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REVIEW ARTICLE

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Combination of chemotherapy and endocrine treatment in breast cancer — is it still a taboo?

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ABSTRACT

For many years, it has been believed that a combination of endocrine therapies with chemotherapeutic agents should not be used in clinical practice as the treatment for either early or advanced breast cancer. These conclusions resulted from clinical trials conducted several decades ago, which combined a selective estrogen receptor modulator (tamoxifen) with polychemotherapy regimens in early breast cancer patients. However, recent results of clinical trials and cohort studies that evaluated combinations of novel chemotherapy regimens with aromatase inhibitors or fulvestrant demonstrated that chemoendocrine therapy is feasible, safe, and active in patients with HR+ breast cancer at various stages of the disease. This article reviews the available data on the safety, activity, and clinical utility of systemic treatment approaches based on the simultaneous administration of endocrine agents with mainly metronomic chemotherapy.

Keywords: chemoendocrine, metronomic, chemotherapy, endocrine treatment, breast cancer

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Introduction

Expression of steroid receptors — mainly estrogen receptor (ER) but also progesterone receptor (PR) — is a characteristic feature of luminal breast cancers representing approximately 80% of all breast cancer cases [1]. Therefore, endocrine and chemotherapeutic agents, active in luminal tumors, are undoubtedly the most commonly used therapies for treating breast cancer (BC) both in curative and palliative settings. However, despite the activity of both strategies in luminal breast cancer, combining them in the treatment of ER+ BC patients is deemed highly inappropriate [2–5]. This consensus is based on the assumption that both approaches display opposite mechanisms of action. On the one hand, chemotherapy-induced impairment of cell cycle machinery exerts an irreversible blockade of cellular proliferation leading to cancer cell death [6]. Conversely, endocrine therapy inhibits the steroid receptor-mediated gene expression and intracellular signaling cascade leading to tumor cell senescence [7, 8]. The consensus is that the higher the tumor proliferation rate, the higher the chemotherapy's cytotoxic potential [9]. However, since endocrine therapies inhibit cellular proliferation by directly targeting steroid receptors (SERMs, SERDs) or depleting systemic estrogens (gonadotropin agonists, aromatase inhibitors), cancer cells may become less susceptible to chemotherapy-induced cell death [10, 11]. Early *in vitro* studies provided conflicting results showing synergistic antitumor activity when tamoxifen was combined with antimetabolites such as methotrexate [12] or 5-fluorouracil [13] but antagonistic when combined with melphalan [14]. Despite contradictory and unconvincing preclinical data, many clinical trials evaluating the combination of endocrine therapy with chemotherapy (HCT) in early breast cancer patients have been conducted in the last two decades of the 20th century.

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Adjuvant therapy

Several studies evaluated HCT activity in the adjuvant setting. Pico et al. [15] compared a combination of tamoxifen and four cycles of epirubicin + cyclophosphamide (EC + TAMx) with a sequential treatment (4 × EC → tamoxifen) in 474 post-menopausal patients. The study has not demonstrated any differences in overall (OS) or disease-free survival (DFS). Similarly, a randomized study by Bedognetti et al. [16] evaluated a concurrent and sequential treatment with tamoxifen in 431 pre- and post-menopausal BC patients receiving adjuvant chemotherapy [6 × fluorouracil + epirubicin + cyclophosphamide (FEC) → cyclophosphamide + methotrexate + fluorouracil (CMF)]. This study also did not demonstrate significant differences between study groups regarding DFS or OS [sequential *vs.* concurrent arm: hazard ratio (HR) of death = 1.06; 95% confidence interval (CI) 0.78–1.44; p = 0.76; HR of relapse = 1.16; 95% CI 0.88–1.52, p = 0.36]. However, in a subgroup analysis, in patients with extensively advanced disease (pN3), a significant benefit of concurrent HCT was observed — HR for OS = 2.05 (1.11–3.78). In a large phase III study involving 1177 post-menopausal BC patients, Albain et al. demonstrated intriguing, albeit non-significant, differences between concurrent and sequential adjuvant HCT based on 6 × fluorouracil + doxorubicin + cyclophosphamide (FAC) and five years of tamoxifen [17]. The 10-year DFS and OS rates were 60% *vs.* 53% and 68% *vs.* 62% for sequential and concurrent HCT, respectively. Del Mastro et al. [18] retrospectively analyzed two randomized clinical trials MIG1 and MIG5 conducted by the GONO-MIG group, which involved 2269 pre- and post-menopausal BC patients treated with 6 × FEC or 6 × dose-dense FEC (MIG1) and 6 × FEC *vs.* 4 × epirubicin + paclitaxel (ET) (MIG5) [18]. In both studies, 1096 patients received tamoxifen administered concurrently or following chemotherapy. The analysis did not show any statistically significant differences between the simultaneous and sequential arms regarding OS or DFS. However, the study provided an interesting observation in premenopausal patients receiving the sequential endocrine treatment, who demonstrated an increased risk of death compared to patients taking tamoxifen concurrently with chemotherapy (HR for death = 1.39; 95% CI 0.7–2.75) [18]. Although all these studies and retrospective analyses did not confirm significant differences between sequential and simultaneous HCT, patients at high risk of recurrence and death (premenopausal, N3) seemed to benefit more from concurrent than sequential tamoxifen-based HCT. This observation was additionally confirmed in a meta-analysis summarizing the studies on concurrent HCT [19]. In summary, the available data on concurrent tamoxifen-based HCT does not support using this strategy in adjuvant settings outside of clinical trials, irrespectively of the risk of recurrence.

Neoadjuvant therapy

Unlike in studies on adjuvant HCT which were based on tamoxifen, concurrent HCT regimens evaluated in neoadjuvant trials utilized aromatase inhibitors alone or in combination with ovarian suppression. Torrisi et al. [20] retrospectively assessed the impact of combining endocrine treatment (letrozole plus GnRH analog) with neoadjuvant chemotherapy in pre-menopausal ER+ BC patients and compared it to an unmatched group of patients treated with neoadjuvant chemotherapy (CT) and subsequent adjuvant hormone therapy [tamoxifen plus aGnRH (HT)]. They demonstrated that concurrent HCT, compared to neoadjuvant CT alone, was associated with a 5-fold increase in the complete pathological response (pCR) rate (5.0% *vs.* 1.1%) and a significant decrease in the proliferation rate as assessed by Ki67 expression. Five-year DFS was 78 *vs.* 41% in the experimental and control groups, respectively (adjusted HR = 0.46; 95% CI 0.27–0.79). However, the difference in long-term outcomes could be related to the fact that patients treated with concurrent HCT received adjuvant letrozole for five years, whereas the chemotherapy-only group was treated with adjuvant tamoxifen.

A randomized phase III trial evaluated neoadjuvant chemotherapy alone or in combination with letrozole in post-menopausal locally advanced BC patients [21]. The study included 101 patients, of whom 34% were ER–. Chemotherapy comprised 3–5 cycles of FAC regimen administered every three weeks. Concurrent neoadjuvant HCT compared to CT resulted in significantly increased pCR rates in the general population (25.5% *vs.* 10.2% p = 0.049), and in ER+ BC patients (31.2% *vs.* 10.0%; p = 0.040). Combination of endocrine therapy with chemotherapy had a similar safety profile as CT, with hot flushes being the only adverse event (AE) significantly more frequent in HCT-treated patients (23.4% *vs.* 6.1%; p = 0.016).

In another trial (CBCSG-036), 249 BC patients received neoadjuvant chemotherapy (4 × EC or 3 × FEC followed by 4 × or 3 × docetaxel with less intensive treatment in elderly patients) and were randomized to CT alone or letrozole-based HCT arms (with aGnRH in premenopausal patients) [22]. Neoadjuvant HCT was associated with an insignificantly increased pCR rate (7.2% *vs.* 4.0%) compared to CT. There was an intriguing suggestion that the efficacy of concurrent HCT regarding pCR and DFS could have been associated with high pretreatment Ki67 expression (> 20%).

In another prospective study, Matsunuma et al. [23] randomized 70 patients to neoadjuvant chemotherapy [12 × paclitaxel → 4 × doxorubicin + cyclophosphamide/epirubicin + cyclophosphamide (AC/EC)] alone or combined with concurrent endocrine therapy (anastrozole ± aGnRH). The study did not demonstrate any significant differences in the pCR rate; however,

numerically, the pCRs were more frequent in patients receiving CT alone (9.7% *vs.* 3.0%). On the other hand, a complete lack of pathological response was observed in 6.5% and 0% of patients receiving CT and HCT, respectively.

A large neoadjuvant phase III trial NSABP B-52 enrolled 311 pre- and post-menopausal patients with HER2-positive, ER+ breast cancer, who were randomized in a 1:1 ratio to 6 cycles of standard TCHP therapy (docetaxel plus carboplatin plus trastuzumab plus pertuzumab) alone or combined with concurrent estrogen deprivation [24]. The study did not demonstrate a significant improvement in the pCR rate, which, however, it was higher in patients treated with concurrent endocrine therapy (46% *vs.* 41%), especially in post-menopausal patients (45% *vs.* 35%). The NSABP B-52 study demonstrated no added toxicity in patients receiving concurrent HT and indicated at least some additive activity when standard therapy in HER2-positive patients was administered simultaneously with endocrine treatment.

In conclusion, the available data on concurrent aromatase inhibitor-based neoadjuvant therapy suggests the need for further evaluation of this strategy in well-designed larger clinical trials such as the ongoing GIM-10-CONSENT [25].

Palliative setting

There is no doubt that the dissemination process involves adaptation and multidirectional evolution of cancer cells, which can lead to the synchronous presence of metastatic lesions that differ significantly despite stemming from the same primary neoplastic cell [26, 27]. Those differences (on genomic, epigenomic, or metabolic levels) may cause significant changes in tumor cell biology leading to activation of novel signaling pathways, development of chemoresistance, loss of immunogenicity, or loss of estrogen dependency [28, 29]. The phenomenon of distinct systemic therapy response patterns in different metastatic lesions is well known to oncologists experienced in the treatment of advanced BC (ABC) patients [30]. It is not rare that in ER+ ABC patients, endocrine therapy can lead to objective responses in bone metastases without any effect on liver metastases. Still, upon treatment switch and administration of chemotherapy, liver metastases respond, whereas bone metastases start to progress. This phenomenon represents a good rationale for considering the combination of chemotherapy and endocrine treatment in ER+ ABC patients. It may sound controversial, but the ultimate mechanism of action of CDK4/6 inhibitors (CDK4/6i) — partners of choice for endocrine agents in ER+ ABC, is typical for phase-specific cytotoxic agents such as vinorelbine, capecitabine, or methotrexate routinely used in various metronomic regimens [31–37]. Indeed, the CDK4/6i used as monotherapy demonstrated moderate antitumor activity in many endocrine-insensitive tumors [31]. Still, when used in conjunction with first or second-line endocrine treatment, they significantly improve outcomes of ER+ HER2– ABC patients [38–40]. Intensive research into CDK4/6i mechanisms of action indicated that besides their phase-specific inhibition of tumor cell proliferation, they also impair tumor-induced angiogenesis [41] and positively modulate the immune system [42–44]. However, it is not a unique feature of CDK4/6i since this phenomenon is a classical mechanism of action associated with chronic administration of classic cytotoxic drugs in so-called metronomic chemotherapy [33, 45, 46]. Therefore, the efficacy of CDK4/6i combined with endocrine treatment may not only be related to their specific molecular features but also to how they are administered in a chronic daily low-dose fashion.

Several articles and case reports seem to confirm this assumption. In a single-arm phase II study, 41 ABC patients following ≤ 1 line of endocrine treatment without previous chemotherapy received metronomic capecitabine combined with fulvestrant [47]. Administration of concurrent HCT induced 24.5% of objective responses and 58.5% of clinical benefit rate. Median PFS and OS were 14.98 and 28.65 months, respectively, which compares favorably to the outcomes observed in pivotal clinical trials on CDK4/6i. The treatment was well tolerated, with hand-foot syndrome being the most common G3 adverse event observed in 7.3% of patients.

A retrospective study by Aurilio et al. [34] evaluated the combination of fulvestrant with metronomic chemotherapy (cyclophosphamide plus methotrexate) in 32 heavily pretreated ER+ ABC patients. Concurrent HCT led to one partial response and disease stabilization in 17 patients (53%). Again the study showed promising clinical activity of HCT with an excellent safety profile.

In a phase II study, Rashad et al. [48] evaluated a combination of capecitabine-based chemotherapy with endocrine treatment (letrozole or tamoxifen) as the first-line treatment of ER+ ABC patients. Concurrent HCT was associated with objective response and clinical benefit rates in 60% and 82.5% of patients, respectively. Median PFS and OS for the whole population were 10.0 and 23.3 months, respectively. In patients treated with the capecitabine and letrozole combination, median PFS and OS were higher (by 4.0 and 3.0 months, respectively) than in patients receiving capecitabine and tamoxifen combination.

In a retrospective analysis conducted at the Jagiellonian University-Medical College Hospital, 39 pretreated ABC patients received a FulVEC HCT regimen combining fulvestrant and metronomic polychemotherapy

(capecitabine, vinorelbine, cyclophosphamide) [49]. Most patients (74%) previously received ≥ 3 lines of systemic treatment involving endocrine therapy and chemotherapy. The clinical benefit rate (CBR) was 87% in the whole population, and median PFS and OS were 8.5 months and 25.5 months, respectively. None of the treated patients stopped the treatment due to toxicity, and slight metronomic chemotherapy dose modifications were needed in 46% of patients.

In a large retrospective analysis, Shi et al. [50] evaluated the outcomes of 407 ER+ ABC patients treated in the first line with an aromatase inhibitor alone (n = 305) or combined with capecitabine (n = 102). The median PFS and OS rates in the combination group were 22.0 and 66.0 months and differed significantly compared to the endocrine treatment alone group (median PFS and OS — 14.0 and 49.0 months, respectively) [50].

Conclusions

There is still a lot of controversy regarding the concurrent chemoendocrine treatment of breast cancer, and lack of solid data supporting its use justifies this reluctance in the curative setting. This is somehow similar to the current situation of CDK4/6i in adjuvant and neoadjuvant settings. Although CDK4/6 inhibitors were shown to be highly successful in the palliative setting, their efficacy in adjuvant treatment by now is modest, with only abemaciclib approved in this indication [51–53]. Unlike CDK4/6 inhibitors, which have been studied in several large phase III clinical trials in ABC patients, data on palliative concurrent HCT are far less robust. However, similarities in general mechanisms of action between the CDK4/6i and classical cytotoxic drugs administered in a metronomic fashion (inhibition of cell-cycle progression, immunomodulation, inhibition of angiogenesis), along with available clinical and preclinical data, justify using metronomic chemoendocrine therapy in advanced ER+ BC patients. This strategy may be of critical importance in low and middle-income countries, where CDK4/6 inhibitors are not reimbursed and thus not available to the majority of ER+ ABC patients [54]. Additionally, novel active endocrine agents, such as oral SERD — elacestrant that are currently being studied in combination with targeted therapies such as CDK4/6 or PI3K inhibitors, will increase the costs of treating ER+ ABC beyond acceptable limits, thus making the state-of-the-art endocrine therapy unavailable for even more patients worldwide. Therefore, wise and reasonable decisions to study the well-known available intramuscular SERD with metronomic chemotherapy may make the endocrine-based combined strategies far more cost-effective and humanitarian.

Generally, metronomic chemotherapy, due to its multidirectional mechanism of action, may become an affordable alternative for many targeted agents, not only for CDK4/6 inhibitors but also for antiangiogenic agents. Additionally, its excellent safety profile allows for combining agents given to patients in a metronomic fashion with standard, intravenously administered cytotoxic, targeted, or immunotherapeutic agents [55]. Recent data from the METEORA-II study provided robust evidence for metronomic chemotherapy potentially in early lines of advanced BC treatment. In this phase II randomized study, metronomic chemotherapy [vinorelbine plus cyclophosphamide plus capecitabine (VEC)] was compared to weekly paclitaxel in 1st or 2nd line of advanced BC treatment [35]. Administration of VEC chemotherapy was associated with significantly improved PFS (HR = 0.67; 96% CI 0.46–0.96) without differences in OS. The low toxicity of metronomic chemotherapy and endocrine agents allows for their safe and well-tolerated combination. In many patients with disseminated BC, the concurrent administration of endocrine drugs and metronomic chemotherapy allows for complex control of highly heterogeneous diseases demonstrating distinct chemosensitivity and endocrine dependency. Concluding, the combination of endocrine treatment and chemotherapy is still not ready for prime time in the curative setting. Still, in the case of ER+ advanced breast cancer, it represents an important but underestimated treatment modality.

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Author contributions

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Conflict of interest

The author declares that there are no conflicts of interest.

Supplementary material

None.

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