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Focus On

Pre-operative endocrine therapy: focus on the clinical and biological results of the IMPACT trial

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Introduction

The main indication for neoadjuvant endocrine therapy in post-menopausal hormone receptor positive breast cancer is to downstage large primary tumours thus avoiding mastectomy or enabling surgery in previously inoperable cancers [1]. This treatment approach may also be used as an alternative to surgery especially in patients with pre-existing medical conditions. In addition treating patients in the neoadjuvant setting enables the development of short-term surrogate clinical, pathological and molecular end-points within clinical trials, which may then be utilised to predict long-term outcome in adjuvant trials. Serial core biopsies may be obtained during neoadjuvant therapy thus aiding research on the molecular mechanisms responsible for sensitivity and resistance to treatment. As an example of these approaches the clinical and biological results of the neoadjuvant endocrine IMPACT trial are discussed in this review.

IMPACT trial

The Immediate Preoperative Anastrozole, Tamoxifen, or Combined with Tamoxifen (IMPACT) trial is the neoadjuvant equivalent of the adjuvant ATAC (Arimidex, Tamoxifen Alone or in Combination) trial [2]. IMPACT was designed as a double-blind, double-dummy, multi-centre trial with post-menopausal women being randomly assigned to receive daily doses of either tamoxifen 20 mg, anastrozole 1 mg or the combination for 3 months prior to surgery [3]. The primary clinical aim of this trial was to compare the response of each treatment arm, including the down-staging of tumours and consequent avoidance of mastectomy. The main biological end-points were to determine whether short-term surrogate biological end-points could be utilised to predict response in the adjuvant ATAC trial. These included proliferation, assessed by Ki67, between 2 and 12 weeks. Three hundred and thirty three patients were recruited: 113 women were randomised to the anastrozole alone group; 108 to the tamoxifen alone; and 109 to the combination group. All had confirmed oestrogen receptor (ER) positive, invasive breast carcinoma and the median age was 73 years. Post-menopausal patients with small breast carcinomas, not necessarily requiring mastectomy, were also eligible for trial entry and the median tumour size was 4 cm for each treatment group.

Clinical results

Clinical objective response rates assessed using calliper measurements, in the intent-to-treat population, were 37%, 36% and 39% respectively, for the anastrozole, tamoxifen and combination groups. No significant difference was observed between the three treatment groups. Ultrasound response rates were 24%, 20% and 28% respectively, for each group, again with no significant difference between the three groups. Progressive disease was documented in 9%, 5% and 5% of each group respectively.

Two hundred and twenty women (67%) had baseline pre-treatment surgical assessments documented

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as requiring either mastectomy or breast conserving surgery (BCS). A subgroup of 124 (56%) patients were categorised as requiring mastectomy at baseline and 96 (44%) as eligible for BCS. Of those 124 women assessed as requiring mastectomy at baseline, 44% of patients received BCS following anastrozole compared with 31% after tamoxifen ($P = 0.23$). However, this difference became significant for women deemed feasible for BCS by their surgeon, 46% for anastrozole and 22% for tamoxifen ($P = 0.03$).

HER2 results

Two hundred and thirty nine women had tumours that were assessable for HER2, and 34 (14%) of these patients were HER2 positive (immunohistochemistry 3+). Objective responses were seen in 7 out of 12 (58%) in the anastrozole group, 2 out of 9 (22%) in the tamoxifen and 4 out of 13 (31%) in the combination group. Despite the small numbers the difference between those treated with anastrozole and tamoxifen was almost significant ($P = 0.09$).

Changes in proliferation

An important aim of the IMPACT trial was to determine whether changes in proliferation, assessed using MIB-1 antibody, following 2 and 12 weeks of therapy were different in the three treatment arms and could predict for long-term outcome difference in favour of anastrozole demonstrated in the ATAC trial [4]. A significant reduction in Ki67 expression was observed in all three arms. These differences were significantly greater for anastrozole compared with tamoxifen or the combination, as assessed using geometric mean ratios of the changes in Ki67 after 2 weeks of therapy ($P = 0.04$) and following 12 weeks ($P = 0.001$). No significant difference was observed between the tamoxifen and the combination arm. A non-significant trend towards greater change in Ki67 in responders compared to non-responders at 2 weeks (geometric mean change −75.3 vs. −61.7%) and 12 weeks (geometric mean change −73.2 vs. −67.3%) was documented.

Other related trials

Eiermann and colleagues have reported the results of a similar multi national double-blind trial randomising 337 post-menopausal women to either neoadjuvant letrozole or tamoxifen [5]. These patients had tumours that were ER and PgR positive and all would have otherwise required mastectomy or were deemed inoperable (14%). A significantly higher clinical objective response rate, the primary end-point of this trial, was observed in the letrozole arm (55%) compared to the tamoxifen arm (36%, $P < 0.001$). In addition letrozole was more effective than tamoxifen when response was assessed by mammography (34% vs. 16%, $P < 0.001$) and by ultrasound (35% vs. 25%, $P = 0.042$). Disease progression was observed in 12% of women treated with letrozole and 17% in those treated with tamoxifen. The rate of BCS was also significantly higher in the group treated with letrozole (45%) compared to tamoxifen (35%, $P = 0.022$). A further important result in this trial was the finding that 15 out of 17 (88%) women whose tumours over expressed HER1 and/or HER2 responded to letrozole compared with 4 out of 19 (21%) with tamoxifen ($P = 0.004$) [6]. However, when HER1 and HER2 tumours were removed from the analysis of response, the numerically higher response rate of letrozole compared to tamoxifen was retained (54% vs. 42%, $P = 0.078$).

Although the population studied and the neoadjuvant therapy differed between the letrozole and IMPACT trials, the data generated by both strongly support that aromatase inhibitors may be more effective than tamoxifen in treating HER2 over expressing, ER positive, early breast cancer.

The PROACT trial (PReOperative Anastrozole Compared with Tamoxifen) trial randomised 451 post-menopausal women with operable or locally advanced but potentially operable hormone receptor positive breast cancer to receive either anastrozole or tamoxifen for 3 months prior to surgery [7]. Around 30% of patients were also treated with concurrent chemotherapy. In the subgroups treated with endocrine therapy alone, ultrasonagraphical and clinical response rates for anastrozole and tamoxifen respectively, were 36% vs. 27% ($P = 0.07$) and 50% vs. 40% ($P = 0.08$). In the 262 women treated with endocrine therapy alone and who on trial entry would have required mastectomy or had locally advanced disease, significantly higher ultrasound and clinical response rates were observed in the anastrozole group; ultrasound response rates were 37% for those treated with anastrozole and 25% for tamoxifen ($P = 0.03$), clinical response rates were 49% and 36% respectively ($P = 0.04$). Additionally in this subgroup of 262 patients, improvement in surgical status (inoperable to mastectomy or mastectomy to BCS) was possible in 47% of the anastrozole group and 38% in the tamoxifen group ($P = 0.15$) and actually occurred in 43% and 31% respectively ($P = 0.04$).

Conclusion

The IMPACT trial confirmed other findings that neoadjuvant aromatase inhibitors are more effective than tamoxifen in downstaging large ER-positive cancers in post-menopausal women to avoid mastectomy.

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In contrast to a similarly designed neoadjuvant letrozole trial, anastrozole did not achieve a significantly higher clinical response rate than tamoxifen; the contribution of small cancers and difficulty in measuring clinical response accurately in these may have contributed to this. The IMPACT trial did however suggest strongly that HER2-positive cancers respond better to anastrozole than tamoxifen at least in the short term, reinforcing the findings of the neoadjuvant P24 letrozole trial.

The IMPACT trial also showed that changes in Ki67 after 2 and 12 weeks treatment in favour of anastrozole reflected similar long-term outcome findings in favour of adjuvant anastrozole in the ATAC trial. Further similar comparative studies are indicated to validate whether short-term Ki67 changes can be used to predict long-term outcome in adjuvant trials of novel therapies.

References

1. Dixon JM, Anderson TJ, Miller WR. Neoadjuvant endocrine therapy of breast cancer: a surgical perspective. *Eur J Cancer* 2002; **38**: 2214–2221.
2. ATAC Trialists' Group. Anastrozole alone or in combination with tamoxifen versus tamoxifen alone for adjuvant treatment of postmenopausal women with early breast cancer: first results of the ATAC randomised trial. *Lancet* 2002; **359**: 2131–2139.
3. Smith IE, Dowsett M, Ebbs SR, *et al*. Neoadjuvant treatment of postmenopausal breast cancer with anastrozole, tamoxifen, or both in combination: the Immediate Preoperative Anastrozole, Tamoxifen, or Combined with Tamoxifen (IMPACT) multicenter double-blind randomized trial. *J Clin Oncol* 2005; **23**: 5108–5116.
4. Dowsett M, Smith IE, Ebbs SR, *et al*. Short-term changes in Ki67 during neoadjuvant treatment of primary breast cancer with anastrozole or tamoxifen alone or combined correlate with recurrence-free survival. *Clin Cancer Res* 2005; **11**: 951s–958s.
5. Eiermann W, Paepke S, Appfelstaedt J, *et al*. Preoperative treatment of postmenopausal breast cancer patients with letrozole: a randomized double-blind multicentre study. *Ann Oncol* 2001; **12**: 1527–1532.
6. Ellis MJ, Coop A, Singh B, *et al*. Letrozole is more effective neoadjuvant endocrine therapy than tamoxifen for ErbB-1- and/or ErbB2-positive, estrogen receptor-positive primary breast cancer: evidence from a phase III randomized trial. *J Clin Oncol* 2001; **19**: 3808–3816.
7. Cataliotti L, Buzdar A, Noguchi S, Bines J. Efficacy of PReOperative Arimidex (anastrozole) Compared with Tamoxifen (PROACT) as neoadjuvant therapy in postmenopausal women with hormone receptor-positive breast cancer. *Eur J Cancer* 2004; **2**(Suppl): 69 [Abstract 46].

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