

Sessão Multidisciplinar em carcinoma ductal in situ

Atualizações sobre tratamento adjuvante

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Sessão Multidisciplinar em carcinoma ductal in situ

Atualizações sobre tratamento
adjuvante

Prognóstico do CDIS?

**Objetivo do tratamento
sistêmico?**

Qual medicação utilizar?

Qual dose ?

Tratamento anti-HER2?

Prognóstico do CDIS?

Objetivo do tratamento sistêmico?

Qual medicação utilizar?

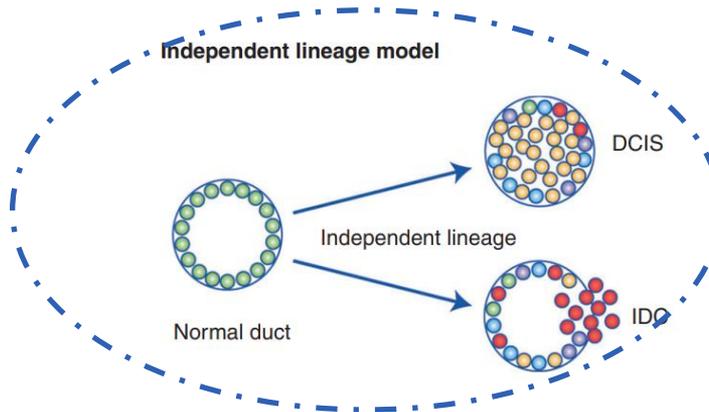
Qual dose ?

Tratamento anti-HER2?

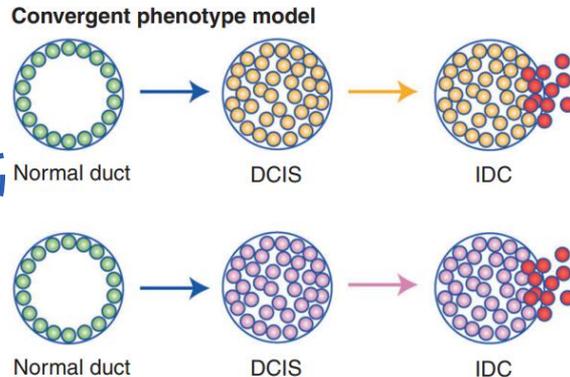
Sessão Multidisciplinar em carcinoma ductal in situ

Atualizações sobre tratamento adjuvante

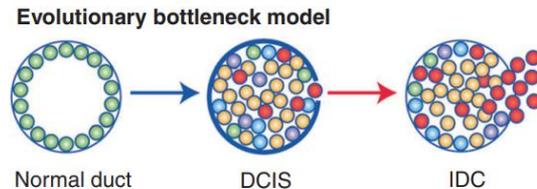
Prognóstico do Carcinoma ductal in situ



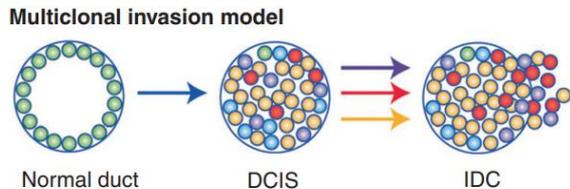
Potentially all cells can develop to DCIS and IDC in parallel



Combination of molecular features of all cells within the duct give rise to invasive properties with the same phenotype



All individual cells in the DCIS duct accumulate different genetic features. Only a specific profile is able to invade



Multiple clones have the ability to escape the duct and to become invasive

Prognóstico do Carcinoma ductal in situ

Research

Original Investigation

Breast Cancer Mortality After a Diagnosis of Ductal Carcinoma In Situ

Steven A. Narod, MD, FRCP, Javad Iqbal, MD, Vandy Ganamales, MPH, Victoria Sopik, MSc, Ping Sun, PhD

IMPORTANCE: Women with ductal carcinoma in situ (DCIS), or stage 0 breast cancer, often experience a second primary breast cancer (DCIS or invasive), and some ultimately die of breast cancer.

OBJECTIVE: To estimate the 10- and 20-year mortality from breast cancer following a diagnosis of DCIS and to establish whether the mortality rate is influenced by age at diagnosis, ethnicity, and initial treatment received.

DESIGN, SETTING, AND PARTICIPANTS: Observational study of women who received a diagnosis of DCIS from 1988 to 2011 in the Surveillance, Epidemiology, and End Results (SEER) 18 registries database. Age at diagnosis, race/ethnicity, pathologic features, date of second primary breast cancer, cause of death, and survival were abstracted for 108 196 women. Their risk of dying of breast cancer was compared with that of women in the general population. Cox proportional hazards analysis was performed to estimate the hazard ratio (HR) for death from DCIS by age at diagnosis, clinical features, ethnicity, and treatment.

MAIN RESULTS AND MEASURES: Ten- and 20-year breast cancer-specific mortality

RESULTS: Among the 108 196 women with DCIS, the mean (range) age at diagnosis of DCIS was 53.8 (15-69) years and the mean (range) duration of follow-up was 7.5 (0-23.9) years. At 20 years, the breast cancer-specific mortality was 3.3% (95% CI, 3.0%-3.6%) overall and was higher for women who received a diagnosis before age 35 years compared with older women (7.8% vs 3.2%; HR, 2.58 [95% CI, 1.85-3.60]; $P < .001$) and for blacks compared with non-Hispanic whites (7.0% vs 3.0%; HR, 2.55 [95% CI, 2.17-3.01]; $P < .001$). The risk of dying of breast cancer increased after experience of an ipsilateral invasive breast cancer (9.8, 95% CI, 14.0-23.6; $P < .001$). A total of 517 patients died of breast cancer following a DCIS diagnosis (mean follow-up, 7.5 [range, 0-23.9] years) without experiencing an in-breast invasive cancer prior to death. Among patients who received lumpectomy, radiotherapy was associated with a reduction in the risk of ipsilateral invasive recurrence at 10 years (0.5% vs 4.9%, adjusted HR, 0.47 [95% CI, 0.42-0.53]; $P < .001$) but not of breast cancer-specific mortality at 10 years (0.8% vs 0.9%; HR, 0.86 [95% CI, 0.67-1.10]; $P = .22$).

CONCLUSIONS AND RELEVANCE: Important risk factors for death from breast cancer following a DCIS diagnosis include age at diagnosis and black ethnicity. The risk of death increases after a diagnosis of an ipsilateral second primary invasive breast cancer, but prevention of these recurrences by radiotherapy does not diminish breast cancer mortality at 10 years.

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JAMA Oncol. doi:10.1001/jamaoncol.2015.290
Published online August 20, 2015.

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Figure 1. Twenty-Year Breast Cancer-Specific Survival After Ductal Carcinoma In Situ (DCIS) by Race/Ethnicity

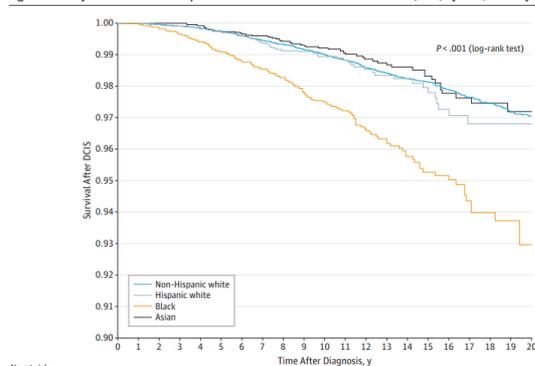


Figure 2. Twenty-Year Breast Cancer-Specific Survival After Ductal Carcinoma In Situ (DCIS) by Estrogen Receptor (ER) Status

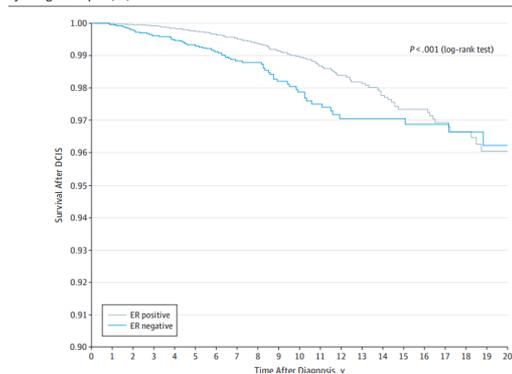


Table 1. Standardized Mortality Ratios (SMRs) of Breast Cancer Following a Diagnosis of Ductal Carcinoma In Situ, by Age at Diagnosis

Age at Diagnosis, y	Person-years	Follow-up, Mean (SD), y	Deaths, No.		SMR (95% CI)
			Observed	Expected	
30-34	8 830.1	9.0 (6.2)	22	8.5	17.0 (10.9-25.3)
35-39	35 503.3	8.9 (6.0)	62	8.5	7.3 (5.6-9.3)
40-44	103 719.2	8.0 (5.7)	112	35.7	3.1 (2.6-3.8)
45-49	142 083.6	7.7 (5.5)	144	67.4	2.1 (1.8-2.5)
50-54	149 541.9	7.5 (5.4)	157	91.7	1.7 (1.4-2.0)
55-59	138 475.9	7.3 (5.2)	145	103.9	1.4 (1.2-1.6)
60-64	120 619.5	7.1 (5.3)	138	107.3	1.3 (1.1-1.5)
65-69	113 118.3	7.3 (5.3)	162	118.0	1.4 (1.2-1.6)
All	811 891.8	7.5 (5.4)	942	533.8	1.8 (1.7-1.9)

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Atualizações sobre tratamento adjuvante

Prognóstico do CDIS?

Risco baixo de morte ~3%
Maior risco em jovens, negras e com ER negativo

Objetivo do tratamento sistêmico?

Qual medicação utilizar?

Qual dose ?

Tratamento anti-HER2?

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Objetivo do tratamento

ARTICLES

Articles

Tamoxifen in treatment of intraductal breast cancer: National Surgical Adjuvant Breast and Bowel Project B-24 randomised controlled trial

Bernard Fisher, James Dipnum, Norman Wolmark, D Lawrence Wickerham, Edwin R Fisher, Eleftherios Mamounas, Roy Smith, Mirsada Begovic, Nikolai V Dimitrov, Richard G Margolese, Carl G Kardinal, Maureen T Ravankar, Louis Fehrenbacher, Robert H Doshi

Summary

Background We have shown previously that tamoxifen with radiation therapy was more effective than tamoxifen alone for the treatment of ductal carcinoma in situ (DCIS). We did a double-blind randomised controlled trial to find out whether tamoxifen, radiation therapy, and tamoxifen was more effective than tamoxifen and radiation therapy alone for DCIS.

Methods 1804 women with DCIS, including those whose resected sample margins were involved with tumour, were randomly assigned tamoxifen, radiation therapy (50 Gy), and placebo (n=602), or tamoxifen, radiation therapy, and tamoxifen (20 mg daily for 5 years, n=602). Median follow-up was 74 months (range 57–93). We compared annual event rates and cumulative probability of invasive or non-invasive ipsilateral and contralateral tumours over 5 years.

Findings Women in the tamoxifen group had fewer breast cancer events at 5 years than did those on placebo (8.2 vs 13.4%, p<0.0009). The cumulative incidence of all invasive breast cancer events in the tamoxifen group was 4.1% at 5 years; 2.1% in the ipsilateral breast, 1.8% in the contralateral breast, and 0.2% at regional or distant sites. The risk of ipsilateral-breast cancer was lower in the tamoxifen group even when sample margins contained tumour and when DCIS was associated with comedonecrosis.

Interpretation The combination of tamoxifen, radiation therapy, and tamoxifen was effective in the prevention of invasive cancer.

Lancet 1999; 353: 1993–2000
See Commentary page 1996

National Surgical Adjuvant Breast and Bowel Project (NSABP), University of the Health Sciences & Humphrey Center, Suite 402, Pittsburgh, PA 15223-3224, USA (E R Fisher, et al); **Department of Biostatistics** (J Dipnum) and **NSABP Biostatistical Center** (D Wickerham), University of Pittsburgh, Pittsburgh; **Allegheny General Hospital, Pittsburgh** (N Wolmark); **University of Pittsburgh Medical Center, Pittsburgh** (E R Fisher); **Mount Sinai Center for Breast Health, Cleveland, OH** (M Mamounas); **Michigan State University, East Lansing, MI** (R Smith); **Novartis Oncology, East Hanover, NJ** (N Dimitrov); **Alton General Hospital, Buxton, Ontario, Canada** (R Margolese); **Alton Debrae Medical Foundation, New Orleans, LA** (C Kardinal); **Boston Medical Center, Boston, MA** (M Ravankar); **Kaiser Permanente, Southern California Region, CA** (L Fehrenbacher); **University of Michigan, Ann Arbor, MI** (R Doshi)

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THE LANCET • Vol 353 • June 12, 1999

1993

Articles

Effect of tamoxifen and radiotherapy in women with locally excised ductal carcinoma in situ: long-term results from the UK/ANZ DCIS trial

Jack Cuzick, Inara Sestak, Sarah I Pinder, Ian D Ellis, Sharon Forsyth, Nigel Bundred, John F Forbes, Hugh Bishop, Ian S Fentons, William D George

Summary

Background Initial results of the UK/ANZ DCIS (UK, Australia, and New Zealand ductal carcinoma in situ) trial suggested that radiotherapy reduced new breast events of ipsilateral invasive and ductal carcinoma in situ (DCIS) compared with no radiotherapy, but no significant effects were noted with tamoxifen. Here, we report long-term results of this trial.

Methods Women with completely locally excised DCIS were recruited into a randomised 2x2 factorial trial of radiotherapy, tamoxifen, or both. Randomisation was independently done for each of the two treatments (radiotherapy and tamoxifen), stratified by screening assessment centre, and blocked in groups of four. The recommended dose for radiation was 50 Gy in 25 fractions over 5 weeks (2 Gy per day on weekdays), and tamoxifen was prescribed at a dose of 20 mg daily for 5 years. Elective decision to withhold or provide one of the treatments was permitted. The endpoints of primary interest were invasive ipsilateral new breast events for the radiotherapy comparison and any new breast event, including contralateral DCIS and DCIS, for tamoxifen. Analysis of each of the two treatment comparisons was restricted to patients who were randomly assigned to that treatment. Analyses were by intention to treat. All trial drugs have been completed and this study is in long-term follow-up. This study is registered, number ISRCTN9518370.

Findings Between May 1996 and August 1995, 1701 women were randomly assigned to radiotherapy and tamoxifen, radiotherapy alone, tamoxifen alone, or to no adjuvant treatment. Seven patients had protocol violations and thus 1694 patients were available for analysis. After a median follow-up of 12.7 years (IQR 10.9–14.7), 376 (163 invasive [122 ipsilateral vs 39 contralateral], 197 DCIS [174 ipsilateral vs 17 contralateral], and 16 of unknown invasiveness or laterality) breast cancers were diagnosed. Radiotherapy reduced the incidence of all new breast events (hazard ratio [HR] 0.41, 95% CI 0.30–0.56; p<0.0001), reducing the incidence of ipsilateral invasive disease (0.32, 0.19–0.56; p<0.0001) as well as ipsilateral DCIS (0.38, 0.22–0.63; p<0.0001), but having no effect on contralateral breast cancer (p=0.4), or 4.1–5.8; p=0.6). Tamoxifen reduced the incidence of all new breast events (HR 0.71, 95% CI 0.58–0.88; p<0.002), reducing recurrent ipsilateral DCIS (0.70, 0.51–0.86; p<0.03) and contralateral tumours (0.44, 0.25–0.77; p<0.005), but having no effect on ipsilateral invasive disease (0.95, 0.66–1.38; p=0.8). No data on adverse events except cause of death were collected for this trial.

Interpretation This updated analysis confirms the long-term beneficial effect of radiotherapy and reports a benefit for tamoxifen in reducing local and contralateral new breast events for women with DCIS treated by complete local excision.

Funding Cancer Research UK and the Australian National Health and Medical Research Council.

Introduction

Ductal carcinoma in situ (DCIS) is usually an asymptomatic disorder that is characterised by a clonal proliferation of epithelial cells confined within the lumens of mammary ducts.¹ Screening has led to a substantial increase in the incidence of DCIS over the past two decades; the disorder represents 10% of all lower cumulative incidences of both types of intraductal-breast cancer because of tamoxifen and radiation therapy.² At 8 years, findings were confirmed of lower cumulative incidences of both types of intraductal-breast cancer because of tamoxifen and radiation therapy for ipsilateral-mammographically-detected DCIS.³ The study concluded that, because of the low recurrence rate of invasive ipsilateral-breast cancer, mastectomy was not warranted in women who had DCIS similar to that of B-17 participants.

Management options for DCIS include surgery, radiotherapy, and hormonal therapy.⁴ The effectiveness of radiotherapy in reducing recurrences has been examined in four clinical trials.^{5–8} In all these studies, radiotherapy reduced in situ or invasive recurrences by about 50%. Although radiotherapy is associated with substantial

reductions in local recurrence, no differences have been reported in metastatic disease or overall survival.^{5–8}

The role of tamoxifen in the management of DCIS has been investigated in the UK, Australia, and New Zealand (UK/ANZ) DCIS trial⁹ and also in the National Surgical Adjuvant Breast and Bowel Project B-24 (NSABP B-24) trial.¹⁰ In the NSABP trial, patients with DCIS received radiotherapy and were then randomised to tamoxifen (20 mg/day) or placebo. After just over 6 years of follow-up, a significant reduction in all new breast events was reported in the tamoxifen group compared with the placebo group (rate ratio 0.61, 95% CI 0.47–0.83; p<0.0009). The use of other endocrine treatments for DCIS is under investigation in the International Breast Cancer Intervention Study 11 (IBIS-11) and the NSABP B-35 trial.¹¹



Lancet Oncol 2001; 2: 29–39

Published Online
December 8, 2000
DOI:10.1056/NEJM
200012082937

See Commentary p 27

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2 estudos randomizados

- Tratamento local TMX vs não TMX

- Avaliação de novos eventos em mamas

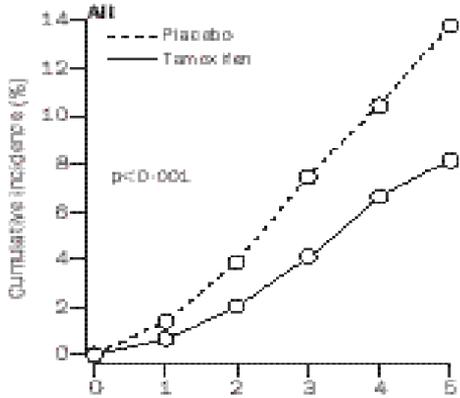
- Mortalidade câncer específica e geral

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LACOG - GBECAM 2003

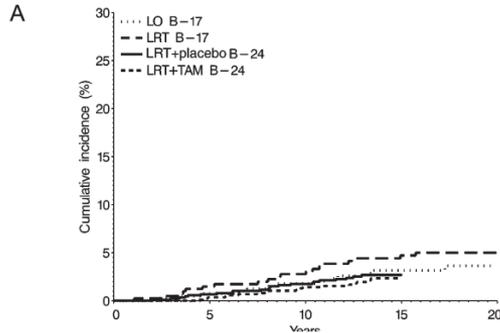
Eventos em mamas ipsi e contra-lateral



HR0.71 (0.58–0.88)

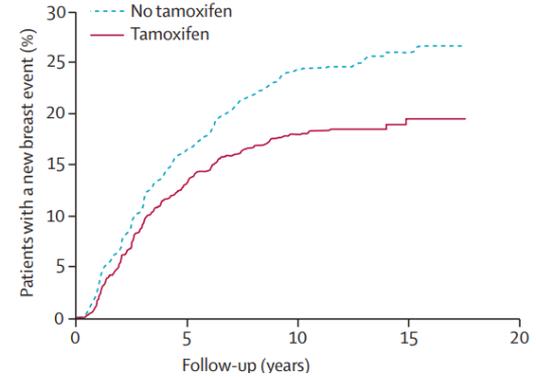
HR0.70 (0.50–0.98)

Mortalidade geral e câncer de mama específica



Articles

Effect of tamoxifen and radiotherapy in women with locally excised ductal carcinoma in situ: long-term results from the UK/ANZ DCIS trial



	No adjuvant treatment (n=544)	Tamoxifen (n=567)	Radiotherapy (n=267)	Radiotherapy and tamoxifen (n=316)	Total (n=1694)
Breast cancer	11 (2%)	19 (3%)	4 (1%)	5 (2%)	39 (2%)
Other cancer	14 (3%)	19 (3%)	10 (4%)	14 (4%)	57 (3%)
Cardiovascular	1 (0%)	3 (1%)	5 (2%)	3 (1%)	12 (1%)
Cerebrovascular	3 (1%)	1 (0%)	0	2 (1%)	6 (0%)
Thromboembolic	3 (1%)	1 (0%)	0	2 (1%)	6 (0%)
Other	20 (4%)	15 (3%)	7 (3%)	17 (5%)	59 (3%)
Total	52 (10%)	58 (10%)	26 (10%)	43 (14%)	179 (11%)

Table 5: Causes of death

[Intervention Review]

Postoperative tamoxifen for ductal carcinoma in situ

Helen Staley¹, Iain McCallum¹, Julie Bruce²

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Editorial group: Cochrane Breast Cancer Group.
Publication status and date: New, published in Issue 10, 2012.

Citation: Staley H, McCallum I, Bruce J. Postoperative tamoxifen for ductal carcinoma in situ. *Cochrane Database of Systematic Reviews* 2012, Issue 10. Art. No.: CD007847. DOI: [10.1002/14651858.CD007847.pub2](https://doi.org/10.1002/14651858.CD007847.pub2).

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Background

Ductal carcinoma in situ (DCIS) is a non-invasive carcinoma twenty years, largely as a result of the introduction of prophylactic surgery with or without radiotherapy to prevent recurrent postoperative hormonal treatment (tamoxifen) after surgery.

Objectives

To assess the effects of postoperative tamoxifen in women having local surgical resection of DCIS.

Search methods

We searched the Cochrane Central Register of Controlled Trials (CENTRAL, The Cochrane Library), the Cochrane Breast Cancer Group's Specialised Register, and the World Health Organization's International Clinical Trials Registry Platform (WHO ICTRP) on 16 August 2011.

Selection criteria

Published and unpublished randomised controlled trials (RCTs) and quasi-randomised controlled trials comparing tamoxifen after surgery for DCIS (regardless of oestrogen receptor status), with or without adjuvant radiotherapy.

Data collection and analysis

Two authors independently assessed trial quality and extracted data. Statistical analyses were performed using the fixed-effect model and the results were expressed as relative risks (RRs) or hazard ratios (HRs) with 95% confidence intervals (CIs).

Main results

We included two RCTs involving 3375 women. Tamoxifen after surgery for DCIS reduced recurrence of both ipsilateral (same side) DCIS (HR 0.75; 95% CI 0.61 to 0.92) and contralateral (opposite side) DCIS (RR 0.59; 95% CI 0.28 to 0.87). There was a trend towards decreased ipsilateral invasive cancer (HR 0.79; 95% CI 0.62 to 1.01) and reduced contralateral invasive cancer (RR 0.57; 95% CI 0.39 to 0.83). 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 detected in all cause mortality (RR 1.11; 95% CI 0.89 to 1.39). Only one study, involving 1799 participants followed-up for 163 months (median) reported on adverse events (i.e. toxicity, mood changes, deep vein thrombosis, pulmonary embolism, endometrial cancer) with no significant difference between tamoxifen and placebo groups, but there was a non-significant trend towards more endometrial cancer in the tamoxifen group.

Postoperative tamoxifen for ductal carcinoma in situ (Review)

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Figure 3. Forest plot of comparison: Outcome: 1.1 DCIS ipsilateral.

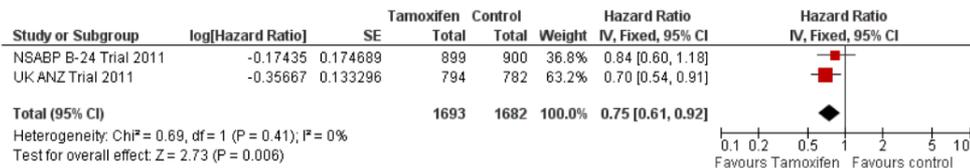
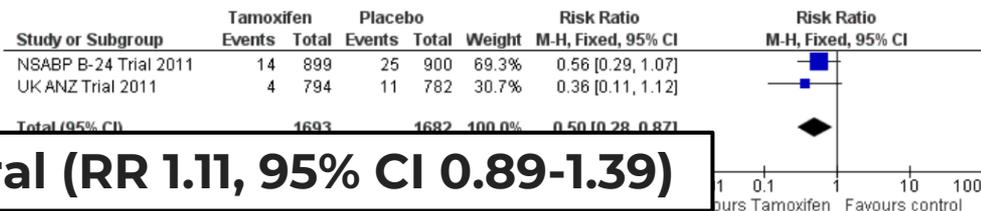


Figure 4. Forest plot of comparison: Outcome: 1.2 DCIS contralateral



Mortalidade geral (RR 1.11, 95% CI 0.89-1.39)

Figure 5. Forest plot of comparison: Outcome: 1.3 Invasive, ipsilateral breast cancer

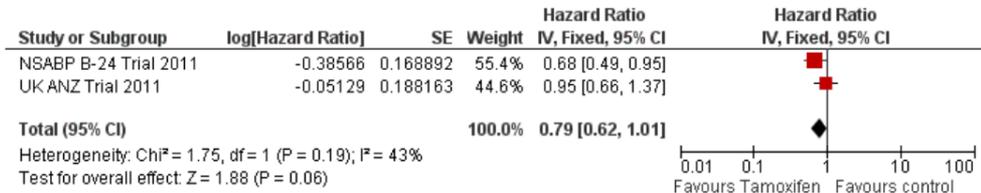


Figure 6. Forest plot of comparison: Outcome: 1.4 Invasive, contralateral breast cancer



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Prognóstico do CDIS?

**Objetivo do tratamento
sistêmico?**

**Reduzir novos eventos em mama ipsi
e contra-lateral**

Qual medicação utilizar?

Qual dose ?

Tratamento anti-HER2?

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Qual medicação utilizar?

Articles

Anastrozole versus tamoxifen in postmenopausal women with ductal carcinoma in situ undergoing lumpectomy plus radiotherapy (NSABP B-35): a randomised, double-blind, phase 3 clinical trial

Rickard G Mangione, Renes S Cecchini, Thomas B Julian, Patricia A Ganz, Joseph P Costantino, Laura A Vallbo, Kathy S Albain, Patrick W Whitworth, Mary E Cranfoco, Adam M Boufky, Howard M Goos, Gemini S Soot, Judith O Hopkins, Louis Fehrenbacher, Kern Strutz, Timothy F Whelan, Thomas E Sey, Efthymios P Mamounas, Norman Wolmark

Summary

Background Ductal carcinoma in situ is currently managed with excision, radiotherapy, and adjuvant hormone therapy, usually tamoxifen. We postulated that an aromatase inhibitor would be safer and more effective. We therefore undertook this trial to compare anastrozole versus tamoxifen in postmenopausal women with ductal carcinoma in situ undergoing lumpectomy plus radiotherapy.

Methods The double-blind, randomised, phase 3 National Surgical Adjuvant Breast and Bowel Project (NSABP) B-35 trial was done in 113 participating NSABP centres in the USA and Canada. Postmenopausal women with hormone-positive ductal carcinoma in situ treated by lumpectomy with clear resection margins and whole-breast irradiation were enrolled and randomly assigned (1:1) to receive either oral tamoxifen 20 mg per day (with matching placebo in place of anastrozole) or oral anastrozole 1 mg per day (with matching placebo in place of tamoxifen) for 5 years. Randomisation was stratified by age (<60 vs ≥60 years) and patients and investigators were masked to treatment allocation. The primary outcome was breast cancer-free interval, defined as time from randomisation to any breast cancer event (local, regional, or distant recurrence, or contralateral breast cancer, invasive disease, or ductal carcinoma in situ), analysed by intention to treat. This study is registered with ClinicalTrials.gov, number NCT00653898, and is complete.

Findings Between Jan 1, 2003, and June 15, 2006, 3104 eligible patients were enrolled and randomly assigned to the two treatment groups (1552 to tamoxifen and 1552 to anastrozole). As of Feb 28, 2015, follow-up information was available for 3083 patients for overall survival and 3077 for all other disease-free endpoints, with median follow-up of 9.0 years (IQR 8.2–10.0). In total, 212 breast cancer-free interval events occurred: 122 in the tamoxifen group and 90 in the anastrozole group (HR 0.73 [95% CI 0.56–0.96], p=0.0234). A significant time-by-treatment interaction (p=0.0410) became evident later in the study. There was also a significant interaction between treatment and age group (p=0.0379), showing that anastrozole is superior only in women younger than 60 years of age. Adverse events did not differ between the groups, except for thrombosis or embolism—a known side-effect of tamoxifen—for which there were 17 grade 4 or worse events in the tamoxifen group versus four in the anastrozole group.

Interpretation Compared with tamoxifen, anastrozole treatment provided a significant improvement in breast cancer-free interval, mainly in women younger than 60 years of age. This finding means that women will benefit from having a choice of effective agents for ductal carcinoma in situ.

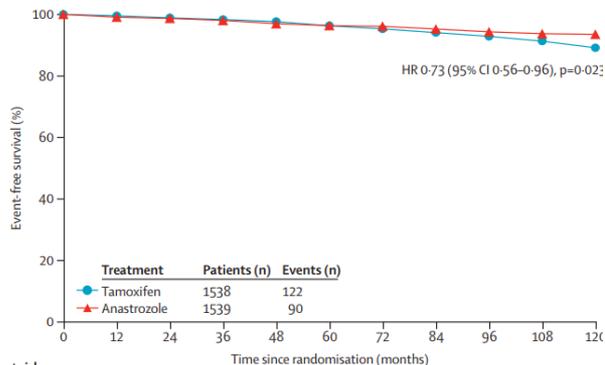
Funding US National Cancer Institute and AstraZeneca Pharmaceuticals LP.

Introduction With continuing improvements in screening mammography and diagnostic breast imaging during the past three to four decades, ductal carcinoma in situ is now identified more frequently and its management has become an increasingly challenging problem. Originally called early or minimal breast cancer, ductal carcinoma in situ is now classified as stage 0 breast cancer and is regarded by some experts as a precancerous entity. As a result, debate is ongoing as to whether ductal carcinoma in situ should be treated as a malignancy or as a precursor of cancer.

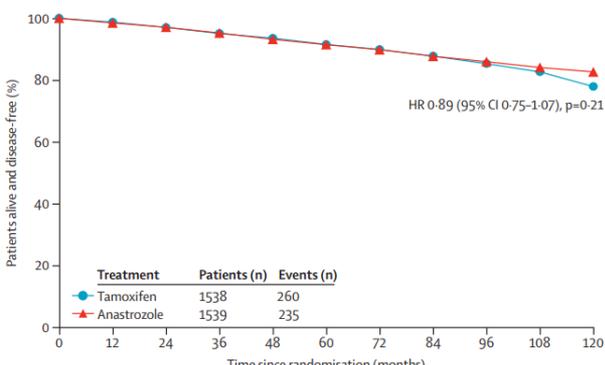
Randomised clinical trials of invasive breast cancer have established that breast-conserving surgery and whole-breast irradiation provide the same long-term survival rates as total mastectomy.^{1,2} This shift in surgical management has also been adopted for ductal carcinoma in situ, following publication of National Surgical Adjuvant Breast and Bowel Project (NSABP) B-17,³ a randomised prospective clinical trial of lumpectomy versus mastectomy and radiotherapy for ductal carcinoma in situ. However, breast-conserving therapy leaves open the chance for a local recurrence, which can manifest itself as another ductal carcinoma in situ or as invasive recurrence.

Published Online
December 10, 2015
http://dx.doi.org/10.1016/S0140-6736(15)01158-X
See Online for Articles
http://dx.doi.org/10.1016/S0140-6736(15)01158-X
NSABP Oncology/Breast and Bowel Project (NSABP), Pittsburgh, PA, USA
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- Estudo duplo cego, randomizado
- 3104 pacientes
- Anastrozol 1mg/d versus Tamoxifeno 20mg/d
- EP 1ario → Intervalo livre de cancer de mama
- EP 2ario → Sobrevida livre de doença
- Estratificação por idade (< 60 anos versus > 60 anos)



**HR 0.73 (IC95% 0.56-0.96)
p=0.023**



**HR 0.89 (IC95% 0.75-1.07)
p=0.21**

www.thelancet.com Published online December 10, 2015; http://dx.doi.org/10.1016/S0140-6736(15)01158-X

Sessão Multidisciplinar em carcinoma ductal in situ

Atualizações sobre tratamento adjuvante

Prognóstico do CDIS?

Objetivo do tratamento sistêmico?

Qual medicação utilizar?

Tamoxifeno ou anastrozol
Alto risco ou pós menopausa com menos de 60 anos podem beneficiar-se de anastrozol

Qual dose ?

Tratamento anti-HER2?

Sessão Multidisciplinar em carcinoma ductal in situ

Atualizações sobre tratamento
adjuvante

Prognóstico do CDIS?

Objetivo do tratamento
sistêmico?

Qual medicação utilizar?

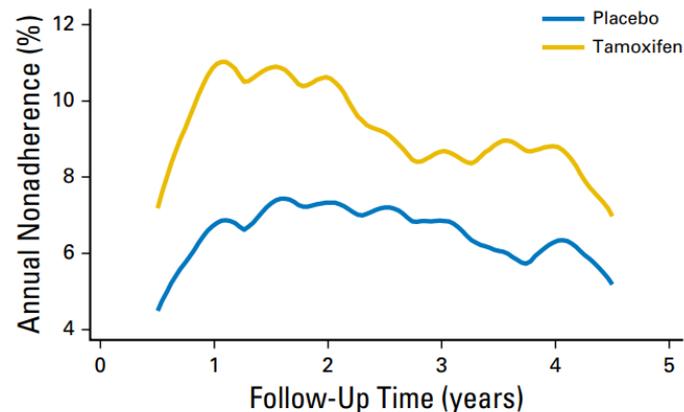
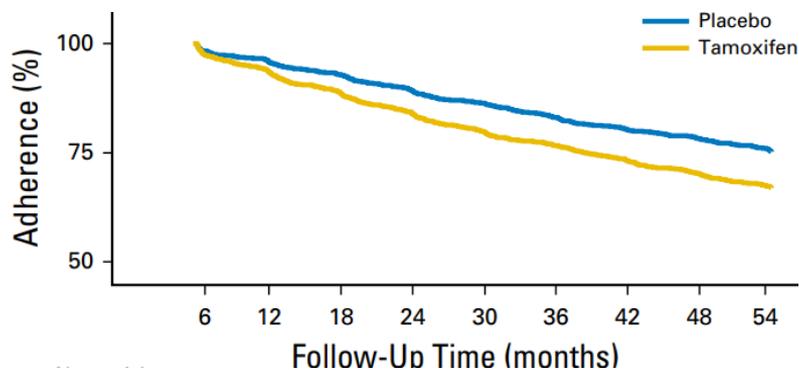
Qual dose ?

Tratamento anti-HER2?

Qual dose?

Aderência abaixo do desejado

- Cerca de 1 em cada 3 pacientes em uso de TMX torna-se não-aderente
- Não aderência diretamente relacionada aos sintomas
- 1º e 2º anos crucial para aderência



Qual dose?

Ausência de benefício em mortalidade

+

Efeitos colaterais com baixa aderência

=



Estratégias de de-escalonamento

ARTICLES

A Randomized Trial of Low-Dose Tamoxifen on Breast Cancer Proliferation and Blood Estrogenic Biomarkers

Andrea Decensi, Chris Robertson, Giuseppe Viale, Francesca Pigatto, Harriet Johanson, Elton R. Kisanga, Paolo Veronesi, Rosalba Torrisi, Maximiliano Cazzaniga, Serena Mora, Maria T. Sandri, Giuseppe Pelosi, Alberto Laini, Aron Goldhirsch, Ernst A. Liem, Umberto Veronesi

Background: Tamoxifen reduces the risk of breast cancer in women at high risk for the disease but increases the risk for endometrial tumors and venous thromboembolisms, possibly in a dose-dependent fashion. We compared the effects of tamoxifen at 1 mg/day and 5 mg/day with those of the standard dose of 20 mg/day on breast cancer proliferation using a surrogate endpoint marker (Ki-67 expression) and blood biomarkers associated with breast cancer, cardiovascular disease, and bone fracture risk. **Methods:** We randomly assigned 120 women with estrogen receptor (ER)-positive breast cancer to tamoxifen at 1, 5, or 20 mg/day for 4 weeks. Expression of the tumor proliferation marker Ki-67 and of biomarkers of breast cancer (insulin-like growth factor-I, sex hormone-binding globulin), cardiovascular disease (cholesterol, triglycerides, ultrasensitive C-reactive protein, fibrinogen, antithrombin-III), and bone fracture (type I collagen C-telopeptide) risk were determined before (baseline) and after treatment. All levels were compared with those in two nonrandomized control groups (34 women with ER-negative breast cancer and 29 additional women with ER-positive breast cancer). Data were analyzed by analysis of covariance. All statistical tests were two-sided. **Results:** Expression of Ki-67 decreased in all three tamoxifen groups, with no difference in the magnitude of reduction among groups ($P = .81$). Relative to baseline, Ki-67 expression decreased by a median of 15.6% (95% confidence interval = 0.0% to 24.1%) among the tamoxifen groups but increased by 12.4% (95% confidence interval = 0.0% to 19.6%) among the nonrandomized control groups. Several blood biomarkers showed dose-response relationships with tamoxifen, including decreased insulin-like growth factor-I, increased sex hormone-binding globulin, and decreased low-density lipoprotein-cholesterol, ultrasensitive C-reactive protein, fibrinogen, and antithrombin-III levels. **Conclusions:** The effects on Ki-67 expression of lower doses of tamoxifen were comparable to those achieved with the standard dose, although the effects on blood biomarkers were variable. The effects of lower doses of tamoxifen should be assessed further in randomized trials. *J Natl Cancer Inst* 2003;95:775-80

Tamoxifen, a selective estrogen receptor (ER) modulator, decreases mortality in patients with ER-positive breast cancer (1) and breast cancer incidence in healthy women at increased risk (2). However, the partial estrogenic activity of tamoxifen is an important limiting factor in its clinical use. Indeed, tamoxifen

use has been associated with drug resistance in women with advanced disease (3) and with a detrimental trend in disease-free survival after treatment for more than 5 years in the adjuvant setting (4). Although the estrogenic agonistic activity of tamoxifen reduces osteoporotic bone fractures (5), tamoxifen has been associated with an increased risk of endometrial tumors (1,5), including uterine sarcomas (6) and with venous thromboembolic events (5,7).

Several factors influence the complex antagonism/agonist effects of tamoxifen in humans, including differences in target tissue ER co-regulator recruitment (8), endocrine milieu (9,10), dose (11), and duration of exposure (4). For example, in the subgroups of premenopausal women (5) and women on hormone replacement therapy (7) assigned to tamoxifen or placebo, no difference in endometrial cancer and venous thromboembolic events was observed between arms, suggesting that tamoxifen pharmacodynamics may be influenced by the woman's endocrine environment. Furthermore, there is evidence that the endometrial cancer risk is time- and dose-dependent (1,12), which provides the rationale for a reduction in an administered tamoxifen dose.

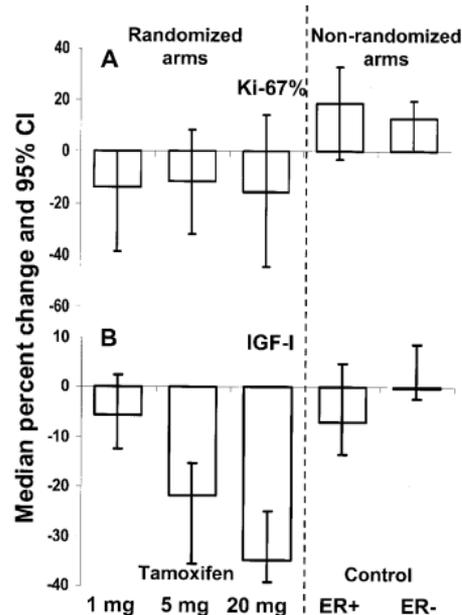
Although tamoxifen is a prototypical designer drug that binds to a specific molecular target, the ER, and follows saturation kinetics (13,14), its early clinical development has been characterized by the search for the maximum tolerated dose rather than the optimal biologic dose. However, when a 20 mg/day dose of tamoxifen was compared with higher doses, their efficacies were similar in lowering recurrence of and mortality from breast cancer (1). Furthermore, results from animal studies have suggested that reducing the tamoxifen dose to an equivalent of 1 mg/day

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Correspondence to: Andrea Decensi, M.D., Division of Chemoprevention, European Institute of Oncology, via Ripamonti, 435, 20141 Milan, Italy (e-mail: andrea.decensi@ieo.it).

See "Notes" following References.

Journal of the National Cancer Institute, Vol. 95, No. 11, October 14, 2003
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5mg/dia não foi inferior a 20 mg/d para inibir marcadores de proliferação de cancer de mama

- Δ ki67 foi similar $\rightarrow p = 0.81$
- IGF sérico pós tratamento discretamente superior $\rightarrow p = 0.001$

Qual dose?

Randomized Placebo Controlled Trial of Low-Dose Tamoxifen to Prevent Local and Contralateral Recurrence in Breast Intraepithelial Neoplasia

Andrea DeCensi, MD¹; Matteo Puntoni, PhD¹; Alana Guerrieri-Gonzaga, MSc¹; Silvia Cariglia, MSc¹; Franca Avio, MD¹; Laura Cortesi, MD¹; Cristiana Tavemili, MSc²; Maria Grazia Paquola, MD¹; Fabio Falini, MD¹; Marcella Guliano, MD¹; Maria Digenmaro, MD¹; Anna Carello, MD¹; Katia Capossi, MD¹; Grazia Pirotti, MD¹; Matteo Lazzeroni, MD¹; Davide Serrano, MD¹; Daniela Bianchi, MSc¹; Sara Campora¹; Marielena Petrea, PhD¹; Tania Buttner Weeber, RN¹; Luca Boni, MD¹; and Bernardo Bonanni, MD¹

PURPOSE Tamoxifen administered for 5 years at 20 mg/d is effective in breast cancer treatment and prevention, but toxicity has limited its broad use. Biomarker trials showed that 5 mg/d is not inferior to 20 mg/d in decreasing breast cancer proliferation. We hypothesized that a lower dose given for a shorter period could be as effective in preventing recurrence from breast intraepithelial neoplasia but have a lower toxicity than the standard dose.

PATIENTS AND METHODS We conducted a multicenter randomized trial of tamoxifen, 5 mg/d or placebo administered for 3 years after surgery in women with hormone-sensitive or unknown breast intraepithelial neoplasia, including atypical ductal hyperplasia and lobular or ductal carcinoma in situ. The primary end point was the incidence of invasive breast cancer or ductal carcinoma in situ.

RESULTS Five hundred women 75 years of age or younger were included. After a median follow-up of 5.1 years (interquartile range, 3.9-6.3 years), there were 14 neoplastic events with tamoxifen and 28 with placebo (11.6 v 23.9 per 1,000 person-years; hazard ratio, 0.48; 95% CI, 0.26 to 0.92; $P = .02$), which resulted in a 5-year number needed to treat of 22 (95% CI, 20 to 27). Tamoxifen decreased contralateral breast events by 75% (three v 12 events; hazard ratio, 0.25; 95% CI, 0.07 to 0.88; $P = .02$). Patient-reported outcomes were not different between arms except for a slight increase in frequency of daily hot flashes with tamoxifen ($P = .02$). There were 12 serious adverse events with tamoxifen and 16 with placebo, including one deep vein thrombosis and one stage I endometrial cancer with tamoxifen and one pulmonary embolism with placebo.

CONCLUSION Tamoxifen at 5 mg/d for 3 years can have the recurrence of breast intraepithelial neoplasia with a limited toxicity, which provides a new treatment option in these disorders.

J Clin Oncol 37:1629-1637. © 2019 by American Society of Clinical Oncology

Guest Editor: Giovanni Tribuzio. Non-Commercial Use: Downloaded 4/10/2020



INTRODUCTION

is effective in the adjuvant treatment of hormone receptor-positive breast cancer¹ and for the prevention of breast cancer in at-risk women on the basis of the Gail model, including those with ADH and LCIS whose risk of subsequent invasive cancer is 10 to 13 per 1,000 per year, respectively.² However, the toxicity of tamoxifen, including venous thromboembolic events and endometrial cancer, is a significant problem and may explain the low uptake of tamoxifen as preventive therapy.³ The increase of menopausal symptoms during tamoxifen therapy, including vasomotor symptoms and sexual and gynecologic disturbances, is also a cause of decreased quality of life and treatment withdrawal.^{4,5} The lack of a demonstrated breast cancer mortality benefit for tamoxifen given for

preventive therapy, including low-dose tamoxifen, among women at high risk of breast cancer.⁶ Current National Comprehensive Cancer Network guidelines also recommend low-dose tamoxifen after DCIS if the patient is symptomatic on the 20 mg dose once daily or if the patient is unwilling or unable to take the standard dose.⁴ Recent data from US centers show that low-dose tamoxifen is the most popular choice of preventive therapy in women with high-risk lesions, with low

ASSOCIATED CONTENT
See accompanying Editorial on page 1595
Appendix
Data Supplements
Author affiliations and support information (applicable at the end of this article)
Accepted on February 11, 2019 and published at jco.org on April 11, 2019.
DOI: [10.1200/JCO.2018.01.0779](https://doi.org/10.1200/JCO.2018.01.0779)
Clinical trial information: [NCT01383772](https://clinicaltrials.gov/ct2/show/study/NCT01383772)

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Journal of Clinical Oncology[®]

Volume 37, Issue 19 1629

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CÂNCER DE MAMA
LACOG - GBECAM 2023



Randomized Placebo Controlled Trial of Low-Dose Tamoxifen to Prevent Recurrence in Breast Noninvasive Neoplasia: A 10-Year Follow-Up of TAM-01 Study

Matteo Lazzeroni, MD¹; Matteo Puntoni, PhD¹; Alana Guerrieri-Gonzaga, MSc¹; Davide Serrano, MD¹; Luca Boni, MD¹; Tania Buttner Weeber, RN¹; Mariana Fray, PhD¹; Irene M. Briata, MSc¹; Livia Giordano, MD¹; Maria Digenmaro, MD¹; Laura Cortesi, MD¹; Fabio Falini, MD¹; Patricia Serra, PhD¹; Franca Avio, MD¹; Francesco Milla, MD¹; Katia Capossi, MD¹; Elisa Galliani, MD¹; Alessia Di Simone, Anna Carello, MD¹; Giuseppe Aprile, MD¹; Maria Renne, MD¹; Bernardo Bonanni, MD¹; Andrea DeCensi, MD^{1,16}

abstract

Clinical trials frequently include multiple end points that mature at different times. The initial report, typically based on the primary end point, may be published when key planned co-primary or secondary analyses are not yet available. *Clinical Trial Updates* provide an opportunity to disseminate additional results from studies, published in JCO or elsewhere, for which the primary end point has already been reported.

PURPOSE Five-year data of the phase III trial TAM-01 showed that low-dose tamoxifen at 5 mg once daily administered for 3 years in women with intraepithelial neoplasia (IEN) reduced by 52% the recurrence of invasive breast cancer or ductal carcinoma in situ (DCIS), without additional adverse events over placebo. Here, we present the 10-year results.

METHODS We randomly assigned 500 women with breast IEN (atypical ductal hyperplasia, lobular carcinoma in situ [LCIS], or hormone-sensitive or unknown DCIS) to low-dose tamoxifen or placebo after surgery with or without irradiation. The primary end point was the incidence of invasive breast cancer or DCIS.

RESULTS The TAM-01 population included 500 women (20% atypical ductal hyperplasia, 11% LCIS, and 69% DCIS). The mean (±SD) age at the start of treatment was 54 ± 9 years, and 58% of participants were postmenopausal. After a median follow-up of 9.7 years (IQR, 8.3-10.9 years), 66 breast cancers (15 in situ; 51 invasive) were diagnosed: 25 in the tamoxifen group and 41 in the placebo group (annual rate per 1,000 person-years, 11.3 with tamoxifen v 19.5 with placebo; hazard ratio [HR], 0.58; 95% CI, 0.35 to 0.95; log-rank $P = .03$). Most recurrences were invasive (77%) and ipsilateral (59%). Regarding contralateral breast cancer incidence, there were six events in the tamoxifen arm and 16 in the placebo arm (HR, 0.36; 95% CI, 0.14 to 0.92; $P = .025$). The number needed to be treated to prevent one case of breast event with tamoxifen therapy was 22 in 5 years and 14 in 10 years. The benefit was seen across all patient subgroups. There was a significant 50% reduction of recurrence with tamoxifen in the DCIS cohort, which represents 70% of the overall population (HR, 0.50; 95% CI, 0.28 to 0.91; $P = .02$). No between-group difference in the incidence of serious adverse events was reported during the prolonged follow-up period.

CONCLUSION Tamoxifen 5 mg once daily for 3 years significantly prevents recurrence from noninvasive breast cancer after 7 years from treatment cessation without long-term adverse events.

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ASSOCIATED CONTENT
See accompanying Editorial on page 1595
Appendix
Data Supplements
Author affiliations and support information (applicable at the end of this article)

INTRODUCTION

We conducted a randomized phase III trial in women with excised atypical ductal hyperplasia (ADH), lobular carcinoma in situ (LCIS), and ductal carcinoma in situ (DCIS), showing that tamoxifen 5 mg once daily given for 3 years halved recurrence without exceeding adverse events, resulting in a more favorable cost-benefit profile than 20 mg once daily.¹ In 2019, ASCO Clinical Practice Guidelines included low-dose tamoxifen as an option in women after noninvasive disease² and the US

Preventive Services Task Force advocated the use of preventive therapy, including low-dose tamoxifen, among women at high risk of breast cancer.³ Current National Comprehensive Cancer Network guidelines also recommend low-dose tamoxifen after DCIS if the patient is symptomatic on the 20 mg dose once daily or if the patient is unwilling or unable to take the standard dose.⁴ Recent data from US centers show that low-dose tamoxifen is the most popular choice of preventive therapy in women with high-risk lesions, with low

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Journal of Clinical Oncology[®]

Estudo de fase III, multicêntrico, randomizado, com 500 pacientes

Pacientes com CDIS, Hiperplasia ductal atípica e CLIS incluídos

TMX 5mg/dia versus placebo → por 3 ano

EP lario : Incidência de Carcinoma invasivo ou CDIS

EP 2ario : toxicidades, incidência de CLIS e hiperplasia, cancer endometrial.

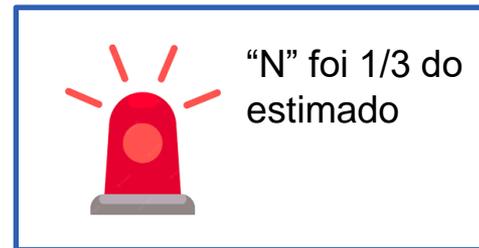
1ª publicação – 5.1 anos de follow-up 2ª publicação – 10 anos de follow-up

Aderência → 85% em 6 meses

Characteristic	Tamoxifen (n = 253)	Placebo (n = 247)
Age, years, mean (SD)	54 (9.6)	54 (9.1)
Menopausal status, No. (%)		
Pre	110 (43)	99 (40)
Post	143 (57)	148 (60)
Age at menopause, years, mean (SD)	50 (4.6)	49 (5.8)
Body mass index, kg/m ² , mean (SD)	25.7 (4.8)	25.3 (4.2)
Waist to hip ratio, mean (SD)	0.86 (0.1)	0.86 (0.1)
Endometrial thickness, mm, mean (SD)	5.1 (3.7)	4.7 (3.2)
1st/2nd degree breast/ovarian cancer FH, No. (%)	94 (37)	95 (38)
Histologic type, No. (%)		
ADH (DIN 1b)	51 (20)	50 (20)
LCIS (LIN 2-3)	27 (11)	25 (10)
DCIS grade 1 (DIN 1c)	42 (17)	40 (16)
DCIS grade 2 (DIN 2)	72 (29)	87 (35)
DCIS grade 3 (DIN 3)	60 (24)	45 (18)

Type of surgery, No. (%)		
Conservative (Q/L)	213 (84)	203 (82)
Mastectomy	40 (16)	44 (18)
Comedo, No. (%)	29 (12)	24 (10)
Necrosis, No. (%)	64 (25)	60 (24)
Multifocal neoplasia, No. (%)	73 (29)	67 (27)
ER %, median (IQR)	90 (60-95)	90 (65-95)
PgR %, median (IQR)	70 (20-90)	60 (14-90)
HER2/neu, No. (%)		
0-2	79 (79)	89 (81)
3+	21 (21)	21 (19)
Ki67%, median (IQR)	10 (5-20)	10 (5-18)
Radiotherapy, No. (%)	108 (45)	107 (45)

Características globais de bom prognóstico, porém braços bem balanceados
 65% das pacientes no braço tamoxifeno foram consideradas aderentes
 61% das pacientes no braço placebo foram consideradas aderentes



Aderência

Braço TMX → 65%

Braço placebo → 61%

Eventos:

66 eventos de neoplasia da mama

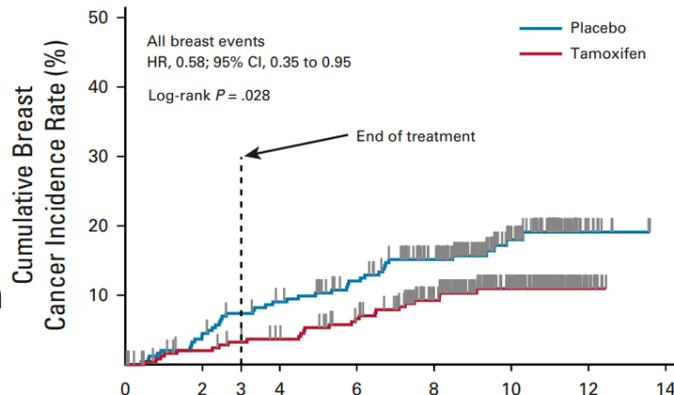
15 in situ

51 invasivos

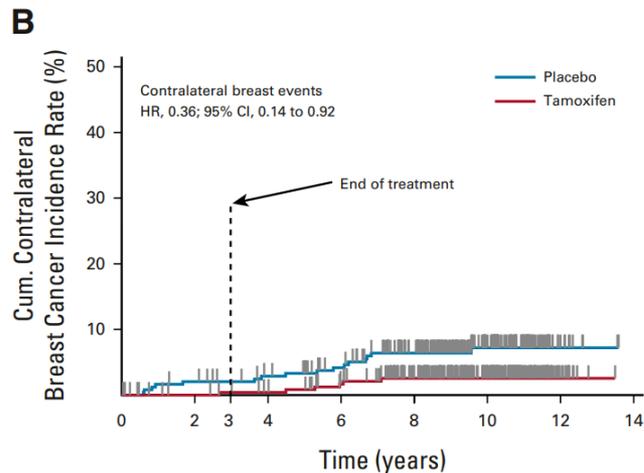
Braço TMX → 25

Braço placebo → 41

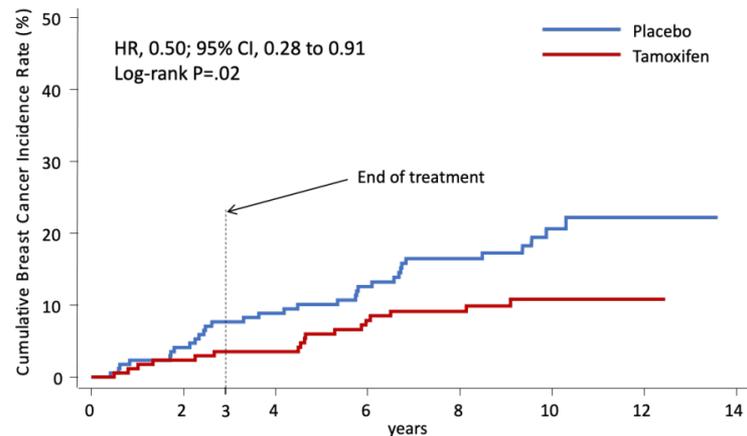
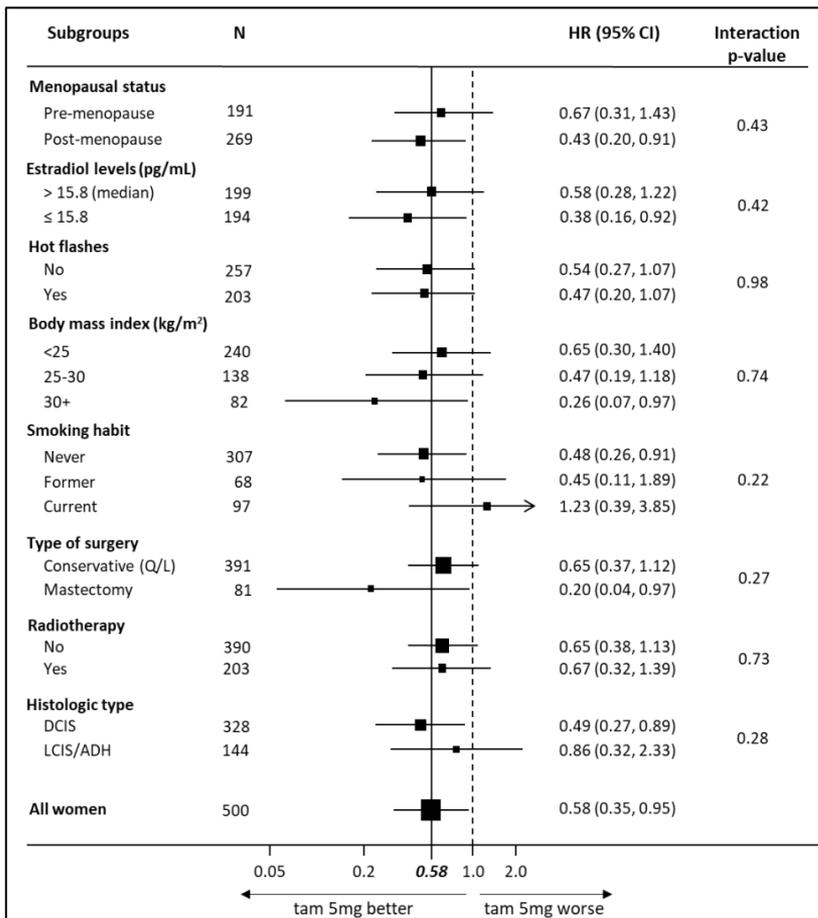
NNT em 10 anos: 14 pacientes



HR 0.58
IC95% 0.35-0.95
p 0.03



HR 0.36
IC95% 0.14-0.92
p 0.025



	Tamoxifen N=25	Placebo N=41	p-value
Invasiveness, n (%)			
Invasive	21 (41)	30 (59)	0.38
DCIS	4 (27)	11 (73)	
Site of recurrence, n (%)			
Ipsilateral	16 (41)	23 (59)	0.35
Contralateral	6 (27)	16 (73)	
Distant	3 (60)	2 (40)	

Sem diferença em incidência de efeitos adversos !!

TABLE 2. Adverse Events by Allocated Arm

Adverse Event	Tamoxifen (n = 249)	Placebo (n = 246)	P
Deep vein thrombosis or pulmonary embolism, No. (%)	1 (0.4)	1 (0.4)	1.0
Superficial phlebitis, No. (%)	2 (0.8)	0	.50
Coronary heart disease, No. (%)	2 (0.8)	2 (0.8)	1.0
Bone fracture, No. (%)	4 (1.6)	2 (0.8)	.69
Cataract, No. (%)	5 (2.0)	5 (2.0)	1.0
Endometrial polyps, No. (%)	20 (8.0)	13 (5.3)	.28
Endometrial cancer, No. (%)	1 (0.4)	0	1.0
Other malignancies, No. (%)	16 (6.4)	9 (3.7)	.22
Thyroid	1	2	
Parathyroid	1	1	
Lungs	1	1	
Melanoma	3	2	
Kidney	—	1	
Bladder	1	—	
Colon	1	—	
Appendiceal	1	—	
Cervix	1	—	
Ovary	1	2	
Lymphoma	4	—	
Mveloma	1	—	
Death from breast cancer, No. (%)	1 (0.4)	2 (0.8)	.62
Death from other causes, No. (%)	4 (2.0)	3 (1.2)	.45
Lung cancer	1	—	
Ovarian cancer	1	—	
Pneumonia	—	1	
Acute renal failure	1	—	
Myocardial infarction	—	1	
Car accident	1	1	
Other serious adverse events, No. (%)	3 (1.2)	6 (2.4)	.34



Sessão Multidisciplinar em carcinoma ductal in situ

Atualizações sobre tratamento adjuvante

Prognóstico do CDIS?

Objetivo do tratamento sistêmico?

Qual medicação utilizar?

Qual dose ?

TAM-01 ou BabyTam mostrou benefício compatível ao usar 5mg ao invés de 20mg

Tratamento anti-HER2?

Sessão Multidisciplinar em carcinoma ductal in situ

Atualizações sobre tratamento
adjuvante

Prognóstico do CDIS?

Objetivo do tratamento
sistêmico?

Qual medicação utilizar?

Qual dose ?

Tratamento anti-HER2?

Não há dados para uso de bloqueio do HER2 em CDIS

Original Article

Biologic and Immunologic Effects of Preoperative Trastuzumab for Ductal Carcinoma In Situ of the Breast

Henry M. Kuerer, MD, PhD¹, Aman U. Buzdar, MD², Elizabeth A. Mittendorf, MD³, Francisco J. Esteva, MD, PhD⁴, Anthony Lucas, MD⁵, Luis M. Vinco, PhD⁶, Laszlo Radvanyi, PhD⁷, Funda Meric-Bernstam, MD⁸, Kelly K. Hunt, MD⁹, and William Fraser Symmans, MD¹

BACKGROUND: Through this study, the authors sought to investigate the biologic and immunologic effects of preoperative trastuzumab in patients with ductal carcinoma in situ (DCIS) of the breast. **METHODS:** Patients with DCIS were enrolled in this open-label phase 2 trial and tested for HER2. Trastuzumab was given by intravenous infusion (8 mg/kg). The patients then had surgery 14 to 28 days after treatment. Tissue and peripheral blood samples were obtained before therapy and at the time of surgery to examine residual disease and immunologic response. **RESULTS:** Median age of the 69 enrolled patients was 53 years, mean mammographic size of the DCIS lesions was 5.2 ± 1.2 cm, and 24 patients (35%) were found to have HER2 overexpression/amplification (12 received trastuzumab and 12 untreated patients provided tissue for blinded, controlled biomarker analyses). No overt histologic evidence of response was noted. No significant change in mean pretherapy staining for Ki-67 (44.3 ± 3.4%) and cleaved caspase-3 (2.6 ± 0.8%) was noted when surgical specimens from drug-treated patient samples were compared with those not treated. Trastuzumab significantly augmented antibody-dependent cell mediated cytotoxicity (ADCC) in 300% of patients; this was demonstrated to be mediated through CD56⁺ degranulating natural killer cells ($P < .01$). One patient developed a significant anti-HER2 humoral CD4⁺ T-cell response. **CONCLUSIONS:** Single-dose monotherapy with trastuzumab for patients with HER2-positive DCIS does not result in significant, clinically overt, histologic, anti-proliferative, or apoptotic changes, but does result in the ability to mount ADCC mediated through natural killer cells and may also induce T-cell dependent humoral immunity. Further studies of trastuzumab for DCIS appear warranted. *Cancer* 2011;117:39-47. © 2010 American Cancer Society.

KEYWORDS: DCIS, trastuzumab, apoptosis, neoadjuvant systemic therapy, immune response.

Ductal carcinoma in situ (DCIS) is the fourth leading cause of cancer among women in the United States, with approximately 64,000 cases diagnosed annually.¹ There is a critical need for the development and investigation of agents that can either eradicate DCIS, thereby averting surgery and radiation, or prevent frankly invasive disease in most patients.

Several lines of evidence suggest the logic in studying trastuzumab, a monoclonal antibody targeting HER2/neu (HER2), for the treatment of DCIS. Neoadjuvant trastuzumab may be able to prevent the development of invasive breast cancer in patients with DCIS in much the same way that tamoxifen markedly decreases the risk of breast cancer development in women with high-risk proliferative lesions such as atypical ductal hyperplasia.² A further rationale for studying neoadjuvant trastuzumab for DCIS relates to the scarcity of effective medical treatments for estrogen receptor (ER)-negative DCIS. Additional support for studying the efficacy of trastuzumab against DCIS comes from promising results from trials of neoadjuvant trastuzumab for invasive breast cancer. Gennari et al showed that administration of a short, preoperative course of single-agent trastuzumab to 11 patients with early stage invasive breast cancer resulted in a complete pathologic response in 1 patient and partial responses in 4.³ The in vivo mechanism of action of trastuzumab is not completely

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The investigators are grateful to Aurore Madrigal, RN, and Rebekah Hubbard for assisting with patient accrual and processing of specimens and to Dr. David Jamison for performing the cell-based ELISA for the quantification of trastuzumab.

DOI: 10.1002/cncr.20399. Received: January 18, 2010. Revised: February 22, 2010. Accepted: March 9, 2010. Published online August 24, 2010 in Wiley Online Library (<http://onlinelibrary.wiley.com>).

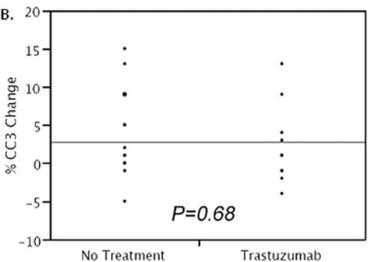
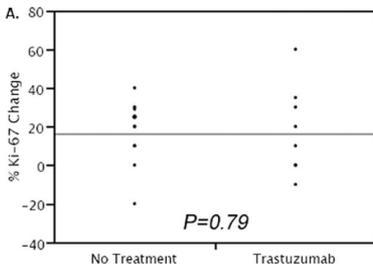
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Estudo de fase II Pacientes com CDIS HER2+ foram incluídos

Trastuzumabe 8mg/kg dose única → cirurgia 2 a 4 semanas após

Avaliação de espécimen cirúrgico e sangue periférico



Ausência de mudança no ki67

Ausência de mudança em marcadores de apoptose

Sessão Multidisciplinar em carcinoma ductal in situ

Atualizações sobre tratamento adjuvante

Prognóstico do CDIS?

Objetivo do tratamento sistêmico?

Qual medicação utilizar?

Qual dose ?

Tratamento anti-HER2?

NÃO

E assinatura genômica ?

- Oncotype Dx DCIS Score

→ 12 genes avaliados

→ 7 genes ligados a proliferação celular (Ki-67, AURKA/ STK15, BIRC5/survivin, CCNB1, MYBL2, PGR, and GSTM1) e 5 genes de referencia (ACTB, GAPDH, RPLPO, GUS, e TFRC)

→ Score de 0 a 100

Baixo Risco : Score até 38

Risco intermediário: Score entre 39 e 54

Risco alto : Score acima de 55

→ Avaliação de risco de evento ipsilateral em 10 anos

Não foi desenvolvida para risco contra-lateral e predição de beneficio de tratamento sistêmico

Conclusões

Sessão Multidisciplinar em carcinoma ductal in situ

Atualizações sobre tratamento
adjuvante



Sessão Multidisciplinar em carcinoma ductal in situ

Atualizações sobre tratamento
sistêmico profilático

Prognóstico do CDIS?

Risco baixo de morte ~3%
Maior risco em jovens, negras e com ER negativo

Objetivo do tratamento sistêmico?

Reduzir novos eventos em mama ipsi e contra-lateral

Qual medicação utilizar?

Tamoxifeno ou anastrozol com benefícios semelhantes. EAs diferentes

Qual dose ?

TMX : 5mg ou 20mg
Anastrozol: 1mg

Tratamento anti-HER2?

HER2 é um biomarcador prognóstico e não preditivo



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