Acta Oncologica, 2013; 52: 861–882

informa
healthcare

LETTERS TO THE EDITOR

Breaking away: High fracture rates may merit a new trial of adjuvant endocrine therapy in Scandinavian breast cancer patients

HÅVARD SØILAND[1,3], KARI BRITT HAGEN[4], JENNIFER GJERDE[5], TONE HOEL LENDE[1] & ERNST A. LIEN[2,5]

[1]*Stavanger University Hospital, Department of Surgery, Section for Breast and Endocrine Surgery, Stavanger, Norway,* [2]*University of Bergen, Institute of Medicine, Bergen, Norway,* [3]*University of Bergen, Institute of Surgical Sciences, Bergen, Norway,* [4]*Haukeland University Hospital, Department of Breast and Endocrine Surgery, Bergen, Norway and* [5]*Haukeland University Hospital, Hormonlaboratoriet, Bergen, Norway*

To the Editor,

Results from the multinational randomized controlled trials demonstrate that adjuvant treatment of postmenopausal breast cancer patients with aromatase inhibitors (AIs) have a longer disease free survival compared to tamoxifen treatment [1,2], but less commonly show improvement in overall survival (OS). A secondary analysis of the ATAC (Arimidex, Tamoxifen Alone or in Combination) trial showed that increased age and number of comorbidities were associated with a substantially increased risk of death without recurrence in women with node-negative breast cancer [1].

The BIG 1–98 randomized trial [2] compares five-year adjuvant treatment of breast cancer patients with the AI letrozole versus 1) tamoxifen for two years followed by letrozole, or 2) letrozole for two years followed by tamoxifen. The absolute differences in disease free survival (DFS) were more discernable among patients at the higher end of the risk spectrum than at the lower end [3]. About half the patients were node-negative, i.e. a low-risk group. In this group of patients the OS favored tamoxifen treatment, although insignificantly. Osteoporosis and bone fractures were increased on letrozole compared to tamoxifen monotherapy [2]. Similar results have been demonstrated in other studies (reviewed in [4]).

Results from the multinational randomized controlled trials challenge their global external validity. Such trials often enroll patients who are younger, healthier, better educated, and have less comorbidity than a population who carry the majority burden of the disease [5].

If the therapy studied in a trial has another impact on people outside the trial than people within the trial, then the results of the trial may not generalize to the population using the drug [5].

In older patients the presence of concomitant diseases is of major importance for the OS of breast cancer patients [6]. The Scandinavian countries have a high rate of osteoporosis and serious bone fractures, such as hip fractures. These fractures often result in invalidity and death in elderly people. Notably, the incidence of hip fractures has been reported to be as high as 4.4% per 1000 person years in Scandinavia whereas the rates in southern, eastern and western Europe were 1.4%, 0.6%, and 0.8%, respectively [7]. Compared with the hip fracture rate in other continents, the Scandinavian countries (Norway, Sweden and Denmark) are at the top. This rate increases sharply with age. Accordingly, in Norway the 10-year probability of hip fracture in women in the age groups 60, 70, and 80 years was 2.9%, 9.0%, and 17.7%, respectively [8].

The high fracture rate in the Scandinavian population compared with other parts of Europe might reduce the external validity of BIG 1–98 applied to the Scandinavian cohort of elderly breast cancer patients. If this is the case the results of BIG 1–98 may not relate to Scandinavian women, as they are more sensitive to fracture than the majority of the women enrolled in the trial.

Correspondence: H. Søiland, Stavanger University Hospital, Department of Surgery, Section for Breast and Endocrine Surgery, Stavanger, Norway. E-mail: hsoiland@gmail.com

(Received 16 August 2012; accepted 14 October 2012)

ISSN 0284-186X print/ISSN 1651-226X online © 2013 Informa Healthcare
DOI: 10.3109/0284186X.2012.742963

Due to the positive effects of tamoxifen on bone fracture rate it may be the drug of choice in endocrine treatment of elderly node-negative breast cancer patients in Scandinavia.

Consequently, a sub-study in elderly Scandinavian breast cancer patients with osteoporosis, history of fractures, or low bone mineral density may be warranted to address differences in bone health between tamoxifen and AIs.

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

References

[1] Forbes JF, Cuzick J, Buzdar A, Howell A, Tobias JS, Baum M. Effect of anastrozole and tamoxifen as adjuvant treatment for early-stage breast cancer: 100-month analysis of the ATAC trial. Lancet Oncol 2008;9:45–53.

[2] Regan MM, Price KN, Giobbie-Hurder A, Thurlimann B, Gelber RD. Interpreting breast international group (BIG) 1–98: A randomized, double-blind, phase III trial comparing letrozole and tamoxifen as adjuvant endocrine therapy for postmenopausal women with hormone receptor-positive, early breast cancer. Breast Cancer Res 2011;13:209.

[3] Viale G, Regan MM, Dell'Orto P, Mastropasqua MG, Maiorano E, Rasmussen BB, et al. Which patients benefit most from adjuvant aromatase inhibitors? Results using a composite measure of prognostic risk in the BIG 1–98 randomized trial. Ann Oncol 2011;22:2201–7.

[4] Amir E, Seruga B, Niraula S, Carlsson L, Ocana A. Toxicity of adjuvant endocrine theraphy in postmenopausal breast cancer patients: A systematic review and meta-analysis. J Nat Cancer Inst 2011;103:1299–309.

[5] Toft Sorensen H, Lash T, Rothman K. Beyond randomized controlled trials: A critical comparison of trials with non-randomized studies. Hepatology 2006;44:1075–82.

[6] Patnaik JL, Byers T, Diguiseppi C, Denberg TD, Dabelea D. The influence of comorbidities on overall survival among older women diagnosed with breast cancer. J Natl Cancer Inst 2011;103:1101–11.

[7] Ismail AA, Pye SR, Cockerill WC, Lunt M, Silman AJ, Reeve J, et al. Incidence of limb fracture across Europe: Results from the European Prospective Osteoporosis Study (EPOS). Osteoporos Int 2002;13:565–71.

[8] Kanis JA, Johnell O, De Laet C, Jonsson B, Oden A, Ogelsby AK. International variations in hip fracture probabilities: Implications for risk assessment. J Bone Miner Res 2002;17:1237–44.