Opinion after ASCO 2005

What is the Role of Letrozole in Adjuvant Breast Carcinoma Setting?

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A meeting for Letrozole clinical investigators was organized in Orlando, joined to ASCO Conference, 2005, in order to review the newest data in adjuvant breast cancer trials. Trials were organized by IBCSG (International Breast Cancer Study Group) and by BIG (Breast International Group). After the encouraging results Novartis provided a meeting to discuss the data achieved so far.

The *MA-17 protocol* was started with a five-year adjuvant tamoxifen treatment and followed by two randomized arms: placebo (2586 patients) and letrozole (2582 patients). The main aim of this study was to compare disease-free survival (DFS), and appearance of new metastatic or primary lesions. Secondary end points were: overall survival time (OS) and toxicity. After the first publication,[1] the study gave further information on toxicity, and on follow-up (more than 40 months). DFS increased in the letrozole group (p=0.00004). Recurrence rates were higher in the placebo group compared to letrozole group: 155 vs. 92 (distant metastases: 94 vs. 54, loco-regional: 33 vs. 18, new primary lesion: 28 vs. 17). The toxicity of letrozole was mild: hot flashes, bone and muscle pain and osteoporosis. The lipoid profile did not change significantly in observation period.[2]

This was the second report on *BIG I-98 protocol* after the St. Gallen conference in January, 2005.[3] In this study 8028 postmenopausal women with hormone receptor positive cancer were randomized after surgery and chemo- and/or radiotherapy. (Hungarian investigators randomized more than 334 patients.) This study had 4 arms: (a) tamoxifen for 5 years, (b) letrozole for 5 years, (c) tamoxifen for 2 years, followed by letrozole for 3 years, (d) letrozole for 2 years, followed by tamoxifen for 3 years. The primary end point was DFS, and the second end points were OS, systemic disease-free survival (SDF), distant disease-free survival and safety. DFS was higher in the letrozole group (84.0%) vs. tamoxifen group (81.4%); and letrozole significantly reduced the number of local and distant recurrences. Analyzing the data, hazard ratio showed significant difference in favor of the letrozole group: DFS = 0.81, OS = 0.86, SDFS = 0.83, time to distant metastases = 0.73, time of recurrence = 0,72. Analyzing the subgroups, OS and DFS were higher in the letrozole group when chemotherapy was administered, lymph nodes were positive, and the hormone status was ER+/PR-. The common toxicity of letrozole were bone fracture and osteoporosis. Comparing the two arms, the frequency of cardiovascular events was significantly higher in the letrozole group, while more thromboembolic complications were detected in the tamoxifen group. Cholesterol level increased during tamoxifen therapy in 19.1% of cases, and in 43.5% of cases in the letrozole group.

These results supported the role of aromatase inhibitors in the adjuvant setting of hormone receptor positive breast cancers. Further analyses may determine the optimal sequence of these agents.

References

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