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Original Research

Treatment decisions and the impact of adverse events before and during extended endocrine therapy in postmenopausal early breast cancer

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Abstract ***Background:*** Extended endocrine therapy beyond 5 years for postmenopausal breast cancer has been studied within multiple phase III trials. Treatment compliance in these trials is generally poor. In this analysis, we aimed to determine factors that were associated with participation in the phase III Investigation on the Duration of Extended Adjuvant Letrozole (IDEAL) trial and with early treatment discontinuation, and how this influenced survival outcome.

Methods: In the IDEAL trial, postmenopausal patients were randomised between 2.5 or 5 years of extended letrozole, after completing 5 years of endocrine therapy for hormone receptor-positive early breast cancer. A subgroup of this population participated earlier in the Tamoxifen Exemestane Adjuvant Multinational trial (5 years of exemestane or 2.5 years of tamoxifen followed by exemestane as primary adjuvant therapy) in which we explored which factors were determinative for enrolment in the IDEAL study. In the IDEAL cohort, we evaluated which factors predicted for early treatment discontinuation and the effect of early treatment discontinuation on disease-free survival (DFS).

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Results: Nodal status, younger age and adjuvant chemotherapy were significantly associated with higher enrolment in the IDEAL trial. In the IDEAL cohort, adverse events (AEs), the type of primary endocrine therapy and the interval between primary and extended therapy were associated with early treatment discontinuation. Among the reported AEs, depressive feelings (56%) were most frequently associated with early treatment discontinuation. Early treatment discontinuation was not associated with worse DFS (hazard ratio [HR] = 1.02, 95% confidence interval = 0.76–1.37).

Conclusions: In this analysis, we found that risk factors were most strongly associated enrolment in the IDEAL trial. In contrast, patient experiences were the most significant factors leading to early treatment discontinuation, with no effect on DFS.

1. Introduction

Extended endocrine therapy for hormone receptor-positive (HR+) early breast cancer, beyond the standard 5 years, is more frequently being used over the recent years. After 5 years of tamoxifen, it has been shown that extended therapy with either 5 additional years of tamoxifen or 5 years of an aromatase inhibitor (AI) has clinical benefit, particularly in high-risk (lymph node positive) disease [1–5]. However, less data are available on the value of extended adjuvant endocrine therapy after primary adjuvant therapy including an AI. Recently, results of trials studying extended therapy after an optimal primary adjuvant regimen (including AIs during the first 5 years) were presented and partly published, showing no significant benefit of extended therapy for the total group and suggesting that mainly high-risk subgroups might benefit from this extended therapy [6,7].

One of the problems regarding adjuvant endocrine therapy, both during primary and extended therapy, is early treatment discontinuation. In the trials reporting on 5 years of extended therapy, patient compliance (finishing 5 years of extended therapy) was consistently low [4,6–8]. In most studies, this is considered to be attributed to the side-effects of endocrine therapy. However, in the placebo-controlled National Surgical Adjuvant Breast and Bowel Project (NSABP) B42 trial, in which patients after 5 years of AI-based therapy were randomised between 5 years of letrozole or placebo, the early treatment discontinuation in the placebo arm was similar as in the letrozole group (62% and 60% on therapy at 5 years) [8]. A similar effect was observed in the MA.17 trial, in which patients were randomised between 5 years of letrozole or placebo after 5 years of tamoxifen, reporting a discontinuation rate of 9.9% versus 9.8% in the letrozole and placebo groups, respectively [3,9]. This indicates that other factors than actual treatment toxicity also play a role in the early discontinuation of extended adjuvant endocrine therapy. Knowledge of these factors would enable the clinician and healthcare workers to tailor the support of patients during extended adjuvant endocrine therapy to decrease early treatment discontinuation.

In the Dutch 'Investigation on the Duration of Extended Adjuvant Letrozole' (IDEAL) trial in which postmenopausal patients were randomly allocated to either 2.5 or 5 years of letrozole after 5 years of any type of adjuvant endocrine therapy, 629 (35%) patients stopped therapy earlier than planned (27% in 2.5 years group, 43% in the five-year group), of which the majority (59%) reported side-effects as the main reason for early treatment discontinuation [7]. A preliminary evaluation after 2.5 years of follow-up suggested that nodal status, type of earlier endocrine therapy and the interval between primary and extended adjuvant therapy could influence patient compliance [10]. A number of patients in the IDEAL trial earlier participated in the Tamoxifen Exemestane Adjuvant Multinational (TEAM) trial, in which postmenopausal early breast cancer patients were randomised between either 5 years of adjuvant exemestane or a sequential scheme of tamoxifen for 2.5 years followed by 2.5 years of exemestane [11,12]. At that time, extended adjuvant therapy was not yet standard of care in the Netherlands, but Dutch TEAM patients were allowed to be enrolled in the IDEAL study thereafter.

The present analyses were performed to explore factors contributing to treatment decisions at enrolment in and during the course of the IDEAL trial. The first aim was to identify which factors were associated with enrolment in the IDEAL trial after participation in the TEAM trial. The second aim was to identify which baseline factors were associated with early treatment discontinuation in the IDEAL trial. The third aim was to assess which specific adverse events (AEs) are associated with either the decision to extend endocrine therapy after TEAM participation and early treatment discontinuation during the IDEAL trial. Finally, we investigated the effect of AE-based early treatment discontinuation on disease-free survival (DFS).