Review

Is Adjuvant Endocrine Therapy Indicated for DCIS Patients After Complete Surgical Excision?

HIBA EL HAGE CHEHADE and KEFAH MOKBEL

The London Breast Institute, The Princess Grace Hospital, London, U.K.

Abstract. Data derived from pathological analysis, natural history, radiological characteristics, genomic profiling, and clinical outcome indicate that ductal carcinoma in situ (DCIS) is a heterogeneous disease; meaning that no single therapeutic strategy is best, but rather that treatment should be personalised and entail a rigorous multidisciplinary approach. The role of adjuvant endocrine therapy after surgical excision has been the subject of scientific debate in view of the in situ nature of this neoplasm. We reviewed the literature and summarised the evidence regarding the need for adjuvant endocrine therapy following complete surgical excision of DCIS through the identification of the most important outcomes, evaluation of quality of evidence, and assessment of the trade-offs involved. There is no scientific evidence that adjuvant endocrine therapy reduces the incidence of ipsilateral breast invasive recurrence or breast cancer mortality in the context of adequate local treatment of DCIS in the form of breast conserving surgery with clear surgical margins plus adjuvant radiotherapy or total mastectomy. Therefore, its routine use is not indicated. However, adjuvant endocrine therapy can be considered after a rigorous multidisciplinary discussion and patient counselling in a carefully selected subgroup of patients with high-risk estrogen receptor-positive DCIS.

Search Strategy

Relevant articles were identified using the electronic database PubMed. Articles published up to December 2017 with no upper limit were included in the study. The following free text terms were used to search for relevant literature: “ductal carcinoma in situ or DCIS” and “endocrine therapy” or “postoperative or adjuvant endocrine therapy” or “Tamoxifen” or “aromatase inhibitors”. Only articles published in English were selected. Studies identified were screened for those that were centered on the role, safety, and controversies of adjuvant endocrine therapy in DCIS patients, which is the focus of this review. Reference articles in this review were selected to provide a balanced and representative overview of a complex subject with an extensive base of published work.

Adjuvant Endocrine Therapy and Clinical Outcome

It was observed that in many institutions the treatment of DCIS is now almost as aggressive as that of the invasive disease (4), especially after the introduction of systemic adjuvant anti-hormone therapy. In 2000, tamoxifen, a selective estrogen receptor modulator (SERM), has gained approval by the Food and Drug Administration (FDA) to be used as an adjuvant endocrine therapy in DCIS patients (8). This was based on the first of the several clinical trials that have suggested potential benefits of endocrine therapy in cases of DCIS, the National Surgical Adjuvant Breast and Bowel Project NSABP B-24 trial (8-12). NSABP B-24 (8) was double-blinded, randomized, and so on.

This article is freely accessible online.

Correspondence to: Prof. Kefah Mokbel, The London Breast Institute, The Princess Grace Hospital, 42-52 Nottingham Place, London W1U 5NY, U.K. e-mail: kefahmokbel@hotmail.com

Key Words: Ductal Carcinoma in situ, endocrine therapy, review.
controlled trial enrolling 1804 DCIS patients who had previously undergone breast conserving surgery and whole breast radiotherapy. It randomized patients to receive tamoxifen versus placebo. Upon 5-year follow-up, less ipsilateral and contralateral breast cancer events were seen in the tamoxifen group than in the placebo group (8.2% vs. 13.4% respectively, \( p=0.0009 \)). In a follow-up study (9), the benefit was seen mainly in estrogen receptor (ER) positive DCIS patients. The second clinical trial to highlight the importance of tamoxifen in the setting of DCIS was the UK/ANZ DCIS trial (10). It enrolled 1701 DCIS patients who had undergone surgical excision to achieve negative margins. They were then randomized into 2×2 factorial trial of radiotherapy, tamoxifen, or both. Upon a median follow-up of 12.7 years, tamoxifen reduced the incidence of all new breast events (HR=0.71, 95%CI=0.58-0.88; \( p=0.002 \)), reducing the risk of ipsilateral DCIS (HR=0.71, 95%CI=0.51-0.86; \( p=0.03 \)) and contralateral tumors (HR=0.44, 95%CI=0.25-0.77; \( p=0.005 \)), but having no effect on ipsilateral invasive disease (HR=0.95, 95%CI=0.66-1.38; \( p=0.8 \). Nonetheless, tamoxifen had no apparent benefit among the cohort of patients who received radiotherapy (13). In view of the recent evidence that aromatase inhibitors are superior to tamoxifen in the treatment of postmenopausal women with ER positive invasive breast cancers (14), two large, double-blinded, randomized clinical trials were carried out to compare the performance of anastrozole versus tamoxifen in the adjuvant management of hormone-receptor positive, postmenopausal women with DCIS (11, 12). In the NSABP B-35 trial (12), 3104 DCIS patients with established clear surgical margins after breast conserving surgery and radiotherapy were enrolled in this study and randomized into either tamoxifen or anastrozole treatment arms. After a median follow-up of 9 years, there was a significant difference in the breast cancer-free interval in favour of the anastrozole group (HR=0.73, 95%CI=0.56-0.96); however, this was mainly seen in the subgroup of postmenopausal patients younger than 60 years. The IBIS II trial (11) enrolled 2980 postmenopausal women with hormone- receptor positive postmenopausal breast cancer to achieve negative surgical margins (7.4% (15)). This would highlight the importance of tamoxifen in the treatment of DCIS that the decrease in the ipsilateral invasive disease is not established in previous trials. In their meta-analysis of tamoxifen vs. no additional treatment in DCIS patients, Staley et al. (17) showed that while tamoxifen after surgery treatment of DCIS reduced the risk of both ipsilateral and contralateral DCIS (HR=0.75; 95%CI=0.61-0.92 and RR=0.50; 95%CI=0.28-0.87), respectively, as well as contralateral invasive cancer (RR=0.57; 95%CI=0.39-0.83), there was no significant reduction in ipsilateral invasive cancer (HR=0.79; 95%CI=0.62-1.01). Moreover, there was no evidence of a difference in all-cause mortality (RR=1.11; 95%CI=0.89-1.39).

**Conclusion**

In summary, we believe that the routine use of adjuvant endocrine therapy in DCIS patients is questionable, provided that a thorough histopathological examination is performed and invasive malignancy is excluded, an issue that can be challenging in extensive DCIS lesions. These anti-hormonal drugs have well-established side-effects with a significant impact on patient’s quality of life (11). Most frequently reported side-effects of endocrine therapy are those related to menopausal symptoms like hot flashes, vaginal dryness, dyspareunia, loss of libido, mood swings, and night sweats. Other adverse effects associated with tamoxifen use include vaginal bleeding or discharge, cataract, venous thromboembolic events, ischemic cerebrovascular events, and endometrial cancer. On the other hand, cardiac failure and other cardiovascular events, hypercholesterolemia, musculoskeletal disorders, including new-onset osteoporosis, fractures, and arthralgia are recognised adverse effects of aromatase inhibitors (18-24). DCIS is an in situ disease with an excellent 10-year survival rate of 98% (4). Although the annual risk of developing a contralateral in situ or invasive disease is elevated at 0.6% in the absence of genetic aberration (25), the risk is very small, and the patients are
routinely followed-up with the ability to detect and manage recurrent or new breast malignancy at an early stage. Since studies have shown that tamoxifen may reduce ipsilateral DCIS but not invasive breast cancer (17), and DCIS recurrence does not influence overall survival, most patients with DCIS can be safely spared endocrine therapy. DCIS theoretically should not metastasize nor relapse in distant organs; therefore, the management should focus on local disease control (8, 26) rather than bombarding the body with systemic overtreatment. The benefits established with tamoxifen in terms of decreasing the risk of contralateral all breast events and possibly ipsilateral DCIS (17) may be explained in a chemoprevention context rather than an actual treatment where tamoxifen seems to have an impact on the prevention of invasive breast cancer among high risk women in general and in women with DCIS only on the “normal” breast” or contralateral breast (4). This potential chemoprevention benefit should be considered in the context of the adverse effects of endocrine therapy and regular surveillance of patients with DCIS during the evaluation of trade-offs. However, the evidence does not exclude the use of tamoxifen in carefully selected cases. Studies have shown that DCIS recurrence is associated with younger age, higher grade, large tumors, and positive or close margins (27-30). This group of DCIS patients as well as those not undergoing postoperative radiotherapy when indicated may be offered adjuvant endocrine therapy after testing for DCIS receptors, multidisciplinary discussion, and careful patient counselling. Furthermore, in addition to the consideration of the clinical picture, future research should focus on accurate molecular and genomic profiling of DCIS in order to guide precise individualized management and avoid overtreatment and hence a rather collateral damage of breast cancer screening.

Conflicts of Interest
The Authors report no conflicts of interest.

Acknowledgements
This review was funded by grants from the Breast Cancer Hope Foundation (London, U.K.).

References


Received December 12, 2017
Revised January 1, 2018
Accepted January 3, 2018