Keynote Lecture

767

Biological insights into breast cancer: results from the ATAC and prevention trials

A. Howell. *Christie Hospital, Department of Medical Oncology, Manchester, United Kingdom*

The results of clinical trials usually give new insight and understanding of a disease and the ATAC and prevention breast endocrine trials are no exception. Together, with our knowledge of cell and molecular biology and epidemiology the results can lead to new hypotheses to be tested in future trials towards our aim of eliminating micrometastatic disease and primary breast cancer. The ATAC trial design of a randomised comparison of anastrozole (n=3125) with tamoxifen (n=3116) or a combination of the two endocrine therapies (n=3125) is well known. Recently the results of the trial were updated when the median follow-up was 47 months. The probability of recurrence was significantly reduced by anastrozole compared with tamoxifen (p=0.007) with the combination arm being non-significantly worse than the tamoxifen arm of the study. The absolute difference between the two monotherapy arms had increased to 2.6% compared with 1.8% at the 33 month analysis. In addition contralateral breast cancers were significantly reduced by anastrozole. The aromatase inhibitors may be superior for a number of reasons which include prevention of receptor activation by growth factor pathways, effectiveness at lower or different oestrogen progesterone receptor profiles or absence of a tumour agonist effect sometimes seen with tamoxifen.The combination of endocrine agents may have been inferior because of data which suggest that tamoxifen is more likely to be an agonist in a low oestrogen environment. However there were failures on anastrozole and recent data suggest that one of the mechanisms is an increased sensitivity of cells to low concentrations of oestradiol associated with increased activity of signal transduction pathways suggesting that combination of inhibitors of these pathways with anastrozole may be the future of endocrine adjuvant therapy. The first tamoxifen prevention trial began in 1986 and three other trials have subsequently been reported. The mean reduction in risk of breast cancer when all trials are combined in an overview analysis is 38%. The MORE trial of raloxifene compared to placebo in osteoporotic women showed a reduction in breast cancer risk of over 60%. We await the results of a further raloxifene trial with over 10,000 women entered (RUTH) and of the North American comparison of tamoxifen and raloxifene (n =19,000:STAR). Importantly both the NSABP P1 tamoxifen trial and the MORE trial showed that the reduction in risk was seen only in oestrogen receptor positive tumours. In addition it was shown that raloxifene was effective only in women with measureable serum oestrogen levels. Several epidemiological studies indicate that greater oestrogen exposure (ie early menarche, late first pregnancy, nulliparity and late menopause, and postmenopausal obesity) are associated with the development of oestrogen receptor positive tumours and these factors may be used to predict who should be treated by endocrine prevention. Although the genesis of oestrogen receptor negative tumours is not known, risk factors for this subtype and possible cell origins and treatment will be discussed. In addition the new prevention trials with aromatase inhibitors will be highlighted.