What is the role of chemotherapy in estrogen receptor-positive, advanced breast cancer?

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Most breast tumors depend on female sex hormones for development and growth, thus being amenable to endocrine therapies. In the management of estrogen receptor (ER)-positive, advanced breast cancer, conventional wisdom dictates the use of endocrine therapy for patients with good prognostic features, whereas chemotherapy is recommended for the treatment of visceral crisis. There is, however, considerable uncertainty regarding the best initial strategy for patients with poor prognostic features other than visceral crisis, such as small-volume visceral involvement and a short disease-free interval after adjuvant therapy. In this article, we examine the role of chemotherapy in ER-positive, advanced breast cancer. Our review of the literature suggests that, in the absence of visceral crisis, endocrine agents should always be considered a major option for the initial treatment of ER-positive, metastatic breast cancer due to their proven efficacy and favorable toxicity profile. Although certain chemotherapy agents can induce higher response rates and more rapid responses, which are desirable effects in particular situations, the up-front use of chemotherapy does not seem to influence the overall outcome of the disease. In the subset of patients with epidermal growth factor type 2-positive disease, on the other hand, current data still do not support the use of endocrine agents alone.

Key words: antineoplastic combined chemotherapy protocols, aromatase inhibitors, breast neoplasms, drug therapy, estrogen, fulvestrant, receptors

introduction

Breast cancer differs from most tumors because of its dependence on female sex hormones for development and growth [1]. At least for the most frequent histological type of breast cancer, infiltrating ductal carcinoma, breast tumors that express estrogen receptors (ERs) represent nearly 65% of cases among women diagnosed before menopause and 80% among postmenopausal patients [2]. Since postmenopausal women account for nearly 75% of patients with breast cancer [3], a rough estimate of the epidemiology of ER-positive disease suggests that this subtype of breast cancer accounts for approximately three-quarters of cases of this neoplasm. In Brazil, where the estimated annual incidence of breast cancer approaches 50 000 cases [4], nearly 37 000 women with ER-positive disease are expected to be diagnosed every year.

Although nearly 90% of patients with breast cancer are diagnosed when the disease is still potentially curable [5], more than half of women diagnosed with early-stage disease and treated with local and adjuvant therapies are destined to develop systemic recurrences [6]. Both for women with metastatic disease upon diagnosis and for those who develop systemic recurrences after initial therapy, treatment has a palliative intent, given the fact that the vast majority of patients will die of their disease [7, 8]. Treatment may include chemotherapy, endocrine therapy, epidermal growth factor type 2 (HER-2)-targeting agents, and antiangiogenic therapy, depending on tumor and patient characteristics [9].

Chemotherapy plays a key role in the management of patients with advanced breast cancer and is the initial therapeutic modality of choice for patients with hormone receptor (HR)-negative disease [7–9]. Regardless of HR expression, recent studies have shown that the addition of trastuzumab leads to improved survival, in comparison with chemotherapy alone, when HER-2 is overexpressed [10, 11]. Given the established role of trastuzumab in the first-line treatment of HER-2-positive breast cancer, and the fact that these tumors are less responsive to endocrine agents [12], the following discussion will not take such cases into consideration. It is therefore assumed that chemotherapy combined with trastuzumab remains the first-line treatment of choice for HER-2-positive, advanced breast cancer.

In contrast with the management of ER-negative, advanced breast cancer, the clinician is frequently faced with a decision regarding the best initial therapy for a woman with ER-positive disease. For such patients, conventional wisdom dictates the use of endocrine therapy, at least for patients with a less
aggressive phenotype, such as those with predominance of bone and soft-tissue metastasis [7, 9]. On the other hand, patients with visceral crisis, frequently defined as the presence of lymphangitic lung metastases, bone marrow replacement, carcinomatous meningitis, or significant liver metastases [13, 14], are recommended to be treated with chemotherapy, even in the case of ER-positive disease [15]. However, for patients without visceral crisis but with poor prognostic features, such as visceral involvement or short disease-free interval after adjuvant therapy, both chemotherapy and hormonal therapy are options. It is very important to recognize that the simple presence of visceral metastasis should not be considered definitive indication for chemotherapy, as many patients may present with small-volume liver or lung disease with very little clinical manifestations and be adequate candidates for endocrine strategies. In this article, we attempt to examine the role of chemotherapy in ER-positive breast cancer, particularly in the subset of patients with advanced disease.

**ER-positive disease: brief overview of endocrine therapies**

Based on the seminal observation by George Beatson of breast tumor regression following oophorectomy [16], more than a century of laboratory and clinical research has demonstrated the role played by estrogen in the natural history of breast cancer. As a consequence, several therapies have been developed to reduce estrogen levels or to block signaling through the ER [17]. These therapies include tamoxifen and other selective ER modulators, the third-generation aromatase inhibitors, and the selective ER downregulator fulvestrant. Single-agent endocrine therapy is considered the treatment of choice for patients with ER-positive disease, with sequential use of further endocrine agents at the time of disease progression [7, 8]. The current range of endocrine therapies offers the opportunity for prolonging benefit from treatment and delaying tumor progression and the ultimate initiation of chemotherapy.

Since its approval by the Food and Drug Administration in 1977, tamoxifen remained the mainstay of endocrine therapy for breast cancer until the late 1990s [18, 19]. After the demonstration of the role of aromatase inhibitors in the second-line endocrine therapy of postmenopausal women with ER-positive, advanced breast cancer [20, 21], randomized trials have shown that aromatase inhibitors are superior to tamoxifen in the first line [22, 23]. More recently, fulvestrant has been shown to provide a safety and efficacy profile comparable to those of the aromatase inhibitors anastrozole and exemestane [24–26]. The expanding endocrine arsenal and the integration of fulvestrant into the therapeutic sequence may further extend the treatment window during which chemotherapy is postponed, with potential improvement in quality of life in advanced breast cancer [27].

The potential clinical benefits of using sequential endocrine agents, as opposed to the use of chemotherapy, should be based on considerations of efficacy, safety, and cost-effectiveness. It is therefore critical to examine the efficacy of chemotherapy in advanced, ER-positive breast cancer in the context of clinical trials. Specifically, it would be important to review the evidence for or against the use of chemotherapy as the initial therapy of choice for women with ER-positive disease.

**Chemotherapy results in ER-positive, HER-2-negative breast cancer advanced disease**

Following the initial observation of a possibly increased [28, 29] or decreased [30] response rate among ER-positive tumors, the relationship between ER expression and response to chemotherapy in the metastatic setting has received relatively little attention in the literature. Contemporary randomized trials of chemotherapy in advanced breast cancer have included patients regardless of ER or progesterone receptor expression. For example, selected phase III trials comparing single agents versus combination chemotherapy in patients failing an anthracycline enrolled between 35% and 45% of women with HR-positive disease [31–34]. To our knowledge, chemotherapy treatment results in the subgroup of women with HR-positive tumors have not been reported separately or adequately compared with those with HR-negative disease in the setting of advanced breast cancer.

Similarly, clinical trials of chemotherapy in advanced breast cancer have not made an explicit attempt to include patients with symptomatic visceral involvement or short disease-free interval after adjuvant therapy. It is conceivable, however, that such patients are overrepresented in these trials because patients with a more indolent disease course would preferentially be treated with endocrine agents. On the other hand, many of the women with HR-positive disease included in chemotherapy trials have received endocrine agents or have become endocrine-refractory before chemotherapy. Therefore, the merit of using cytotoxic chemotherapy as opposed to endocrine therapy in aggressive cases cannot be properly ascertained from these trials.

Regardless of disease aggressiveness, a few randomized trials have compared endocrine agents with chemotherapy in the setting of metastatic disease. Priestman et al. compared cytotoxic and endocrine therapies in 92 patients and found higher response rates (49% versus 21%) in the former group. In addition, a significantly longer survival was ascribed to cytotoxic treatment in the subgroup of premenopausal women; in contrast, endocrine treatment produced response rates and survival equivalent to those produced by cytotoxic drugs in postmenopausal patients with predominantly soft-tissue disease [35]. In a larger randomized trial among postmenopausal patients, 75% of whom had unknown ER status, investigators from Australia and New Zealand compared doxorubicin plus cyclophosphamide (AC) followed by tamoxifen after progression versus tamoxifen followed by AC. Although the initial response rate to tamoxifen (22%) was lower than that to AC (45%), the overall survival (OS) was almost identical in both arms. Adverse prognostic factors for survival, regardless of treatment group, were liver metastases, short disease-free interval, poor performance status, and prior adjuvant chemotherapy. In no subgroup was initial chemotherapy associated with a significantly better survival [36]. In a second randomized trial comparing combination chemotherapy followed by tamoxifen after progression or the reverse...
sequence, Taylor et al. [37] reported a higher response rate and longer response duration with the endocrine agent. Finally, in 60 patients with advanced disease refractory to tamoxifen, Dixon et al. [38] found a higher response rate (23% versus 13%) but no significant differences in median time to tumor progression, response duration, or OS, when mitoxantrone was compared with megestrol acetate.

The results of these studies have been combined with those from other published and unpublished trials comparing endocrine therapy alone with chemotherapy alone in advanced breast cancer. The meta-analysis of these trials found no significant difference in terms of OS, when endocrine therapy was compared with chemotherapy [39]. Interestingly, over 50% of the women included in these trials had visceral disease, one of the features commonly regarded by clinicians as an indication for chemotherapy. The pooled reported response rates suggested a significant advantage for chemotherapy over endocrine therapy, but the two largest trials [36, 37] in the meta-analysis showed trends in opposite directions, and a test for heterogeneity was significant, thus questioning this observation. There was little information on toxicity or quality of life, but six of the seven fully published trials commented on increased toxicity with chemotherapy.

It should be noted that the trials included in the meta-analysis were published from 1963 to 1995 and some of them have included patients with ER-negative or ER-unknown tumors. In addition, those trials investigated endocrine agents no longer considered as first-line choices and most chemotherapy regimens used in the trials are currently outdated. Therefore, the comparative efficacy of chemotherapy and endocrine therapy in patients with ER-positive, advanced breast cancer treated with contemporary agents remains uncertain. Moreover, the specific merit of chemotherapy in the subgroup of patients with aggressive disease cannot be ascertained with precision, given the fact that clinical trials have not selected participants on the basis of disease aggressiveness. Given the paucity of data regarding the comparative efficacy between chemotherapy and endocrine therapy as first-line treatment of choice in advanced breast cancer, it may be interesting to examine the current evidence regarding the role of chemotherapy in ER-positive, early breast cancer.

early disease

In contrast with advanced breast cancer, the relationship between ER expression and response to chemotherapy in early-stage disease has been the subject of several subgroup analyses in recently reported studies, being suggested that the benefit from chemotherapy is significantly greater in, or even restricted to, patients with ER-negative disease, in comparison with patients with ER-positive breast cancer. In the International Breast Cancer Study Group Trial V, there was a marked benefit from the use of chemotherapy among postmenopausal patients with HR-negative tumors, whereas postmenopausal patients with HR-positive tumors and premenopausal patients had no benefit from this treatment [40]. In Trial IX, conducted by the same group, the addition of chemotherapy to tamoxifen improved disease-free survival and OS only in the subgroup of women with ER-negative tumors [41]. Similar results were observed in a subgroup analysis of Intergroup Trial 0100, indicating that chemotherapy adds no benefit in patients with a stronger expression of ER [42]. In node-negative, ER-positive disease, a retrospective analysis of the National Surgical Adjuvant Breast and Bowel Project Trial 20 has shown that the addition of combination chemotherapy with cyclophosphamide, methotrexate, and fluorouracil to tamoxifen is beneficial only in the subgroup of patients with a high risk of recurrence, as determined by a 21-gene panel recurrence score [43]. Albeit without a reference treatment arm containing endocrine therapy only, a retrospective study, including 6644 node-positive breast cancer patients from Cancer and Leukemia Group B and US Breast Cancer Intergroup trials, showed significantly lower reductions in the risks of recurrence and death, when patients with ER-positive tumors were compared with those with ER-negative disease [44]. However, subgroup analyses of other randomized trials comparing various adjuvant chemotherapy regimens and doses found no preferential benefit for the optimization of chemotherapy regimens and schedules according to ER expression [45–48].

Similar to the observations in the adjuvant setting, several reports have suggested that ER-negative tumors derive more benefit from neoadjuvant chemotherapy than their ER-positive counterparts [49–53]. Selected results from such reports are shown in Table 1 and suggest that ER-positive tumors display lower rates of pathological complete response to neoadjuvant chemotherapy than ER-negative tumors. In addition, ER expression was found to be an independent predictor of pathological complete response in a recently developed nomogram for neoadjuvant chemotherapy [54]. It should be noted that neoadjuvant endocrine therapy with aromatase inhibitors may result in rates of objective response and breast-conserving surgery similar to those seen with chemotherapy in postmenopausal women with HR-positive tumors [55].

### endocrine therapy results in HER-2-positive breast cancer

HER-2 overexpression has been shown to confer an overall worsened prognosis in breast cancer [56]. HER-2 is overexpressed in ~10% of ER-positive breast tumors [57]. Preclinical data indicate that HER-2 overexpression may lead to endocrine resistance in human breast cancer [58, 59]. From the clinical standpoint, however, such resistance seems more

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<tr>
<th>First author</th>
<th>n (% with positive ER/HR)</th>
<th>pCR in ER/HR-positive (%)</th>
<th>pCR in ER/HR-negative (%)</th>
</tr>
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<tbody>
<tr>
<td>Bear [49]</td>
<td>2286 (45)</td>
<td>8.2</td>
<td>16.7</td>
</tr>
<tr>
<td>Ring [50]</td>
<td>435 (71)</td>
<td>8.1</td>
<td>21.6</td>
</tr>
<tr>
<td>von Minckwitz [52]</td>
<td>904 (68)</td>
<td>6.2</td>
<td>22.8</td>
</tr>
<tr>
<td>Colleoni [51]</td>
<td>399 (43)</td>
<td>7.6</td>
<td>33.3</td>
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<tr>
<td>Guarnieri [53]</td>
<td>1719 (67)</td>
<td>7.8</td>
<td>23.7</td>
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<td>1719</td>
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ER, estrogen receptor; HR, hormone receptor; pCR, pathological complete response.
evident in studies of tamoxifen. Elledge et al. [60] found an association between the overexpression of HER-2 and resistance to tamoxifen in 205 ER-positive patients enrolled on Southwest Oncology Group 8228. In addition, Arpino et al. [61] observed a significantly shorter time to treatment failure and OS for HER-2-positive, advanced breast cancer patients treated with tamoxifen, in comparison with HER-2-negative patients. Aromatase inhibitors, on the other hand, have been shown to provide improved response rates, in comparison with tamoxifen, in the neoadjuvant treatment of HER-2-positive breast cancer [62, 63]. Selected results of two randomized trials comparing aromatase inhibitors with tamoxifen in the neoadjuvant setting are shown in Table 2. In the metastatic setting, the TAnDEM trial randomized 208 patients with HER-2-positive, HR-positive, metastatic breast cancer to receive anastrozole alone or in combination with trastuzumab until disease progression. Crossover to trastuzumab was actively offered to all patients who progressed on anastrozole alone. Clinical benefit rate was significantly higher in the combination group (42.7% versus 27.9%; \( P = 0.026 \)), which also had a longer progression-survival benefit rate (median of 7.7 versus 3.8 months; \( P = 0.00006 \)) [65].

Finally, Robertson et al. [64] investigated the activity of fulvestrant in 102 patients with HER-2-positive, ER-negative disease, 42% of whom had previously received trastuzumab. The clinical benefit rate was 42%, with median duration of 14.5 months. The results of these studies suggest that endocrine agents, alone or combined with trastuzumab, play a role in selected patients with HER-2-positive, HR-positive breast cancer. However, there are no known clinical predictors of benefit from endocrine therapy in such patients, and an individualized decision seems more appropriate at this point in time.

**Discussion**

In recent years, it has become clear that breast cancer is not one single biological entity, but rather a collection of distinct malignant subtypes arising from the breast epithelium. The taxonomy of breast cancer is currently undergoing profound changes due to the availability of techniques that allow the systematic investigation of expression patterns of thousands of genes in tumors using complementary DNA microarrays [66]. The classification of breast tumors based on gene expression profiles has prognostic implications [67, 68]. One important finding from genomic studies was the separation of ER-positive and ER-negative tumors, with gene expression profiles having prognostic implications [67, 68]. This separation has important implications for both clinical and research settings.

**Table 2.** Selected results of studies assessing the efficacy of endocrine agents in HER-2-positive, HR-positive breast cancer

<table>
<thead>
<tr>
<th>First author</th>
<th>Setting</th>
<th>n with HER-2-positive disease</th>
<th>Agent</th>
<th>Response rate (%)</th>
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</thead>
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<tr>
<td>Ellis [62]</td>
<td>Neoadjuvant</td>
<td>23</td>
<td>Tamoxifen</td>
<td>17</td>
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<td></td>
<td></td>
<td>16</td>
<td>Letrozole</td>
<td>69</td>
</tr>
<tr>
<td>Smith [63]</td>
<td>Neoadjuvant</td>
<td>9</td>
<td>Tamoxifen</td>
<td>22</td>
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<tr>
<td></td>
<td></td>
<td>12</td>
<td>Anastrozole</td>
<td>58</td>
</tr>
<tr>
<td>Robertson [64]</td>
<td>Metastatic</td>
<td>102</td>
<td>Fulvestrant</td>
<td>9</td>
</tr>
</tbody>
</table>

HER-2, epidermal growth factor type 2; HR, hormone receptor.

remains to be investigated whether these and other findings bear implication in clinical practice, where decisions are still based on phenotypic tumor features and patient profile. Recent studies already suggest that responses to neoadjuvant chemotherapy correlate with gene expression profile, with tumors displaying the ER-positive gene signatures being less likely to respond than other types of breast cancer [70].

While we still do not have an answer to this question, our review of the literature suggests that the use of chemotherapy may be optimized by selecting those patients most likely to benefit from it. In the neoadjuvant and adjuvant settings, it seems clear that patients with ER-negative tumors are the ones accruing the most benefit from the use of chemotherapy. If the lower response rates to neoadjuvant chemotherapy seen in ER-negative tumors are not to be interpreted as a reason to withhold such treatment, nor should chemotherapy be withheld in patients with ER-positive tumors treated adjuvantly, the smaller relative benefit from chemotherapy in such patients, in comparison with their ER-negative counterparts, should be factored into the decision regarding indication of the chemotherapy. This recommendation becomes even more critical for postmenopausal patients as the relative benefit from chemotherapy diminishes with increasing age [6]. Ultimately, only properly designed clinical trials addressing these questions prospectively will be able to answer these issues. Two ongoing international initiatives (Microarray In Node negative Disease may Avoid ChemoTherapy [MINDACT] and TaylorX) are prospectively using gene expression platforms in the attempt to select a subgroup of endocrine-responsive patients who may be spared chemotherapy [71, 72].

Important treatment goals in advanced breast cancer include symptom control and an improved quality of life. Although treatment of systemic recurrence may prolong survival and improve the quality of life, it is not curative. Therefore, treatments associated with minimal toxicity, such as endocrine therapies, are preferred whenever reasonable [9]. Our review of the literature suggests that in the absence of visceral crisis, endocrine agents should always be considered a major option for initial treatment of ER-positive, metastatic breast cancer. Due to its proven efficacy and favorable toxicity profile, the presence of poor prognostic features, such as visceral involvement and a short disease-free interval after adjuvant therapy, should not be regarded as contraindications for the use of hormonal therapy first.

Although certain chemotherapy agents or combinations can induce high response rates and rapid responses, which are desirable effects in particular situations, especially in the case of symptomatic visceral involvement, the up-front use of chemotherapy does not seem to influence the overall outcome of the disease. Whether this strategy may be advantageous over the use of hormonal agents first in those specific settings is surely possible, but this hypothesis is difficult to be proven or rejected in the context of a controlled clinical trial.

Therefore, considering that most patients frequently utilize both endocrine agents and chemotherapy during the course of their disease, clinicians should carefully select the situations in which aggressive treatments will be indicated. This is particularly important in the postmenopausal setting, considering the lack of evidence on the benefit of chemotherapy.
over endocrine therapy, regardless of the presence or absence of poor prognostic features [35, 36]. On the other hand, our review indicates that current data still do not support the use of endocrine agents alone in the subset of patients with HER-2-positive disease. Despite the encouraging preliminary results with fulvestrant monotherapy, the role of this agent in the treatment of ER-positive, HER-2-positive, advanced breast cancer remains to be tested in randomized clinical trials.

In conclusion, for women with potentially endocrine-responsive disease, even those with poor prognostic features, the comparative efficacy of current generation chemotherapy and endocrine therapy should be further investigated. For those patients with indolent disease and ER-responsive disease, endocrine therapy is considered the treatment of choice, given its proven efficacy and favorable toxicity profile [73]. And finally, for those patients with ER-positive, HER-2-negative disease, trastuzumab, alone or in combination with chemotherapy, is still the better treatment option.

references


46. Barrios et al. Volume 20


