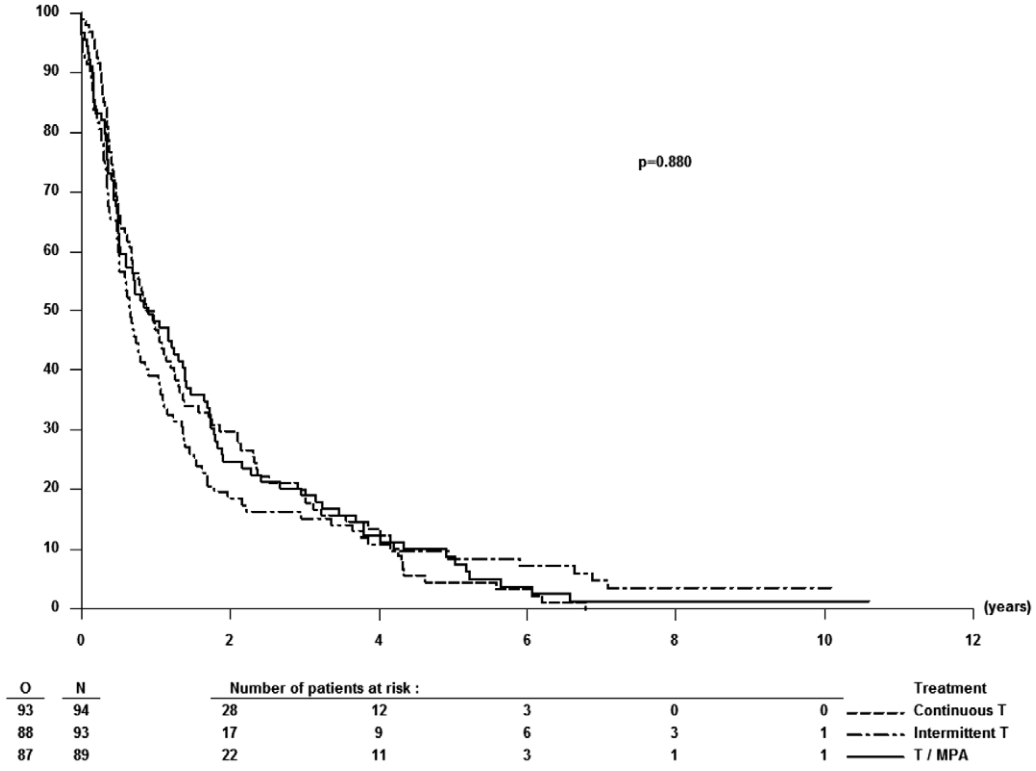

Fig. 2 – Estimated progression free survival from time of randomisation.

Table 3 – Reasons for failure to demonstrate resistance to tamoxifen

	Continuous tamoxifen (N = 94)	Intermittent tamoxifen (N = 93)	Intermittent/ alternated tamoxifen and MPA N = 89	
Proven resistance to tamoxifen	79 (84%)	65 (69.9%)	49 (55.1%)	Arm 1 *versus* 2 $p = 0.024$
Non-proven resistance to tamoxifen	15 (16%)	28 (30.1%)	40 (44.9%)	Arm 2 *versus* 3 $p = 0.04$
				Arm 1 *versus* 3 $p < 0.0001$
				(Fisher exact test)
Reasons off study without proven resistance to tamoxifen:				
Death without established resistance to tamoxifen	7 (7.4%)	9 (9.6%)	6 (6.7%)	
Treatment refused	2 (2.1%)	2 (2.1%)	6 (6.7%)	
Toxicity	0	0	4 (4.4%) (2 related to MPA therapy)	
Non-adherence to protocol	6 (6.4%)	17 (18.3%)	24 (26.9%)	

tamoxifen/MPA treated patients might have been biased by the large number of patients in this group in which this resistance to tamoxifen was not determined. It appeared during the study that strict adherence to this part of the protocol, especially in the intermittent/alternating arm, was frequently violated by uncertainty of investigators and patients (Table 3). On the other hand, patients progressive during continuous and intermittent tamoxifen were candidates for second line endocrine therapy, including MPA, restoring a potential shorter overall survival time as compared with the third treatment arm, in which MPA was already included.

6.1. *Intermittent therapy*

This study intended to demonstrate a prolonged hormone sensitivity when anti-hormone therapy was not given continuously. This assumption was based on experiments in which 'complete' ligand depletion enhanced, whereas incomplete ligand depletion delayed tumour dedifferentiation to hormone independent growth in mammary and also prostate cancer[3,5]. Mechanisms for these experimental observations may be (immunogenic) interactions between hormone dependent- and independent cell clones in heterogeneous tumours[13–15] or adaptive mechanisms in ligand depleted hormone sensitive

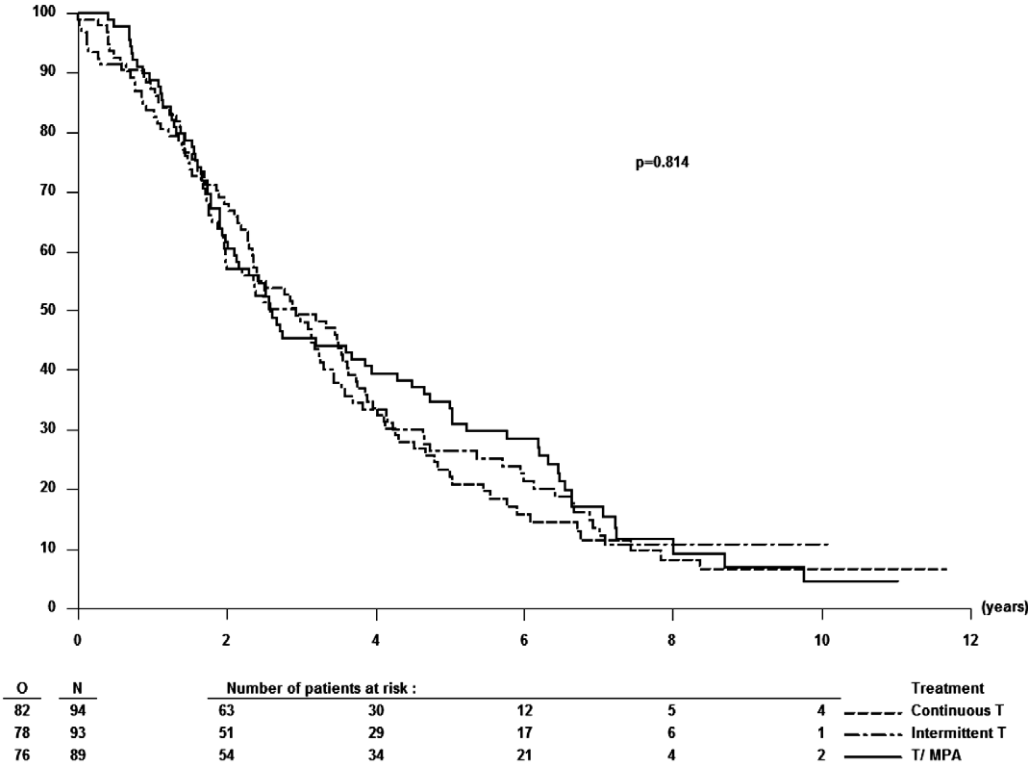

Fig. 3 – Estimated overall survival from time of randomisation.

tumour (stem) cells[16,17]. Acquired resistance against oestrogen deprivation therapy or tamoxifen may be the consequence of increased ER activity and sensitivity and ER activation by growth factor interaction[18]. One of the conditions to prevent this type of resistance may be combined treatment of oestrogen deprivation and growth factor blockade[19,20]. Other strategies could focus on the prevention of (both nuclear and membrane located) ER hypersensitivity by treatment with ER down regulators, as fulvestrant, instead of oestrogen deprivation or SERM's[21], or, as we did in this study, by intermittently allowing ligand receptor interactions. Endocrine treatment of breast and prostate cancer results in a wide spectrum of some to almost complete ligand depletion or blockade. In advanced disease, more pronounced continuous ligand depletion or blockade enhances objective remission rates without any or only marginal effect on survival times. This was seen in breast cancer for tamoxifen with or without aminoglutethimide[22–24], and for luteinising hormone releasing hormone (LH-RH) with or without tamoxifen[25] and in prostate cancer for gonadal suppression with or without anti-androgens[26]. Treatment with tamoxifen at progression after its use as adjuvant therapy and repeated courses of tamoxifen in advanced breast cancer does not exclude subsequent responses[7,27]. Those clinical data indirectly underscore that continuous (maximal) endocrine therapy, at least in cases of tumour regression, may not be necessary and even may be a selective force for the development of hormone independent disease. Several authors described that PSA-levels titrated intermittent androgen deprivation or blockade in patients with prostate cancer is not inferior to continuous treatment and may extend hormonal dependency.[28–30] The design of those studies was different from ours: androgen deprivation therapy was given during 6 months or longer and a complete response on the basis of normalisation of PSA levels should have been reached before stopping therapy. Reinstitution of androgen deprivation occurred when PSA levels increased. However, no such data are available for patients with breast cancer. In our study, the outcome of intermittent tamoxifen therapy was similar compared to classical continuous treatment.

6.2. *Alternating therapy*

Sequencing endocrine modalities before progression may postpone development of endocrine resistance as such or the development of resistance to the individual drugs.

Adjuvant studies with sequenced tamoxifen and aromatase inhibitors have demonstrated improved disease-free survival, and preliminary survival data indicate that this approach may be associated with postponement of endocrine resistance[31–33]. However in advanced disease, data from the present study and the study by Gunderson and colleagues[34], comparing sequential tamoxifen and high dose MPA every 8 weeks with continuous tamoxifen, do not support this hypothesis. Although in the latter study response rates in the sequential group were significantly higher as compared to those in the continuous treatment arm, the authors reported similar durations of response and survival with the two strategies. Beltrán and colleagues[35] compared continuous tamoxifen treatment with weekly alternated tamoxifen and tamoxifen plus MPA. They found less non-responders and a longer time to progression in the alternating arm, without significant differences in objective remission rates and duration.

Of note, in both studies no real alternating strategy was investigated because MPA was given during the long-term washout period of tamoxifen[10] when tamoxifen was still available for the ER[36] or during tamoxifen itself.

Unfortunately, in the present study, time to resistance to tamoxifen in the intermittent and intermittent/alternating arms could not be determined accurately, due to frequently incorrect handling in this part of the trial.

6.3. *Side effects*

In general, well-known toxicity of tamoxifen, including flare-up phenomena, was mild and did not differ in the continuous and intermittent treatment arms. However, MPA doubled registered toxicity in the third treatment arm. This also may have hampered compliance to this strategy.

7. Conclusions

Despite some imperfections of this study, it appears that the efficacy of intermittent and intermittent/alternating strategies used is not superior but also not inferior to continuous tamoxifen therapy. Noteworthy, the study proved that intermittent and intermittent/alternating endocrine treatment strategies in advanced breast cancer can safely be applied. The concept of intermittent ligand depletion in endocrine related cancer surely needs further exploration, using modern drugs as aromatase inhibitors, LH-RH analogues or receptor down regulators and growth factor inhibition strategies.

Conflict of interest statement

For all authors, there is no potential conflict of interest, relevant to this article.

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