Comments on the IES (Intergroup Exemestane Study) 031

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The updated analysis of the IES 031 study appeared in *The Lancet* in February 2007 [Coombes RC, Kilburn LS, Snowdon CF, et al.: Survival and safety of exemestane versus tamoxifen after 2–3 years' tamoxifen treatment (Intergroup Exemestane Study): a randomised controlled trial. *Lancet* 2007;369:559–570]. In the IES 031 study, 4,740 patients were randomized following a two- to three-year adjuvant tamoxifen therapy and treated with either exemestane or with tamoxifen until 5 years of treatment were completed. 4,724 patients were evaluable.

The first interim analysis after a median follow-up of 30.6 months showed a significant improvement in disease-free survival, relatively by 32%, absolutely by 4.7%. The updated interim analysis after a median follow-up of 37.4 months, which appeared in December 2004, showed the following data for the patient group treated with exemestane: a significant improvement in disease-free survival by 27% with an absolute risk reduction by 3.75%, connected with a significant improvement of breast cancer-free survival by 30% as well as a significant risk reduction in contralateral breast cancer by 50%. Further, exemestane proved to be significantly more efficient than tamoxifen in almost all subgroups, in particular in the subgroups with node-positive patients and in those who previously received chemotherapy, which had less favorable prognoses.

A look at the most important endpoint of this study, the question of improvement of overall survival, was interesting. Under exemestane, distinctly fewer deaths associated with breast cancer and deaths reported altogether were seen than in the tamoxifen group. In the updated evaluation in 2004, this corresponded to a 17% overall survival benefit in patients treated with exemestane. In this context, the fast positive development between the interim analysis after 30.6 months with a risk reduction of 12% and the interim analysis after 37.4 months with a risk reduction of 17% was impressive. It was to be expected that a significant improvement of overall

survival can be achieved with exemestane after an even longer follow-up.

The updated evaluation published in the *Lancet* in 2007 covered a median follow-up of 55.7 months. A total of 809 events contributing to the analysis of disease-free survival had been reported, with a relative improvement of disease-free survival in the exemestane treatment arm of 24% and an absolute benefit of 3.3%. This difference was statistically significant. Likewise, a 17% relative improvement of overall survival in patients treated with exemestane was seen. After exclusion of estrogen receptor-negative tumors and adjustment for nodal status, chemotherapy use, and HRT use, this difference achieved statistical significance with a p-value of 0.04 (fig. 1). The benefit was consistent in all subgroups (fig. 2). However, the relatively low number of events in the individual subgroups must be taken into account in this context.

With a view to adverse events, 18.4% of the cases showed degree III or IV adverse events in patients treated with exemestane and 17.6% in patients treated with tamoxifen. Thromboembolic events were less frequent in patients treated with exemestane than in patients treated with tamoxifen. Likewise, the incidence of cardiovascular events did not differ between the two treatment arms. The cardiac infarct rate was 1.3% in the exemestane group and 0.8% in the tamoxifen group. However, the analysis showed that 70.1% of the patients given exemestane who suffered a heart attack manifested hypertonia in the course of the baseline anamnesis, whereas this was only the case with 31.6% of the patients with tamoxifen. The number of serious gynecological events was lower in patients treated with exemestane than in those treated with tamoxifen. On the other hand, musculoskeletal pain, carpal tunnel syndrome, paresthesia, and arthralgia occurred more frequently in patients with exemestane. The fracture rate per 1,000 women/year was 19.2 under exemestane and 15.1 under tamoxifen.

Fig. 1. Exemestane improves overall survival.

These new results were taken into account both in the course of the production of the new guideline of the AGO (Working Group of Gynecological Oncology) and the consensus panel of the 2007 St. Gallen Conference. The St. Gallen Conference, which is held every two years, is one of the forward-pointing events with regard to recommendations on the treatment of breast cancer. Here, 39 leading international experts agreed on a consensus on the therapy options which are to be recommended according to the current state of research.

Relative to an endocrine adjuvant therapy in the postmenopausal situation, there was a clear vote in favor of sequential therapy. 89% of the experts approve a switch to an aromatase inhibitor after 2–3 years of tamoxifen. In direct comparison of the 3 therapy regimes with an aromatase inhibitor (upfront, sequential or extended therapy), the majority of the panel was in favor of the sequential therapy. Almost 2/3 of the experts selected this option (early sequential therapy: 63%, upfront: around 31%, extended: nearly 6%).

Fig. 2. The overall survival benefit of exemestane was consistent in all subgroups.

The AGO, in which German experts produce guidelines for the treatment of breast cancer, also assesses sequential therapy with a double plus, which corresponds to the highest recommendation level in its therapy recommendations.

Conclusion for Clinical Practice

Following St. Gallen 2007, the use of aromatase inhibitors is to be regarded as an integral part of adjuvant endocrine therapy of postmenopausal hormone-sensitive breast cancer. The experts have agreed that the various aromatase inhibitors should be used in precisely the therapy scheme in which they proved their efficacy in large, randomized studies in question and according to which they have been given corresponding registration approval.

According to the current state of the data situation, a change to an aromatase inhibitor such as exemestane or anastrozole after 2–3 years of tamoxifen therapy is connected with a statistically significant survival benefit and is regarded as being sensible by international and also national experts.