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Review article

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

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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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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