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Review

Postoperative Tamoxifen for ductal carcinoma in situ: Cochrane systematic review and meta-analysis

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ABSTRACT

This review aimed to assess the effects of postoperative Tamoxifen following surgical resection of ductal carcinoma in situ (DCIS). Data on local DCIS recurrence, new invasive carcinoma, distant disease, mortality and adverse effects were extracted from randomised controlled trials (RCTs) comparing Tamoxifen after surgery for DCIS (regardless of oestrogen receptor (ER) status), with or without adjuvant radiotherapy. Meta-analysis was performed using the fixed-effect model and the results expressed as relative risks (RRs) or hazard ratios (HRs) with 95% confidence intervals (CIs). Two RCTs which recruited 3375 women were included. Tamoxifen after surgery for DCIS reduced recurrence of ipsilateral DCIS (HR 0.75; 95% CI 0.61-0.92) and contralateral DCIS (RR 0.50; 95% CI 0.28-0.87). Contralateral invasive cancer was reduced (RR 0.57; 95% CI 0.39-0.83), and there was a trend towards decreased ipsilateral invasive cancer (HR 0.79; 95% CI 0.62-1.01). The number needed to treat in order for Tamoxifen to have a protective effect against all breast events is 15. There was no evidence of a difference in all-cause mortality (RR 1.11; 95% CI 0.89-1.39). Only one trial involving 1799 participants followed-up for 163 months (median) reported on adverse events with no significant difference in event rate between Tamoxifen and placebo groups, but there was a non-significant trend towards more endometrial cancer in the Tamoxifen group. This review concludes that while Tamoxifen after local excision for DCIS, with or without adjuvant radiotherapy, reduced the risk of recurrent DCIS, it did not reduce the risk of all-cause mortality.

Introduction

The detection and hence incidence of ductal carcinoma in situ (DCIS) has increased with mammographic screening for breast carcinoma. A Dutch study of 1767 screen-detected cases of DCIS estimated an increased incidence from 3/100 000 person/years to 34/100 000 person-years following the introduction of screening [1]. The current management of DCIS is either wide local excision (WLE) with radiotherapy for isolated DCIS, or mastectomy for widespread disease. The aim of surgical treatment with or without radiotherapy is local control of the disease, and prevention of ipsilateral recurrent DCIS or invasive carcinoma, particularly invasive recurrence which is associated with poor 5-year survival [2,3].

Tamoxifen is a hormonal treatment for 'oestrogen receptor (ER) positive' breast cancer. Tamoxifen works by its binding to ER positive breast cancers. Tamoxifen and several of its metabolites (4-hydroxyTamoxifen and endoxifen) bind to nuclear oestrogen receptors in oestrogen-sensitive tissues, obstructing oestrogen from binding to its receptor. However, there are known side effects: Tamoxifen has been shown to increase the risk of stroke, endometrial cancer and venous thromboembolic events [4–6]; although these side effects are rare.

The role of Tamoxifen as an adjuvant treatment of invasive breast cancer is well established: adjuvant treatment for 5 years after WLE or mastectomy confers benefit in overall mortality and incidence of ipsilateral recurrence and contralateral carcinoma in women with ER positive cancers and cancers of unknown ER status. Survival benefit is greatest in those with node-positive disease at surgery, with absolute mortality decreases of 10.9% (standard deviation (SD) 2.5) at 10 years for node-positive disease and 5.6% (SD 1.3) in node-negative disease [7].

Cells in DCIS express the same oestrogen receptors in a proportion of tumours. Approximately 50% of local recurrences are invasive rather than recurring DCIS [8]; and retrospective studies of

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low grade DCIS have shown that after 20 years of follow-up, approximately 33% of patients will have an invasive recurrence [9]. One group reviewed recurrences of DCIS and found concordant histology and identical marker expression in 63% [10]. This may suggest a progressive, stepwise model of carcinogenesis, and assuming that anti-cancer manipulations can arrest this process, adjuvant treatment in the 'pre-malignant' setting can be rationalised.

Randomised controlled trials (RCTs) have been conducted to investigate Tamoxifen treatment after surgical resection of DCIS; however, consensus on its use has not been reached. This paper is based on a Cochrane systematic review and meta-analysis published in the Cochrane Library and aims to inform clinicians regarding the optimal treatment of DCIS [11].

Methods

We searched the Cochrane register of controlled trials (2011), Cochrane Breast Cancer Groups specialised register (2011), and the World Health Organisation's International Trials Registry Platform (2011). A combination of medical subject headings and key words were used: "ductal carcinoma in situ", "DCIS", "Tamoxifen", "intraductal carcinoma", "endotherapy". Bibliographies of included studies were reviewed to identify potentially relevant articles. We contacted authors of included studies to enquire about unpublished data.

Inclusion criteria

Eligible studies were RCTs comparing Tamoxifen treatment after surgery for DCIS, either ER positive or ER negative, with or without adjuvant radiotherapy in women aged 18 years or more. Comparisons included mastectomy or WLE for DCIS with or without Tamoxifen. Patients who have had previous long-term hormonal treatment were excluded.

Outcome measures

Primary outcome measures were local recurrence of DCIS, defined as the detection of further DCIS during follow-up when original surgical margins were clear; new primary ipsi- or contralateral invasive carcinoma; distant disease, defined as regional or distant nodal disease and metastases; and all-cause mortality. Secondary outcomes were the adverse effects of treatment e.g. endometrial carcinoma, thromboembolic events, stroke.

Quality assessment and data extraction

All review authors independently examined the title and abstracts of articles identified in the search, and full versions of all potentially relevant articles were obtained. Duplicate publications were removed and the most recently published data were included in the review. Two reviewers (HS and JB) independently extracted data and assessed study quality using risk of bias assessments according to the Cochrane Handbook [12]; disagreements were resolved by a third reviewer (IM). The following information was obtained from each study: Publication details, study design, patient population, details of intervention, outcome measures, length and method of follow-up, proportion followed-up.

Statistical analysis

Meta-analysis was performed using the fixed-effect model in the RevMan 5.1 software. Assessment of statistical heterogeneity was undertaken using the χ^2 test and the I^2 statistic. Data were expressed as relative risks (RRs) or hazard ratios (HRs) with 95% confidence intervals (CIs). The χ^2 test was used to explore subgroup differences; statistical significance was set at $p \leq 0.05$. We considered the following thresholds for I^2 values: whereby 0%–40% is not considered important; 30%–60% may represent moderate heterogeneity; 50%–90% may represent substantial heterogeneity, and 75%–100% considerable heterogeneity.

Results

Of the 43 potentially relevant trials identified and screened, 24 papers were retrieved for full critical appraisal. Two trials were included in the review: The National Surgical Adjuvant Breast and Bowel Project (NSABP) B-24 trial [13] and The UK ANZ DCIS Trial [14] (Table 1).

National Surgical Adjuvant Breast and Bowel Project (NSABP B-24 trial 2011) [13]

This multicentre trial recruited 1804 women with DCIS or lobular carcinoma in situ (LCIS) from centres in the USA and Canada. Participants were recruited between May 1991 and April 1994. All women recruited underwent local excision without axillary dissection and were then randomised to receive either (a) radiotherapy and placebo or (b) radiotherapy and Tamoxifen 10 mg twice daily for 5 years. Approximately 25% of the patients involved in this study had lumpectomy margins reported as either involved or of uncertain status. The primary outcomes were the occurrence of invasive or non-invasive ipsilateral breast cancer or contralateral breast cancer.

UK ANZ DCIS trial (UK ANZ trial 2011) [14]

This 2 × 2 factorial trial recruited 1701 women from centres in the UK, Australia and New Zealand between May 1990 and August 1998. Participants with completely excised DCIS were entered into separate randomisation schedules. The first schedule was a 2 × 2 randomisation of (a) Tamoxifen only; (b) radiotherapy and Tamoxifen; (c) radiotherapy only; or (d) no adjuvant treatment. The second schedule involved a preference-based strategy whereby a choice was firstly made to receive radiotherapy or not or Tamoxifen or not, and then participants were randomised to receive the other treatment. Within the 2 separate 2-way randomisations, the choice of treatment was based upon surgeon discretion or patient preference (after discussion with the surgeon) about whether the alternative treatment should be given in addition to their randomly allocated treatment. The dose of Tamoxifen was prescribed as 20 mg once daily for 5 years and the primary outcome was the incidence of subsequent ipsilateral and contralateral DCIS.

Primary outcomes

Local recurrence of ipsilateral and contralateral DCIS

Both trials reported rates of local recurrence of DCIS, both in the ipsilateral and contralateral breast for a total of 3375 participants. For ipsilateral recurrence, there was a statistically significant reduction in the ratio of events in patients who had received Tamoxifen (HR 0.75; 95% CI 0.61–0.92; $I^2 = 0\%$) (Fig. 1). There was also a statistically significant reduction in the rate of contralateral DCIS events after Tamoxifen compared to no Tamoxifen treatment (RR 0.50; 95% CI 0.28–0.87; $I^2 = 0\%$) (Fig. 2).