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Letter

An open randomised trial of second-line endocrine therapy in advanced breast cancer: comparison of the Aromatase inhibitors letrozole and anastrozole

We were surprised to read in the conclusion of the article by Rose and colleagues [1] comparing anastrozole with letrozole as second-line treatment for advanced breast cancer that 'advanced breast cancer is more responsive to letrozole than to anastrozole' when no differences were reported for the primary endpoint and five of six secondary endpoints in this study. Rather, we would suggest that this study failed to demonstrate improved efficacy of letrozole over anastrozole and instead indicated that marginal differences in potency seen between the two agents did not translate into greater efficacy.

The primary endpoint of this study was time to progression (TTP), which was a median of 5.7 months for both anastrozole and letrozole ($P = 0.92$). In addition, no differences between treatments were seen for the secondary endpoints of time to treatment failure, duration of response, duration of clinical benefit, overall survival, World Health Organisation (WHO) performance status, or safety. The only secondary endpoint that did show an advantage for letrozole was objective response rate (ORR). If differences in potency between anastrozole and letrozole were of genuine clinical relevance, we would expect this advantage to be apparent across more of the efficacy endpoints.

This was an open-label study, likely to be subject to bias, particularly in relation to subjective endpoints such as ORR. Measurement of ORR can vary between investigators and can also be influenced by prior experience. However, most surprisingly, the advantage for letrozole was no longer apparent in the subgroup of patients whose tumours were known to be hormone-receptor positive, the population in whom endocrine therapy is considered appropriate. Moreover, this subgroup made up only 48% of the total, with the hormone-receptor-unknown group constituting a large proportion of the total trial (52%). In addition, in this subgroup analysis, the median TTP for anastrozole was 6.5 months versus 5.8 months for letrozole, thus *anastrozole* showed a marginal advantage in the primary endpoint in the target population. It is also in this hormone-receptor-positive subgroup of patients that differences in efficacy as a result of differing degrees of oestrogen suppression would be anticipated to be most apparent, rather than less as reported. This is in contrast to the rather intriguing suggestion of Rose and colleagues that 'in hormone-receptor poor tumours, it is possible that a higher degree of oestrogen deprivation... could lead to a better response [1], although no additional evidence is put forward to support this suggestion. In this regard, we note that studies of letrozole in the adjuvant setting are only being performed in patients with hormone-receptor-positive tumours, which suggests a degree of confusion regarding the potential benefits of letrozole in hormone-receptor poor tumours.

In summary, we were surprised that so much of the discussion was dedicated to one of six secondary endpoints, for which no significant differences between treatments were seen in what is considered to be the target population for endocrine therapy. In advanced breast cancer, the main aims of endocrine treatment are to prolong survival, delay disease progression and palliate symptoms, with the aim of improving quality of life. The results of this study suggest that letrozole confers no benefit over anastrozole in achieving these goals.

Reference

1. Rose C, Vtoraya O, Pluzanska A, *et al.* An open randomised trial of second-line endocrine therapy in advanced breast cancer: comparison of the aromatase inhibitors letrozole and anastrozole. *Eur J Cancer* 2003, **39**, 2318–2327.

J.S. Tobias
A. Howell
Meyerstein Institute of Clinical Oncology
Middlesex Hospital
Mortimer Street, W1N 8AA
London, UK
Tel.: +44-20-7380-9214
fax: +44-20-7436-0160
E-mail address: j.tobias@ucLH.org

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