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CLINICAL BREAST CANCER, NEW DEVELOPMENTS IN SELECTION AND ENDOCRINE TREATMENT OF PATIENTS

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Summary—Breast cancer is the most common malignant tumor among women, comprising an estimated 24% of all cancer cases and 18% of all cancer deaths. At least half of the patients with primary breast cancer will ultimately die by metastatic disease. The tumor characteristics, the natural course of the disease and the response to therapy vary strongly. A number of recently detected cell biological parameters such as oncogenes/suppressor genes, growth factors and secretory proteins are more or less important prognostic factors, because they influence the characteristics and behavior of a tumor with respect to metastatic pattern, extent of cellular differentiation, growth rate and response to treatment. However, there is no clear consensus how best to identify patients at high or low risk. In our experience c-*myc* amplification and pS2 protein are strong prognosticators for relapse rate, while in advanced disease (apart from a negative estrogen/progesterone receptor/pS2 status) amplification of HER2/*neu* is a good prognosticator for failure to endocrine therapy. In the diagnosis of breast cancer, *in vivo* imaging of tumors by labeled hormones or other factors also forms a new development which might have implications for treatment too. With respect to treatment both endocrine and chemotherapy can cure a minority of patients with micrometastases, but in patients with advanced disease only a prolongation of (progression-free) survival can be reached. Response rates decrease with increasing tumor load. In the past decade a number of interesting new endocrine agents has been developed such as new (pure) (anti)steroidal agents, vitamins, aromatase inhibitors, analogs of peptide hormones, prolactin inhibitors and growth factor antagonists. However, less is known on the (potential) interaction between hormones, chemotherapeutic agents, retinoids, cytokins, growth factor antagonists and irradiation. Rapid detection of new powerful combination therapies are needed to improve treatment results during the nineties.

INTRODUCTION

Breast cancer is the most common malignant tumor among women, with an estimated 135,000 new cases and 58,000 recorded deaths per year in the European Community [1]. It comprises an estimated 24% of all cancer cases and 18% of all cancer deaths. Ultimately about 1 out of 12 women will get breast cancer during her life, in the U.S. presently even 1 out of 9. At least half of these patients will sooner or later die as a consequence of metastatic disease. Even in node-negative primary breast cancer patients, one third of them will have a (distant) recurrence within 10 years, since occult disseminated disease had been present at the time of the diagnosis. Although by multiple bone marrow aspirations tumor cells can be detected in 20–25% of the cases, it remains difficult to detect the patients with occult (micro)metastases and to predict prognosis. In addition, the natural course of disease and the response of breast cancer to therapy varies strongly. Adjuvant systemic therapy with chemotherapeutic drugs or antihormones has been shown to result in a 25% reduction in annual odds of death, meaning an absolute decrease in deaths of 4 and 10% in node-negative and node-positive patients, respectively [2–4]. However, it must be concluded that the majority of the patients with primary breast cancer will be overtreated in case of adjuvant therapy. Both efficacy and cost effectiveness of adjuvant systemic therapy are presently important subjects of debate [5, 6]. Identification of high-risk and low-risk patients is therefore a major issue. For patients with breast cancer a large series of classical and modern prognostic factors have been reported (see reviews [7–10]). These factors concern patient characteristics,

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parameters determined in blood and tumor characteristics. Most of these factors have been evaluated with respect to relapse free survival (RFS) and overall survival but very few with respect to response to hormonal or chemotherapy in metastatic disease. However, also for patients with recurrent disease (macrometastases) prognostic factors and predictors for response to treatment are clinically important for reaching decisions concerning type of therapy. In general, the presence of both estrogen receptor (ER) and progesterone receptor(PgR) in the primary breast tumor indicates a relatively good prognosis but the differences between ER-positive and ER-negative cancer patients with respect to 5-year RFS is relatively small (8–10%). ER and PgR status have been shown to define those patients with advanced breast cancer, who are more likely to respond to hormonal therapy [11]. Nonetheless half of the receptor-positive patients fail to benefit from hormonal therapy whereas few receptor-negative patients do, indicating that ER and PgR status is an imperfect predictor of response and prognosis. Recently a great number of modern cell biological parameters such as oncogenes/suppressor genes, growth factors and secretory proteins, appear to strongly influence the behavior of a tumor with respect to metastatic pattern, extent of cellular differentiation, growth rate and the development of therapy resistance [8]. Assessment of the value of these biological parameters as prognosticator, predictor of response to therapy or as possible point of action for new treatment modalities, is important. Therefore characterization of individual tumors is increasingly relevant. In this context we studied the significance of several oncogenes, growth factors, receptors for hormones and growth factors, and of some estrogen regulated proteins. In addition, we and others tested new treatment modalities. In this paper we will give a short overview of these new developments, focusing on our own results.

PROGNOSTIC FACTORS AND PREDICTORS OF RESPONSE TO THERAPY

Oncogenes

In breast cancer especially HER2/*neu*, c-*myc* and int-2 appeared to be important oncogenes with respect to incidence and prognostic value [12–21]. In DNA isolated from homogenates of 1052 human breast cancer samples we determined the incidence of oncogene amplification by Southern analysis [18]. In addition, we studied the prognostic value with respect to RFS and overall survival [20] as well as the predictive value for response to endocrine and chemotherapy [19] in subgroups of patients.

In our series of 975 evaluable tumors HER2/*neu* amplification was observed in 19% which is in agreement with data reported in the literature [14–16, 21] both for HER2/*neu* amplification and (over)expression (20.6 vs 19.2%), which parameters are strongly correlated with each other (Table 1). A strong negative relationship with ER and PgR was observed [17]. Generally there is no consensus on the prognostic value of HER2/*neu* in primary breast cancer [14–16, 20]. In our experience HER2/*neu* amplification was not associated with RFS, but weakly with shorter overall survival only in univariate analysis [20]. HER2/*neu* amplification appeared to be of much greater value in patients with metastatic disease i.e. HER2/*neu*-positive tumors showed a poor response to endocrine therapy but a good response to subsequent chemotherapy [19].

In 17 papers c-*myc* amplification has been reported to occur in 1–41% of primary breast cancers [13, 18]. These publications reported totally on 1518 tumors, of which 324 (21%) were amplified. In our series of nearly 1000 tumors c-*myc* amplification was observed in 17% and significantly related to PgR-negative tumors, but not to ER-negative tumors [18]. A strong negative association between c-*myc* and HER2/*neu* amplification was found. Overall c-*myc* amplification appeared to be a much more powerful prognosticator than HER2/*neu* amplification with respect to RFS and overall survival especially in ER-positive patients [20]. Regarding metastatic disease, c-*myc* amplified tumors showed a worse response to chemotherapy but not to endocrine therapy when compared to non-amplified tumors [19].

Oncogene amplification of int-2/bcl-1 was observed in 14% of our series of patients and appeared to be related to ER-positive tumors [18].

Receptors for hormones and growth factors

Previously we reported extensively on the prognostic value of ER, PgR [8, 10, 22, 23] the somatostatin-receptor (SS-R) [24, 25], IGF-1-R [24, 25] and EGF-R [8, 24–26]. Patients with ER+, PgR+ or SS-R+ tumors showed a better prognosis than patients having tumors

Table 1. Amplification and overexpression of HER-2/*neu* in human breast cancer

Author	Year	Patients All	Patients Overexpression or amplification *n* (%)	Status	Assay
Slamon *et al*	1987	189	53 (28%)		S
	1987	86[a]	34 (40%)	N+	S
Van de Vijver *et al.*	1987	95	15 (16%)		S
Zhou *et al.*	1987	86	15 (17%)		S
Varley *et al*	1987	41	7 (17%)		S
Ventner *et al*	1987	36	12 (33%)		S
Cline *et al.*	1987	53	8 (15%)		H
Varley *et al.*	1987	57	7 (19%)		H
Tal *et al*	1988	21	2 (10%)		S
Berger *et al*	1988	51	13 (25%)		S
Van de Vijver *et al.*	1988	189	27 (14%)		H
Barnes *et al.*	1988	195	17 (9%)		H
Gusterson *et al*	1988	95	12 (13%)		H
Ali *et al.*	1988	122	12 (10%)		S
Slamon *et al.*	1989	526	146 (28%)		H
Tandon *et al.*	1989	350	59 (17%)	N+	W
		378	59 (16%)	N−	W
Tavassoli *et al.*	1989	52	15 (29%)		S
Ro *et al.*	1989	66	13 (20%)	N−	S
Tsuda *et al.*	1989	176	28 (16%)		S
Zhou *et al.*	1989	157	17 (11%)		S
Zeilinger *et al*	1989	291	52 (18%)		S
Wright *et al.*	1989	185	31 (17%)		H
Adnane *et al.*	1989	219	45 (21%)		S
Thor *et al*	1989	290	39 (13%)		H
Walker *et al*	1989	85	14 (16%)		H
Roux-Dosseto *et al*	1989	143	40 (28%)		S
Lacroix *et al*	1989	57[a]	11 (19%)		S
		53	14 (26%)		W
Seshadri *et al.*	1989	73	17 (23%)		S
Makar *et al.*	1990	44	19 (43%)		H
Querzoli *et al*	1990	50	32 (64%)		H
Meyers *et al*	1990	99	9 (9%)		S
Paik *et al*	1990	292	62 (21%)		H
Iglehart *et al*	1990	130	30 (30%)		S
	1990	111[a]	29 (26%)		W/H
Borg *et al.*	1990	300	51 (17%)	N+	S
	1990	300[a]	57 (19%)	N+	W
Winstanley *et al.*	1990	463	103 (22%)		H
Lovekin *et al*	1990	678	112 (17%)		H
Heintz *et al.*	1990	50	17 (34%)		S
Parkes *et al.*	1990	62	19 (39%)		H
Tsutsumi *et al.*	1990	37	11 (30%)		S
Broullet *et al*	1990	140	32 (23%)		S
Barnes *et al*	1991	70	20 (29%)		H
Soomro *et al.*	1991	149	16 (11%)		H
Borg *et al*	1991	539	102 (19%)		S
		290[a]	70 (24%)	N+	S
Kury *et al.*	1990	77	24 (31%)		S
Borresen *et al.*	1990	89	20 (22%)	prim	S
		24	12 (50%)	meta	S
Anbazhagan *et al.*	1991	211	29 (14%)	N+	H
Paterson *et al.*	1991	230	27 (12%)	N−	S
Clark and McGuire	1991	362	120 (33%)		S
Winstanley *et al.*	1991	465[a]	104 (22%)		H
O'Reilly *et al.*	1991	172	39 (23%)		H
Lovekin *et al.*	1991	782[a]			H
		497[b]	75 (15%)		
		180	36 (20%)		
Berns *et al.*	1991	975	182 (19%)		S
Rilke *et al.*	1991	1210	279 (23%)		H
Total update		11,408	2,264 (20%)		

N: nodal status; S: Southern blotting; H: (immuno)-histochemical techniques; W: Western blotting.

[a]Subgroup derived from the same study, mentioned above.

[b]497 Primary operable breast cancer patients and 180 with advanced breast cancer.

Note: references can be provided by the authors on request.

without these receptors. Receptors for IGF-1 were demonstrated by us [24] and two other groups [27, 28] in 93, 87 and 50–67% of primary breast cancers, respectively. Our study on 214 patients showed no relationship between IGF-1-R and RFS, but recently Bonneterre *et al.* [29] demonstrated in a study of 277 patients a longer RFS in a small subgroup

Table 2. Relationship between prognostic factor and response at endocrine therapy in advanced disease

Prognostic factor	Relative tumor response
ER+	Good
PR+	Good
AR+	Good
pS2+	Good
cathepsin-D	No value
EGF-R+	Poor
Aneuploidy	Poor
High Labeling Index	Poor
HER2/*neu*+	Poor
C-*myc*+	?

of patients (±15%) with very low levels of IGF-1-R than in those with high levels.

There is much more debate on the prognostic value of EGF-R [8, 26]. Sainsbury *et al.* [30] indicated that by multivariate analysis EGF-R status was the most important variable in predicting RFS and overall survival in lymphnode-negative patients and the second most important variable in lymphnode-positive patients. We only found a tendency ($P = 0.09$) to a negative relationship between EGF-R and RFS [24]. Reviewing the literature EGF-R-positivity was shown to be present in 2500 (48%) of 5232 breast tumors of 40 different series of patients [26]. The mean of the percentages of EGF-R-positivity in the individual series is 45% (range 14–91%). Five of 9 different groups of investigators showed significant prognostic value of EGF-R after short-term (1–4 year) follow-up indicating that patients with EGF-R-positive tumors have a poor prognosis. However, 3 or 5 groups with a maximal follow-up of at least 6 years found only a tendency to such relationship between EGR-R status and long-term outcome. With respect to metastatic disease EGF-R-positive tumors appeared to respond significantly worse to first-line endocrine treatment compared to EGF-R-negative tumors.

Estrogen regulated proteins

Interesting new prognostic markers are pS2 protein and cathepsin-D [8, 10, 31–36]. Previously we reported that pS2 is a very powerful prognostic factor in both node-negative and node-positive patients, and in patients with ER-positive primary tumors [31]. With respect to recurrent disease, Schwartz *et al.* [33] showed in a preliminary study on 72 patients that pS2 expression may define a subset of ER-positive patients that are more likely to respond to hormonal treatment. In a quite large series of 289 patients, recently we did the same observation by quantitative assessment of pS2 i.e. pS2-positive tumors responded better to endocrine therapy than pS2-negative tumors [32]. The metastase marker, cathepsin-D did not appear to have predictive value with respect to response to endocrine therapy in metastatic disease. A summary of the predictive value of several parameters with respect to response to endocrine therapy in (advanced) disease is indicated in Table 2.

ENDOCRINE TREATMENT OF BREAST CANCER

Many steroid and peptide hormones, growth factors and other trophic substances are involved in the growth regulation of breast cancer (Table 3) [37]. Endocrine treatment of breast cancer is designed to decrease plasma concentrations of one or more of these hormones and growth factors or to antagonize the biological effects of these trophic substances directly at the level of tumor cells. Also stimulation of the production of tumor growth inhibitory factors might play an important role. The involvement of so many hormones and other factors offers many points of action for endocrine therapy, both directly and indirectly [38, 39]. Endocrine therapy of breast cancer consists of a variety of both medical and surgical ablative treatment modalities [38–43], but ablative therapy is increasingly replaced by medical treatment. Most endocrine therapies have more than one endocrine effect, frequently together with direct growth-inhibitory actions. In the past decade the number of available endocrine agents has been drastically increased. Novel approaches to the endocrine therapy of breast cancer are

Table 3 Hormones and other factors involved in the growth regulation of breast cancer (directly and indirectly)

1. Steroid hormones	: estrogens, progesterone, androgens, glucocorticosteroids
2. Peptide hormones	. prolactin, growth hormone, insulin, somatostatin, calcitonin, (LH, FSH, ACTH).
3. Other trophic factors	: iodothyronines (T4, T3), vit. D, retinoids, polyamines, melatonine.
4. Growth factors	: insulin-like growth factors (IGF-1, IGF-2), epidermal growth factor (EGF), transforming growth factors (TGF-α, en β), platelet-derived growth factor (PDGF), fibroblast growth factors (FGF), mammary derived growth factor 1 (MDGF-1).
5. Secretory proteins	

Table 4. (Potential) advantages of "pure" antiestrogens compared to tamoxifen

1.	Higher affinity for ER.
2	Better antiestrogenic–estrogenic ratio
3.	Different half-lives ($T_{\frac{1}{2}}$)
4(a)	Higher antitumor efficacy?
(b).	More effective in bone?
5	Inhibition of tamoxifen-stimulated growth of MCF-7 cells *in vitro* and endometrial tumors grown in athymic mice.
6.	Effective in some patients who failed with tamoxifen.
7	Effective in other ER-negative experimental tumors?
8	Good tolerance of high dosages
9	Less hepatocarcinogenicity in rats.
10.	Lower risk on endometrial cancer during long-term (adjuvant) therapy?
11.	Less tumor flare?
12	Reversal of multidrug resistance (MDR) at high dosages?

Questions:
—risk on development of pituitary tumors?
—higher risk on osteoporosis or unfavorable plasma lipid spectrum due to less estrogen agonistic properties?
—development of hormone-refractory cells?

application of new antiestrogens, new aromatase inhibitors, luteinizing hormone-releasing hormone analogs (LHRH-A), somatostatin analogs, inhibitors of prolactin secretion, vitamins and growth factor antagonists.

Relationship between efficacy of endocrine therapy and tumor stage

Adjuvant systemic therapy by means of ovarian ablation or long-term treatment with tamoxifen has been shown to result in a 25% reduction in annual odds of death in pre- and postmenopausal patients with primary breast cancer, respectively [2–4]. This is related to an absolute decrease in deaths of 4% in node-negative and of 10% in node-positive patients after 10 years of follow-up. This means that endocrine therapy can not only be palliative, but also curative on condition that the treatment will be started early during the disease, when only very small micrometastases might be present. Based on an extensive meta-analysis [4] and on a recent randomized British trial [44], adjuvant chemotherapy is as effective as surgical castration, which might indicate that in premenopausal patients the main mechanism of action of adjuvant chemotherapy is an endocrine one i.e. chemical castration.

In patients with advanced disease (macrometastases) cure is scarcely possible, mainly temporary tumor remissions or inhibition of tumor growth can be reached. Response rates decrease with increasing stage. Tamoxifen as primary therapy in elderly women caused an objective response (CR + PR) in 62% of 385 patients [42]. This response rate decreases to 30–45% for first-line tamoxifen treatment in unselected patients with metastatic disease and to 15–25% for second-line treatment (although up to 50% in patients responding to first-line endocrine therapy). Generally, within stage IV, the efficacy of endocrine and chemotherapy decreases with increasing tumor load and the number of metastases [45]. Therefore, some investigators aim to start with endocrine therapy even before detection of primary tumors in women at high risk for breast cancer i.e. endocrine chemoprevention [46].

Antiestrogens

Tamoxifen is now the standard first-line therapy for postmenopausal metastatic breast cancer and is even accepted as an alternative to oophorectomy in premenopausal patients [42]. However, the stimulatory effect on the pituitary–ovarian function in the latter group with the occurrence of sometimes very high plasma estradiol levels is a point of concern and discussion. Nevertheless, based on 8 phase II and 2 phase III studies concerning totally 348 premenopausal patients treated with tamoxifen an objective response was observed in 103 (30%). In the 2 randomized trials the efficacy of tamoxifen appeared not to be significantly different from that of oophorectomy, but larger randomized trials are needed for definite conclusions. With respect to postmenopausal patients the response rate increases slightly with age up to 45% in elderly patients.

At present, various new "pure" antiestrogens with less estrogenic agonistic properties than tamoxifen have been developed and are under investigation in experimental models and in the clinic [42, 47–49]. The (potential) advantages of these new antiestrogens compared to tamoxifen are summarized in Table 4. Most interesting is the observation that some of these new antiestrogens such as toremifene and ICI 164,384 have growth inhibitory effects on tumor cells being resistant for tamoxifen or even stimulated in growth by tamoxifen. In experimental models ICI 164,384 showed also a greater antitumor efficacy than tamoxifen in the absence of any (partial) estrogen agonistic actions.

LHRH analogs

Based on 13 phase II studies, treatment with "medical castration" by LHRH analogs [50, 51] caused an objective response in 161 (39%) of totally 419 patients [52]. The objective response rate in ER-positive tumors was 50% and the reported longest duration of response is 5 years. In 135 postmenopausal patients reported in 8

Table 5. Antitumor effects of treatment with the antiprogestin mifepristone (RU 486) in postmenopausal pretreated breast cancer

	Treatment	n	PR	MR/NC	PD
1 Romieu *et al* (1987)	200 mg/day (third-line)	22	3	9	10
2 Klijn *et al* (1989)	200–400 mg/day	11	1	6	4
	In total	33	4 (12%)	15 (46%)	14 (42%)
PgR-positive tumors (all ER+)		7	3	3	1
PgR-negative tumors (5 ER+)		8	0	3	5

Improvement in patients resistant to progestin therapy (1): 3 out of 5
Improvement in patients resistant to tamoxifen therapy (2): 1 out of 11

papers the response rate was 10% [52]. These responses in postmenopausal metastatic breast cancer might be explained by direct antitumor effects in view of (a) the presence of LHRH-like material in mammary tumor cells; (b) the finding of specific LHRH binding sites in 52–67% of primary breast cancers and (c) the observation of direct growth inhibitory effects of LHRH analogs on tumor cell lines *in vitro* [53, 54]. However, Dowsett *et al.* [43] also showed decrease of postmenopausal ovarian androgen secretion by LHRH agonist treatment and consequently a decrease of peripheral synthesis of estrogens, which endocrine effect could explain tumor remissions too.

Presently depot preparations, which cause medical castration for at least 3 months, are available making this type of treatment convenient for the patients [55]. Recently very potent new LHRH *anta*gonists have been developed [56]. These antagonists have a more rapid and longer duration of action than agonists and maybe a greater antitumor efficacy, but are more expensive and cause more side-effects than agonists.

Of great interest is the application of LHRH analogs in combination with other endocrine agents. Previously, we [57] and Nicholson *et al.* [58] reported that the combination of buserelin or goserelin with antisteroidal treatment increased the duration of response as assessed in non-randomized studies. This is very recently confirmed by the first randomized trial [59] showing that Zoladex plus Nolvadex caused longer progression-free survival than Zoladex alone in the absence of a significant difference in response rate (34 vs 28%). In DMBA-induced mammary tumors we demonstrated favorable antitumor effects of combined treatment with buserelin and antiprogestins [60], while Szende *et al.* [61] showed additional antitumor effects of LHRH and somatostatin analogs in MXT mammary tumors. Stein *et al.* [62] observed favorable endocrine effects (a decrease of estradiol from 24 to 6 pmol/l) by adding an aromatase inhibitor (4OHA) to treatment with Zoladex.

Aromatase inhibitors

Aminoglutethimide (AG) is the classical and only freely available aromatase inhibitor [42, 43, 63–67]. Low dose AG (125–375 mg daily) is somewhat less toxic [42, 64], but causes lower response rates (16–19%), while additional responses in 18–23% of patients have been shown after dose escalation to 750 or 1000 mg per day, especially when glucocorticoids are added. A significant positive relationship was found between tumor aromatase activity (determined in about 70% of primary breast cancers) and response to treatment with AG but not to tamoxifen [68].

The new very potent aromatase inhibitors such as 4OHA, CGS 16949A, CGS 20267 and R76713 need much lower dosages to reach similar reduction (50–80%) in plasma and urinary estrogen levels compared to AG [42]. However, in postmenopausal breast cancer the antitumor efficacy seems not different from that caused by conventional AG treatment regimens. An advantage of these new compounds might be less toxicity and maybe some efficacy in premenopausal patients based on preclincial studies.

Antiprogestins

Antiprogestins form a new category of antihormonal agents being of potential interest in the treatment of cancer. *In vitro* [69] and in rats with mammary tumor clear growth inhibitory effects were demonstrated [60, 70–73]. Very interestingly, combination treatment with tamoxifen aiming blockade of both PgR and ER showed additive growth inhibitory effects [60, 74]. In a preliminary clinical study using mifepristone (RU 486) we demonstrated endocrine and clinical antiglucocorticoidal side-effects resulting in stimulation of pituitary–adrenal function followed by increased plasma estradiol levels as a consequence of

peripheral conversion of adrenal-derived androgens by aromatase activity [74]. In spite of these unsuitable endocrine effects, antitumor efficacy of second or third-line treatment with mifepristone was observed (Table 5) [74, 75], especially in patients with PgR-positive tumors indicating the presence of direct growth inhibitory action. More specific antiprogestins with less antiglucocorticoidal side-effects are in an advanced phase of development [72, 73].

Somatostatin analogs and prolactin (PRL) inhibitors

Single treatment with dopamine agonists (PRL inhibitors) appeared not to be successful in the treatment of metastatic breast cancer. In one clinical study, the addition of bromocriptine to high dose progestins (MPA) showed a slight additive growth inhibitory effect [76], but in combination with tamoxifen another study did not show any extra beneficial result [77]. The possible favorable effects of suppression of PRL secretion could be overruled by growth stimulatory effects induced by growth hormone (GH) binding to the lactogenic receptors. Therefore and in view of the observation that (a) somatostatin analogs can decrease GH and IGF-1 secretion [78–80]; (b) these analogs can inhibit growth of human tumor cells *in vitro* [81] and of mammary tumors in animal models [61] under condition that somatostatin receptors are present [82] and (c) somatostatin receptors have been demonstrated in about 40–50% of primary breast cancers [83, 84], clinical treatment with somatostatin analogs might be worthwhile, especially in combination with PRL inhibitors and antisteroidal agents. However, thusfar only a few results of treatment have been published [42, 85–88] showing a low response rate in heavily pretreated patients (Table 6). Studies on the efficacy of combination therapies with somatostatin analogs in previously untreated patients are warranted.

Therapies interfering with growth factor-mediated pathways

Plasma growth factor concentrations (especially IGF-1) can be decreased by somatostatin analogs [89] or tamoxifen [90]. Potentially, the administration of growth inhibitory growth factors (TGF-β) or analogs might inhibit breast cancer growth, when sufficient amounts of these agents will be available. Growth factor antagonists can inhibit tumor growth *in vitro* and *in vivo* by blocking growth factor receptors for their respective growth factors [91, 92]. In our experience the aspecific growth factor antagonist suramin caused growth inhibition of several human breast cancer cell lines *in vitro*, but low concentrations of this drug can stimulate growth of some, especially EGF-R-rich tumor cell types [92]. In a few heavily pretreated patients with metastatic breast cancer we observed no objective response. However, more specifically acting growth factor antagonists (not also inhibiting growth inhibitory growth factors) are needed. Other developments involve binding of cytostatic drugs linked to growth factors, radiolabeled growth factors, antibodies against growth factor receptors, growth factor receptor tyrosine kinase inhibitors and ultimately gene therapy [38, 39].

Table 6 Antitumor efficacy of sandostatin in (heavily) pretreated patients with metastatic breast cancer

First author	Dose (μg/d)	CR	PR	SD	PD	In total
Morten[a] (1988)		—	—	1	5	6
Vennin (1989)	200	—	—	3	11	14
Manni[a] (1989)	200–400	—	—	1	9	10
Holtkamp[a] (1990)	300	1	—	—	7	8
In total		1	—	5	32	38

[a]In combination with bromocriptine CR/PR/SD = 16%

Hormonal recruitment of tumor cells prior to chemotherapy

We [93–95] and others [42] showed that hormonal recruitment of tumor cells into S-phase increased the cytotoxicity of chemotherapy. However, in clinical studies the benefit from estrogen priming appeared to be absent or modest [42, 96]. New regimens have to be tested in randomized trials.

Future aspects

Apart from newly developed agents with a new mechanism of action, especially combined therapies might be of value to improve treatment results. This concerns not only combinations of endocrine agents, but also combinations of endocrine-, chemo-, immuno- and radiotherapy. However, less is known on the (potential) interaction between hormones, growth factor antagonists, retinoids, interferons, interleukines, chemotherapeutic agents and irradiation. All these treatment modalities have different effects on various cell biological parameters, cell function, the cell cycle, DNA synthesis and DNA damage. Certain simultaneous and/or sequential combinations of treatment modalities may prevent DNA repair and increase tumor cell kill. Therefore, in view

of the fact that it is clearly impossible to test clinically all the possible combination therapies within a reasonable time period, a better understanding of the biological principles involved and a rapid preclinical screening of powerful combination therapies are needed in order to improve the results of breast cancer therapy in the nineties.

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