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The HOBOE-2 multicenter randomized phase III trial in premenopausal patients with hormone-receptor positive early breast cancer comparing triptorelin plus either tamoxifen or letrozole or letrozole + zoledronic acid

F. Perrone[1], M. De Laurentiis[2], S. de Placido[3], M. Orditura[4], S. Cinieri[5], F. Riccardi[6], A.S. Ribecco[7], C. Putzu[8], L. Del Mastro[9], E. Rossi[10], B. Daniele[11], A.M. Mosconi[12], F. Di Rella[2], G. Landi[2], F. Nuzzo[2], C. Pacilio[2], R. Lauria[3], L. Arenare[1], M.C. Piccirillo[1], C. Gallo[13]

[1]Clinical Trials Unit, Istituto Nazionale Tumori – I.R.C.C.S - Fondazione Pascale, Naples, Italy, [2]Senology, Istituto Nazionale Tumori – I.R.C.C.S - Fondazione Pascale, Naples, Italy, [3]Medical Oncology, AOU Policlinico Federico II, Naples, Italy, [4]Department of Internal and Experimental Medicine, Università degli Studi della Campania Luigi Vanvitelli, Naples, Italy, [5]Medical Oncology, Perrino Hospital, Brindisi, Italy, [6]Oncologia Medica, Ospedale Cardarelli, Naples, Italy, [7]Medical Oncology, Ospedale S. Giovanni di Dio, Florence, Italy, [8]Oncologia Medica, Università di Sassari, Sassari, Italy, [9]Internal Medicine, IRCCS AOU San Martino - IST-Istituto Nazionale per la Ricerca sul Cancro, Genoa, Italy, [10]Oncologia Medica, Azienda Ospedaliera S. Giuseppe Moscati, Avellino, Italy, [11]Oncology, Azienda Ospedaliera G. Rummo, Benevento, Italy, [12]Oncology-Hematology Dept., Azienda Ospedaliera di Perugia S. Maria della Misericordia, Perugia, Italy, [13]Medical Statistics, Università degli Studi della Campania Luigi Vanvitelli, Naples, Italy

Background: Role of aromatase inhibitors and zoledronic acid as adjuvant treatment of premenopausal endocrine-responsive breast cancer patients is debated. Letrozole has never been tested in this clinical setting.

Methods: Following surgery and eventual neoadjuvant or adjuvant chemotherapy, premenopausal patients (last menses within 1 yr) were randomly assigned 1:1:1 to Triptorelin 3.75 mg every 4 weeks plus either Tamoxifen 20 mg/die (T), or Letrozole 2.5 mg/die (L) or Zoledronic acid 4mg iv every 6 months + Letrozole 2.5 mg/die (ZL), for 5 years. The primary end-point was disease-free survival (DFS) including locoregional or distant recurrence, second breast or non-breast invasive cancer and death without cancer as event. Analysis was based on intention-to-treatment. Pairwise comparisons (with Bonferroni-Holm correction) were allowed if overall test was statistically significant. The IDMC suggested final analysis be done after 5yrs median follow-up, independently of number of events.

Results: From March 2004 to August 2015, 1065 patients were randomized (T: 354, L:356, ZL: 355) in 16 centres in Italy. Median age was 45; 68% had a pT1 tumor; 55% had negative nodes; 63% had received chemotherapy. After 65 months median follow-up, there were 58, 44, and 32 DFS events and 5 yrs DFS probability was 0.85, 0.93 and 0.93 in the T, L and ZL arms, respectively ($P = 0.008$). Pairwise comparison was statistically significant for ZL vs T (HR 0.52, 95% CI 0.34-0.80, $P = 0.003$) but not for L vs T (HR 0.72, 95% CI 0.48-1.07, $P = 0.06$) and ZL vs L (HR 0.70, 95% CI 0.44-1.12, $P = 0.22$). ZL was more effective than T in all subgroups, but for HER2-positive cases (interaction $P = 0.002$). Twenty-six (7%) patients with T, 26 (7%) with L and 59 (17%) with ZL stopped assigned treatment before 5 yrs due to toxicity or refusal. Grade 3-4 side-effects were reported in 4%, 7% and 9% of patients with T, L and ZL, respectively; there were 4 cases of osteonecrosis of the jaw in the ZL arm.

Conclusions: HOBOE shows that, in premenopausal early breast cancer patients, the ZL+triptorelin combination is more effective than T+triptorelin in terms of DFS.

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