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Switching to anastrozole versus continued tamoxifen treatment of early breast cancer: Long term results of the Italian Tamoxifen Anastrozole trial

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Abstract The Italian Tamoxifen Anastrozole (ITA) trial investigated the efficacy of switching to anastrozole for women who were already on adjuvant tamoxifen since 2–3 years. Relapse-free survival (RFS) was the primary end-point; event-free survival (EFS), overall survival (OS) and safety were secondary end-points. Herein, we report an update on the long term results of this trial.

At a median follow-up time of 128 months (range14–168 months), 94 events have been recorded in the tamoxifen group compared with 71 events in the anastrozole group (hazard ratio (HR) = 0.71; 95% confidence interval (CI), 0.52–0.97; $p = 0.03$). RFS was also significantly longer in the anastrozole group (HR = 0.64; 95% CI, 0.44–0.94; $p = 0.023$); no statistically significant difference between study arms concerning OS was shown, but the trial was not powered enough in respect to this end-point. The incidence of serious adverse events (SAE) like bone fractures was comparable (four in each arm), while gynaecological problems were still significantly more numerous among the women continued on tamoxifen (21 patients developed a SAE in this

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group, including eight endometrial cancers, compared to three patients who suffered from a SAE, including one endometrial cancer, in the anastrozole group: $p < 0.000$).
Present data confirm that switch is safe and can provide long-term gain in terms both of RFS and of EFS, which persists even several years since treatment discontinuation.

1. Introduction

For more than two decades, tamoxifen has represented the gold standard for the management of patients affected by endocrine-responsive early breast cancer, being that this anti-oestrogen was largely demonstrated to significantly reduce the risk of recurrence and death in these patients.[1] Indeed, tamoxifen represents the standard for endocrine-responsive, premenopausal early breast cancer.[2] and still a valuable option for postmenopausal women.[3] However, the long-term use of this anti-oestrogen is associated with potentially life-threatening adverse events like endometrial carcinoma or thromboembolic events.[4,5] Moreover, a relevant proportion of breast cancers can be primarily resistant to tamoxifen or may eventually become resistant to this anti-oestrogen even if they express high oestrogen receptor (ER) levels.[6,7] These two considerations have provided the rationale for introducing aromatase inhibitors in the adjuvant treatment of endocrine-responsive postmenopausal breast cancer in view of the different way through which these compounds target ER driven pathways in breast cancer.[6–8] As a result of this large research work, current guide-lines recommend the use of aromatase inhibitors either as an alternative to tamoxifen or following a few years of tamoxifen administration.[3,9] Both approaches have proven to be cost-effective in individual randomised trials and in meta-analyses when the benefits were compared to those achievable by tamoxifen single therapy.[10–17] We firstly investigated the potential superiority of switching to an aromatase inhibitor over continuing tamoxifen by sequencing the anti-oestrogen with aminogluthetimide, the only aromatase inhibitor available at the time we conceived this approach.[18] As we were encouraged by the preliminary results of this trial showing the feasibility of switching and some clinical benefits for the switch recipients, we embarked on a new trial, which included replacing low dose aminogluthetimide with anastrozole in the frame of a multi-centre, nationwide prospective trial known as Italian Tamoxifen Anastrozole (ITA). Clinically relevant improvements in relapse-free survival (RFS) were observed in patients who were switched to anastrozole, already at 36-month median follow-up time.[13] These preliminary results were later confirmed, at a median follow-up time of 64 months.[19] Herein, we provide an additional update on the long term results of this trial, with a median follow-up time currently exceeding 120 months.

2. Patients and methods

2.1. Study design and end-points

Details about study rationale, eligibility criteria, reasons for limiting trial entry to node-positive women, assigned treatments, treatment allocation procedures and patient monitoring procedures have been previously reported.[13,19] Briefly, 448 postmenopausal women with histologically confirmed, ER positive (or unknown) breast cancer with positive axillary nodes and no evidence of recurrent or metastatic disease who had already been on adjuvant tamoxifen for 2–3 years were randomly allocated to continue tamoxifen (20 mg daily) or to switch to anastrozole (1 mg daily). In both groups, the assigned treatment was continued up to the 5th year or until patient relapse, death, undue toxicity or refusal. As it is detailed in the first results communication, no patient allocated to continue tamoxifen was crossed over to anastrozole before completing the assigned treatment up to the 5th year.[13] Written informed consent was obtained from all subjects after trial approval by the ethics committees of all participating centres. Disease recurrence, including both loco-regional and distant recurrences (except contra-lateral breast cancer) was the primary end-point. Loco-regional recurrences had to be confirmed cytologically or histologically and included tumour relapse in the homo-lateral breast, thoracic wall, axilla or supra-clavicular nodes. All other events, besides disease recurrences, including second primaries or contra-lateral breast cancers, and deaths occurring in the absence of breast cancer recurrence, were considered secondary end-points. Deaths were considered secondary end-points, regardless of the cause. Lastly, adverse events were also considered secondary end-points.

2.2. Data collection and ethical aspects

The trial was initially sponsored by Astra Zeneca (Basiglio, Milan, Italy) which provided study drugs and funded clinical monitoring for the first 8 years since patient randomisation. However, official sponsoring by the Company was discontinued thereafter. Thus, in order to perform the present analysis we had to implement a specific observational study (Italian Drug Agency – AIFA-RSO ID 576) and to request new authorisation from the ethics committee of participating centres to allow us to update the follow-up data. Since such a long time had elapsed since trial activation, we were able to