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ENDOCRINE THERAPY OF ADVANCED BREAST CANCER

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Abstract

Recent research has resulted in several new options for endocrine treatment of advanced breast cancer. Since one of the most intriguing characteristics of endocrine therapy is that new remissions can be achieved when using subsequent endocrine modalities it is of importance to evaluate their optimal sequence. Tamoxifen has become the most commonly used endocrine therapy of advanced breast cancer due to its few side effects and an overall response rate of 35%, which has been obtained in randomized trials of tamoxifen compared with either ablative, additive or inhibitive treatment approaches. Crossover data from these trials indicate that the highest overall response rate is obtained when tamoxifen is used as first line endocrine therapy. Furthermore, it seems that oophorectomy in premenopausal and aminoglutethimide or progestins in postmenopausal patients are equally effective as second line endocrine therapy. Despite an obvious clinical rationale for combined endocrine therapy most trials exploring this concept have failed to show any benefit. Although data from trials combining tamixofen with prednisolone or androgens seem exciting, the use of combined endocrine therapy still have to be considered experimental.

Key words: Advanced breast cancer, endocrine therapy, review of trials.

Treatment of advanced breast cancer is palliative. Optimal efficacy of cytotoxic therapy has been reached by achieving response rates of 60% and median times to progression of 8–12 months. This has resulted in a renewed interest in the various endocrine therapies used either alone, in combination with each other or in addition to cytotoxic therapy. Recently, a number of trials have demonstrated that endocrine therapy with tamoxifen followed by cytotoxic therapy upon progression is as effective in terms of overall response rate and survival as cytotoxic treatment and tamoxifen given simultaneously or sequentially to postmenopausal patients with advanced breast cancer (1, 5, 37, 45, 49).

One of the characteristics of the various forms of endocrine therapy is that a response can be predicted by the presence of estrogen and/or progestrone receptors in the patient's tumor tissue. All the different endocrine modalities have a lower acute toxicity and a lower long-term morbidity than the cytotoxic approaches. Moreover, one of the most intriguing characteristics of endocrine therapy is that subsequent remissions can be obtained with successive endocrine therapies. It is therefore of clinical importance to evaluate whether there is an optimal sequence in which these therapies can be administered. A rational approach to such an evaluation would be the conductance of carefully designed phase III studies in receptor positive patients with a crossover of all patients upon progression. No such trials have ever been performed. We are therefore forced to analyze data from anecdotal reports, phase II trials and comparative trials with crossover data from a minority of the patients. Several comprehensive reviews have been published in which available data have been pooled (12, 26, 39, 44 and unpublished data by Rose, Løber and Mouridsen) (Table 1). There are, however, objections to this approach. Different criteria for response have been used to access the outcome of therapy and different selection criteria for patients have evolved with time. Furthermore, prognostic variables are not equally represented in the different trials and since most of the data in these reviews stem from phase II trials, in which determination of response rate is the only aim, valid knowledge about time to progression is not available. Moreover, data on cross sensitivity and non-cross resistance are not necessarily reliable due to a possible withdrawal response. These problems can partly be overcome by a restriction of the analysis to random-

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ized trials in which a minority of the patients have been crossed over to treatment with the comparative therapy.

The efficacy and low toxicity of tamoxifen has been established in comparative trials with other ablative, additive, or inhibitive treatment approaches (36). Although none of these trials have included a large enough number of patients to allow detection of even great differences in response rate (10–20%), these trials have been of prime importance in placing tamoxifen as the treatment of choice for first line endocrine therapy. Furthermore, a number of trials have explored the possibility of an increased efficacy by combining tamoxifen with other endocrine approaches.

In the following we will therefore first analyse data from trials between tamoxifen and other endocrine therapies. Secondly, we will review trials of combined endocrine therapy where tamoxifen is used as one of the endocrine modalities. All randomized trials reviewed here meet the following selection criteria:

1) at least 20 patients in each treatment group,
2) similar response criteria,
3) information concerning relevant data, such as response rate, toxicity, time to progression, and survival.

In the analysis of the trials we have focused upon treatment efficacy and side effects.

Efficacy of endocrine therapy

The efficacy of the various endocrine therapies can be assessed by considering time to progression, response rate, and crossover data (cross sensitivity and non-cross resistance). Furthermore, treatment efficacy can be evaluated in relation to prognostic factors as for example estrogen receptor (ER) status. Since only a few studies give data regarding time to progression, only response rates will be compared within the various trials.

Tamoxifen has been compared with other endocrine modalities in 26 randomized trials which are summarized in Table 2. Premenopausal patients have been randomized to either tamoxifen or oophorectomy in 2 trials (4, 16). Both yielded similar response rates and revealed no major differences in other treatment endpoints. Adrenalectomy vs. tamoxifen has been compared in a single trial (29). A non-significant difference in response rate in favor of adrenalectomy was obtained. A rate of response in the order of 30–35% has been found, regardless of whether treatment has been tamoxifen, aminoglutethimide and hydrocortisone (20, 41), estrogens (2, 10, 13, 22, 33, 42), medroxyprogesterone acetate (MPA) (3, 8, 9, 21, 30, 34, 40, 48) or megestrole acetate (MA) (6, 14, 24, 27). In the 3 trials analyzing the relative efficacy of androgens vs. tamoxifen (17, 28, 51) there is a trend towards a lower response rate for patients treated with androgens as first line endocrine therapy.

Table 1

Response data from comprehensive reviews

Therapy	n	Response rate (%)	Reference
Ablative			
Ovx	1 674	33	Henderson et al. (12)
Adx	3 739	32	Henderson et al. (12)
Hypx	1 174	36	Henderson et al. (12)
Inhibitive			
AG+H	1 153	31	Stuart-Harris et al. (44)
Additive			
Estrogens	1 683	26	Henderson et al. (12)
Progestins	1 746	29	Rose et al.*
Androgens	2 250	21	Henderson et al. (12)
Glucocorticoids	756	25	Santen et al. (39)
Competitive			
Tamoxifen	1 269	32	Mouridsen et al. (26)

Ovx = oophorectomy, Adx = Adrenalectomy, Hypx = hypophysectomy, AG+H = aminoglutethimide + hydrocortisone.

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Table 2

Response to tamoxifen compared to other endocrine modalities in advanced breast cancer. Summary of 26 randomized trials

No. of trials	Tamoxifen		Comparative therapy		
	n	(%)	n	(%)	
2	81	(25)	79	(27)	Ovx
1	26	(35)	25	(52)	Adx
6	248	(27)	249	(28)	Estrogens
3	123	(26)	136	(18)	Androgens
12	696	(34)	762	(35)	Progestins
2	99	(33)	93	(32)	AG+H

Table 3

Terminology of crossover data

	First line therapy	
	R	NR
Second line therapy		
R	Cross sensitivity	Non-cross resistance
NR	Non-cross sensitivity	Cross resistance

R = responders, NR = non-responders.

Crossover data

It is important to evaluate the cross sensitivity and non-cross resistance (Table 3) between 2 endocrine treatment modalities given sequentially, since such information can elucidate the proper sequence of the various therapies.

Table 4

Cross sensitivity between tamoxifen (TAM) and other endocrine therapies (ET)

No of trials	Response to TAM in responders to comparative ET		Response to comparative ET in responders to TAM		
	n	(%)	n	(%)	
1	7	(14)	5	(40)	Ovx
1	6	(17)	2	(50)	Adx
4	11	(36)	22	(36)	Estrogens
5	15	(13)	7	(33)	Progestins
3	20	(25)	26	(39)	AG+H

Table 5

Non-cross resistance between tamoxifen (TAM) and other endocrine therapies (ET)

No. of trials	Response to TAM in non-responders to comparative ET		Response to comparative ET in non-responders to TAM		
	n	(%)	n	(%)	
1	11	(9)	10	(30)	Ovx
1	9	(22)	7	(57)	Adx
4	52	(21)	41	(17)	Estrogens
1	20	(15)	10	(10)	Estrogens
5	53	(6)	104	(10)	Progestins
3	42	(7)	61	(12)	AG+H

Table 4 shows the available data on cross sensitivity. Although the number of patients in each trial is small, it is obvious that the response rate to second line treatment with tamoxifen in patients who have responded to a previous endocrine treatment is lower than that to any other second line endocrine therapy in patients, who have first responded to tamoxifen. For patients who have not responded to first line endocrine therapy, rates of response to second line therapy is essentially independent of treatment modality and is approximately 10% (Table 5). There is, however, a tendency towards a higher rate of response when tamoxifen is given as the first therapy.

Response and ER-status

Only a few of the randomized phase III studies we are considering here have correlated the response to endocrine therapy with the presence of ER. In all these studies, only a small subset of the total group of patients has ER-analysis performed, and the different investigators have used different techniques and cut-off limits. Furthermore, none of these studies distinguish between receptor analysis performed on tumor tissue from the primary tumor vs. that from a metastases. The response rate in ER-positive patients range from 0–57% in the various studies. In the corresponding ER-negative group the response rate is only about 10%. However, it is of importance for this analysis that response rate in relation to ER status seems to be independent of the form of endocrine therapy used.

Side effects or problems with endocrine therapy

The only reliable comparison between the different endocrine therapies with regard to side effects would have to be based upon knowledge of the number of patients, who had to discontinue treatment or who had to have the dose reduced. Only a few of the trials analyzed herein give such information. Furtermore, the toxicity profiles are so different from the various therapies that a direct comparison is almost meaningless. A more or less subjective assessment must therefore be given. Since the surgical procedures are irreversible, they have to be restricted to those patients with a relatively high probability of response. Side effects from treatment with estrogens or androgens in the form of congestive heart failure and/or virilization are considered by many to be more serious than the lethargy or fluid retention recorded in patients treated with aminoglutethimide or a progestin.

Relative cost of endocrine therapies

Based upon analysis of the relative efficacy of the various endocrine treatment modalities and their toxicity, it seems justified that tamoxifen currently is considered the drug of choice for first line endocrine therapy. However, all societies have to be concerned about the cost-effectiveness of medical treatments of nearly identical efficacy and toxicity. In order to be able to compare ablative procedures with pharmacological therapies, we have therefore estimated the cost of a response to various endocrine therapies in both the UK and Denmark. Based upon a response rate of 35% for the various therapies and a median time to progression of 8 months it seems that surgical procedures are expensive in comparison with any pharmacological treatment. When only the latter therapies are compared it appears that the cost of a response obtained with MPA and the LHRH-agonists Buserelin or Zoladex is about 3–5 times that obtained either by aminoglutethimide and hydrocortisone, MA, halotestin (HAL), or tamoxifen. Without exception, even high doses of diethylstilbestrol (DES) is the most inexpensive treatment of all pharmacological therapies of breast cancer. As a further example, the price of tamoxifen is about 7 times that of DES in the United States. Finally, it can be shown that the cost of a response obtained by actinic castration is in the same order as pharmacological treatment with HAL or tamoxifen.

Evaluation of the possible candidates for endocrine therapy

On the basis of the relative efficacy, side effects and price, the various options for endocrine therapy of pre-

Table 6

Randomized trials comparing tamoxifen with oophorectomy in advanced breast cancer

References	Treatment (daily dose)	Response rate		Response duration median (days)	Time to treatment failure median (days)	Survival median (days)
		(CR+PR)/n	(%)			
Ingle et al. (16)	TAM (20 mg)	7/26	(27)	453	160	749
	Oophorectomy	10/27	(37)	476	144	722
Buchanan et al. (4)	TAM (40 mg)	13/55	(24)	600	–	450
	Oophorectomy	11/52	(21)	210	–	750

Table 7

Randomized trials comparing tamoxifen and estrogens in advanced breast cancer

References	Treatment (daily dose)	Response rate		Response duration, median (days)	Time to treatment failure, median (days)	Survival, median (days)
		(CR+PR)/n	(%)			
Stewart et al. (42)	TAM (10 mg×3)	9/29	(31)	266	–	–
	DES (5 mg×3)	6/27	(22)	228	–	–
Ingle et al. (13)	TAM (10 mg×2)	23/69	(33)	238	171	735
	DES (5 mg×3)	30/74	(41)	393	142	>1 140
Ribeiro (33)	TAM (20 mg)	13/47	(28)	720	–	–
	DES (3 mg)	14/45	(31)	720	–	–
Gockerman et al. (10)	TAM (10 mg×2)	3/54	(6)	–	150	1 020
	DES (5 mg×3)	5/50	(10)	–	180	1 050
Beex et al. (2)	TAM (20 mg×2)	10/30	(33)	330	–	750
	EE_2 (3 mg)	9/29	(31)	360	–	930
Matelski et al. (22)	TAM (20 mg)	10/19	(53)	–	–	–
	EE_2 (3 mg)	6/24	(25)	–	–	–

DES = diethylstilbestrol; EE_2 = ethinylestradiol.

and postmenopausal advanced breast cancer will be considered separately.

Premenopausal advanced breast cancer. Castration, either by surgery or by irradiation, is the oldest form of endocrine therapy, and until recently it was considered to be the treatment of choice in all premenopausal patients with metastatic disease. The overall response rate in 1674 premenopausal patient was 33% (12). Surgical or actinic castration have never been compared in a randomized trial. However, actinic castration has produced similar rates of response as those obtained by oophorectomy (7, 19). It is therefore reasonable to believe that ovarian ablation by radiotherapy can substitute the surgical procedures due to comparable efficacy and a lower cost. Rather high doses of estrogens have been tried in premenopausal patients and seem to be without effect (18). Androgens can be used to induce menostasia, but this requires high doses, which in most cases lead to unacceptable virilization. Table 6 shows in greater detail the only 2 randomized comparisons between tamoxifen and oophorectomy. Although the numbers are small, similar rates of response are obtained and none of the 2 studies demonstrate any difference in survival.

Postmenopausal advanced breast cancer. Due to the favorable cost-effectiveness relationship for treatment with estrogens, the randomized comparisons between tamoxifen and DES or ethinylestradiol are summarized in Table 7. It appears that the various treatment endpoints are comparable between the 2 treatment options and without significant differences. It is well known that estrogen therapy display a variety of toxicities. Although some of the side effects of estrogen treatment are claimed to be less severe with continued treatment, it is clearly demonstrated in all 6 randomized trials that the toxicity of tamoxifen is milder and generally without importance. In addition, treatment with estrogens had to be discontinued due to side effects in about 50% of patients in 2 of the trials (22, 42). Even in the study by Ribeiro (33) using only

Table 8

Randomized trials of tamoxifen in combination with androgens in advanced breast cancer

References	Treatment (daily dose)	Response rate (CR+PR)/n	(%)	Response duration, median (days)	Time to treatment failure, median (days)	Survival, median (days)
Tormey et al. (46)	TAM (2–100 mg/m^2×2)	8/52	(15)	230	64	330
	TAM (2–100 mg/m^2×2) FLU (7 mg/m^2×2)	21/56	(37)	212	180	380
Twito et al. (47)	TAM (10 mg×2)	50/119	(42)	–	199	860
	TAM (10 mg×2) FLU (10 mg×2)	62/120	(52)	–	364	917
Rose et al. (35)	TAM (10 mg×3)	32/94	(34)	720	300	720
	TAM (10 mg×3) FLU (5 mg×4)	36/87	(44)	720	330	720
Wallgren et al. (50)	TAM (20 mg×2)	36/145	(25)	615	–	964
	TAM (20 mg×2) FLU (10 mg×2)	51/139	(37)	>720	–	696
Heinonen et al. (11)	TAM (10 mg×3)	24/49	(49)	–	>390	870
	TAM (10 mg×3) NAND (100 mg i.m./w/2.w.)	22/49	(45)	–	>360	750

FLU = fluoxymesterone; NAND = nandrolone.

Table 9

Randomized trials of tamoxifen in combination with inhibitive endocrine therapy or glucocorticoids in advanced breast cancer

References	Therapy (daily dose)	Response rate (CR+PR/n	(%)	Response duration, median (days)	Time to treatment failure, median (days)	Survival, median (days)
Powles et al. (32)	TAM (10 mg×2) TAM (10mg×2)	34/111	(31)	675	–	1 440 (CR+PR)
	AG+H (250 mg×3+ 20 mg×2) Danazol (100 mg×3)	48/111	(43)	540	–	690 (CR+PR)
Milsted et al. (23)	TAM (10 mg×2) TAM (10) mg×2)	5/26	(19)	–	–	–
	AG+H (250 mg×4+ 10 mg×2)	6/26	(23)	–	–	–
Ingle et al. (15)	TAM (10 mg×2) TAM (10 mg×2)	21/49	(43)	452	216	657
	AG+H (250 mg×4+ 100 mg×40)	25/51	(49)	447	227	827
Rose et al. (35)	TAM (10 mg×3) TAM (10 mg×3)	32/94	(34)	720	300	720
	AG+H (250 mg×4+ 20 mg×3)	24/83	(29)	720	240	720
Stewart et al. (43)	TAM (10 mg×2)	9/72	(13)	390	–	360
	TAM (10 mg×2) Pred. (5 mg×2)	26/73	(36)	390	–	630
Rubens et al. (38)	TAM (10 mg×2)	24/77	(31)[+]	360	–	NS
	TAM (10 mg×2) Pred. (5 mg×2)	39/85	(46)[+]	720	–	NS

[+] = ref.: R. D. Rubens: Personal communication, NS = not significant.

3 mg of DES daily, 15% of the patients had to stop treatment. Nevertheless, even such a substantial proportion of patients stopping treatment because of side effects did not seem to influence the therapeutic outcome of treatment with estrogens.

Combined endocrine therapy

The clinical experience of partial cross sensitivity and a lack of complete cross resistance between the different endocrine treatment modalities indicate that these therapies may not share the same ultimate modes of action (36). Thus there is a rationale for the simultaneous application of the different endocrine therapies. In Denmark we have performed 3 randomized clinical trials, comparing treatment with tamoxifen alone and tamoxifen in combination with either additive or inhibitive endocrine treatment in postmenopausal patients with advanced breast cancer (26, 37).

The results from these 3 trials in postmenopausal patients with progressive breast cancer demonstrated that first line endocrine therapy with tamoxifen was just as effective as treatment with tamoxifen in combination with either MPA, DES, aminoglutethimide and hydrocortisone, or HAL. Toxicity was more pronounced and severe in the combined treatment groups in all 3 trials. Other investigators have explored the effect of combined endocrine therapy in randomized trials and the results of combining tamoxifen with an androgen or aminoglutethimide and hydrocortisone are shown in Tables 8 and 9 respectively. In 4 out of 5 trials analyzing the addition of androgen to tamoxifen a trend for an increased response rate is demonstrated. Preliminary data from the largest of these trials (50) even suggest a survival advantage for the combined approach.

The addition of aminoglutethimide and hydrocortisone to tamoxifen has been analyzed in 4 trials (Table 8). By combining both tamoxifen, aminoglutethimide, hydrocortisone and danazol, Powles et al. (32) obtained a 12% increase in response rate. However, this increase was not translated into a prolongation of either response duration or survival. The addition of prednisolone to tamoxifen has been demonstrated to increase the response rate in 2 consecutive trials performed by the same group (38, 43). Based upon the results in these 2 trials it can be predicted that the response rate to tamoxifen in combination with prednisolone will be 10–40% higher than to tamoxifen alone. In the latter trial, it appears from a preliminary analysis that the higher rate of response was translated into a prolongation of time to progression and survival.

Conclusion

Considering efficacy, side effects, and cost of the various options for single agent endocrine therapy, and assuming that every patient with metastatic disease should have at least one trial of endocrine therapy, it seems justified that tamoxifen is the treatment of choice for first line endocrine therapy in both pre- and postmenopausal breast cancer patients. Current knowledge about cross sensitivity and price suggests that actinic castration among premenopausal women and aminoglutethimide and hydrocortisone or MA for postmenopausal women is a reasonable choice for second line endocrine therapy in previous responders to tamoxifen. If third line endocrine therapy is to be considered aminoglutethimide and hydrocortisone, MA or DES might be of use.

Despite an obvious clinical rationale for combined endocrine therapy most trials exploring this concept have failed to show any benefit. Although data from trials combining tamoxifen with prednisolone or an androgen seem exciting, the use of combined endocrine therapy cannot at present be recommended outside the context of randomized clinical trials.

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