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Review

Use of maintenance endocrine therapy after chemotherapy in metastatic breast cancer

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Abstract ***Background:*** For women with oestrogen receptor+ metastatic breast cancer (MBC), the options for systemic treatment include endocrine therapy (ET) and chemotherapy. For women whose disease is also HER2+, anti-HER2 therapies are also routinely used either with chemotherapy or less commonly with ET. Where chemotherapy is used as initial therapy, treatment is often discontinued due to cumulative toxicity in the absence of disease progression. In this setting, there is the option of introducing ET with the aim of prolonging response and delaying relapse.

Methods: Literature review revealed four trials addressing the question of whether there is a benefit from introducing ET following chemotherapy for MBC. We also sought evidence for alternative approaches, including concurrent chemotherapy and ET and continuing chemotherapy until disease progression.

Results: The evidence for the use of ET after chemotherapy in MBC is limited, and the trials done were small. Furthermore, they were performed at a time when both the chemotherapy regimens and ET were different from those used currently. Despite these limitations, there is probably a modest improvement in time to progression for the sequential use of ET after chemotherapy but with no overall survival benefit. An alternative approach, particularly considering agents with relatively low toxicity, such as orally bioavailable fluoropyrimidines, is to continue chemotherapy until disease progression.

Conclusion: Where chemotherapy for MBC is discontinued due to toxicity, in the absence of progression, the use of ET, with its relatively low toxicity, is a reasonable approach with the aim of delaying relapse.

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1. Introduction

Breast cancer is the most common cancer among women in the western world and is one of the leading causes of cancer mortality. Although almost 90% of patients present with early-stage disease [1], 20–30% of those treated will ultimately relapse with metastatic disease despite the use of adjuvant therapies [2]. The majority of breast cancers express oestrogen receptors (ERs) occurring in 65% of premenopausal and 80% of postmenopausal patients [3].

For women with ER+ metastatic breast cancer (MBC), the options are either endocrine therapy (ET) or chemotherapy. Additionally for HER2+ ER+ MBC, anti-HER2 therapies are routinely used either with chemotherapy or less commonly with ET.

ET is often used as first-line treatment for metastatic disease in those who have soft tissue, bone predominant, or low-volume visceral disease, reserving chemotherapy for those with more aggressive disease or visceral crisis. This is supported by the updated 2014 ESMO consensus guidelines for ER+ Advanced Breast Cancer (ABC), which state that 'ET is the preferred option for hormone receptor (HR)–positive disease, even in the presence of visceral disease, unless there is concern or proof of endocrine resistance or there is disease needing a fast response' [4].

There is, however, less certainty about the choice of therapy in those with small volume visceral involvement or where there has been a relatively short disease-free interval (DFI) following adjuvant treatment, suggesting a poorer prognosis. Many of these patients will do relatively well with ET, and reviews of the literature suggest that although chemotherapy induces better response rates and has longer time to progression (TTP), there is no overall survival (OS) benefit [5]. The relative expression of ER can also affect response rates to both chemotherapy and ET, with higher ER expression being associated with better response rates to hormonal therapy and lower ER associated with more chemosensitive disease [6–8].

Where chemotherapy is used as initial therapy, further treatment depends on whether chemotherapy is used for a fixed number of cycles (as is often the case with agents such as docetaxel), whether toxicity has halted chemotherapy or whether chemotherapy is used until disease progression. In the first two scenarios, there is the option of introducing ET after chemotherapy, and in this manuscript, we discuss the evidence for this approach, as well as the other options of maintenance chemotherapy and concurrent chemo-ET.

2. Method

We performed a literature review to identify studies regarding maintenance hormonal therapy after chemotherapy treatments in MBC. PubMed was searched for published studies, between January 1995 and December 2015, using the following search terms alone or in combination, in MeSH major topics, subheadings, terms, and article title/abstract: breast cancer, hormone therapy and maintenance. Reference lists of relevant papers were also searched for additional publications. Only four papers were identified which will be discussed below.

3. Evidence for the benefit of ET after chemotherapy

As a consequence of the expected cumulative toxicity associated with some palliative chemotherapy, a fixed number of cycles is often used, even in the absence of disease progression. Though commonly considered, there are few data with regard to evidence for benefit from the use of 'maintenance' endocrine therapy (MET) after discontinuation of chemotherapy in such circumstances.

Three published studies [9–11] specifically looking at this question have shown a modest improvement in TTP but no significant benefit in terms of OS. These studies will be discussed in more detail below. Only one of these studies was randomised, and all involved relatively small numbers of patients. A further older study [12] investigating prognostic factors in metastatic patients with objective response or stable disease after epirubicin chemotherapy also assessed the impact of MET and found it had a positive outcome in terms of survival. These studies are summarised in Table 1.

In a phase III randomised trial investigating the use of medroxyprogesterone acetate (MPA) in patients responding to chemotherapy for ABC, Kloke *et al.* [9] selected patients with anthracycline and progestin-naïve ABC who were progressing and treated them with epirubicin and ifosfamide. Patients without disease progression after six cycles of chemotherapy were then randomly assigned to no treatment or MPA 500 mg od until progression. Enrolled patients were not selected for ER positivity, but HR status was one of the stratification criteria. Ninety patients were randomised: 46 to MPA and 44 to observation. Seven patients discontinued MPA due to side-effects. Median TTP was 4.9 months for MPA versus 3.7 months for the observation arm in an intent-to-treat analysis ($p = 0.02$) and 4.9 v 3.0 months in the final efficacy analysis, completed after enrolment of 90 patients. Quality of life (QoL) scores were similar in the two groups. There was no difference in OS, with a median survival from randomisation was 17.4 months for those receiving MPA and 18.0 months for the observation cohort ($p = 0.39$). There was no significant difference in TTP between those with HR-positive and those with HR-negative disease. Treatment with MPA was the only significant factor associated with longer TTP after adjustment for covariates. Response to prior chemotherapy was associated with a trend to improved TTP.