Commentary

Estrogen as therapy for breast cancer

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Abstract

High-dose estrogen was generally considered the endocrine therapy of choice for postmenopausal women with breast cancer prior to the introduction of tamoxifen. Subsequently, the use of estrogen was largely abandoned. Recent clinical trial data have shown clinically meaningful efficacy for high-dose estrogen even in patients with extensive prior endocrine therapy. Preclinical research has demonstrated that the estrogen dose–response curve for breast cancer cells can be shifted by modification of the estrogen environment. Clinical and laboratory data together provide the basis for developing testable hypotheses of management strategies, with the potential of increasing the value of endocrine therapy in women with breast cancer.

Keywords: breast cancer, dose–response, endocrine therapy, estrogen

Introduction

High-dose estrogen was the endocrine treatment of choice in postmenopausal women with advanced breast cancer prior to the introduction of tamoxifen in the 1970s. Cole *et al*. reported the first clinical trial of tamoxifen in women with late or recurrent breast cancer [1], and compared their findings with those from another similarly conducted trial in which women received diethylstilbestrol (DES) or an androgen. They concluded that the level of response was of the same order for the three agents but that an advantage for tamoxifen was the low incidence of 'troublesome side effects'.

Consistent with these early findings, the acceptance of tamoxifen as preferable to estrogen therapy was based not on a superior efficacy, but rather on an improved tolerability demonstrated in phase III trials [2,3]. It is common practice to employ a series of endocrine agents in patients who remain candidates for such therapy on the basis of sites, extent, and tempo of disease and clinical status. It is remarkable given the prior importance of estrogens that, following the establishment of tamoxifen as the standard, estrogens largely disappeared from the endocrine therapy mindset of practicing oncologists, being relegated to the end of a list of agents that included aromatase inhibitors (AIs), progestins, and androgens.

We have recently updated our trial of DES versus tamoxifen. Although the trial is small in size by today's standards, it provided mature survival data in that 95% of the 143 eligible patients had died [4]. There was no significant difference between the two agents in terms of response rates and time to progression. However, survival was modestly and significantly better for women initially treated with DES (adjusted $P = 0.039$), with median survivals of 3.0 years versus 2.4 years, and 5-year survivals of 35% and 16%, respectively.

Estrogen as salvage endocrine therapy

A recent report by Lønning *et al*. described the use of high-dose DES in women with prior endocrine exposure [5]. This was a prospective phase II clinical trial that used well-established (Union Internationale Contre le Cancer)

AI = aromatase inhibitor; DES = diethylstilbestrol; E2 = estradiol; LTED = long-term estrogen-deprived.

criteria for patient assessment. Eligibility criteria included a requirement for evidence of endocrine sensitivity as indicated by a prior response or 6 months of disease stability on an endocrine agent.

Thirty-two patients were entered in the trial with a median of four prior endocrine regimens (range, two to 10 regimens). Three or more endocrine regimens had been employed in almost all (i.e. 29) of the patients, and 20 patients (62%) had also received prior chemotherapy. This population of patients can thus be considered heavily pretreated. Considering hormonal receptor status, one-quarter had either estrogen receptor-negative and progesterone receptor-negative tumors (two patients), or the receptors were unknown (six patients). From the standpoint of patient outcomes, it is remarkable that 10 patients (31%) achieved either a complete response (four patients, 12%) or a partial response (six patients, 19%), with one-half of these responses lasting for longer than 1 year. Although all but two patients had the responses in 'local regional' disease, the longest responder (>124 weeks) was a patient with visceral metastasis.

The fact that high-dose estrogens are not tolerable in all patients is illustrated by the fact that six patients (19%) stopped therapy because of side effects. This proportion is of the same order as our experience in the first-line treatment setting [2], where nine out of 74 patients (12%) discontinued DES because of side effects. It has become the present author's experience that a step-wise escalation of the estrogen dose over 1–2 weeks, and in some cases longer, will ameliorate the toxicity and make the treatment tolerable. A previous report also identified efficacy for DES in a smaller group of 11 patients, in whom all but one had received at least two prior therapies and four achieved a complete response or a partial response [6].

Interpreting the Lønning *et al*. estrogen trial

Care must be taken in attempting to place the results of the Lønning *et al*. phase II trial [5] in the proper context because this involves the perilous process of cross-study comparisons. This is particularly the case when utilizing the parameter of response rate, as this can be greatly modulated by patient selection. Some observations are possible, however, regarding levels of response seen with the most efficacious endocrine agents available today, albeit in less heavily pretreated patient populations.

Two trials evaluated third-generation AIs in patients who had disease progression after tamoxifen and megestrol acetate. Jones *et al*. evaluated the steroidal AI exemestane in 91 patients and identified a response rate (complete response + partial response) of 13% [7]. Letrozole was evaluated in a similar population and in 45 patients treated at the recommended dose of 2.5 mg/day; the response rate was 18% using different criteria [8].

Two studies have also evaluated exemestane but in patients who had prior nonsteroidal AI exposure. Thürlimann *et al*. studied exemestane at 200 mg/day, which is eight times the recommended dose, in 78 patients with progressive disease on aminoglutethimide, and with most patients also on tamoxifen [9]. They found a response rate of 26%. Lønning *et al*. used the currently recommended dose of 25 mg/day in a large phase II trial of exemestane in 241 patients [10]. The prior AI in this study had been a third-generation, nonsteroidal agent (anastrozole, letrozole, or vorozole) in 44% of patients, with the remainder having received prior aminoglutethimide. Three-quarters of the patients had received two prior endocrine agents, and 22% had received three prior endocrine agents. The response rate was more modest in this trial, being 6.2%.

In a second-line endocrine therapy setting in patients having received prior tamoxifen, the response rates observed for the third-generation AIs anastrozole, exemestane, and letrozole were 10% [11], 15% [12], and 24% [13], respectively. These rates were observed in phase III studies in comparison with megestrol acetate. The 31% objective response rate observed in the Lønning *et al*. trial with DES [5] is thus remarkable and encouraging even considering all the cautionary caveats regarding interpretation of a small phase II trial.

Resistance to endocrine therapy

The mechanisms by which a patient's cancer becomes resistant to endocrine therapy are poorly understood. Insights into potential mechanisms come from the work of Masamura *et al*. [14], who hypothesized that the response observed to subsequent endocrine therapy could be related to increased sensitivity to estradiol (E2), due to adaptation by tumor cells to E2 deprivation. These investigators grew MCF-7 cells in serum-free medium to eliminate E2, and these cells were designated long-term estrogen-deprived (LTED) cells.

When the E2 dose–response curve was generated, a typical bell-shaped curve was seen with an initial increase in stimulation at lower doses, a peak stimulation, and a progressive diminution in stimulation at higher E2 concentrations. The LTED cells showed maximal stimulation at 10^{-14} mol/l E2. This represented a shift to the left in the dose–response curve, in that the curve for the wild-type MCF-7 cells had maximal stimulation of 10^{-10} mol/l, which represents a 10,000-fold higher concentration compared with the LTED cells.

Masamura *et al*. also studied the concentration of a pure antiestrogen (ICI 164384) necessary to inhibit growth by 50%. They found that it was substantially lower in the LTED cells (10^{-15} mol/l) than in the wild-type MCF-7 cells (10^{-9} mol/l).

The results of these studies provide a potential explanation for loss of efficacy of agents that act to lower or block E2. The explanation is that the breast cancer cells can adjust to the agent-induced lower E2 environment by becoming more sensitive to a given E2 concentration.

Use of a shifting estrogen dose–response curve for therapeutic purposes

One can hypothesize from the preceding discussion that, in the clinical setting, long-term estrogen deprivation could shift the estrogen dose–response curve of a tumor to the left and increase the sensitivity to estrogen therapy. In considering this hypothesis, a case from the author's clinic is of note.

A 62-year-old patient was diagnosed with estrogen receptor-positive stage I breast cancer and was given adjuvant tamoxifen. The patient developed metastatic disease 2 years later, which was treated for more than 1 year with a third-generation nonsteroidal AI and then with a steroidal AI without response. On subsequent progression, the patient elected another endocrine trial. The patient received high-dose estrogen and achieved almost complete clearing of pleural metastasis, which has been maintained for longer than 1 year.

It is plausible that the year-long treatment with AIs represents the clinical equivalent of long-term estrogen deprivation seen in the laboratory. The third-generation AIs such as letrozole and anastrozole are potent, and they have been found to substantially suppress total-body aromatization (>99.1% and 97.3%, respectively) and plasma E2 levels (87.8% and 84.9%, respectively) [15].

The clinical observations combined with the laboratory data noted earlier support further study of high-dose estrogen following maximal estrogen deprivation in appropriately selected patients.

Song *et al*. studied LTED and wild-type MCF-7 cells with regard to the potential mechanism of action of high-dose estrogen [16]. Apoptosis was induced by high concentrations (≥0.1 nM) of E2 in LTED cells, with a sevenfold increase over vehicle-treated controls and a concomitant 60% decrease in growth, but not in wild-type MCF-7 cells. The authors presented data showing that only LTED cells expressed Fas protein, and they suggested that high-dose estrogen may induce tumor regressions in postmenopausal women through activation of Fas-mediated apoptosis.

Clinical responses to a wide range of estrogen doses have been seen in breast cancer. Responses to DES in a double-blind, randomized clinical trial were observed over a 3-log range from 1.5 to 1500 mg daily [17]. Substantial tumor regressions have been seen with even relatively minor modifications in estrogen levels, as in withdrawal of physiologic estrogen replacement [18]. Howell addressed the issue of a shifting estrogen dose–response curve in a patient's tumor [19] and discussed potential strategies of preventing resistance such as fixed alternating endocrine therapies and stepwise modifications of estrogen levels.

Conclusions

The use of high-dose estrogen as therapy in selected patients with metastatic breast cancer and prior endocrine exposure has merit, based on the efficacy demonstrated in a prospective clinical trial conducted by Lønning *et al*. [5]. Although the potential for toxicity exists with estrogen therapy, the tolerability in the majority of patients is better than with chemotherapy.

There are important implications of these clinical data when considered in conjunction with recent laboratory findings related to shifting of estrogen dose–response curves for breast cancer cells with alterations of the hormonal environment. Together, they suggest testable hypotheses of management strategies that have the potential for increasing the value of endocrine therapy for women with breast cancer.

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