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Extended adjuvant chemotherapy in endocrine non-responsive disease☆

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A B S T R A C T

Introduction and aims: There is a biological rationale for expecting benefit from longer duration therapy in the subpopulation of patients with endocrine non-responsive disease. Such tumors have a rapid cell proliferation and are associated with a high risk of relapse despite adjuvant chemotherapy. Moreover, prolonged duration of chemotherapy may be particularly relevant for patients with triple negative disease to inhibit the growth of tumors that are not susceptible to the effects of endocrine therapies due to lack of steroid hormone receptors, or to the effects of anti-HER2 target treatment.
Methods and results: The question of duration of adjuvant chemotherapy for breast cancer has been directly addressed in several trials herein presented. Most of these were small and, therefore, unsuitable for detecting differences of modest magnitude in intrinsic biological subtypes. In addition, a number of trials examine regimens which differ in duration of therapy, but also in the drugs given. In these trials the effects of duration and choice of drug are inextricably confounded. However incremental chemotherapy strategies, compared with less extensive therapies, were more effective in past studies particularly in patients with endocrine non-responsive disease.
Conclusions: The evidence resulting from past trials indicates that conventional-dose chemotherapy for 4–6 months is an adequate option in patients whose tumors present a low or no expression of steroid hormone receptors. These tumor subtypes are part of a highly heterogeneous subgroup (e.g., basal-like, molecular apocrine, claudin-low, HER-enriched). Tailored research through international cooperation is key to solidify consensus on how to treat individual patients with endocrine non-responsive breast cancer.

Introduction

Endocrine non-responsive breast cancer represents a group particularly relevant for tailored treatment investigations on adjuvant chemotherapy. In fact adjuvant chemotherapy may be particularly relevant to inhibit the growth of these tumors that are not susceptible to the effects of endocrine therapies due to lack of estrogen receptor (ER). In recent years, the concept of heterogeneity of breast cancer has been widely elucidated and emphasized, but the latest information is that, even within subtypes, tumors are heterogeneous. This is remarkably true for those tumors with negative hormone receptors [2]. Patients with HER2-positive and ER-negative disease in the pre-trastuzumab era were considered in the global pool of ER-negative in past trials. Only recently, after the introduction of trastuzumab, this subgroup of patients is considered as a distinct entity candidate to targeted adjuvant therapy of prolonged duration with a significant impact on their prognosis [1].

Endocrine non-responsive breast carcinomas are generally recognized as having a more rapid cell proliferation and consequently a high responsiveness to adjuvant chemotherapy. In particular, the triple-negative subtype is characterized by high expression of the proliferation cluster of genes [3] and by a higher proliferative index as measured by Ki-67 LI expression when compared with the endocrine-responsive subtype [4]. Recently, some biologically distinct triple-negative subgroups were identified using the transcriptome data set from 21 independent breast cancer studies. Different clusters were recognized based on mesenchymal features, immune system–related genes, DNA damage response genes, and activated androgen receptor signaling supporting the hypothesis that triple-negative represents an hetereogeneous group of diseases [5].

Potential targets for chemotherapeutic agents are present in triple-negative tumors, the majority of which overexpress EGFR and endothelial growth factors [6,7]. In vitro chemosensitivity

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studies have found that human cells lacking BRCA1, and to some extent other triple-negative cells, may be sensitive to drugs that cause double-strand breaks in DNA [8] such as alkylating agents. In recent years, PARP-inhibitors were enthusiastically investigated in triple negative tumors and although initial trials were promising [9] the foreseen benefits were not confirmed in randomized trials [10].

In the neoadjuvant setting, higher benefit from the introduction of chemotherapy can be expected among patients whose tumors do not contain steroid hormone receptors compared with those tumors defined as endocrine receptor positive [11,12]. Nevertheless patients with triple negative disease who are refractory to neoadjuvant chemotherapy tend to relapse early, with a peak of metastases occurring at 1 year [13], indicating that these patients probably belong to a subgroup within the triple negatives that should be better investigated with new agents, since it does not respond to chemotherapy with conventional drugs. Studies in the adjuvant setting in the node-positive population showed that patients with ER-negative disease derived a greater benefit from modern improvements in chemotherapy regimens when compared with those with ER-positive disease [14,15].

There are additional reasons to investigate the question of treatment duration in endocrine non-responsive breats cancer. Subjectively, shorter duration of chemotherapy is related to a lower incidence of side effects. A course of three cycles of CMF was better tolerated, and associated with more rapid improvement in quality of life than 6 cycles [16,17]. Less toxicity was observed with three cycles of CMF in study conducted by the GBSG [18]. Finally, shorter duration treatments are less costly than longer durations of the same agents.

Lessons learned from previous studies

The question of duration of adjuvant chemotherapy for breast cancer has been directly addressed in several trials [19–22]. Most of these were small and therefore unsuitable for detecting differences of even modest magnitude. Many trials examine regimens which differ in duration of therapy but also in the schedule and drugs given, being the effects of duration and choice of drugs confounded.

Mature studies were designed in an era when adjuvant therapies were selected according to the stage of the disease and where factors predictive of response (i.e. hormone receptor expression and HER2 overexpression\amplification) were uncommonly taken into consideration. Breast cancer is now recognized as a heterogeneous disease in which the chance that one treatment program will benefit all is not realistic [23]. The association between duration of chemotherapy and outcome may be confounded in retrospective analyses by the inclusion of both endocrine responsive and non responsive disease. As a matter of fact, the results of subgroup analyses should be treated with caution, especially because some of the subgroups had small sample sizes.

In premenopausal women, cytotoxic therapy is thought to exert its effects both by direct tumor cell kill and by an endocrine effect secondary to suppression of ovarian function [24]. The extent to which chemotherapy may exert such an endocrine effect will depend on the type of chemotherapy, the age of the patient [24,25], and on the hormone receptor expression of the tumor [26]. Other types of endocrine therapy such as tamoxifen [27] and medical suppression of ovarian function are prescribed concurrently or sequentially, so the optimal duration of chemotherapy in endocrine responsive breast cancer may also depend on whether or not such treatments are used. Therefore extended duration of chemotherapy should be better evaluated in patients with ER-negative tumors, where the cytotoxic rather than endocrine effects of chemotherapy in the absence of other endocrine treatments, might be larger.

Data from past series include information on several aspects of the disease collected in the earlier period, when the various prognostic and predictive factors were not available as they are today. Historically, patients were classified as having ER-negative ($<$10 fmol mg/cytosol protein or $<$10% of positive cells) and ER-positive ($\geq$10 fmol mg cytosol protein or $\geq$10% of positive cells) tumors to facilitate prediction of response to endocrine therapies. However, there is evidence that tumors with less than 10% of weakly positive cells may still experience tumor response, compared with those who had no detectable ER staining [28].

Extended adjuvant chemotherapy (more than 6 months)

The question of duration beyond 6 months of adjuvant chemotherapy has been directly addressed in several trials. Some of these investigated substantially long treatments, such as the SAKK and Milan studies (24 and 12 months of CMF, respectively) [29,30]. However most of these trials were small and, therefore, unsuitable for detecting differences of modest magnitude [20–22,31]. A meta-analysis of six of these trials comparing longer regimens versus at least 6 months of the same polychemotherapy showed that shorter treatment duration (6 months) was substantially as effective as a longer duration with a non-significant further reduction in recurrence with longer therapy that was not reflected in any apparent difference in survival [32].

A more recent EBCTCG overview evaluated 6000 women included in trials that directly compared longer versus shorter polychemotherapy with a mean treatment duration of 10·7 vs 5·0 months [33]. The overall results indicate little long-term advantage from longer treatment (HR for recurrence rates 0·95, 95% CI 0·88–1·02). Although there might be some advantage from longer treatment, extended chemotherapy should not be considered outside a clinical trial.

Dose-dense chemotherapy

A hypothesis that has been addressed is that a more frequent administration of chemotherapy might be more effective than schedules with classical time periods. Chemotherapy schedules were applied every three weeks since this time interval represents the time needed for bone marrow recovery for the majority of patients. It emerged that administration of selected drugs every two weeks, might be more effective than less frequent (every three weeks) delivery [34].

A dose-dense chemotherapy approach using concurrent doxorubicin and cyclophosphamide followed by paclitaxel was assessed in the Cancer and Leukemia Group B 9741 trial, a phase III randomized study on patients with node-positive operable breast cancer [35]. This trial showed a significant improvement in disease-free survival (DFS) and overall survival (OS) for the dose-dense chemotherapy arm and has become a treatment option in the treatment of node positive patients [23]. In a subsequent meta-analysis [36], dose-dense chemotherapy had a statistically significant benefit with respect to DFS only in receptor-negative patients (HR of relapse = 0.71; 95% CI = 0.56 to 0.89; I2 = 0%) [37]. These data support the hypothesis that a prolonged duration of chemotherapy is not an issue when a dose-dense approach is used.

About 6 months of adjuvant chemotherapy vs. shorter duration

As previously mentioned the question of duration of adjuvant chemotherapy for breast cancer (2–6 months) has been addressed in several trials that differ in duration of therapy, but also in the drugs combinations given. One of the most frequently used

anthracycline-containing adjuvant therapy schedules, four courses of intravenous doxorubicin and cyclophosphamide (AC) combination given once every 3 weeks, is administered within 63 days. In a direct comparison, six courses of classical CMF (154 days) and four courses of AC yielded super imposable results despite the different durations [38,39]. Similarly, in an Intergroup study, a short and complex 16-week regimen (including a continuous administration of cytotoxics during the period of treatment) provided results marginally superior to those observed with six courses of cyclophosphamide, doxorubicin and fluorouracil (CAF) [40]. The CALGB 40101 trial compared four and six courses of AC or paclitaxel (administered in the majority of cases in a dose-dense fashion) in women with breast cancer and 0–3 positive nodes. They found no difference in relapse-free survival or OS between four-course and six-course regimens. Unplanned subset analyses showed no interaction between the number of courses of therapy and tumor ER or HER2 status [41]. On the other hand, the US Intergroup performed a trial where the addition of 4 cycles of paclitaxel following four cycles of AC demonstrated a small but significant improvement DFS and OS using the longer, different regimen [31]. This improvement was seen mainly among patients with ER-negative tumors who did not receive tamoxifen. The NSABP B30 evaluated patients with operable, node-positive, breast cancer randomized to receive four courses of AC followed by four courses of docetaxel, four courses of doxorubicin and docetaxel or four courses of concurrent doxorubicin, cyclophosphamide, and docetaxel. Patients treated with sequential chemotherapy had a significant reduction in relapse or death as compared with those who received a shorter duration of therapy. No evidence of interaction between treatment effect and ER status was noted [42]. Similar results in terms of significant reduction in risk of relapse for extended chemotherapy were observed in the NSABP B28 study comparing four courses of AC followed by four courses of paclitaxel versus four courses of AC alone [43]. When the difference in duration was of smaller magnitude (four courses of AC followed by four courses of docetaxel vs. 6 courses of TAC) no difference was detected in another study [44]. The Breast International Group 02–98 trial compared sequential vs. concurrent administration of doxorubicin and docetaxel. Patients with four or more positive lymph nodes and patients with hormone receptor – negative disease showed the largest absolute improvement in 5-year DFS (7%) when the sequential docetaxel arm (doxorubicin, followed by docetaxel, followed by CMF) was compared with the control arms, although the difference was not statistically significant [45].

Timing and benefit of adjuvant chemotherapy

Based on early biological models attempting to portray effective adjuvant chemotherapy [46,47], several clinical trials were designed in the past to test the hypothesis that a treatment gap during the first 6 months of chemotherapy might improve therapeutic results. It was hypothesized that the gap would allow tumor cells to move from dormant to active phase and thus become more susceptible to additional chemotherapy courses based upon a modified Gompertzian model of tumor development with a stochastic growth rate [48,49].

IBCSG Trials 13–93 and 14–93 [50,51] were designed to prospectively evaluate whether the introduction of a 16-week gap would be beneficial for patients with node-positive breast cancer. Overall, the results indicate that treatment with and without a gap yielded similar DFS and OS. Exploratory subgroup analysis noted a trend towards decreased DFS for gap compared with no gap for women with ER-negative tumors not receiving tamoxifen, especially evident during the first 2 years [52]. The observation that a trend for an adverse outcome in ER-negative patients reflected early events is in line with the reported higher risk of relapse during the early years after surgery in patients with ER-negative disease [53]. Data from these studies raises the hypothesis that, for patients whose tumors are not endocrine responsive, chemotherapy should be delivered with no interruption during the first 6 months from surgery in order to maximize its effects.

Conclusions

Proper duration of adjuvant chemotherapy in the endocrine non-responsive setting is far from being defined with major issues of controversy still needing a resolution. Many different regimens were used and no clear indication for a particular regimen exist. Although no standard duration of chemotherapy was identified in clinical studies, incremental chemotherapy strategies compared with less extensive therapies were more effective across trials, especially in patients with endocrine non-responsive disease. Therefore it is reasonable to offer to patients with endocrine non responsive disease a chemotherapy regimen for duration of 4–6 months.

The efficacy of adjuvant systemic therapy for early breast cancer depends on variable features, including those of the tumor, the patient, and the treatment itself. Endocrine non-responsive disease (triple negative and non luminal HER2-positive disease) is substantially controlled by the direct cytotoxic effects of chemotherapy. Therefore future studies on the benefit of extended adjuvant chemotherapy might best be studied in this setting of patients. Indeed, this is particularly true for the triple negative subtype in the absence of endocrine effects of therapies and in the absence of the effects of prolonged anti-HER2 treatment.

It should be however emphasized that these tumor subtypes still include heterogeneous groups of tumors (e.g., basal-like, molecular apocrine, claudin-low, HER-enriched) and that within these groups there are many differences in terms of gene expression, mutations and druggable pathways. Tailored treatment investigations on tumor subtypes more likely to benefit from extended chemotherapy through international cooperation, is key to make progress and solidify consensus on how to treat individual patients with endocrine non-responsive breast cancer.

Conflict of interest statement

None declared.

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