Maturitas 95 (2017) 11–23

Contents lists available at ScienceDirect

Maturitas

journal homepage: www.elsevier.com/locate/maturitas

Review article

The use of high-dose estrogens for the treatment of breast cancer

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ARTICLE INFO

Article history:
Received 1 September 2016
Received in revised form 7 October 2016
Accepted 18 October 2016

Keywords:
Estrogen
Breast cancer
Endocrine resistance
Estrogen gap

ABSTRACT

Estrogens are known to stimulate the growth of breast cancer but they are also an effective treatment for this disease (this has been termed the 'estrogen paradox'). The fact that estrogens can be an effective treatment for breast cancer is something that has almost been forgotten, whereas the fear for estrogens remains. This paper reviews the use of estrogens for the treatment of breast cancer and identifies possible applications. The data summarised in this review demonstrate that high-dose estrogens are effective for the treatment of advanced breast cancer, both as first-line treatment as well as for treatment after occurrence of endocrine resistance to TAM and AIs. Essential for efficacy is an extended period of estrogen deprivation before the tumour is subject to estrogen treatment (the gap hypothesis). Research on the mechanism of action has shown that apoptosis induced by estrogens is regulated via the estrogen receptor and growth factor signalling pathways. High-dose estrogens have a negative safety image, especially in terms of side-effects and increased rates of cardiovascular disease, but the safety data reviewed in this paper do not give rise to major concerns. Taking into account their side-effect profile together with their observed clinical efficacy, high-dose estrogens should be considered a valuable alternative to chemotherapy in selected patients.

Contents

1. Introduction

Efficacy of synthetic estrogens for the treatment of advanced breast cancer was first described by Haddow et al., 1944 [1]. Fourteen patients with advanced breast cancer, between 31 and 80 years of age, were treated orally or by intramuscular injection with

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http://dx.doi.org/10.1016/j.maturitas.2016.10.010

diethylstilbestrol (DES) for a period of several months. Five subjects (36%) showed alterations in tumour growth. Patients who responded to treatment were between 57 and 80 years of age. Side effects reported were nausea, pigmentation of mammary areola, uterine bleeding and edema in low extremities. Some patients also experienced improved appetite, weight gain and reduced pain. In the same year, Binnie [2] also reported a beneficial effect of DES in patients (36–76 years) with advanced breast cancer, especially when it was combined with radiotherapy. The patients tolerated doses of DES between 6 and 10 mg for a longer period (several months). Most frequently reported side effects were nausea, weight increase and for some women menorrhagia, which tended to diminish with the continuation of treatment. Interestingly, some patients also reported a feeling of well-being despite the nausea.

The results of the trials of Haddow et al. [1] and Binnie [2] were a paradox, as breast cancer was considered to be dependent on estrogens for growth. In the following years, other clinicians such as Kennedy [3–6], Kautz [7] and Stoll [8] continued research on high dose estrogens (HDE) for the treatment of breast cancer, making estrogens the standard of care in postmenopausal patients with advanced breast cancer from the early 1960s onwards.

In the 1970s, trials with antiestrogens, specifically tamoxifen (TAM), were performed. Randomized trials comparing estrogens (DES and ethinyl estradiol (EE)) versus TAM in postmenopausal women with advanced breast cancer showed similar regression rates, but less toxicity with TAM [9–11]. From that time onwards TAM was used as the preferred first-line treatment for postmenopausal women with advanced breast cancer and almost completely replaced the use of estrogens.

As of the 1990s, the use of estrogens for the treatment of breast cancer was revisited as HDEs showed good efficacy in patients who were exposed to multiple prior hormone therapies. Since then, several clinical trials were conducted with different estrogens (DES, EE, estradiol (E2)). Results of these trials showed high responses, especially in patients who became resistant to hormone therapy [12–18]. The authors suggested to further explore the use of HDEs for the treatment of patients with advanced breast cancer refractory to hormone treatment as an alternative treatment option for chemotherapy.

An overview of the different clinical trials performed with HDEs over the time period 1944–2015 is provided in Table 1. The aim of this review paper is to discuss the use of HDEs for the treatment of patients with advanced breast cancer over the years starting as of 1944, compare HDEs with TAM, aromatase inhibitors (AIs) and the pure antiestrogen fulvestrant (FUL) and identify possible applications for the use of HDE in the future.

2. The use of high dose estrogens in the past (1940s–1970s)

Following Haddow et al. [1] and Binnie [2], Kennedy and Nathanson [3] published a paper in 1953 on the side effects observed when patients were treated with estrogens for advanced breast cancer. DES was the estrogen most frequently used, at a dose level of 15 mg per day (oral administration), but treatments between 5 and 400 mg were also used. Most frequently reported gastrointestinal side effects were anorexia, nausea and vomiting. Pigmentation of the nipples was reported in about 80% of the patients treated with estrogens. HDE produced amenorrhea in premenopausal women, whereas postmenopausal women (mainly younger postmenopausal women) experienced vaginal bleeding. Another side effect of HDE included urinary urgency and incontinence. Fluid retention has also been reported with the use of HDE, which in some patients led to congestive heart failure. Hypercalcemia in patients treated with estrogens in their study was rare, but it occurred in two out of the 235 patients, so it is considered important to monitor serum calcium concentrations in patients treated with HDEs, especially in patients with bone metastasis.

In 1960, Kautz [7] published the results of a very large study in which they assessed the effects of androgens and estrogens for the treatment of advanced breast cancer. The study was initiated in 1947 and lasted 12 years. In total, 364 mainly postmenopausal women with advanced breast cancer were included in the study. Most patients were treated with 15 mg DES per day (oral administration), but also EE (3 mg per day, oral administration) and some other estrogens (e.g. chlorotrianisene, conjugated estrogenic substances and dienestrol) were used. Tumour regression was observed in 134 patients (36.8%), all postmenopausal patients. Estrogen treatment was more effective when its use started later (>5 years) after menopause.

Kennedy [4] in 1962, had published data from a study in which they treated 23 premenopausal women (aged 33–54 years) with advanced breast cancer with high dosages of DES. According to their theory, tumour regression with HDE treatment in postmenopausal women was caused by inhibition of the pituitary gland, but the authors did not specify this further. In order to get the same effect in premenopausal women, a much higher dose was considered to be necessary to inhibit the pituitary gland, so therefore they treated the patients with oral dosages of 400–1000 mg DES per day. Four patients out of the 23 (17%) showed an objective clinical response (tumour regression), which lasted for 6–21 months. In two patients (9%), the cancer remained stable. The cancer continued to progress in a normal way in 15 patients and 2 patients showed an accelerated tumour growth. Side effects reported initially were nausea and vomiting. Most patients experienced amenorrhea, but occasionally monthly vaginal spotting occurred. The two patients with an accelerated tumour growth also showed hypercalcemia as a side effect. Other side effects were pigmentation, ankle edema, drowsiness, fatigue and engorgement of normal breast. The side effects were no more intense and possibly milder, than those reported with 15 mg of DES in postmenopausal women with advanced breast cancer. Kennedy [5,6] also performed a study in which he compared DES versus testosterone propionate in postmenopausal patients with advanced breast cancer. In total 55 patients were treated with DES (orally, three times 5 mg per day) and 16 patients showed an objective regression (29%). In the group of women >5 years postmenopausal, the objective regression rate (15/38, 39%) was significantly higher (p 0.028) as compared to the group of women who were less than 5 years postmenopausal (1/17, 6%). The median duration of the response was 11+ months. The objective response rate in patients treated with DES was significantly higher than for patients treated with testosterone propionate (29% vs 10%). Gastrointestinal complaints were frequently reported; nausea occurred in 69% of the patients, and half of these patients also reported vomiting. Prolonged administration of DES produced pigmentation of the nipples, areolae, axillae and scars in about 60% of the patients. Mastodynia and nipple tenderness were also reported, but these events were not considered to be bothersome by the patients. Vaginal spotting/bleeding occurred in about a quarter of the patients. When vaginal bleeding persisted, the treatment was discontinued for 7 days and subsequently resumed. About half of the patients reported fluid retention (leg and ankle edema), which resulted in a congestive heart failure in one patient. Diuretic treatment was successfully used in controlling this problem. Fluid retention frequently subsided when the treatment was prolonged. About 40% of the patients reported urinary incontinence. Hypercalcemia, the most serious side effect reported, was induced in two patients at the onset of the treatment, but eventually subsided.

Stoll and Ackland [19] in 1970 performed a retrospective survey in women with breast cancer over 70 years of age (70–95 years). Patients were treated with estrogens (15 mg DES or 1.5 mg EE per day) when surgery or radiotherapy was insufficient to control the

Table 1
Overview of clinical trials performed with HDEs over the time period 1944–2015.

Reference	Line of therapy	Treatments	Population	ORR (%)	CBR (%)
Haddow *et al* 1944 [1]	Prior radiotherapy	DES	N = 14; pre- and postmenopausal women, aged 31–80	5/14 (36)	*ND*
Binnie, 1944 [2]	Prior hormone therapy and/or radiotherapy	DES: 2–7 mg/day	N = 4; aged 36–76	*ND*	*ND*
Kautz, 1960 [7]	Partly untreated and partly pre-treated	DES: 15 mg/day EE: 3 mg/day	N = 364; DES N = 155, EE N = 62; pre- and postmenopausal women	134/364 (37)	*ND*
Kennedy, 1962 [4]	Mostly untreated and 2 prior hormone therapy (testosterone propionate).	DES: 400–1000 mg/day	N = 23; premenopausal women, aged 33–54	4/23 (17)	6/23 (26)
Kennedy, 1965 [6]	No details present.	DES: 5 mg, three times a day	N = 55; postmenopausal women	16/55 (29)	*ND*
Stoll and Ackland 1970 [19]	Prior radiotherapy.	DES: 15 mg/day EE: 1.5 mg/day	N = 170; postmenopausal women, aged 70–95	45/92 (49)	*ND*
Cole *et al* 1971 [21]	Majority had been pre-treated with hormones or alkylating agents and radiotherapy.	DES: 5 mg, three times a day	N = 64; postmenopausal women, >5 yrs after menopause	16/64 (25)	*ND*
Cole *et al* 1971 [21]	Majority had been pre-treated with hormones or alkylating agents and radiotherapy.	TAM: 10 mg, once or twice daily	N = 46; postmenopausal women	10/46 (22)	*ND*
Heuson *et al* 1975 [11]	7/49 patients received prior hormone (excluding estrogens and anti-estrogens) therapy, chemotherapy or both.	EE: 1 mg, three times a day	N = 49; postmenopausal women, >2 yrs after menopause, aged 45–89 (median 64 yrs)	7/49 (14)	*ND*
Carter *et al* 1977 [20]	No prior hormone therapy.	DES: 0.5 mg, three times a day DES: 5 mg, three times a day DES: 50 mg, three times a day DES: 500 mg, three times a day	N = 523; postmenopausal women, median age in each treatment group 59 to 61 yrs.	10 15 17 21	*ND*
Stewart *et al* 1980 [25]	No prior systemic therapy other than prophylactic or failed therapeutic oophrectomy.	DES: 5 mg, three times a day	N = 56; postmenopausal women under the age of 80. Subjects received both DES and TAM in a cross over design.	6/27 (22)[a]	*ND*
Stewart *et al* 1980 [25]	No prior systemic therapy other than prophylactic or failed therapeutic oophrectomy.	TAM: 10 mg, three times a day	N = 56; postmenopausal women under the age of 80. Subjects received both DES and TAM in a cross over design.	9/29 (31)[a]	*ND*
Ingle *et al* 1981 [9]	No prior hormone therapy Prior chemotherapy 22/69	DES: 5 mg, three times a day	N = 74; postmenopausal women, >5 yrs after last menses, aged 46–84 (median 64.5 yrs)	30/74 (41)	62/74 (84)
Ingle *et al* 1981 [9]	No prior hormone therapy Prior chemotherapy 22/74	TAM: 10 mg, two times a day	N = 69; postmenopausal women, >5 yrs after last menses, aged 50–82 (median 60.4 yrs)	23/69 (33)	54/69 (78)
Beex *et al* 1981 [10]	Majority no prior treatment. Some received chemotherapy or androgens	EE: 0.5 mg/day increasing within 5 days to 3 mg/day	N = 31; postmenopausal women, >2 yrs after menopause, aged 54–77 (median 63 yrs)	9/29 (31)	11/29 (38)
Beex *et al* 1981 [10]	Majority no prior treatment. Some received chemotherapy, androgens or therapeutic ovariectomy	TAM: 20 mg, two times a day	N = 32; postmenopausal women, >2 yrs after menopause, aged 44–82 (median 63.5 yrs)	10/30 (33)	12/30 (40)
Matelski *et al* 1985 [26]	No prior hormone therapy	TAM: 10 mg, two times a day	N = 19; postmenopausal women >5years after menopause, aged 58–83 (median 64)	10/19 (53)[a]	*ND*
Matelski *et al* 1985 [26]	No prior hormone therapy	EE: 1 mg/day increasing within 7 days to 3 mg/day DES: equivalent to 3 mg/day EE	N = 24; postmenopausal women (>5 years after menopause, n = 22), aged 48–81 (median 65)	6/24 (25)[a]	*ND*
Gockerman *et al* 1986 [27]	No previous estrogen or antiestrogen treatment. Prior treatment consisted of chemotherapy or adrenalectomy/hypophysectomy	DES: 5 mg, three times a day	N = 44; postmenopausal women, aged 45–86 (median 71.2)	10%	83%
Gockerman *et al* 1986 [27]	No previous estrogen or antiestrogen treatment. Prior treatment consisted of: chemotherapy or hormonal (androgens/progestational agents) therapy or both	TAM: 10 mg, two times a day	N = 46; postmenopausal women, aged 41–95 (median 69.6)	6%	84%

Table 1 (*Continued*)

Reference	Line of therapy	Treatments	Population	ORR (%)	CBR (%)
Boyer and Tattersall, 1990 [28]	Previous hormone therapy, chemotherapy or both	DES: 10–20 mg/day	N = 11; postmenopausal women, aged 46–80 (median 63 yrs)	4/11 (36)	9/11 (82)
Lønning *et al* 2001 [12]	Patients should have received and become resistant to previous hormone therapy. Previous chemotherapy was allowed.	DES: 5 mg, three times a day	N = 32; postmenopausal women, aged 45–87 (median 68 yrs)	10/32 (31)	12/32 (38)
Agrawal *et al* 2006 [13]	Patients should have received and become resistant to previous hormone therapy. EE as 3rd to 7th line hormone treatment	EE: 1 mg/day	N = 12; postmenopausal women, aged 49.1–85 (median 75.1 yrs)	3/12 (25)	4/12 (33)
Ellis *et al* 2009 [18]	Previous systemic therapies allowed: hormone treatments and one line of chemotherapy.	E2: 2 mg, three times a day	N = 34; postmenopausal women, aged 36.3–83.8 (median 54.7 yrs)	3/34 (9)	10/34 (29)
Ellis *et al* 2009 [18]	Previous systemic therapies allowed: hormone treatments and one line of chemotherapy.	E2: 10 mg, three times a day	N = 32; postmenopausal women, aged 39.4–77.7 (median 59.5 yrs)	1/32 (3)	9/32 (28)
Mahtani *et al* 2009 [14]	Most patients received multiple prior lines of therapy: hormone and chemotherapy.	DES: 5 mg, three times a day E2: 10 mg, three times a day E2: 2 mg, three times a day	N = 26; postmenopausal women, aged 42–92 (median 59 yrs)	5/20 (25)	9/20 (45)
Iwase, 2013 [15]	Previous treatment with AI and sequential hormone therapies including chemotherapy	EE: 1 mg, three times a day	N = 18; postmenopausal women, aged 51–83 (median 63 yrs)	9/18 (50)	10/18 (56)
Chalasani *et al* 2014 [16]	Patients should have received and become resistant to previous hormone therapy (AI).	E2: 6 mg/day	N = 13; postmenopausal women, aged 49–85 (median 68 yrs)	3/13 (23)	6/13 (46)
Zucchini *et al* 2015 [17]	Patients should have received and become resistant to previous hormone therapy (AI).	E2V: 2 mg/day	N = 19; postmenopausal women, aged 49–90 (median 67)	0/19 (0)	5/19 (26)

[a] Response to primary therapy; ND = not determined.

disease. In total, 170 patients in this age group were treated with estrogens of which 18 patients (11%) discontinued treatment due to side effects (mainly severe nausea or fluid retention causing cardiac embarrassment). Of the 92 patients who could be assessed for tumour response, 45 patients (49%) had an objective response (tumour regression) with an average survival after initial treatment of 28 months versus 16 months in non-responders.

Carter et al. [20] performed a randomized, double blind, study with four different oral dosages of DES (1.5 mg, 15 mg, 150 mg and 1500 mg given over three portions per day) in postmenopausal patients with advanced breast cancer (1977). In total 523 postmenopausal patients (median age 59–61 years) who did not receive any prior hormonal therapy were included in the study. Higher dosages produced significant higher regression rates, 21%, 17%, 15% and 10% for the 1500 mg, 150 mg, 15 mg and 1.5 mg dose respectively. No regression in tumour size was observed in patients (17 in total) who were less than one year postmenopausal. Gastrointestinal toxicity increased in frequency and severity with increasing dose. Also nipple or areolar pigmentation was dose-related. Uterine bleeding occurred three times more often in the lowest dose group as compared to the other groups, whereas withdrawal bleedings occurred three times more often in the three higher dose groups as compared to the lowest group. However at all dosages, withdrawal bleedings were uncommon. Other side effects reported were urinary symptoms (stress incontinence), edema, congestive heart failure and hypercalcemia. Severe side effects (e.g. pulmonary embolism, phlebitis) were reported for 16 out of the 523 subjects (3%). In total four patients died due to side effects, two patients because of pulmonary embolism and two patients because of hypercalcemia.

3. The introduction of antiestrogens

Cole et al. [21] in 1971 were the first who reported the use of the non-steroidal antiestrogen tamoxifen (TAM) for the treatment of advanced breast cancer. In total, 46 postmenopausal patients with advanced breast cancer were treated with 10 or 20 mg of TAM per day. Ten patients (22%) showed a clear response, 17 patients (37%) showed an incomplete response and 19 patients (41%) failed to respond to treatment. Side effects reported were hot flushes, gastrointestinal intolerance, tumour pain, pruritis vulvae, ankle edema, vaginal bleeding and lassitude. Two patients (4%) discontinued treatment prematurely due to side effects. There was no evidence of hepatoxicity or hypercalcemia. Cole et al. [21] also treated patients with advanced breast cancer with DES (15 mg per day) (unpublished results). This data was used for comparison when evaluating the results of TAM treatment. Sixty-four patients were treated with DES, of whom 16 (25%) patients responded. Twelve patients (18%) discontinued the treatment due to side effects. Gastrointestinal intolerance, fluid retention, vaginal bleeding were the most frequently side effects reported. Although the response rate of TAM was comparable to the response rate seen with estrogen treatment, the incidence of side effects leading to discontinuation of treatment was lower in the TAM treatment group. Subsequently several trials using TAM for the treatment of patients with advanced breast cancer were performed by different clinicians [22–24].

In 1975, Heuson et al. [11] performed a clinical study in postmenopausal patients with advanced breast cancer in which they compared the efficacy and side effects of the non-steroidal estrogen antagonist nafoxidine (60 mg, three times a day, oral administration) with EE (1 mg, three times a day, oral administration). All patients were at least 2 years past menopause, either natural or surgical. Several patients had received previous hormonal or cytotoxic therapy. Objective remissions were obtained in 15 out of 49 (31%) patients treated with nafoxidine and 7 out of 49 (14%) treated with EE. Eight patients in the EE group, discontinued treatment prematurely due to side effects hypercalcemia (2 patients), gastrointestinal intolerance (4 patients), uncontrolled fluid retention (1 patient) and acute dyspnoea (1 patient) versus three patients

in the nafoxidine group (hypercalcemia, digestive intolerance and liver toxicity). Nafoxidine produced fewer serious side effects but produced very specific side effects as ichthyosis, partial hair loss and phototoxicity of the skin which occurred in almost all patients limiting it's practical usefulness as treatment for breast cancer.

Stewart et al. [25] performed a double-blind cross-over study with TAM (10 mg, three times a day) and DES (5 mg, three times a day) in 56 postmenopausal women with advanced breast cancer (1980). The hormones were given consecutively for 90 days with a 4 week wash-out between the treatments. No significant difference in the rate or the duration of response was seen between the two compounds. Some patients showed a lack of response on the first treatment, but responded on the second treatment suggesting that the treatments might have a different mode of action. In total 9 out of the 29 subject in the TAM group (31%) and 6 out of the 27 subject in the DES group (22%) responded to primary therapy. Receptor status was known for some of the patients and an association between positive estrogen receptor (ER) status and response to treatment was confirmed in this small group of patients. Intolerance to drug treatment was higher in patients on DES treatment than on TAM treatment, so the authors suggested to make TAM the first choice of treatment for postmenopausal women with advanced breast cancer.

In 1981, Beex et al. [10] published data from a randomized study in which they compared TAM (20 mg twice daily) versus EE (3 mg per day) for the treatment of advanced breast cancer in postmenopausal women. EE treatment was always combined with chlorothiazide (500 mg daily) to prevent fluid retention. The median age of the patients in both treatment groups was 63 years. Nine out of the 29 patients in the EE group (31%) and ten out of the 30 patients in the TAM group (33%) achieved an objective remission, so remissions were similar between the two treatment groups. Furthermore, in each group, two patients had a stable disease for 6–36 months during therapy. Objective responses occurred in both treatment groups only in estrogen receptor (ER) positive patients or in patients for which the ER status was unknown. No responses were observed in ER negative patients. Two patients in the EE group had to discontinue treatment due to cholelithiasis considered to be related to drug treatment. In the TAM group, also two patients discontinued treatment due to drug related side effects (persistent nausea). Most frequently reported side effects in both treatment groups were nausea or vomiting. Hot flushes and vulvovaginitis were only reported by subjects in the TAM group, whereas vaginal spotting and withdrawal bleeding was only observed in patients in the EE group. Three patients (one in the EE group and two in the TAM group) had hypercalcemia which was successfully treated in both groups with hydration and furosemide. All patients continued treatment. One patient in the EE group developed a deep venous thrombosis with multiple non-fatal embolisms of the lungs. Two patients in the TAM groups developed a superficial phlebitis of the leg. In summary, there was no significant difference in efficacy between EE and TAM treatment in postmenopausal women with advanced breast cancer. However side effects in TAM treated patients were less serious as compared to EE treatment.

In the same year, a randomized clinical trial was conducted by Ingle et al. [9] in postmenopausal women with advanced breast cancer in which they compared DES (3 times 5 mg per day) versus TAM (two times 10 mg per day). In total 151 patients were entered into the study, of which 143 were considered to be evaluable. Eight patients were excluded because of major protocol violations. Postmenopausal status was defined as five or more years since last menstrual period. Patients had received no prior hormonal therapy, but prior chemotherapy was allowed and was received by about 22% of the patients in each group. ER data was available for 14 patients in each group, 12 patients in each group were ER positive. Out of the 74 patients in the DES group, 30 patients (41%) showed an objective response versus 23 patients (33%) out of the 69 in the TAM group. The overall objective regression rate for DES was higher than for TAM, but the difference was not statistically significant. In both groups more than 40% of the patients had a stable disease (43% in the DES groups versus 45% in the TAM group). Also median times until treatment failure showed no significant difference between the groups (142 days in DES group versus 171 days in TAM group). Patients in the DES group had significant more toxicities than patients in the TAM group. Most frequently reported side effects in the DES group were edema, nausea, emesis, anorexia, vaginal bleeding, diarrhoea and incontinence. Most frequently reported side effects in the TAM group were hot flushes, nausea, anorexia, leukopenia, emesis, edema and diarrhoea. Nine patients in the DES group (12%) discontinued treatment because of side effects versus none in the TAM group. Events leading to discontinuation in the DES group were congestive heart failure (three patients), gastrointestinal intolerance (four patients), thrombophlebitis (one patient) and refractory lower extremity edema with superficial ulcerations (one patient). Hypercalcemia occurred in two patients taking TAM.

So the study of Ingle et al. [9] who compared DES versus TAM showed similar results as the study of Beex et al. [10], who compared EE versus TAM; similar efficacy but less serious side effects with TAM. Ingle et al. [9] suggested that since there was no statistically significant difference between the treatment groups in efficacy, but less toxicity with TAM, TAM should be taken forward as the preferred treatment for the treatment of advanced breast cancer. From that time onwards TAM was used as the preferred first-line treatment for postmenopausal women with advanced breast cancer and almost completely replaced the use of estrogens.

Matelski et al. [26] have performed a randomized trial of high dose estrogens (EE or DES) versus TAM with a cross-over to the alternative treatment in case of progressive disease. In total 43 evaluable postmenopausal women with advanced breast cancer were included in the study; 19 patients were randomized to TAM and 24 to estrogen treatment. No prior hormonal therapy was allowed. Patients were treated with 10 mg TAM, twice daily or 1 mg EE, three times a day. Two patients in the estrogen group received DES at an equivalent dose of 3 mg/day EE. Ten of the 19 patients in the TAM group (53%) and six out of the 24 patients in the estrogen group (25%) responded to primary therapy. Responses were related to the presence of the ER, particularly in the TAM group, but in the estrogen group also three ER negative patients showed a response. Major side effects of estrogen treatment were nausea, vomiting and peripheral edema. Hypercalcemia was reported in one patient in the TAM group.

In 1986, Gockerman et al. [27] also performed a randomized study in which they compared DES versus TAM. In total, 90 postmenopausal women with ER-positive or ER-unknown advanced breast cancer were treated with DES (5 mg three times per day) or with TAM (10 mg twice a day). Efficacy was similar between the treatment groups. The Objective Response Rates (ORR, patients with a complete response (CR) plus partial response (PR)) observed were 10% and 6% for the DES and TAM group, respectively. Stable disease (SD, <50% decrease or <25% increase) was present in 73% of the DES users and 78% of the TAM users. The authors suggested that the presence of the ER is more frequently associated with DES response than with TAM response, but the difference was not statistically significant. Side effects (nausea, emesis, leg edema and breast tenderness) were more frequently reported with DES than with TAM. Three patients in the DES group developed congestive heart failure, but this was not considered to be related to the treatment and one patient had a stroke while receiving DES. Although side effects were more frequent in the DES group, they usually occurred in the first weeks, were mild in intensity and not life-threatening. According to the opinion of the authors,

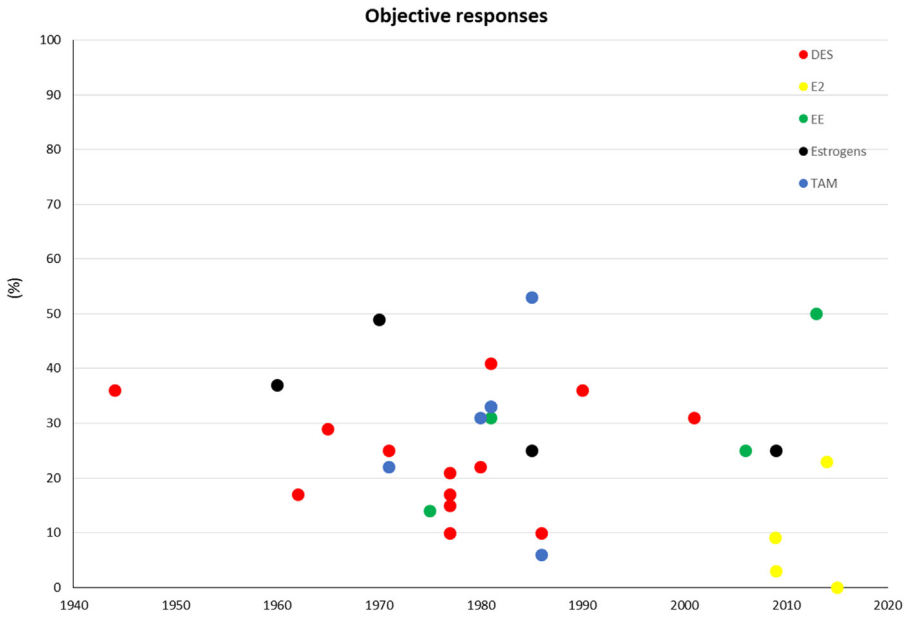

Fig. 1. Objective responses observed in clinical trials with HDEs and TAM over the time period 1944–2015.

based on cost-effectiveness DES was the preferred agent of choice for the treatment of postmenopausal women with ER-positive or ER-unknown advanced breast cancer. However, the results of this study did not change the increasing preference for the use of TAM in the management of advanced breast cancer.

4. Estrogen treatment in patients resistant to hormone therapy

As of the 1990s, the use of estrogens for the treatment of advanced breast cancer was revisited as HDEs showed efficacy in patients who were exposed to multiple prior hormone therapies. In 1990, Boyer and Tattersall [28] treated 11 postmenopausal patients with disseminated breast cancer with DES after they had observed an impressive response to DES in a breast cancer patient with pulmonary metastasis resistant to several other hormone therapies. The dose of DES ranged between 10 and 20 mg per day. Of the 11 patients treated, 4 patients (36%) showed an objective response to the DES treatment (one CR and three PRs), five patients had a SD and 2 patients showed a progressive disease. Interestingly, patients whose tumours had previously been unresponsive to several hormone therapies showed a response to DES. Most frequently reported side effect was nausea. Two patients developed cardiac failure of which one was leading to discontinuation of DES treatment. The other case was controlled with diuretics and DES was continued. Hypercalcemia was not observed. The authors concluded that DES remains a useful drug for the treatment of advanced breast cancer in postmenopausal women and that it may be of particular interest for elderly breast cancer patients by delaying the need for cytotoxic treatment.

In 2001, Lonning et al. [12] performed a study in which they evaluated whether DES treatment (5 mg three times a day) was efficacious in breast cancer patients becoming refractory to hormone treatment. Postmenopausal patients were included in the study and patients should have received and become resistant to previous hormone therapy. Previous chemotherapy was allowed. Ten out of the 32 patients included in the study (31%) demonstrated an objective response. In addition, two patients showed stabilization of the disease $\geq$6 months, resulting in 12 patients (38%) to benefit from treatment (Clinical Benefit Rate (CBR), patients with a CR, PR and SD). Ten patients were ER-positive, one patient was ER-unknown and one patient was ER-negative. One patient died following 19 weeks on DES treatment from a myocardial infarction, not considered to be related to treatment. Six patients (19%) discontinued treatment due to side effects. Side effects leading to discontinuation were bleeding, vaginal discharge and mastalgia, nausea, diarrhoea, abdominal bloating, arthralgia, dizziness and lethargy. Two patients developed hypercalcemia of which one had the calcium levels normalized with clodronate treatment. The authors concluded that DES is an effective treatment option for breast cancer patients with hormone sensitive tumours heavily exposed to hormone therapy and might be an valuable alternative to chemotherapy in selected patients.

Agrawal et al. [13] in 2006, assessed efficacy of EE (1 mg per day) in heavily pre-treated postmenopausal women with advanced breast cancer. Twelve patients with a median age of 75.1 years were identified in their database. Three patients (25%) showed an objective response (all PR), while one patient had a SD for 36 months. In total, 4 patients had benefit from treatment (33%). One patient discontinued treatment within 2 weeks due to a hepato-renal syndrome.

Ellis et al. [18] in 2009, published data from a randomized study in which they compared efficacy of 6 mg E2 versus 30 mg E2 in postmenopausal patients (median age 54.7 year (6 mg) and 59.5 year (30 mg)) with aromatase inhibitor (AI)-resistance advanced breast cancer. Eligible patients had received an AI with at least 24 weeks progression free survival. One line of chemotherapy for advanced disease was allowed. Treatment with fulvestrant (FUL) within 12 months before study initiation was not allowed. Primary endpoint was CBR. In total 66 subjects were enrolled. CBRs were similar between the two treatment groups (29% in the 6 mg group and 28% in the 30 mg group). Most of the patients had a SD response. None of the patients had a CR and 1 patient (3%) in the 30 mg group and 3 patients (9%) in the 6 mg group had a PR. Seven patients were retreated with an AI and three (43%) out of these seven patients experienced again a clinical benefit (2 PR and one SD) on the AI treatment. Side effects reported were nausea, vomiting, electrolyte disturbances (low sodium), pleural effusion, tumour pain and vaginal bleeding. Vaginal bleeding was mainly seen in younger postmenopausal women and was well controlled with progestin treatment either orally or with an intrauterine device. There was no evidence that the use of a progestin interacted with the response.

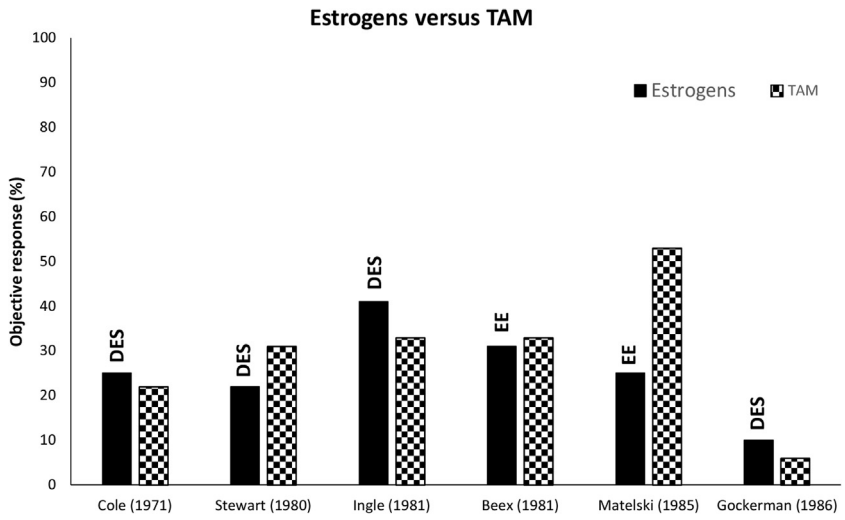

Fig. 2. Objective responses of estrogens versus TAM (comparative trials).
Figure created based on data from Cole et al. [21], Stewart et al. [25], Ingle et al. [9], Beex et al. [10], Matelski et al. [26] and Gockerman et al. [27].

Thrombosis occurred in one patient in each treatment group. Altogether, the 6 mg dose had a significant lower serious side effect rate and fewer side effects impacting quality of life with an similar CBR as compared to the 30 mg dose, so the authors suggested to examine the lower dose in future clinical studies.

Mahtani et al. [14] published their experience with the use of HDEs in postmenopausal patients (median age 59 years) with advanced breast cancer as a retrospective review in 2009. All patients, except one, received multiple lines of prior therapy (both hormone therapy and chemotherapy) in the advanced setting before initiation of HDE treatment. Patients were treated with DES (3 times 5 mg per day) or with E2 (3 times 10 mg per day or 3 times 2 mg per day). Most of the patients were ER-positive and for two patients ER status was unknown. Five (25%) out of the 20 patients had an objective response and four patients (20%) had a SD for ≥6 months, giving a CBR of 45%. Side effects reported were fluid retention, vaginal bleeding, nausea, fatigue and pruritus. Two patients mentioned that estrogen therapy was associated with increased libido. The authors suggested that HDEs despite its limitations should be further considered as a treatment option in heavily pre-treated patients.

Iwase et al. [15] assessed the efficacy and safety of EE (3 mg per day) in heavily pre-treated postmenopausal women with advanced breast cancer resistant to AIs. Eighteen ER-positive patients were included in the study. Nine out of the 18 patients had an objective response (all patients had a PR). One patient had a SD resulting in a CBR of 55%. Three patients (17%) discontinued the study due to early estrogen flare reactions (muscle skeletal pain, nausea and fatigue). No serious side effects were reported. Most frequently reported side effects were nausea and vomiting, nipple/areola pigmentation, endometrial thickening, muscle-skeletal pain, fatigue, vaginal discharge/bleeding and hot flushes. Patients reported also some beneficial effects of the treatment such as improvement of vaginal dryness, skin dryness and lipoprotein profiles. Authors concluded that EE treatment is beneficial for heavily pre-treated postmenopausal with advanced breast cancer women who became resistant to AIs.

Chalasani et al. [16] in 2014 treated postmenopausal women with ER-positive advanced breast cancer whose disease progressed after receiving at least one prior hormone therapy with 6 mg E2 per day. Patients who had not progressed after 3 months were switched to exemestane in order to assess whether short term E2 treatment could reverse hormone resistance and re-sensitize tumours to AI treatment. Of the 13 patients included in the study, 6 patients (46%) had not experienced disease progression (3 PR, 3 SD) at 3 months and they were switched to exemestane. Five out of the six patients on exemestane reported disease progression and one patient had a SD. Frequently reported side effects while on E2 treatment were vaginal spotting, fatigue, nausea and mood changes. No grade 3 or 4 toxicities were observed. In conclusion, short term treatment with 6 mg E2 was not effective at reversing hormone resistance. However, according to the authors E2 should be considered as a therapeutic option for the treatment of patients refractory to hormone treatment as E2 treatment showed good clinical efficacy with minimal toxicity.

Zucchini et al. [17] in 2015, published data of a phase II clinical study with low dose E2 in postmenopausal women with advanced breast cancer resistant to AIs. They hypothesized that estrogen suppression induced by AIs would mimic a more prolonged postmenopausal period, sensitising breast cancer cells to inhibition by low and hopefully more tolerable doses of estrogen. Nineteen postmenopausal women with ER-positive advanced breast cancer patients were included in the study and were treated with low dose estrogen (LDE), 2 mg estradiol valerate (E2 V). Clinical benefit was observed in 5 patients (26%), all five patients had a SD ≥6 months. The CBR was similar as seen with 30 mg and 6 mg E2 by Ellis et al. [18]. Four patients were re-challenged with the same AI as on which the cancer had progressed and three of these patients (75%) showed evidence of re-sensitisation achieving clinical benefit for a second time. Re-sensitisation was also seen in the study of Ellis et al. [18] in 3 out of 7 patients (43%). Four patients (21%) discontinued treatment due to toxicities. Reasons for discontinuation were hypercalcemia, mucositis, headaches and vaginal bleeding. Frequently reported side effects were nausea, lethargy, mastalgia, headache and vaginal bleeding. In summary, 2 mg E2 V showed a similar CBR as higher doses (6 and 30 mg) used in previous trials [18], but the toxicity was higher than expected.

5. Efficacy of AIs and FUL in heavily pre-treated patients with advanced breast cancer

Nowadays, AIs (letrozole and anastrozole (non-steroidal AIs), exemestane (steroidal AI)) and FUL (pure ER antagonist that blocks and accelerates degradation of the ER) are widely used in treating breast cancer in the advanced setting, therefore it is also interesting to compare the efficacy of AI and FUL versus the efficacy of

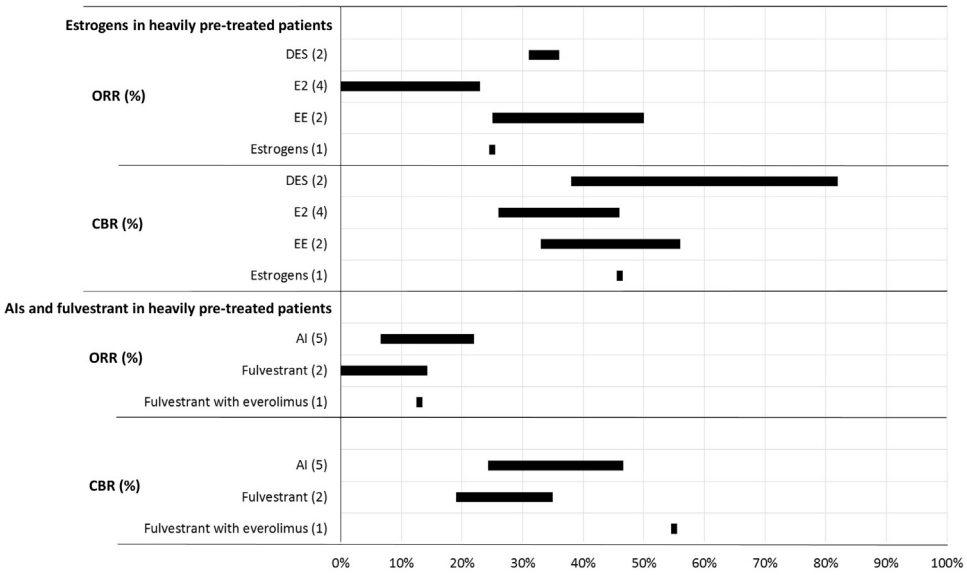

Fig. 3. Objective response and clinical benefit rates of estrogens versus AIs/FUL in heavily pre-treated patients.
Figure created based on data from Boyer and Tattersall [28] and Lonning et al [12] for DES; Ellis et al [18] (two dose levels), Chalasani et al [16] and Zucchini et al [17] for E2; Agrawal et al [13] and Iwase et al [15] for EE; Ingle et al [29] (two dose levels), Jones et al [30], Lonning et al [31], Gennatas et al [34] for AIs; Franco et al [32] and Ingle et al [33] for FULV; Massarweh et al [35] for FULV with everolimus. The number of studies included in this figure for each compound is given between brackets. Different dose levels of the same compounds are seen as separate studies.

HDEs. Unfortunately, no comparative trials of AIs or FUL versus HDEs have been performed so far, so only indirect comparisons can be made. In order to get an impression of the anti-tumour activity of HDEs versus AIs and FUL, trials with AIs and FUL in heavily pre-treated postmenopausal women with advanced breast cancer are summarized below.

Ingle et al. [29] performed a randomized phase II study using two dosages of letrozole (0.5 mg and 2.5 mg per day) as third line hormonal therapy for patients with advanced breast cancer. Patients were required to have failed two prior hormonal therapies. In total, 91 postmenopausal patients, 46 receiving 0.5 mg and 45 receiving 2.5 mg of letrozole per day, were assessable for response. At the lower dose, 9 out of the 46 patients (20%) showed an objective response and 18 patients (39%) showed a clinical benefit. For the high dose group, 10 out of the 45 patients (22%) showed an objective response and 21 patients (47%) demonstrated a clinical benefit. The median times to progression were 97 days for the low dose group versus 154 days for the high dose group. Both treatments were well tolerated. Most frequently reported side effects were nausea, emesis, anorexia, lethargy, headache and hot flushes.

Jones et al. [30] assessed the anti-tumour activity of exemestane (25 mg/day) administered as third-line therapy in postmenopausal women refractory to TAM and megestrol acetate. In total 91 patients were included in the study. Twelve patients demonstrated an objective response (13%, four patients had a CR and eight patients a PR). The overall clinical benefit was 30%. The treatment was well-tolerated. Most frequently reported drug related side effects were mild nausea and hot-flushes.

Lonning et al. [31] evaluated the efficacy and safety of exemestane (25 mg/day) in postmenopausal women with advanced breast cancer who had progressive disease after treatment with a nonsteroidal AIs. In total 241 patients were included in the study, 16 patients (6.6%) demonstrated an objective response (three CRs and 13 PRs) and 24.3% showed a clinical benefit. Exemestane was well tolerated. Most frequently drug related side effects were nausea, fatigue and hot flushes, so similar to what has been reported by Jones et al. [30].

Anti-tumour activity of FUL (250 mg once-monthly intramuscular injection) in heavily pre-treated postmenopausal breast cancer patients with prior hormone therapy and chemotherapy was assessed by Franco et al. [32]. In total 42 postmenopausal women were included in the study. None of the patients demonstrated an objective response, but 8 patients showed a SD resulting in a clinical benefit of (19%). Fulvestrant was well-tolerated. Side effects reported were bone pain, edema of lower extremities, diarrhea and dizziness.

Ingle et al. [33] also evaluated the anti-tumour activity of FUL (250 mg once-monthly intramuscular injection) in postmenopausal patients with disease progression on third generation AIs and at the most one additional hormonal treatment. Out of the 77 eligible patients, 11 patients showed an objective response (14.3%, all PRs) and 16 patients demonstrated a SD for at least 6 months resulting in a CBR of 35%.

Gennatas et al. [34] have assessed the anti-tumour efficacy of exemestane administered as third-line hormonal therapy in postmenopausal women with advanced breast cancer refractory to letrozole and anastrozole. In total 60 postmenopausal women were enrolled of which 12 (20%) showed an objective response. The overall CBR was 38.3%.

Massarweh et al. [35] reported a study in which they assessed the anti-tumour activity of combined FUL and everolimus (10 mg per day) in postmenopausal patients with advanced breast cancer. Everolimus is able to inhibit mTOR, a key signalling pathway in hormone resistance. Prior therapy included TAM and chemotherapy, with 26% of the patients having received 3 or more hormonal therapies. In total 31 evaluable patients were included in the study of which 4 patients (13%, one CR and three PRs) showed an objective response. An additional 13 patients showed a SD resulting in an overall CBR of 55%. Most common dose-limiting toxicity reported was mucositis. In addition, metabolic changes including hyperglycemia and hypercholesterolemia were also frequently reported which may have a potential impact on long-term risk of cardiovascular disease. Altogether the toxicities of everolimus were less than would be expected using chemotherapy, but still greater than hormone therapy alone.

6. Discussion

It is quite remarkable that the concept of treating breast cancer with high doses of estrogens was introduced in 1944 at a time when surgical removal of estrogen producing and estrogen production stimulating endocrine glands (ovaries, adrenals, pituitary) was standard practice for the treatment of advanced breast cancer. As described nicely by Jordan [36] it was possibly a matter of serendipity that Haddow [1] recognised the potential use of HDEs for the treatment of breast cancer. Two concepts are dominating the discussion on this controversial issue since then for more than 70 years and both concepts were already recognised by Haddow. These concepts are "the estrogen paradox" and the "gap hypothesis". The "estrogen paradox" refers to the fact that on the one hand estrogens are known to stimulate the growth of breast cancer, whereas on the other hand high doses of estrogens are an effective treatment for this disease. The "gap hypothesis" refers to the fact that HDEs are only significantly effective when the breast cancer has been devoid of estrogen exposure for a considerable amount of time, either because the patient is postmenopausal for at least five years or due to long term antiestrogen treatment.

In this review an effort is made to summarise the literature data on HDEs for the treatment of breast cancer and both concepts are evaluated. When judging the value of HDEs for advanced breast cancer treatment, one has to distinguish between its efficacy, the potential mechanism of action of estrogens under these circumstances and its side effects. Last but not least there is the question whether at present there is a place for HDEs in the treatment of breast cancer. These four issues will be discussed next.

6.1. The efficacy of HDEs

Until the introduction of TAM in the 1970s, HDE was used as primary hormone treatment of breast cancer. With HDEs, objective response rates (ORRs) up to 50% (judged by tumour regression) were observed (see Fig. 1). Consistently it was found that significant therapeutic effects were only found in women who were at least five years postmenopausal. The ER status of breast cancer patients was still unknown at the time of these early studies.

Fig. 2 shows ORRs of six comparative studies with TAM versus high doses of DES or EE. The response rates varied from 6 to 53% for TAM, from 10 to 41% for DES and from 25 to 31% for EE. Also in these studies efficacy required a postmenopausal status of five years or more. There were no significant differences in efficacy between TAM and the estrogens. However, the consistently superior side effect profile of TAM resulted in the replacement of HDEs for the first line treatment of advanced breast cancer and HDE treatment was abandoned and no longer practised. A remarkable finding in the study of Matelski [26] comparing HDEs and TAM is the efficacy of HDE in three patients with ER negative breast cancer. This finding deserves further investigation in patients with triple-negative breast cancer (TNBC).

HDEs returned in the nineties for the treatment of second or third line hormone treatment in ER positive patients who became resistant to treatment with TAM and/or AIs. Results from clinical trials in which heavily pre-treated patients with advanced breast cancer were treated with HDEs, have shown ORRs between 0 and 50% and clinical benefit rates (CBRs) between 26 and 82%. So, HDE seems to be an effective treatment option in ER positive patients who were exposed to multiple prior hormonal therapies and showed recurrence of the disease. Dose-dependency has not been studied appropriately, but in the study of Ellis et al. [18] no difference was observed between the efficacy of 6 mg E2 versus 30 mg E2, whereas with the 30 mg dose there were more serious side effects impacting quality of life of the patients.

No direct comparative studies are available for HDE versus AIs or FUL. Data from clinical trials with AIs and FUL in heavily pre-treated postmenopausal patients, demonstrated ORRs between 6.6%–22% and CBRs between 19 and 55% (see Fig. 3). The highest CBR (55%) was observed in the study of Massarweh et al. [35] who combined FUL with the mTOR inhibitor everolimus. However, the addition of everolimus also increased toxicity, particularly mucositis, which interferes with drug compliance and may lead to treatment discontinuation. Comparing the results in this heavily pretreated population, HDEs are at least as effective, if not superior to AIs and FUL, and could therefore be considered as a treatment option in patients refractory to hormone treatment.

Although the ORR and CBR are well accepted and useful parameters to judge the clinical effects of anti-cancer treatments, survival with a reasonable quality of life is the most important clinical efficacy issue. Interestingly, in 1999 Peethambaram et al. published long term follow-up data of the patients included in the trial of Ingle et al. [9]. Although the ORR and the median duration of response were not significantly different between the groups, survival was significantly better for patients on DES versus patients on TAM. In the DES arm, the median survival was 3.0 years and the 5-year survival was 35%, whereas in the TAM arm, the median survival was 2.4 years and the 5-year survival 16%. This confirms the efficacy of HDEs for the most important criterion i.e. survival.

The data summarised in this review demonstrate beyond doubt that HDE is effective for the treatment of advanced breast cancer, both for first line treatment as well as for treatment after the occurrence of endocrine resistance to TAM and AIs. This confirms the "estrogen paradox" since the use of estrogens is generally considered to increase the risk of breast cancer and stimulate breast cancer growth. Essential for the efficacy of HDE is the "gap hypothesis". This is an extended period of estrogen deprivation required before the tumour becomes sensitive to high dose estrogen treatment. For first line treatment, patients had to be more than 5 years postmenopausal to obtain significant clinical effects of HDEs. This was already specifically identified as the key factor for efficacy by Kautz [7] and Kennedy [6] in the sixties and confirmed by Haddow [37] in the seventies. HDEs as second or third line treatment with TAM and/or AIs start per definition after a considerable period of estrogen deprivation, creating the "estrogen gap". Santen and Alfred [38] even suggest that the lower incidence of breast cancer observed in the Women's Health Initiative (WHI) estrogen-only study [39,40] could also be explained by an estrogen gap, i.e. the fact that the women in the study were on average 63 years old and long after menopause when they started estrogen-only treatment.

In summary, assuming scientific agreement about the growth-promoting effect of estrogens [41,42], the efficacy data reported in this review for high doses of estrogens confirm both the "estrogen paradox" as well as the "gap hypothesis".

6.2. Mechanism of action of HDE treatment

How to explain the "estrogen paradox" i.e. what is the mechanism of action behind the two "Faces of Janus" of estrogens [43]. Song and Santen et al. [44] developed the long term estrogen deprived (LTED) MCF-7 cell model and showed that high concentrations of estradiol (≥0.1 nM) reduced the growth of LTED cells by 60% and increased apoptosis sevenfold by a Fas death receptor mediated mechanism. They suggest that the tumour regression induced by HDE in breast cancer patients may result from this Fas-mediated apoptosis. Earlier the same group had shown that estrogen deprivation of LTED cells causes hypersensitivity of the cells to estradiol [45] and they introduced the concept of "Adaptive Hypersensitivity" [46], referring to the changing responsiveness of breast cancer cells to various hormonal therapies. In an editorial accompanying the paper of Song and Santen [44], Soto and Sonnenschein [43]

Table 2
Overview of side effects per System Organ Class and side effect.

% AE per System Organ Class and per side effect	DES N = 195	EE N = 82	TAM N = 267	E2[a] N = 98
Blood and lymphatic system disorders	1,5%		3,7%	
Jaundice	0,5%			
Leukopenia	0,5%		3,4%	
Thrombocytopenia	0,5%		0,4%	
Cardiac disorders	4,1%			
Congestive heart failure	4,1%			
Gastrointestinal disorders	67,7%	47,6%	19,9%	39,8%
Abdominal bloating/distress				2,0%
Constipation			1,1%	3,1%
Diarrhea	4,1%		2,6%	3,1%
Nausea/vomiting	63,6%	47,6%	16,1%	31,6%
Hepatobiliarly disorders		4,9%		
Liver function impairment		4,9%		
Infections and infestations		6,1%		13,3%
Flu-like symptoms/fever		6,1%		2,0%
Infection				11,2%
Investigations		4,9%	0,7%	
Weight gain		4,9%		
Weight loss			0,7%	
Metabolism and nutrition disorders	9,2%	1,2%	7,9%	10,2%
Anorexia	6,2%		4,1%	
Hypercalcemia	3,1%	1,2%	3,7%	3,1%
Hyponatremia				7,1%
Neoplasms, benign, malignant and unspecified				3,1%
Tumour flare				3,1%
Nervous system disorders				8,2%
CNS ischemia				1,0%
Dizziness				3,1%
Headache				4,1%
Psychiatric disorders	0,5%		0,4%	13,3%
Psychiatric disorder	0,5%		0,4%	13,3%
Renal and urinary disorders	12,8%		0,4%	
Incontinence	12,8%		0,4%	
Reproductive system and breast disorders	23,1%	81,7%	3,0%	49,0%
Amenorrhea				
Breast pain/nipple tenderness	9,7%	1,2%		20,4%
Endometrial thickening		14,6%		
Libido increased		1,2%		
Spontaneous galactorrhea		1,2%		
Vaginal bleeding/spotting/discharge	12,8%	25,6%	1,5%	26,5%
Vaginal itching			0,4%	2,0%
Vulvovaginitis			1,1%	
Withdrawal bleeding	0,5%	37,8%		
Respiratory, thoracic and mediastinal disorders				5,1%
Cough				2,0%
Dyspnoea				3,1%
Skin and subcutaneous tissue disorders	12,8%	15,9%	0,4%	
Nipple/areola pigmentation	10,8%	15,9%		
Pruritis				
Rash	2,1%		0,4%	
Vascular disorders	2,6%	12,2%	12,0%	2,0%
Hot Flushes	1,5%	8,5%	12,0%	
Phlebitis	1,0%	2,4%		
Thrombosis/embolism		1,2%		2,0%
General and administration site disorders	32,3%	35,4%	7,5%	78,6%
Edema/fluid retention/pleural effusion/lymphoedema	31,3%	15,9%	4,1%	19,4%
Lethargy/lassitude/drowsiness/fatigue	1,0%	12,2%	0,4%	23,5%
Pain (including bone pain)		7,3%	3,0%	35,7%
Musculoskeletal and connective tissue disorders		12,2%		3,1%
Arthralgia		12,2%		3,1%

Table created *based on data from Beex* et al. [10], *Chalasani et al.* [16], *Cole et al.* [21], *Ellis et al.* [18], *Gockerman et al.* [27], *Ingle et al.* [9], *Iwase et al.* [15], *Kennedy* [6], *Matelski et al.* [26], *Stewart et al.* [25] *and Zucchini* et al. [17].

[a] *E2 includes also E2V.*

concluded that since sex steroids may act as mediators of both cell proliferation and cell death, a better understanding of the mechanism behind estrogen-induced apoptosis is important in order to improve the prognosis of breast cancer patients. Several research groups tried to find mechanistic explanations for estrogen induced regression. The group of Soto and Sonnenschein [47] suggested that E9 (PHD zinc finger protein) may be a mediator for estrogen induced regression based on *in vitro* experiments in E8CASS cells (an MCF-7 variant) and in the same year the group of Jordan [48] has studied *in vivo* regression by estrogens in tumours resistant to TAM treatment in athymic mice transplanted with MCF-7 tamoxifen stimulated tumour cell lines. The data of the group of Jordan [48] suggest that long-term TAM exposure also results in adaptation to estrogen-induced apoptosis, which may explain the efficacy of HDEs after the development of TAM resistance and is also complying with the 'gap hypothesis'. Santen and colleagues postulate that enhanced sensitivity of breast cancer tumour cells to estrogens after estrogen deprivation is due to overproduction of growth factor signalling pathways which interact with receptor mediated events [38].

Recently, Jordan [36] and Suba [49] summarized the research that has been performed on exploring the mechanism by which estrogens are able to induce apoptosis of breast cancer cells. From these publications it becomes clear that breast cancer cell growth and breast cancer cell apoptosis are both regulated via the estrogen receptor (ER). According to Jordan [36], the key to trigger apoptosis with estrogens is the selection of breast cancer populations that are resistant to long term estrogen deprivation, because these cells become vulnerable to estrogen-induced apoptotic cell death. Suba [49] explains the mechanism of action of HDEs by the fact that estrogen treatment is capable of restoring estrogen signalling – even after long term antiestrogen therapy – which is important for triggering apoptotic tumour cell death. Especially the review of Jordan [36] provides a very complete and comprehensive summary of the literature and the work of his own group and is advised for further reading. Both for tumour growth and for regression, the estrogen receptor seems to play an important role. Extensive research has been done to investigate the role of ERα, but so far little is known about the potential role of the ERβ.

6.3. The side effects of HDE

Estrogens, certainly high doses, have a negative safety image, especially in terms of side effects and increased risks of cardiovascular disease and breast cancer. All side effects reported with incidence rates in the studies mentioned in this review have been listed in Table 2 per system organ class and side effect. The side effects reported in the comparative studies with TAM are also included in Table 2.

High doses of estrogens have side effects indeed. High incidences were observed for nausea and vomiting (32–64%), vaginal bleeding due to the unopposed estrogen treatment (13–38%) and edema and fluid retention (16–31%). Overall DES showed more side effects than EE and E2 and with 30 mg E2 more side effects occurred than with 6 mg E2, whereas efficacy (measured by the ORR and CBR) was similar. Cardiovascular side effects apart from edema were rare, being congestive heart failure with DES (4%), phlebitis with DES (1%) and with EE (2%), and thrombosis/embolism with EE (1%) and with E2 (2%). Overall the seriousness and intensity of the side effects reported in the studies reviewed and related to HDEs were better than expected and do not give rise to major concerns.

The most important side effects of TAM mentioned in Table 2 were nausea and vomiting (16%) and hot flushes (12%). As mentioned by Gockerman [27], although the side effects with DES were more frequent than with TAM, these usually occurred in the first weeks, were mild in intensity and not life-threatening. Nevertheless in the comparative studies of HDE versus TAM, the investigators consistently reported more side effects with HDEs and therefore and in view of the equal efficacy they concluded that TAM should be preferred above HDEs. These developments marked the end of the use of HDEs as the first line treatment of advanced breast cancer. However, the long term use of TAM as primary or adjuvant treatment has disclosed that TAM acts as an estrogen on the endometrium, causing hyperplasia and endometrial cancer and requiring close supervision of these serious side-effects of TAM [50,51]. Unopposed HDE treatment will cause the same endometrial problems in women with an uterus, which can be counteracted by either regular ultrasound control of the endometrium and occasional progestin withdrawal [52] in case of endometrial growth or prevention by the placement of a progestin-releasing IUD [53].

When patients become resistant to hormonal therapy, the next step is treatment with chemotherapeutic agents. In this setting the goal of care is not just to optimize length, but also quality of life, so treatment-induced toxicity must be carefully considered. Taking into account the side effect profile of HDEs as discussed above together with the observed clinical efficacy, HDEs should be considered as a valuable alternative to chemotherapy in selected patients.

6.4. Is there still a place for HDE?

As argued and demonstrated in this review, treatment of advanced breast cancer with high doses of estrogens is as effective as TAM and AIs and is also effective after the development of resistance to TAM and AIs. However, HDEs have the negative reputation of having side effects, especially related to the cardiovascular system. This review shows that although these side effects are indeed more frequent with HDEs compared to TAM and AIs, these unwanted effects have a low incidence and are relatively innocent. All available estrogens that were investigated (DES, E2 and EE) seem qualitatively similar with respect to pharmacodynamic effects as argued before [54] and have the same side effect profile, although DES may be somewhat worse. Remarkably, conjugated equine estrogens (CEEs) have not been investigated for the treatment of breast cancer, most likely because this mixture of horse urine derived steroids contains many different estrogens with unknown toxicity at higher dose levels. With respect to the pregnancy estrogens, estriol is not suitable for long-term oral treatment due to the very short oral elimination half-life of this estrogen and estetrol has not been investigated for this indication so far.

In summary, HDE is an effective treatment for advanced breast cancer after long-term estrogen deficiency by inducing apoptosis, but the estrogens investigated (DES, E2 and EE) have too many side effects as compared to presently available antiestrogen hormonal preparations making them less suitable as the first line treatment. However, HDEs could be a valuable alternative to chemotherapy when patients become resistant to hormonal therapy and estrogens with less side effects could also be suitable for primary treatment, provided the women treated are at least five years postmenopausal.

Contributors

All authors contributed to the content and development of the manuscript, and the first two authors contributed equally to this review.

Conflict of interest

HJTCB is CEO and shareholder, and CV and AED are employees of Pantarhei Bioscience BV. Pantarhei Oncology BV, an affiliate of Pantarhei Bioscience, is developing estetrol for the treatment of breast cancer and prostate cancer.

JT has no conflict of interest to declare.

Funding

No funding was sought or received for writing this review paper.

Provenance and peer review

This article has undergone peer review.

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