

Benefit of tamoxifen in estrogen receptor positive DCIS of the breast

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Allred and colleagues recently published, in *Journal of Clinical Oncology*, a retrospective analysis which illustrates the benefits of tamoxifen (TAM) in ductal carcinoma in situ (DCIS) according to the estrogen receptor (ER) status (1). The analysis included 41% of the original sample of the NSABP24 trial (2). TAM reduced the hazard of relapse by 50% at 10 years of follow-up among 76% patients resulting ER+ in this trial. No benefit was observed in ER-patients with DCIS. The strength of this analysis was the centralisation of receptor analysis, in the majority of cases, according to standard immunohistochemical analysis.

DCIS diagnosis has increased dramatically with the introduction of breast cancer screening mammography. The aim of treatment for DCIS is to prevent the development of invasive breast cancer. It is common knowledge that TAM reduces the risk of all breast cancer events. The subgroup results of Allred's paper showed that the reduction of ipsilateral and contralateral invasive breast cancer and DCIS are not statistically.

In 2011 we performed a pooled-analysis (3) of 2 DCIS trials [the NSABP B24 (2) and UK-ANZ trial (4)] to study the beneficial effects of TAM when prescribed in addition to surgery and/or radiotherapy. The results showed that TAM significantly reduced only the risk of ipsilateral invasive and contralateral in situ recurrences in women of all ages. There was, however, no difference in the overall survival in the two arms (surgery, radiotherapy and TAM *vs.* surgery and radiotherapy). Data of ER+ patients in our meta-analysis were not available at the moment of publication. These results were to be expected as TAM could have a synergistic effect, in addition to radiotherapy, in preventing local invasive relapse and at the same time preventing contralateral in situ disease.

The results of subgroup analysis of the B24 trial and our

meta-analysis confirm that DCIS has an excellent prognosis when treated with locoregional treatment alone without systemic adjuvant therapy, and TAM adds little or no benefit to risk of recurrence, and only confined to ER+ cases. In particular what is unknown at the moment is which subgroup, among ER+ patients, can benefit more significantly from hormone therapy. In general the characteristics that may predict risk of recurrence include the patient's age, nuclear grade, presence of comedo-type necrosis, tumour size and margin width. The Van Nuys Prognostic Index (VNPI) combines four significant predictors of local recurrence: tumour size, margin width, pathologic classification, and patient age and gives an estimation of individual risk after DCIS surgery. Information obtained from this Index could be used to select high risk patients and offer them both local and systemic therapy for DCIS (5).

Data from 949 patients treated with breast conservation (604 excision alone, 345 excision and radiation therapy) and analysed according to the VNPI revealed a 12-year local recurrence rate for VNPI 4 to 6 (low risk subsets) of 5.5% for excision alone and 2.5% for excision and irradiation (6).

We think that adjuvant TAM could only be given to high risk patients who would probably gain a greater benefit, but there is no data to confirm this hypothesis. Side effects associated with TAM, in particular of a gynaecological and vascular nature, are to be also considered.

Would older patients with low risk ER+ DCIS and comorbidity, really benefit by adjuvant treatment? The question still remains open. The long-term update of the UK ANZ trial has not confirmed a reduction of ipsilateral or contralateral events in patients treated with surgery, radiotherapy and TAM compared to those treated only with surgery and radiotherapy (4). The only subgroups which

gained a benefit from TAM were patients not randomised to radiotherapy who obtained a reduction of both ipsilateral (DCIS only) and all contralateral events. Hence an indication for the treatment with TAM could be a patient who has undergone surgery for DCIS and where radiotherapy is not recommended for medical or logistic reasons.

The data of Allred and colleagues emphasise the crucial importance of patient selection and of a correct pathological analysis. In fact, DCIS is only a risk factor for invasive disease and not for distant spread. An adequate surgical procedure with sufficient margin width and a correct histopathological analysis of size, grade and ER evaluation is the starting point before any decision for adjuvant treatment of DCIS is made. Radiotherapy is one of the cornerstones of adjuvant treatment of DCIS. Despite extensive study, there are no clinical-pathological features of DCIS that reliably predict a sufficiently low rate of local recurrence, with wide excision alone, which can justify patients not undergoing radiotherapy. Even in the NSABP B-17 study (2), in which approximately 80% cancers were small and clinically occult, surgery alone was associated with a relatively high incidence of ipsilateral breast tumour recurrence, reaching 35% after 15 years. Furthermore, of total recurrences, half were invasive, and women who developed an invasive recurrence had a 10-year cumulative risk of dying of breast cancer of 10%. These data provide strong evidence for the inclusion of radiotherapy as a component of treatment in all women with DCIS.

In every case, the choice of treatment - radiotherapy with or without TAM - must be discussed with the patient. In the case of patients with low risk (ER+) DCIS, both radiotherapy and TAM should be explained and offered to patients, drawing their attention to the risk/benefit ratio. With the data available at present, we are unable to select a subgroup of very low risk and ER+ DCIS patients who may not benefit from endocrine therapy.

The retrospective analysis of NSABP24 stresses the importance of a correct histopathological examination of ER status in all excised DCIS as the benefit is only confined to ER+ve patients. The discordance between local and central pathology analysis (about 10%) according to Allred also confirms literature data and emphasises the need for applying a standard pathological examination of ERs.

The decision concerning treatment with TAM must always

be individualised, balancing the expected benefits of TAM with its risks and side effects. Treatment with TAM is unlikely to improve overall survival, even after prolonged follow-up. The outcome of DCIS is excellent if negative margins are obtained independent of radiotherapy (7). The role of TAM in patients who have undergone mastectomy is unknown. Adjuvant trials with aromatase inhibitors will probably provide further and important information in the near future.

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