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Perspectives and Commentaries

Endocrine Therapy of Breast Cancer*

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Abstract—*The aim of this literature study is to evaluate the various endocrine drugs used in the treatment of breast cancer in order to compare their therapeutic efficacy.*

Hormone-dependent metastasized breast cancer of post-menopausal women can be treated with four equivalent drugs: tamoxifen, megestrol, medroxyprogesterone, and—combined with steroid suppletion therapy—aminoglutethimide. Each of these drugs induces (partial) remissions in 50–60% of estrogen receptor-positive tumors.

Because of its relatively few and less serious side-effects tamoxifen is the agent of first choice for soft tissue and lung metastases. Due to its potentially enhanced objective and more pronounced subjective side-effects, aminoglutethimide may be preferred in bone metastases. In view of the only minor activity of hormonal agents in liver metastases, combination chemotherapy with concomitant, sequential or alternating use of hormonal agents should be considered in this condition.

Until now, only tamoxifen seems suitable for the treatment of premenopausal metastasized hormone-dependent breast cancer.

In the adjuvant setting, preoperatively initiated and as soon as possible postoperatively continued endocrine therapy seems to be of the utmost importance to counteract (occult) metastases while reducing the need for extensive surgery.

INTRODUCTION

CELLS of the normal mammary gland contain receptors for estrogens (ER), progestins (PgR), androgens (AR), glucocorticoids (GcR) and prolactin. If these receptors remain present and functional as a tumor develops the tumor will be vulnerable to changes in the endocrine environment [1]. Since the stimulating effect of estradiol (E_2) on this type of tumor is well established, endocrine therapy is preeminently directed against this hormone. In general, four endocrine approaches of breast cancer can be distinguished:

a. additive therapy: progestins, androgens, glucocorticoids, high doses of estrogens;
b. competitive therapy: anti-estrogens;
c. synthesis inhibition: aromatase inhibitors, LHRH agonists, danazol, bromocriptine;
d. ablative therapy: oophorectomia/ovary irradiation, adrenalectomy, hypophysectomy.

In this paper pharmacological considerations in the use of anti-estrogens, progestins, aromatase inhibitors, LHRH agonists and danazol will be followed by reviews of endocrine and chemo-endocrine therapy of metastasized and early stage female breast cancer as well as by a review of male breast cancer.

PHARMACOLOGY

Anti-estrogens

The anti-estrogens tamoxifen (Tam), trioxyphene, clomiphene and nafoxidine are triphenylethylene derivatives, which are, depending upon the species and organ under study, antagonists or (partial) agonists of the circulating estrogens.

The precise mechanism by which Tam and other anti-estrogens counteract estradiol-induced proliferation is still unknown. In recent years, the cytoplasmic estrogen receptor model (binding of Tam to cytoplasmic ER, activation of the complex, translocation to the nucleus and interaction with nuclear acceptors) has been questioned as new findings have indicated that all ER may be located in the nucleus.

The binding of Tam to ER induces conformational changes in the receptor leading to interactions with the chromatin that result in altered protein synthesis and reduced cell proliferaton [2–4].

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Tam inhibits the uptake of E_2 in target tissues like the uterus, vagina, pituitary gland and DMBA (dimethylbenzanthracene)-induced breast cancers both in animals and humans in a dose-dependent manner [2]. Because of structural resemblances to E_2 Tam binds competitively with E_2 to ER [5, 6] with an affinity varying in several studies from 30 to 0.01% (!) of that of E_2 [2]. Furthermore, it has been shown that Tam binds to ER 4 times faster and dissociates from ER 100 times slower than E_2 [7].

Tam binds also to Anti-Estrogen Bindings Sites (AEBS) or more specifically Triphenylethylene Binding Sites [2] that do not bind E_2 [8]. The anti-estrogen and tumor growth inhibiting actions of Tam, however, correlate with its binding affinity for ER but not with that for AEBS, i.e. ER+ and ER− tumors contain equal concentrations of AEBS [3].

Studies on the existence of ER subpopulations could also shed light on the mode of action of the anti-estrogens. Clomiphene and nafoxidine appear to behave as full agonists of the Type I subpopulation while being only very weak agonists of the Type II ER [9, 10].

E_2 causes an increase and subsequent decrease in nuclear ER followed by a.o. PgR synthesis. In marked contrast, nafoxidine causes a persisting increase in ER without PgR synthesis, whereas Tam exhibits a slower and longer lasting increase followed by a slower decrease in ER and synthesis of PgR [2].

Tam inhibits the growth of estrogen and prolactin dependent DMBA-induced rat mamma carcinomas by preventing the binding of E_2 to its receptor. In contrast to E_2, binding of Tam to ER causes an only temporary rise in RNA polymerase levels [2, 11]. The ER concentration of the tumor diminishes during treatment [12].

Other mechanisms by which Tam might exert its growth inhibiting effect are a lowering of the release of gonadotropins and prolactin from the pituitary gland, an inhibition of E_2 synthesis, and an enhancement of the natural killer cell activity (additive to interferon) [2, 13]. In the DMBA model tumor regression is correlated to the tumor cytosol concentrations of Tam and its metabolites. Interestingly, these concentrations cannot be explained from binding to ER alone [14].

In vitro, Tam exerts a tumor growth inhibiting effect on the human breast cancer cell line MCF-7 that can be suppressed by E_2 [15–17]. However, the cytotoxic effect of high doses of Tam cannot be reversed by E_2 [18].

Tumor growth inhibition *in vitro* is evident from a lowering of [^{3}H]thymidine incorporation while the intracellular pool of thymidine is reduced [19, 20], from DNA synthesis arrest [19, 20], from a reduction of DNA polymerase activity [21], from a reduction of DNA content [15, 22] and from a reduction of cell number [15, 20].

Tam and its metabolites cause a dose-dependent decrease in the percentage of cells in S phase, and a relative increase in the number of cells in either G_0/G_1 phase [23, 24] or G_1/G_2 phase [25]. However, cell cycle specific effects of Tam could not be detected in the ER+ and PgR+ cell line TG-1, which is grown in nude mice [26].

Tam also inhibits growth of an E_2-highly sensitive variant of MCF-7, CG-5, and potentiates the effect of progestins [27]. This is probably in agreement with the increase in PgR observed in MCF-7 cells during treatment with low concentrations of Tam [22]. Growth of the T-47D cell line in a medium without endogenous E_2 is stimulated by low concentrations of E_2 and Tam, but inhibited by high concentrations of both compounds [28]. In the ZR-75-1 cell line 17β-estradiol stimulates growth whereas Tam causes E_2-reversible growth inhibition [29].

Some ER− cell lines are also sensitive to Tam [2]. At first sight these effects do not seem to relate to AEBS, because correlations between affinity for AEBS and anti-estrogenicity have not been reported [30, 31]. However, observations indicating that Tam-resistant ER+ clones of MCF-7 do not contain AEBS [32] and that growth inhibition is increased with increasing AEBS content of the tumor [33] stress the importance of AEBS. Tam-induced inhibition of prostaglandin synthetase could also be of importance [34].

Information on Tam's action at the level of protein synthesis is limited but promising. Tam seems to inhibit the synthesis of E_2-regulated stimulatory growth factors while stimulating the synthesis of inhibitory growth factors (see e.g. [35]). Furthermore, PgR synthesis of MCF-7 cells is stimulated or inhibited depending on the administered dose [22] whereas PgR synthesis of ZR-75-1 is not affected [36]. The synthesis of an E-dependent protein of MCF-7 cells is inhibited by Tam. In a Tam-resistant clone of MCF-7 the synthesis of this protein is augmented whereas the synthesis of an E-dependent mRNA remains suppressed [37–41].

Tam is administered orally, is well absorbed, and in the blood stream largely bound, particularly to albumin. Plasma levels correlate well to the administered dose [2, 42–44]. However, no correlations between plasma levels and clinical response have been detected so far [2].

Tam is metabolized in the liver by cytochrome P-450-dependent oxidases to active compounds, among which *N*-desmethyl-Tam (maximum serum level ±60% higher than Tam and affinity for ER comparable to Tam) and 4-OH-Tam (maximum serum level ±2.5% of that of Tam and affinity for

ER 100-fold larger than Tam) have gained the most interest. The half-life of Tam is approximately 7 days with steady state levels appearing in the 4th week of therapy, whereas *N*-desmethyl-Tam has a half life of ±14 days with steady state levels appearing after 8 weeks [2, 45–53].

Tam and its metabolites affect numerous endocrine parameters (Table 1), varying per individual qualitatively and quantitatively. In pre-menopausal patients the Tam-induced blockade of ER may be overcome by a rise in E_2 level, if the anticipated rise in SHBG is insufficient to avoid a rise in percentage free estradiol. However, correlations with the clinical response have not been reported.

Trioxyphene has been studied by a limited number of authors. Its affinity for ER is about 10 times higher than that of Tam [54]. In marked contrast to Tam, it might also possess intrinsic estrogenic activity, inducing e.g. a dose-dependent reduction of LH and FSH levels [55].

Progestins

In order to exert their predominantly differentiating effects progestins need estrogen priming. Progesterone and the 17α-OH-progesterone derivatives megestrol acetate (Ma), medroxyprogesterone acetate (Mpa) and cyproterone acetate exert endometrium transforming, anti-estrogenic, anti-androgenic, anti-gonadotropic and (Mpa > Ma) glucocorticoid-like effects, whereas the testosterone derivative norethisterone and the 19-nortestosterone derivative lynestrenol exert next to endometrium transforming, estrogenic as well as anti-estrogenic, androgenic and anti-gonadotropic effects [74].

These effects result from interactions with PgR, AR and GcR [75, 76]. Correlations between tumor receptor levels and clinical response have been described for ER [77], ER and PgR [78–80] and AR (albeit receptors were mutually correlated as well) [56].

Without affecting ER directly, progestins are capable of influencing E_2-dependent tumor proliferation by (see also Table 1):

a. lowering the ER content (of MCF-7 cells) [81];
b. lowering LH and FSH release, resulting in a diminished steroid synthesis [56–59];
c. slowing down testosterone catabolism (see Fig. 1) [56–59];
d. speeding up E_2 turnover into the less active estriol by catalyzing the activity of, in human breast cancer demonstrated [82], estradiol-17β-dehydrogenase [81–84] (not affirmed in [75]).

A remarkable *in vitro* study using MCF-7 cells has revealed that tumor growth inhibition by the synthetic progestin R5020 cannot be reproduced or distorted by dexamethasone or dehydrotestosterone. This indicates a PgR-dependent mode of action which results in anti-estrogenic effects such as synthesis inhibition of an E_2-induced protein [85].

E-independent mechanisms cannot, however, be ruled out, since progestins inhibit growth of an ER−/PgR+ human breast cancer cell line [86]. They also inhibit growth of a Tam-resistant variant of MCF-7 [85]. Under certain conditions progesterone [87] and Mpa [88] may cause tumor growth exacerbations.

Aromatase inhibitors

The commonly used steroid synthesis inhibitor *aminoglutethimide* (Ag) affects notably cytochrome P-450 containing enzymes of the adrenal gland (Fig. 1) [60]:

a. inhibition of desmolase [89, 90];
b. possibly activation of 3β-OH-steroid dehydrogenase [91];
c. possibly inhibition of C_{21}-hydroxylase [92];
d. possibly inhibition of C_{11}β-hydroxylase [93–95];
e. inhibition of 18-hydroxylase [96–98];
f. inhibition of aromatase [99–109];
g. inhibition of organic binding of iodine in the thyroid gland [110];
h. inhibition of prostaglandin synthetase [111].

The inhibition of steroid synthesis in the adrenal gland causes a reflex release of ACTH from the pituitary gland, through which the inhibition is overcome [112]. To avoid this reflex, Ag (commonly 250 mg 4×/d) is combined with hydrocortisone (Hc) (20 mg 2×/d) or cortisone acetate (25 mg 2×/d).

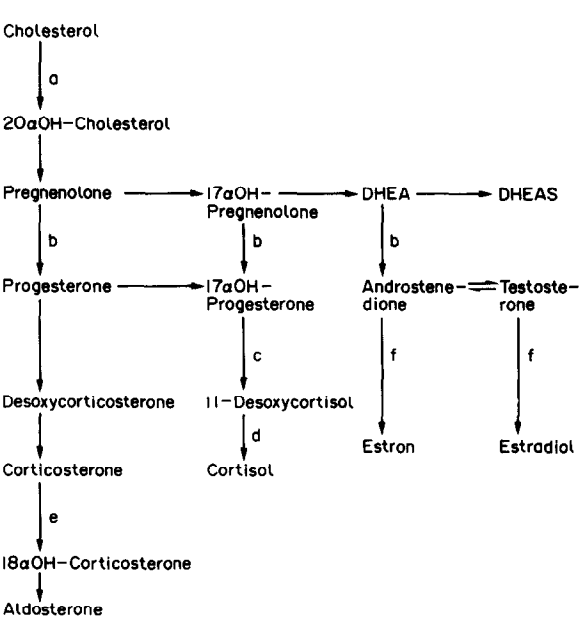

Fig. 1. Influence of aminoglutethimide on steroid synthesis [60].

Table 1. *Influence on endocrine environment*

	Tamoxifen [2]*			Mpa,Ma [56–59]†	Ag/Hc [60,61]‡
	Pre-menopause	Post-menopause	Men	Post-menopause	Post-menopause
Estrogens	↑	=	↑	↓	↓
% free estradiol		↓			
Progesterone	↑	=			
FSH	=	↓	↑	↓	↑ n.s.
LH	=	↓	↑	↓	=
LHRH-induced release of					
FSH	↓/↑	↓/=	=/↑		
LH	↓/↑	↓/↑	=/↑		
ACTH				↓	
Prolactin	=	=/↓	=	↑	=
TRH-induced release		↓		↑	
Bromocriptine release inhibition	↑				
Growth hormone		=		=	
Arginine-induced release					
L-Dopa-induced release		↓			
Bromocriptine release inhibition	↑				
TSH		=		=	↑
T_4					↓
T_3					=
Insulin				↑	
Androstenedione		=	↑	↓	=
DHEAS				↓	↓
Testosterone				↓	↓ n.s.
Cortisol		↑		↓	↓ n.s
Aldosterone					↓
Hydrocortisone				↓	
Cortisol binding globulin		↑			
SHBG		↑		↓	

	Trioxyphene [55,62]§	LHRH agonists [63,64]‖	Chemotherapy [65–67]	
	Post-menopause	Pre-menopause	Pre-menopause	Post-menopause
Estrogens	=	↓	↓	↓ n.s.
% free estradiol	↑/↓			
Progesterone		↓		
FSH	↓	↓	↑	↓ n.s.
LH	↓	↓	↑	↓ n.s.
LHRH-induced release of				
FSH				
LH				
ACTH				
Prolactin	=/↓	↑/↓	↓	=/↓
TRH-induced release	↓			
Bromocriptine release inhibition				

Table 1. Influence on endocrine environment (Continued)

	Trioxyphene [55,62]§ Post-menopause	LHRH agonists [63,64]‖ Pre-menopause	Chemotherapy [65–67]	
			Pre-menopause	Post-menopause
Growth hormone				
Arginine-induced release	↓			
L-Dopa-induced release	↑			
Bromocriptine release inhibition				
TSH	=			
T_4				
T_3				
Insulin				
Androstenedione	=	↑/↓	↑/↓ n.s.	↓ n.s.
DHEAS				
Testosterone		↓		
Cortisol		↑/↓		
Aldosteone				
Hydrocortisone				
Cortisol binding globulin				
SHBG	↑/↓			

*Pre-menopausal midcycle prolactin possible decreased [2]; in post-menopausal patients sustained or temporary decrease in LH and FSH [2]; in males after 7 days FSH and LH on basic levels but both are from the 10th day onwards increased, the same holds for the response to LHRH, with clomiphene the response of males to LHRH is depressed [2].

†Ma causes insulin levels to rise possibly by a direct effect on the pancreas [69]; Mpa decreases Hc, DHEAS and E_2 levels dose-dependently (500–1500 mg/d p.o.) [57].

‡Ag alone: androstenedione ↑, DHEAS = and 17α-OH-progesterone ↑ [60]; compared to Hc alone Hc + Ag results in a significantly lower E_1 level and a non-significantly lower E_2 level while DHEAS remains unchanged [70]; Hc plus high-dose Ag results in comparison to 62.5–125 mg/d Ag in a non-significantly lower estron-sulphate level and unchanged E_1 and E_2 levels [71]; Ag/Hc causes a decrease in prostaglandins F levels [72]; TSH is increased before therapy is started in 35% of patients (possibly due to radiating supra-clavicular lymph nodes), the organic binding of iodine is inhibited [73].

§L-Dopa-induced release of growth hormone is stimulated [55, 68].

‖Temporary rise of hormone levels during ± first 4 days of therapy.

In view of a potentially extensive salt loss, due to a lowering of aldosterone levels, substitution therapy with 0.05–0.10 mg/d fludrocortisone may become necessary, especially in warm climates.

Because the dose required for aromatase inhibition is less than that required for inhibition of the various hydroxylases, aromatase inhibition is thought to be responsible for the anti-tumor action of Ag [113]. Aromatase is responsible for the peripheral conversion of androgens to estrogens, the most important source of estrogens in post-menopausal women [99, 100]. Inhibition of aromatase ranges from 80% at a dosage of 250 mg/d to 95% at 1000 mg/d, although 92% inhibition has been observed at dosages as low as 250 mg/d as well [101, 102]. The resulting reduction of estrogen levels amounts to 60–80% [60].

Ag is well absorbed from the gastro-intestinal tract, and is largely excreted in urine within 72 h [115]. It stimulates its own metabolism—the initial $t_{\frac{1}{2}}$ of 13 h is after one week of treatment 7 h [116, 117]—as well as that of dexamethasone and anti-coagulants but it does not alter the degradation of hydrocortisone and androstenedione [90, 118–120]. After enzyme induction a new metabolite, *N*-OH-Ag, is formed [121]. Ag is also metabolized by non-induced acetylation to the slightly active *N*-acetyl-Ag [122]. Depending upon the speed of acetylation 9–48% of Ag is converted to *N*-acetyl-Ag, but no correlations between the speed of acetylation and toxicity or clinical response have been observed [122].

For the effects of Ag/Hc on endocrine parameters of post-menopausal women the reader is referred to Table 1. The influence on the menstrual cycle varies interindividually, but E_2 levels do not seem to be affected significantly. Only minor changes in LH and FSH levels are observed in the luteal phase. The response to exogenous gonadotropins appears to be reduced [123, 124].

Other drugs affecting steroid synthesis are trilostane, Δ^1-testololactone and 4-OH-androstenedione. *Trilostane* inhibits competitively and reversibly the action of 3β-OH-steroid dehydrogenase

(Fig. 1) [125–127]. In addition, it probably inhibits aromatase [128]. Δ^1-*Testololactone* is an aromatase inhibitor with probably androgenic properties [129]. 4-OH-*Androstenedione* is a more specific and stronger inhibitor of aromatase than AG. It does not inhibit cortisol synthesis and, therefore, substitution therapy is superfluous. It also has less effect on the central nervous system. Furthermore, it exhibits estrogenic effects (depletion of ER in MCF-7 cells and PgR synthesis induction), direct effects on the hypophysis (prevention of negative feedback of E_2) and androgenic effects [130, 131]. Remarkably, the three aromatase inhibitors Ag, Δ^1-testololactone and 4-OH-androstenedione behave additively on microsomal systems [114].

LHRH agonists

Chronic administration of the LHRH agonists, busereline or leuprolide, causes an increase in LH and FSH levels during the first 4 days of therapy which is followed by a persisting decrease in gonadotropin release and, therefore, reduced steroid synthesis [63, 64, 132–134]. The reduction of gonadotropin release is caused by a Ca^{2+}-independent desensitization [132], due to a decrease in LHRH receptors [63, 64, 134]. The anti-tumor effect might be augmented by weak, direct anti-estrogenic and anti-androgenic effects on the gonads, as observed in MCF-7 cells [64, 133, 134].

LHRH agonists are not only capable of inhibiting growth of DMBA-induced mammary cancers but also of preventing the carcinogenic effects of DMBA [135–138].

Pharmacokinetic considerations, however, have prevented large-scale application of LHRH agonists: these peptides are not absorbed from the gastrointestinal tract and possess very short half-lives. They are administered subcutaneously or intranasally several times a day [138–141]. However, intranasal application may cause incomplete suppression of the pituitary–gonadal axis, as exemplified by the persistence of E_2 peaks [64]. Continuous release formulations have been developed, but their efficacy and side-effects do not seem to differ significantly from those of the conventional formulations [35].

Therapy is commonly started in the luteal phase and results in amenorrhea in all pre-menopausal patients (see further Table 1).

Danazol

Danazol blocks the release of gonadotropins, binds possibly to ER, PgR and AR, and inhibits steroid synthesis in the adrenals and ovaries [142–144]. In pre-menopausal women danazol causes amenorrhea [142]; in post-menopausal women the total E_2 concentration remains unchanged [145]. However, danazol and its metabolites ethisterone and 2-OH-methylethisterone increase the percentage of unbound E_2 and unbound testosterone by displacing these hormones from sex hormone binding globulin (SHBG) binding sites, by decreasing the SHBG plasma level or by reducing the binding capacity of SHBG [142].

METASTASIZED BREAST CANCER

Anti-estrogens

Tamoxifen. The efficacy of tamoxifen citrate as monotherapy of metastasized mamma carcinoma has been reviewed by Patterson [146] (Table 2). Remissions are observed in 34% of unselected patients, but especially elderly patients and soft tissue metastases appear to be sensitive to Tam [146].

Favorable prognostic factors are the presence and level of ER [147–149]. However, since ER assays might be falsely positive [150–153], whereas well determined ER might be non-functional, a relatively large number of ER+ tumors do not react to any hormonal treatment. As PgR synthesis is initiated by stimulation of ER, the presence and the concentration of this receptor are better indicators of hormone dependence [153–158].

ER+ and PgR+ tumors are usually smaller and better differentiated with fewer cells in the S phase and less DNA aneuploidy; the incidence of ER+ tumors is higher in elderly women [159–162]. The presence of hormone receptors in a tumor biopsy, however, does not exclude the existence of hormone-independent subpopulations [163].

Other favorable prognostic factors frequently encountered in the literature are related to a lesser tumor burden, e.g. longer disease-free period, fewer metatsases and better performance status.

Tam is administered orally in a dosage of 10 mg 2–4×/d until progression or relapse. A schedule using Tam intermittently induced secondary remissions [164]. Boost doses are likely to be effective in accelerating response and reducing tumor flare [165, 166]. Tumor flare is observed, generally, 2–21 days after starting most hormonal therapies in the following percentages of patients [167]:

a. LHRH agonists 3–10%;
b. androgens 3%;
c. anti-estrogens 2.2%;
d. estrogens 1%;
e. progestins 1%;
f. aminoglutethimide not reported thus far.

A possible explanation for this phenomenon during Tam treatment is that Tam would act as an agonist at low plasma concentrations but as an antagonist as the plasma level gradually increases during chronic administration [168, 169].

Although several studies have indicated that higher doses are unable to induce any remissions

Table 2. Tamoxifen as monotherapy of metastasized mamma carcinoma (data derived from Patterson et al. [146])

Overall response	Number of patients	% CR	% PR	% (CR+PR)	% SD
	2889	7	27	34	19
Response according to estrogen receptor status					
ER+	49	% (CR+PR)	57	% (CR+PR+SD)	
ER−	9		27		
Response according to dominant metastase					
Soft tissue	56	% (CR+PR)			
Bone	33				
Viscera	35		(lung > liver)		
Response according to dose					
20 mg/d	30	% (CR+PR)			
30 mg/d	36				
40 mg/d	40				
30 mg/m^2.d	43				
80 mg/d	38				
Response according to age					
Pre-menopause	28	% (CR+PR)			
≤50 years	36				
51–60 years	40				
61–70 years	43				
>70 years	38				
Response according to pretreatment					
No prior treatment	43	% (CR+PR)			
Chemotherapy	41				
Endocrine and chemotherapy	35				
Prior response to endocrine therapy	59				
Prior failure of endocrine therapy	21				
Tolerance of therapy					
Well tolerated	96.4%				
Dose reduction or temporary withdrawal	0.9				
Drug withdrawal (mainly due to nausea and vomiting)	2.7				

CR = complete remission, PR = partial remission, SD = stabilized disease.

after progression on 20–30 mg Tam/d [170–173], the optimum dosage remains to be settled. In view of Patterson's review (Table 2) and the apparent lack of serious side-effects (Table 3), a conservative approach using 40 mg/d should be recommended.

As Tam may cause severe nausea and vomiting, a rectal application form has been developed. However, this formulation seems to have reduced bioavailability [195].

Response and loss of response on Tam do not correlate to Tam-induced hormonal changes [163]. Nevertheless, relapse on hormonal therapy is often accompanied by a loss of ER and PgR [150–153]. This could be a selective cloning of resistant, i.e. hormone-independent, subpopulations or could be drug-induced, e.g. by adaption of host homeostases to the changed endocrine environment. After a prior hormonal therapy the tumor often retains some of its hormone dependence, since second-line Tam is able to induce remissions in a majority of patients (Table 2). Therefore, it seems likely that pleiotropic drug resistance does not contribute to tumor relapse to a large extent.

Trioxyphene. Two small, non-randomized studies have indicated that trioxyphene mesylate is as effective as Tam with regard to remission rate, stabilization rate and response duration [54, 55]. A favorable prognosis is observed in the same subsets of patients having a favorable prognosis to Tam [54]. Only two of 17 patients who had responded to Tam had a remission on trioxyphene [54]. Side-effects either parallel those of Tam (10, 20, 40 mg/d trioxyphene) [54] or are more severe and more frequently encountered (1–24 mg/m^2.d or 80–200 mg/m^2.d trioxyphene) [55]. Side-effects were seen to be independent of the administered dose and include nausea (in 31%), leucopenia (in 41%), thrombocytopenia (not observed at higher doses!), anemia, edema, vaginal bleedings, hot flushes, tumor flare and hypercalcemia [55].

Progestins: medroxyprogesterone, megestrol, norethisterone

Progestins are mainly used in post-menopausal patients, leading to remissions in ±30% of the treated patients (Table 4). The median duration of the remissions equals that of other hormonal

Table 3. Side-effects of tamoxifen, megestrol, medroxyprogesterone and aminoglutethimide/hydrocortisone

Tam [2,174,175]	vs. placebo [176]	Mpa/Ma [177–183]	Ag/Hc [60,61,73,184–193]
Nausea		Subjective improvement	Subjective improvement
Vomiting		pain relief	pain relief
Hot flushes		less edema	Somnolence
Hematological	n.s.	raised appetite	Dizziness/vertigo
Genito-urinary	n.s.	I.m. local irritation	Ataxia
Infections	n.s.	sterile abscesses	Depression
Gastro-intestinal	n.s.	Weight increase (Ma no	Nausea
Pain	n.s.	fluid retention)	Vomiting
Neurological*	n.s.	Thombosis/hypercoagulation	Erythema
Hypercalcemia†	?	Hypertension	Herpes zoster
Disease flare‡	?	Muscle spasms/tremors	Gastric ulcer activation
Endometrial adenocarcinoma		Nervousness	Gastritis
(seldom)		Fatigue	Depressed appetite
Menstrual cycle		Diabetes	Hypothyroidy
irregular (28%)		Edema	Orthostatic hypotension
amenorrhea (19%)		Vaginal bleedings	Hyponatremia/hyperkalemia
menorrhagia (3%)		Moon face	Myelosuppression
		Nausea	septicemia (case report)
		Transpiration	Liver necrosis (seldom)
		Hot flushes	Myxedema (seldom)
		(Hypercalcemia)	Hot flushes
			Headache
			Weight increase

n.s. = non-significant.

*In one patient depression, lability, cerebellum dysfunction and syncope are attributed to Tam at normal plasma levels of Tam, *N*-desmethyl-Tam and 4-OH-Tam [194].

†Also spontaneously in bone metastases [2].

‡Mainly based on increased pain of bone metastases and other subjective parameters.

therapies and is approximately 1 year [77, 198]. Patients who are more than 5 years after menopause are more sensitive to Ma and Mpa than younger patients [77, 197, 198, 200, 201], probably reflecting the increase in the incidence of hormone-dependent mamma carcinoma with age. With Tam comparable results have also been achieved in patients younger than 60 years of age [178] and—though the efficacy in this subset of patients is generally questioned—even in pre-menopausal patients [77].

Generally, it is felt that prognosis is favorable when ER and/or PgR are present [77–80, 178], but in various studies this link could not be established [56, 197, 201]. Determination of AR might also be of use [56]. Only one or two metastases and, unlike Tam, a disease-free period shorter than 1 year, i.e. fast growing tumors, might also be indicators of a favorable prognosis [178]. Bone and soft tissue metastases appear to be more sensitive than visceral metastases [77, 178, 201], although in one study good results were obtained with visceral and not with bone metastases [197].

After relapse on a prior hormonal treatment progestins induce remissions in 31–54% of patients, lasting approximately a half year [178, 201, 202], whereas tumors resistant to first line endocrine therapy have an objective response rate to secondary Mpa or Ma of ±25% [178, 202–204]. The objective response rate after cytotoxic pretreatment is ±30% [171, 202].

Side-effects of Mpa and Ma are more severe than those of Tam, although seldom requiring drug withdrawal (Table 3). In contradiction, a significant subjective improvement, especially pain relief, is more frequently observed than during Tam treatment [177–183].

The response rate to norethisterone is comparable with those of Mpa and Ma [205–208], but the masculinizing side-effects, due to androgenic properties, limit its use.

The optimal route of application and dosage of Mpa remain to be established. Kauppilla [196] has reviewed 13 studies on this topic. He showed that when doses of less than 1 g/d are considered oral administration yields an objective response about 55% of that of intramuscular administration. Furthermore, dosages over 1 g/d are significantly more effective than lower dosage schedules, whereas at dosages over 1 g/d i.m. and p.o. application appear to be equally effective [196]. The results of several randomized trials (Table 5), however, contrast Kauppila's findings.

An increase in response rate with increasing doses of Mpa corresponds with the dose-dependent effect

Table 4. Progestins as monotherapy of metastasized mamma carcinoma

	Number of studies	Number of patients	% (CR + PR)	% SD	Dose requirements	Reference(s)
Mpa	15	1138	29	27	—	[196]
	10	696	41	?	≥500 mg/d.30d	[177]
Ma	7	583	30	33	—	[77,80, 197–201]

of Mpa on several hormones. Oral administration of 900 mg/d reduces estrogen and androgen plasma levels to a greater extent than does 300 mg/d [59]. It takes, however, 1500 mg/d to completely suppress the pituitary–adrenal axis [57].

Oral application results in interindividually highly variable steady state levels after 2 weeks of therapy, due to differences in intestinal absorption, in entero-hepatic recycling and in distribution volume [214, 215]. Intramuscular application results after 4 weeks of therapy in comparable but interindividually more uniform steady state levels, which are maintained by doses of 500–1000 mg/week [57, 177, 216].

Disadvantages of i.m. administration are the requirement of an induction dose, the possible interference with a second-line therapy upon progression, and local irritation at the injection site in 16–60% of the treated patients [178].

A compromise has been proposed to administer Mpa in the induction phase i.m. as well as p.o. [177, 199]. Indeed this seems warranted provided a meticulous plasma level guidance and a dose of at least 1 g/d administered either p.o. or i.m. An induction schedule of 1 g/d p.o. and 500 mg/d i.m ensures steady state levels are obtained as soon as possible, could avoid interference with second line agents upon tumor progression and enables a simple maintenance of steady state levels in case of absorption problems with i.m. administration upon tumor regression. Furthermore, the high dose of MPA used in this schedule can be expected to yield the highest possible objective response rate.

The orally administered megestrol acetate accumulates in the body during treatment, but 3 days after cessation of therapy already 93% has been excreted [56]. The optimal dosage seems to be 180 mg/d, divided in 3 doses. This amount results in persistingly lowered hormone levels, whereas 90 mg/d results in incomplete suppression and 270 mg/d in too high insulin levels [56].

Aromatase inhibitors

Aminoglutethimide. The efficacy of aminoglutethimide (commonly 1000 mg/d) combined with hydrocortisone (40 mg/d) as first- or second-line therapy of post-menopausal breast cancer is comparable to that of Mpa, Ma or Tam (Table 6). However, Ag/Hc is not capable of reducing hormone levels and inducing remissions in pre-menopausal patients [232, 233].

The beneficial action in post-menopausal women is, in contrast to Tam, Mpa and Ma, independent of age [217]. It is possibly also independent of the site of the metastase(s), although as yet it has to be assumed that Ag/Hc has little effect on liver metastases (Table 6). Ag/Hc induces non-significantly more remissions of bone metastases than Tam [218, 220, 234]. This might be attributed to a more pronounced inhibition of prostaglandin synthetase [72]. In addition, Ag/Hc has a more pronounced subjective effect than Tam; especially with respect to pain relief, even in patients with progression of bone metastases [60, 218, 230].

Duration of response and overall survival of first line Ag/Hc is comparable to the effects of Tam and the progestins: the median duration of response is ±15 months [61, 217, 222]; the median overall survival as from the start of treatment is ±2 years

Table 5. Randomized trials with different dosages of medroxyprogesterone acetate

Therapy		% (CR + PR)		% SD		Reference
1	2	1	2	1	2	
I.m. 500 mg.30d	I.m. 1000 mg.30d	44	41	26	25	[209]
I.m. 500 mg.30d	I.m. 1500 mg.30d	44	43	26	28	[180]
I.m. 500 mg.30d	I.m. 1000 mg.30d	28	35	28	28	[210]
I.m. 500 mg/d	P.o. 600 mg/d	Equal results				[211]
P.o. 600 mg/d	P.o. 1200 mg/d	No additive response				[212]
I.m. 1000 mg/d	I.m. 500 mg twice/wk*	33	15			[213]

*Time to treatment failure and overall survival similar for the two dosage schedules.

for responding patients and less than 10 months for non-responding patients [61, 217, 219]. Ag/Hc has relatively severe side-effects, particularly on the central nervous system (Table 3). Five to nine per cent of patients require withdrawal of the drugs [60, 61, 73, 230]. These side-effects are often temporary, appearing in the 2–6th week of therapy [60, 61, 193], and seem to be dose-dependent [191]. Therefore, attention has recently been focused on dose optimalization.

Five hundred mg/d Ag seems to be equally as effective as 100 mg/d with respect to response rates of specific metastases, in time to response, response duration and overall survival, while it is better tolerated [234]. One hundred and twenty-five mg Ag twice daily with steroid substitution has a response rate similar to conventional dosage schedules. Nausea, vomiting and ataxia are less frequently observed but the incidence of erythema remains unchanged [235]. One hundred and twenty-five mg Ag twice daily without steroid substitution also induces remissions, but the response rate is increased when a higher dose of Ag is combined with cortisone acetate [236]. As little as 62.5–125 mg/d Ag lowers estrogen levels by inhibition of aromatase while causing a minimal suppression of the adrenal cortex [71]. In this study too a response was observed, but, remarkably, the incidence of side-effects appeared to equal that of higher dosage schedules.

Considering the ambiguity of the foregoing results, the harmful or even fatal effect [236] that the omission of glucocorticoids even at low doses of Ag may have and the anti-tumor potential of these steroids themselves [70], combination of Ag with hydrocortisone or cortisone can only be favored. However, the addition of high doses of glucocorticoids may be hazardous, due to an aromatase-stimulating effect [71]. In view of these considerations, the administration of 500 mg/d Ag together with 100 mg/d Hc during an induction period of 14 days seems justified [61, 184, 237].

Trilostane. In a pilot study, 960 mg/d trilostane—together with dexamethasone or hydrocortisone—induced six partial remissions in 23 patients [128].

After hormonal pretreatment only one out of 41 patients responded [238].

Side-effects reported thus far are nausea, vomiting, diarrhea, dyspepsia, hot flushes, dizziness, sleepiness, palpitations, and—to steroids responding—hypercalcemia and hypotension [128, 238].

Δ^1-*Testololactone.* Segaloff has reviewed its efficacy, suggesting a response rate of ±15% [129].

4-OH-*Androstenedione.* In a pilot study, intramuscularly administered 4-OH-androstenedione induced remissions in four of 11 patients; side-effects were local irritability and hot flushes [130].

LHRH agonists

Busereline. Busereline, administered in the first week of therapy either i.v. or s.c. and subsequently intranasally, induced remissions in eight out of nine and four out of 12 pre-menopausal patients [64, 239]. Disease stabilization was observed in four out of 12 patients [64]. Major side-effects were local irritability on the injection site, hot flushes and reduced libido [64].

Leuprolide. Leuprolide, administered daily subcutaneously, induced remissions in 12 out of 31 post-menopausal and in 11 out of 25 pre-menopausal patients [63, 240]. Disease stabilization was reported for three out of 31 and five out of 25 patients, respectively. The optimum dosage was

Table 6. Aminoglutethimide, combined with hydrocortisone, as monotherapy of metastasized mamma carcinoma

	Number of studies	Number of patients	% (CR + PR)	References
Overall response	15	873	37	[61,193,217–228, 279,281,368]
ER+ tumors	6	147	54	[61,191,220–222, 229]
Response according to pretreatment				
Prior response to endocrine therapy	7	157	48	[61,192,193,217, 230,281,368]
Prior failure of endocrine therapy	6	269	24	[61,193,217,230, 281,368]

Percentage CR + PR according to dominant metastases ([61], [217] and [218] respectively):
soft tissue 47, 31, 38;
bone 35, 23, 35;
lung 29, 16, 22;
liver 0, 22, 0.

1 mg/d s.c. [63]. Prognosis was favorable when metastases were located in soft tissue or bone; ER+ and ER− tumors, however, appeared to be equally responsive [63].

The median duration of remissions of pre-menopausal patients was 49 weeks; stabilization was restricted to 33 weeks [63]. Major side-effects were hot flushes, nausea, vomiting, headache, dizziness, taste sensations, increased bone pain, diarrhea and local irritability [63].

Danazol

Danazol induced remissions in two out of seven pre-menopausal and seven out of 37 post-menopausal patients that lasted 3–12 months [144]. Side-effects encountered were hot flushes, water and salt retention and temporary changes in liver function [144].

Other drugs

The efficacy of *androgens* [241–246] and *estrogens* [247–253] is comparable to Tam, but, due to their severe side-effects, they are nowadays only rarely used.

Glucocorticoids are mainly applied in combination with cytotoxic drugs. As single agents they are moderately effective with a response rate ranging from 14 to 33% [70, 254]. Their anti-tumor action possibly results from a decrease in steroid synthesis after a reflex reduction of ACTH release, from their interaction with GcR, from a direct cytolytic action on tumor cells and from G_1 phase arrest [255–257].

Bromocriptine stimulates central dopamine receptors and consequently the synthesis and release of the prolactin inhibiting factor (PIF). Because, besides a tumor differentiating action, a tumor proliferating action of prolactin cannot be excluded, bromocriptine has been used in combination with other endocrine drugs (see below).

Two *cytotoxic-bound hormones* are being used in breast cancer: *estramustine*, an ester of estradiol and *N*-phenylalanine mustard, and *prednimustine*, an ester of prednisolone and chlorambucil. They are supposed to accumulate in tumor cells through binding to hormone receptors, and may be cytotoxic by alkylating DNA. However, it has been shown that estramustine does not bind to ER (and AR) in prostate tissue, but is otherwise specifically bound; it also does not seem to damage DNA, but probably acts as a spindle poison [258]. It, furthermore, exhibits estrogen-like effects, particularly on the heart and blood vessels [259].

The esterification of chlorambucil to prednisolone (P) to form prednimustine can be expected to be beneficial. P is cytotoxic itself and chlorambucil may be accumulated in the tumor to a larger extent as a result of binding to GcR. Furthermore, P is known to sensitize the chromatin to alkylating agents, and since P alleviates hematologic side-effects of cytotoxics higher doses of these drugs can be applicated.

The ester appeared to be more effective than the combination of the two drugs (response 21 vs. 11%, respectively), and appeared to have less hematologic side-effects [260]. Daily administration was as effective as intermittent therapy with higher dosages, but caused less frequently severe gastro-intestinal side-effects [260].

Ablative procedures

Adrenalectomy. Bilateral adrenalectomy of post-menopausal breast cancer patients has no advantage over therapy with Ag/Hc with regard to lowering E_2 levels, objective response rate, response rate of ER+ tumors, response according to site of metastase(s), duration of response and survival [60].

On the contrary, adrenalectomy has a mortality rate of 2.7% [261], causes Addisonian crises under conditions of stress in 6.7% of patients and severe lassitude in 20% [262], necessitates life-long substitution therapy with gluco- and mineralocorticoids, and is—in contrast to Ag/Hc—contraindicated in patients with poor performance status, hypercalcemia etc. Therefore, it seems reasonable to conclude that adrenalectomy of breast cancer patients is obsolete [60].

Oophorectomia. Oophorectomia or ovary irradiation of pre-menopausal patients has an objective response rate of 53% in ER+ tumors [263]; the objective response rate in ER− tumors is generally believed to be less than 10%, although a response rate of 30% has been reported as well [263]. Therefore, it appears to be equally as effective as tamoxifen ([264], comparative study).

Conflicting results have been published on the use of ovariectomy as second line therapy. After failure of Tam, ovariectomy either fails too [264] or induces remissions in 20% of patients [265, 266]. The beneficial effect in the latter studies may reflect the aforementioned potentially adverse rise in E_2 level during Tam treatment, which could render Tam ineffective. After a primary response to Tam ovariectomy would be useless to counteract a relapse [267] or would yield a 50% response rate [266].

Hypophysectomy. Hypophysectomy also has been found to be an effective therapy [62], but no more effective than Tam [268].

Combination therapy

Hormonal or chemo-hormonal therapy with agents differing in their mode of action could potentially affect more tumor subpopulations with less development of drug-resistance. Combinations are mostly based on changes in the endocrine environ-

ment caused by one drug which may potentiate the effect of a second drug (e.g. Tam-induced PgR synthesis) or on adverse effects on the endocrine milieu which may be overcome by the addition of a second drug (e.g progestin-induced prolactin release). Addition of drugs could also be of benefit in counteracting hormonal changes observed immediately before relapse, such as the increase in androgen and estrogen levels observed with Ag/Hc therapy [269].

The choice of drugs in combination therapy, however, is hindered by the impossibility, thus far, of correlating the clinical response to certain changes in plasma levels of specific hormones [270]. Moreover, negative interactions are possible, e.g. Tam-induced G_1 phase arrest may render cell cycle-specific cytotoxics less active, metabolism may be unfavorably altered by e.g. Ag and side-effects such as myelo-suppression may overlap. The uncertainty about which of the drugs have actually contributed to a response may present a problem in defining a second line therapy in case of a relapse.

The most important question to be addressed is whether concomitant use of drugs has any advantage over sequential use of single agents. In this context it should be mentioned that a response during second-line—sequential—therapy imposes a problem as to whether this effect is due to the second-line agent itself or presents a delayed or even withdrawal response to the first agent. Furthermore, it remains to be established whether during therapy of a relapse therapy with the first line agent should be continued in order to keep the initially dominant clone under control or may be stopped because this clone itself has become resistant to the first line agent [271–273].

Tamoxifen and progestins. Tam causes *in vitro* and *in vivo* a temporary rise in PgR [87, 274]. Theoretically, this may potentiate the effect of progestins.

In vitro administration of Mpa concomitant with or 3 or 6 days after Tam inhibits tumor growth to a larger extent than Tam alone [274]. It remains to be investigated whether this may be extrapolated to the *in vivo* situation. In the first place, it is obvious that the anti-tumor actions of progestins only partially depend upon PgR. In the second place, evidence for Tam-induced PgR synthesis is limited to certain breast cancer cell lines, and, moreover, it appears to be only temporary. A possible synergism may, therefore, be confined to several weeks of therapy after which even negative interactions may occur. In this last instance the long $t_{\frac{1}{2}}$ of Tam and *N*-desmethyl-Tam and the depot effect of intramuscular application of Mpa will present serious difficulties. The Mpa-induced increase in $t_{\frac{1}{2}}$ of *N*-desmethyl-Tam [275] even worsens this picture.

On the other hand, combination of Tam and progestins beneficially affects the endocrine milieu: LH and FSH levels are lowered more than with progestins alone, and the level of SHBG increases while estrogen levels remain decreased [101].

The utility in clinical practice has to be, until now, seriously doubted. Combination therapy of Tam and Ma has been reported to be equally effective as sequential therapy, but the duration of response was shortened [276]. Furthermore, a decreased response rate was observed when sequential Tam + Mpa was compared to Tam alone (objective response 17 and 39%, respectively) [277]. However, in a non-randomized study of the same group sequential Tam and Mpa resulted in a response rate of 59% in 44 patients resistant to conventional therapy [278].

Tamoxifen and aminoglutethimide/hydrocortisone. The rationale for this combination is a decrease in E_2 level by Ag, next to a Tam-induced increase in SHBG level [279]. Addition of Tam to Ag/Hc, however, appears to have no beneficial effect with regard to remission rate, response duration and overall survival [218, 280–283].

Aminoglutethimide/hydrocortisone and danazol. Addition of danazol to Ag/Hc has resulted in lower response rates and shorter response durations, possibly because the danazol-induced lowering of the SHBG level counteracts the lowering of the total E_2 level induced by Ag [284, 285].

Tamoxifen, aminoglutethimide/hydrocortisone and danazol. With reference to the foregoing section, the addition of Tam to Ag/Hc + danazol can be assumed to be of benefit as Tam causes the SHBG level to rise [138]. The clinical studies reported thus far have corroborated this hypothesis. The objective response rate was increased when the combination was compared to Tam alone, and, moreover, the simultaneous administration was seen to be more effective than the sequential administration [286, 287]. In view of the results obtained with Tam + Ag/Hc and Ag/Hc + danazol, the use of Ag/Hc in the combination may be questioned.

Medroxyprogesterone and aminoglutethimide. MPA has sufficient corticoid-like effects to replace Hc in Ag treatment [60]. It, also, has a greater anti-tumor potential than the corticoids. Attention should be paid to the 50% lowering of Mpa plasma level by a Ag-induced acceleration of Mpa metabolism [288].

In two pilot studies response rates were 50% and—in heavily pretreated patients—17%, respectively [289, 290]. Of importance is a report indicating a low response (4%) to second-line Ag/Hc in patients previously treated with Mpa [291].

Tamoxifen and androgens. The objective response rate and response duration are increased when

fluoxymesterone is added to Tam [292, 293]. Second-line fluoxymesterone also is capable of inducing remissions in patients who had a prior response to Tam (42%) and in patients in whom Tam previously failed (33%) [62]. Whether combination therapy has an advantage over sequential therapy remains to be elucidated. Despite the high sensitivity of bone metastases to androgens and their explicit palliative effects, relatively severe side-effects as virilization and impaired liver function have to be taken into account.

In marked contrast to fluoxymesterone, the addition of *nandrolone* to Tam does not seem to be beneficial [294, 295]. It is unclear whether this difference is due to different modes of action of these androgens or is caused by differences in study design (e.g. more/less bone metastases; response to Tam alone just 15% in [292]).

Tamoxifen and prednisolone. In two studies a higher response rate was observed when prednisone or prednisolone was added to Tam [296, 297]. However, in these studies the response to Tam alone was remarkably low: 15 and 17%, respectively.

Tamoxifen and busereline. The combination is in contrast to busereline alone unable to cause complete castration. After the addition of Tam buserelin-induced E_2 peaks disappeared in two patients, but in three others progesterone secretion reoccurred with relapsing E_2 peaks [64]. Concomitant use of Tam and busereline has resulted in two remissions in five pre-menopausal patients [64]. After adding Tam to busereline two extra partial remissions and two extra disease stabilizations were observed among 11 pre-menopausal women [64]. Unfortunately, the addition of busereline to Tam was not investigated in this study. However, a beneficial effect can be anticipated, since LHRH agonists may override Tam-induced activation of the pituitary–gonadal axis, which adversely affects the response of pre-menopausal women to Tam.

Combinations with bromocriptine. Therapy with bromocriptine aims at the suppression of a possible tumor growth stimulating effect of prolactin. Combination of bromocriptine and Tam, however, seems of no use [298]. In a randomized study bromocriptine together with Mpa had a 55% remission rate among 69 patients, so an additive effect of these compounds cannot be ruled out [299].

Chemo-hormonal therapy. Combination chemotherapy is, particularly when the actually delivered doses are optimized [300], capable of inducing remissions in a majority of patients. Table 7 briefly reviews the major chemotherapy combinations used concomitantly with endocrine drugs. Since chemotherapy affects hormone-independent as well as hormone-dependent tumor subpopulations, chemo-hormonal combination therapy may be advantageous. The effects on hormone-dependent mamma carcinoma cannot only be attributed to the normal cytotoxic actions but also to chemotherapy-induced changes in the endocrine milieu.

Cytotoxic drugs are toxic to the ovaries. In pre-menopausal women a decrease in estrogen levels and a reflex rise in LH and FSH is observed. In post-menopausal women no significant changes can be detected (Table 1) [65–67].

The addition of prednisolone (see also 'Other drugs' above) causes androgen and corticoid levels to decrease [317]. Addition of Tam, however, causes a rise in estrogen levels in pre-menopausal women through which the rise in LH and FSH is overcome [65–67].

In vitro, Tam acts synergistically with the anti-metabolites methotrexate (M) and 5-fluorouracil (F) [318, 319]. Moreover, two abstracts published several years ago indicated synergism with cyclophosphamide (C) [320], but antagonism with L-phenylalanine-mustard [321]. Mpa, testosterone, nandrolone and prednisolone cause leucocytosis, and, therefore, counteract the leucopenia caused by cytoxicic agents. This enables the application of higher doses of these drugs [322, 323].

It has been demonstrated *in vivo* that the addition of combinations of cytotoxics to Tam increases the response rate from ±30% to ±60% in unselected patients [324–326]. Because combination chemotherapy often has a response rate of ±60% itself these studies do not demonstrate any beneficial effect of Tam in the chemo-hormonal therapies used.

Several authors have investigated the effect of adding endocrine-acting drugs to cytotoxic chemotherapy. Addition of Tam to adriamycin-containing combinations appears to result in similar or increased response rates (Table 8). The addition of progestins or androgens to adriamycin-containing combinations may also be of little value.

On the other hand, addition of endocrine therapeutics to ariamycin-lacking combinations, i.e. CMF-containing combinations, increases response rates significantly by about 25% [340–346]. This increase is observed especially in visceral metastases and in patients beyond the age of 60 years [346].

Addition of Tam to CFP, however, may be of no benefit [347]. The addition of fluoxymesterone [348], diethylstilbestrol [349] and Mpa [345] to CMF-containing combinations also resulted in significantly elevated response rates.

Elevation of response rates cannot be translated readily into a lengthening of response duration and/or survival. For instance, the response rate of CMF + Mpa and that of CMF + Tam have been reported to be similar but significantly higher than that of CMF alone. However, the response duration (±1

*Table 7. Randomized trials of combination chemotherapy in metastasized mamma carcinoma**

Therapy			Number of patients	% CR	% (CR + PR)	Remarks	Reference
1	2	3					
CAF	CMFP		155	17 5	53 53	DR 11.0 v 6.3 m OS 18.6 v 15.8 m	[301]
CAF	CMFVP		106 107	18 8	60 42		[302]
CAF	CMFVP		130		40	CAF minimal OS ↑	[303]
CAF	CMFVP		59 54	20 6	64 37	OS 14 v 20 m	[304]
CAF	CMF		38 40	18 7.5	82 62	DR 10 v 8 m OS 27 v 17 m	[305]
CAV	CMF		42 39	5 0	50 18	Too low doses CMF?	[306]
CAV	CMFP		26 26	16 19	56 65	DR 12 v 12 m OS 22 v 18 m	[307, 308]
CAFVP	CMFVP		76 72	13 11	58 57	OS 33 v 16 m	[309]
CAFM	AC		22 26	32 12	55 50		[310]
CAFM	CMFVb		54 57	2 14	52 44		[311]
AVM	CVF		30 31		30 3		[312]
AF	CAF	CAFM	105 103 105	10 14 11	42 43 49		[313]
AV	AVd		14 11		64 73		[314]
PAV	PAVDbd		92 94	6 2	27 23		[315]
CMFP	CMFVP		208 219		32 39	OS similar	[316]

Abbreviations: A = adriamycin, C = cyclophosphamide, Dbd = dibromodulcitol, F = 5-fluorouracil, M = methotrexate, P = prednisone/prednisolone, V = vincristine, Vb = vinblastine, Vd = vindesine, DR = duration of response, OS = overall survival.
*Comparing non-randomized studies [300]:
CMF 9 studies, % (CR + PR) 16–63%, OS 9–17 m;
CMFP 5 studies, % (CR + PR) 56–70%, OS 15–19 m;
CMFVP 12 studies, % (CR + PR) 27–88%, OS 12–21 m;
CAF 12 studies, % (CR + PR) 12–84%, OS 10–27 m.

year) and overall survival (±2 years) as compared to CMF appeared non-significantly shortened when CMF + Mpa was used and non-significantly lengthened when CMF + Tam was applied [345]. In this study second line therapy with either AV + Tam or AV + Mpa had a response rate of ±20% whereby a significantly prolonged survival was observed for those patients responding to both first- and second-line therapy.

Other reports describe a prolonged [329, 335, 344, 346, 348, 350], unchanged [330, 333, 336, 345, 348, 349] or shortened [344, 347] response duration and/or survival. This variance may in part be explained by differences in patient and tumor characteristics (age, ER+/−, location and number of metastases etc.) and differences in review criteria and methods. Nevertheless, the efficacy of chemo-hormonal therapy in terms of duration of response and survival must be questioned. This is even more so because the results achieved with concomitant chemo-hormonal therapy do not seem to be any better than those achieved with sequential therapy (chemo-hormonal, hormonal-chemo or alternating therapy)[326, 351–354].

In some studies use has been made of cell cycle-specific properties of endocrine therapeutics. Recruitment of tumor cells into the S phase by estrogens—sometimes preceded by Tam-induced synchronization in the G_1 phase—would render cell cycle-dependent cytotoxic agents more effective.

In a randomized study comparing recruitment by DES followed by C, F and epidoxorubicin with C, F and epidoxorubicin alone, some benefit was observed in patients with soft tissue metastasis, with ER− tumors and in whom prior adjuvant therapy failed [355].

In another study, the response on recruitment by ethinylestradiol followed by daily Ag administration and cycles of CAF was 74% [356].

Synchronization by Tam, recruitment by conjugated estrogens (Premarin), subsequently M and finally F resulted in 46% complete and 23% partial remissions among 32 patients with predominantly non-visceral metastases and good performance status [357]. In another study, however, the response rate of heavily pretreated patients to the same schedule was 10% [358]. Tam, Premarin and subsequently CAFM did not have a higher response rate than CAFM alone, but did have a prolonged time to treatment failure and overall survival in patients with a partial remission [359]. This result must not be overestimated since the advantage may result from the non-specific addition of both hormonal agents to the chemotherapy schedule.

Comparative studies and conclusions

Comparative studies reported thus far have failed to demonstrate major differences in effects between Tam, Mpa, Ma and Ag/Hc as monotherapy of ER+

Table 8. Influence on objective response of adding endocrine-acting drugs to adriamycin-containing combination chemotherapy

Hormonal agent	Combination chemotherapy	Influence on objective response	Reference
Tam	CAFV	Increased from 42 to 63%	[324]
Tam	CAFV	Increased from 64 to 80%	[327]
Tam	CAFMV	Increased from 40 to 75%	[328]
Tam	DbdA	Increased from 36 to 55%	[329]
Tam	CA	Unchanged	[330]
Tam	CAFM	Unchanged	[331]
Tam	CAV	Unchanged	[332]
Tam	CAF	Unchanged	[333]
Mpa	CA	Increased from 28 to 44%	[334]
Mpa	CAF	Increased from 55 to 75%	[335]
Mpa	CAF	Increased from 41 to 62%	[336]
Mpa	CAV	Unchanged	[337]
Norethisterone	AV-CMF	Unchanged	[338]
Calusterone	CA	Increased from 53 to 65%	[339]

Abbreviations are as listed under Table 7.

and/or PgR+ post-menopausal advanced breast cancer (Table 9).

It it still too early to draw conclusions with respect to the efficacy of hormonal combination therapy. Apart from the Tam, Ag/Hc and danazol combination results have not been encouraging. Moreover, a higher response rate during combination therapy does not mean that survival will be prolonged too. The same holds for chemo-hormonal therapy. Nevertheless, the significant increase in response rate when combining CMF and Tam is an achievement on its own. In view of the pharmacological and clinical data available scepticism should be the key word when recruitment therapy is considered.

Awaiting further reports, Tam may be preferred in post-menopausal patients, because of its apparent lack of serious and frequent side-effects. Several studies have indicated a—albeit non-significantly—higher response rate of bone metastases to Ag/Hc [218, 220, 280]. Therefore, it seems appropriate to start treatment of bone metastases with Ag/Hc. Only few patients suffering from liver metastases seem to respond to endocrine treatment. In order to increase response rates, more aggressive cytotoxic chemotherapy—possibly with concomitant administration of hormonal agents—seems warranted. In this context it should be considered that a beneficial effect of vincristine in the CMFVP combination is doubtful [316, 369, 370]. Attention should be focused on the administration of cytotoxic agents in optimal doses, i.e. in doses as high as possible [300]. For pre-menopausal disseminated breast cancer Tam, also, should be considered as a first-line agent. If ethically justified, the efficacy of progestins in these patients should be updated.

The exact place of the newly developed LHRH agonists still has to be determined, but their probable clinical effect in post- and pre-menopausal women is promising.

With regard to the various equipotent pharmaceutical alternatives available, adrenalectomy must be considered as being obsolete. Oophorectomia may be considered as second- or third-line therapy.

EARLY STAGE MAMMA CARCINOMA

Drugs are used as an adjunct to surgery and radiotherapy in breast cancer stages I (confined to breast tissue), II (disseminated to ipsilateral lymph nodes) and III (locally advanced breast cancer). Endocrine therapy commonly consists of Tam, administered in a dose of 20–40 mg/d for one or two years, with or without concomitant cycles of CMF ± P.

Like adjuvant radiotherapy [371–375] and chemotherapy [376–387], adjuvant endocrine therapy improves relapse-free survival but, until now, no certainty exists about a prolongation of overall survival (Table 10). On the topic of prognostic factors ambivalent results have been reported (Table 10), especially when menopausal status and ER status are considered. In addition, it remains to be elucidated whether Tam affects loco-regional [399, 411], distant [176, 391], loco-regional and distant [388] or just local and distant [400] relapse. On the other hand, presence of PgR or lymph node metastases and size of the primary tumor >3 cm seem to predict a favorable outcome of adjuvant endocrine therapy.

These discrepancies partly result from differences in study design, e.g. differences in study groups, in diagnostic criteria, in type of operation performed and whether or not radiotherapy was added. Because breast cancer generally does not spread via the loco-regional lymph nodes [373, 378] and since a possibly loco-regional relapse often can be handled

Table 9. Randomized trials comparing tamoxifen, megestrol, medroxyprogesterone and aminoglutethimide/hydrocortisone

Therapy		No. of patients		% (CR + PR)		Remarks	Reference
1	2	1	2	1	2		
Tam	Ma	64	61	33	28	2nd line: 15 v 7% Adjusted OS and TTP of Tam significantly better	[360]
Tam	Ma	39	23	18	35	2nd line: 13 v 18% OS: T → Ma 98 wk, MA → Tam 106 wk Tam better in ER+	[361]
Tam	Ma	48	46	35	30		[362]
Tam	Ma	80	136	22	23	2nd line: 9 v 17% SD 1st and 2nd line ± 50% TTF for OR: 13 v 12 and 3 v 9 m TTF for SD: 9 v 7 and 6 v 7 m	[363]
Tam	Ma		55	26	14	2nd line: 11 v 12.5% Para-menop. OS: 13.2 v 17.3 m Both not effective after prior failure	[199]
Tam	Mpa	43	42	30	26	2nd line: 19 v 17% Mpa failure then Tam no effect	[364]
Tam	Mpa	26	28	19	29		[365]
Tam	Mpa	33	30	52	70	2nd line (resistant to 1st line): 15 v 59%	[366]
Tam	Mpa	26	27	27	37		[367]
Mepitiostane	Mpa	40	37	35	40	Mepitiostane (anti-estrogen androgen) effect ER+ = ER− Soft 50 v 60%, bone 15 v 32%, viscera 29 v 13% Mpa effect ER+ higher than ER−	[322]
Tam	Ag/Hc	39	24	41	42		[279]
Tam	Ag/Hc	32	34	28	47	SD: 28 v 12% Mean DR 15 v 18 m 2nd line: 1st line failure 18 v 7%, 1st line response 31 v 44%	[281]
Tam	Ag/Hc	24	21	42	48	Median DR 13 v 10 m ER+ = 67 v 44% Soft 67 v 30; bone 22 v 54	[220]
Tam	Ag/Hc	60	57	30	30	Median DR 20 v 16 m Soft 32 v 38%, bone obj. 17 v 35%, bone subj. 17 v 26%, lung 25 v 22% Discontinuation 0 v 7% 2nd line: 1st line failure 6 v 21%, 1st line response 0 v 50%	[218,368]

Abbreviations: DR = duration of response, OS = overall survival, SD = stabilized disease, TTF = time to treatment failure, TTP = time to progression.

adequately by local means [412, 413], one is however tempted to assume that an unchanged overall survival after pharmacotherapy particularly reflects patients with loco-regional relapse whereas a prolonged overall survival may particularly reflect patients with distant relapse or with micrometastases at the time therapy was initiated.

One may, however, not lose sight of factors like drug resistance development which may render every drug in whatever situation ineffective. Moreover, the duration of therapy with Tam may be of particular interest. Several studies have shown that Tam initially reduces the rate of relapse but that after 1 year [400] or 3 years [392, 407] the relapse rate is strongly increased. Preliminary results of a study comparing long-term (longer than 5 years) and short-term treatment with Tam seem to support this hypothesis [410].

Furthermore, the timing of therapy may be a decisive factor for prolonging overall survival. Theoretically, preoperative pharmacotherapy has the advantages of:

a. counteracting (micro)metastases in the earliest possible stage;
b. decreasing primary tumors in size, due to which less frequent—and less extensive—

Table 10. *Endocrine therapy as adjunct to surgery and/or radiotherapy in stage I, II and III mamma carcinoma*

Therapy		Patient characteristics	OS/RFS	Prognostic factors	Reference
Endocrine therapy v. control					
Tam		Pre ln+ and Post ln±	RFS ↑ OS ↑	Not menopausal, Ln and ER status	[388]
Tam			RFS ↑	ER−	[389]
Tam		Post III	RFS ↑	50–59 yr, ln > 3 ER+ ⩾ 100 fmol/mg protein	[390,398]
Tam		Post I, II, III	RFS ↑ OS=		[391,174]
Tam		Post	RFS ↑ OS=	>3 cm and ln+	[392]
Tam			RFS ↑	ER+	[393]
Tam		Pre and post	RFS ↑ OS ↑ RFS ↑ OS=	Pre, ln 1–3 Post, ln 1–3	[394]
Tam		Elderly II	RFS ↑ OS ↑	OS (ns) RFS(s) ln > 3, ER+, PgR+, ⩽3 cm, >3 cm	[176]
Tam		Post II	RFS ↑	ln +, PgR+	[395,396]
Tam		Pre and post	RFS ↑	Post	[397]
P + Tam		Post > 65 yr, II	RFS ↑	ER+, ln 1–3	[399]
P + Tam and CMFPTam		Post ⩽ 65 yr, II	RFS ↑	ER+, ln 1–3, ln > 3 CMFPTam beneficial in ER−	[399]
CMFPTam		Post II	RFS ↑		[400]
Ag/Hc		Post	RFS ↑		[401]
Endocrine therapy v. other modalities					
Tam	Ovary irradiation	Pre I, II, III	RFS ↑ OS ↑	OS (ns) 75 v 65%	[391,174]
CMFTam	CMF	Pre and post II	RFS ↑ OS ↑	RFS (s) ER+ and ln ⩾ 4; all post; all ln ⩾ 4; ER+ and > 3cm RFS (ns) ER+ post; all ER+ OS ER + and > 3 cm	
CMFP	CMF	Pre and peri	RFS= OS=	Amenorrhea induction	[406]
PamFTam	PamF	Pre and post II	RFS ↑	post ER+ and PgR+ pre ER− and PgR−	[407, 408]
CMFPTam	CMFP CMF	Pre and post II	RFS=/↑	most recently Tam beneficial	[400, 409]
Tam long	Tam short or not	Post II	RFS ↑	72 v 59 v 33% Relatively much A used in Tam-long group	[410]
Tam + RT	RT	Post II and III	RFS ↑	< 60 yr, ln > 3 (s) ER not important	[398]
Tam + RT	Tam	Post III	RFS ↑	ER ⩾ 100 fmol/mg protein	[390]
Tam	RT	Post II	RFS= OS=		[396]

Abbreviations: pre = pre-menopausal, post = post-menopausal, peri = peri-menopausal, para = para-menopausal, ln = lymph nodes, RT = radiotherapy, ns = non-significant, s = significant; other abbreviations as described earlier.

operations have to be performed;

c. reducing the chance of resistant clones;

d. preventing possible adverse effects of local therapy, e.g. it may bypass a reduced activity of drugs due to a local therapy-induced reduced vascularization.

In practice, indeed, preoperative chemotherapy—usually continued after surgery and/or radiotherapy [414–422]—and perioperative chemotherapy [423] have prolonged relapse-free and overall survival and have reduced the necessity to perform surgery in 25% of patients [422].

With regard to endocrine therapy very little attention has been paid thus far to timing, but, in view of the successes achieved with chemotherapy and in view of the recently published results of a study in which Tam has been used as primary therapy [424], preoperative and subsequently postoperatively continued therapy with a drug with as few side-effects as Tam seems of the utmost importance

for patients with hormone-dependent tumors [425], and especially for post-menopausal patients who in case of development of resistance have several equivalent alternatives to rely upon.

It is obvious that a reduced rate of relapse is a goal in itself. In this respect, combination of radiotherapy and Tam may be considered, since the combination significantly prolongs the relapse-free survival when compared to the separate use of these modalities [390, 398]. This is in agreement with results achieved with combined chemo- and radiotherapy [418, 422, 426–441]. Moreover, these reports suggest that concomitant chemo- and radiotherapy or chemotherapy directly following radiotherapy is acceptable with regard to side-effects, especially when X-ray therapy is restricted to the breast. In view of the potential loss of effects after a delayed start of pharmacotherapy, the concomitant use of Tam and radiation may be fruitful.

The concomitant use of Tam and chemotherapy, also, significantly prolongs relapse-free survival as compared to chemotherapy alone (Table 10). A beneficial effect of prednisone in these combinations and used for this purpose must be questioned [400, 406, 409]. The same holds for vincristine [316, 369, 370].

MALE MAMMA CARCINOMA

Of all cases of breast cancer less than 1% concerns males. A genetic predisposition [442] and, possibly related, high estrogen levels [443] seem to play a role in the etiology. The disease may also result from repeated radiotherapy [444]. Male breast cancer resembles female breast cancer, although the average age of 64 years for men is higher than that for women and in spite of the fact that a large majority of male breast tumors is ER+ [445, 446].

Therapy of men is essentially the same as that of women. Primary therapy, however, is not so much surgery as radiotherapy [447]. Besides, endocrine therapeutics and ablative surgery are being used.

The ablative procedure pre-eminently successful in male breast cancer is orchiectomy with an objective response rate of 38–67% [448–451]. In males too, adrenalectomy can be replaced by Ag/Hc [452]. Tam also is effective with an objective response rate of 48% in 37 men [449, 451] both before and after orchiectomy [448, 453].

Progestins are more successful than Tam. The anti-androgenic progestin cyproterone acetate decreases testosterone and estrogen levels significantly—though not correlating to the clinical response—as well as those of progesterone, LH and FSH [451]. The overall response, including patients with stabilized disease, approximates 100% with a remission duration of ±8 months [451, 454]. Major side-effects are impotence, weight increase, gynecomastia and fatigue [447]. Megestrol and medroxyprogesterone are also effective with an objective response rate of about 80% [451, 455, 456].

For the sake of completeness, it should be mentioned that corticoids sometimes have induced remissions, that leuprolide possibly induces remissions, and that during therapy with estrogens both remissions and exacerbations have been observed [451, 457].

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