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CED-SOS Advice Report 9 EDUCATION AND INFORMATION 2012

Docetaxel plus Cyclophosphamide as Adjuvant Therapy for Early, Operable Breast Cancer

M. Trudeau and J. Franek

A Quality Initiative of the
Program in Evidence-Based Care (PEBC), Cancer Care Ontario (CCO)

Report Date: September 9, 2008

This CED-SOS Advice Report was put in the Education and Information section in 2012. The PEBC has a formal and standardized process to ensure the currency of each document (PEBC Assessment & Review Protocol).

The report, which consists of the Recommendations, is available on the CCO web site (http://www.cancercare.on.ca).

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Docetaxel plus Cyclophosphamide as Adjuvant Therapy for Early, Operable Breast Cancer: Recommendations

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The 2008 guideline recommendations were put in the

Education and Information section

This means that the recommendation will no longer be maintained but may still be useful for academic or other information purposes.

QUESTION

In comparison to a regimen of concurrent doxorubicin plus cyclophosphamide (AC), does adjuvant therapy with concurrent docetaxel (T) plus cyclophosphamide (C) improve outcomes of interest?

OUTCOMES OF INTEREST

Disease-free survival, overall survival, adverse events, and quality of life.

TARGET POPULATION

Women with node-positive or node-negative (tumour size ≥ 1 cm), early, operable breast cancer.

RECOMMENDATIONS

Concurrent docetaxel plus cyclophosphamide (TC), administered intravenously at a dosage of 75 and 600 mg/nm^2, respectively, on day 1 of four 21-day cycles, is recommended in place of concurrent doxorubicin plus cyclophosphamide (AC) for early, operable female breast cancer.

KEY EVIDENCE

- There has been one phase III trial comparing TC (n=506) to AC (n=510) as adjuvant therapy of early, operable female breast cancer that met the inclusion criteria of this evidence review.
- This trial was described in a full report (1) and in two abstracts (2,3). The latest results, at 6.9 years of follow-up, were reported as an abstract at the 2007 San Antonio Breast Cancer Symposium (2). Updated results are presented where possible.
    - Seven-year disease-free survival (DFS), the trial's primary endpoint, was significantly longer for the TC group versus AC (81% versus [vs.] 75%, hazard ratio [HR] 0.74, p=0.033). Seven-year overall survival (OS) was also significantly longer for TC (87% vs. 82%, HR 0.69, p=0.032) (2). The HR for DFS remained significant and in favour of TC in an exploratory analysis where patients were stratified pre-treatment by age (<65 and ≥65 years up to 75 years) (2) and nodal status (48% of total trial population was node-negative) (1).
    - Patients on TC experienced more myalgia, arthralgia, edema, and fever (p<0.01) (1). Patients on TC also experienced near-double febrile neutropenia (4% vs. 2% age<65, 8% vs. 4% age≥65, TC vs. AC) (2). Meanwhile, patients on AC experienced more grade 1 to 4 nausea and vomiting (p<0.01) (1). No formal comparison of cardiac function/toxicity was prospectively planned (1). No patients on TC experienced long-term fatal toxicities, although two patients on TC experienced myocardial infarction (1). In comparison, four patients on AC died of myocardial infarction, and three patients on AC experienced long-term fatal toxicities, with deaths due to congestive heart failure, myelodysplastic syndrome, and myelofibrosis (2). Leukemia was not investigated.

QUALIFYING STATEMENTS

- The majority (71%) of patients had breast cancer that was estrogen receptor (ER) and/or progesterone receptor (PR) positive and thus, the majority of trial participants received adjuvant tamoxifen at some point during initiation of TC (although not prior to TC). Aromatase inhibitors (AIs) were not in general use at the time of trial initiation, and no information regarding their use was recorded (1). Therefore, it is unclear whether TC will behave similarly in patients not receiving tamoxifen, or in patients receiving AIs, although there is currently no evidence to suggest that TC would behave differently.
- Patient enrolment included women with node-negative or node-positive tumours. Unique to this trial, patients whose tumours could be considered low-risk node-negative (e.g., exhibiting none of the following features: estrogen receptor (ER)-/progesterone receptor (PR)-, lymphovascular invasive (LVI)+, grade 3, size ≥ 2 cm, HER2/*neu*+) were also eligible for inclusion, thus extending generalizability of results to this generally under-studied population.
- No patients received neoadjuvant chemotherapy, and no patients had a tumour size less than 1.0 cm, thus limiting the generalizability of results for these patient populations (1).
- Significance levels were properly adjusted for interim analyses (1).
- While cardiac toxicity was not under protocolled investigation in this trial, a phase I and II trial by Trent et al. (4) indicated no cardiac toxicity when TC was used as first-line therapy for metastatic breast cancer.
- While TC has demonstrated survival advantage over AC, TC has not been compared to other regimens commonly used for high-risk, node-negative or node-positive tumours, including anthracycline-taxane regimens (e.g., AC→paclitaxel, dose-dense

AC→paclitaxel; fluorouracil [5FU], epirubicin and cyclophosphamide [FEC]→Docetaxel; Docetaxel+AC) or anthracycline regimens given for more than 4 cycles (e.g., cyclophosphamide, epirubicin, and 5FU [CEF]; FEC-100). Therefore, it is unknown whether TC is equivalent to these regimens with respect to DFS or OS, and it is not possible to make evidence-based recommendations regarding the decision to use TC as opposed to other regimens that have proven superior to AC (e.g., AC→paclitaxel).

METHODS

This advice report, produced by the Program in Evidence-Based Care (PEBC), is a convenient and up-to-date source of the best available evidence on the role of concurrent cyclophosphamide with docetaxel for adjuvant therapy of early, operable breast cancer. For this project, the core methodology used to develop the evidentiary base was the systematic review. The body of evidence in this review is derived from one single, phase III randomized controlled trial. The systematic review and the recommendations are intended to promote evidence-based practice in Ontario, Canada. The PEBC is supported by the Ontario Ministry of Health and Long-Term Care through Cancer Care Ontario. All work produced by the PEBC is editorially independent from its funding source.

Literature Search Strategy

The MEDLINE (1996 through June 2008) and EMBASE (1996 through week 24 2008) databases were searched for relevant evidence. The American Society of Clinical Oncology (ASCO) Annual Conference Proceedings from 2000 through 2008 were searched, as were the San Antonio Breast Cancer Symposium from 2005 to 2007.

Relevant articles were selected and reviewed by one reviewer (JF), and the reference lists from those sources were searched for additional trials.

The search strategy for this review was undertaken as part of a much larger and more comprehensive search than usual for a systematic review of all adjuvant taxane regimens. The OVID search strategy, applied simultaneously to MEDLINE and EMBASE databases, is summarized in Table 1 below.

Table 1. Literature search strategy.

Step	Search Terms	Hits
1	exp breast tumor/	190315
2	((breast or mammary or mammarian) and (cancer? or carcinoma? or neoplasm? or tumo?r? malignan$)).tw.	177837
3	1 or 2	224702
4	exp Meta-Analysis/ or exp "Systematic Review"/ or (meta analy$ or metaanaly$ or systematic review$ or pooled analys?s or statistical pooling or mathematical pooling or statistical summar$ or mathematical summar$).tw.	90973
5	(systematic adj (review$1 or overview$1)).tw.	28436
6	(cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or cinhal or science citation index or scisearch of bids or sigle or cancerlit).ab.	24710
7	(reference list$ or bibliograph$ or hand-search$ or relevant journals or manual search$).ab.	18963
8	(selection criteria or data extraction).ab. and (review.pt. or exp Review Literature/)	13840
9	exp phase 3 clinical trial/ or exp phase 4 clinical trial/ or exp randomized controlled trial/	296366
10	(randomi$ control$ trial? or phase III or phase IV or phase 3 or phase 4).tw.	81088
11	randomization/ or single blind procedure/ or double blind procedure/ or placebo/	160846
12	((single$ or double$ or treb$ or tripl$) adj (blind$3 or mask$3 or dummy)).tw.	102274
13	placebo$.tw.	132241
14	randomly allocated.tw.	12786
15	(allocated adj2 random).tw.	317
16	(rct or random allocation).tw.	5572
17	(allocated randomly or (allocated adj2 random)).tw.	1815

18	(single blind$ or double blind$).tw.	99092
19	4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18	564506
20	exp Clinical Trials/	427666
21	(phase 2 or phase II).tw.	42036
22	(clinic$ adj trial?).tw.	172859
23	(20 or 21 or 22) and random$.tw.	168593
24	19 or 23	587651
25	exp adjuvant chemotherapy/	19822
26	(adjuvant or neoadjuvant or neo adjuvant or post operativ$ or postoperativ$ or pre operativ$ or preoperativ$ or following surgery or after surgery or post surgery or before surgery or prior to surgery or pre surgery or early breast or primary breast or early invasive breast or operable).tw.	502156
27	25 or 26	508544
28	exp taxoids/	13859
29	(taxane? or paclitaxel or docetaxel or taxol or taxotere or taxoid?).tw.	33659
30	exp paclitaxel/	38418
31	exp docetaxel/	12412
32	exp taxane derivative/	5370
33	28 or 29 or 30 or 31 or 32	53459
34	3 and 24 and 27 and 33	993
35	limit 34 to humans	989
36	limit 35 to english language	907
37	36 not (comment or letter or editorial or news or newspaper article or patient education handout).pt.	893
38	exp breast tumor/	190315
39	((breast or mammary or mammarian) and (cancer? or carcinoma? or neoplasm? or tumo?r? malignan$)).tw.	177837
40	38 or 39	224702
41	exp Meta Analysis as Topic/ or (meta analy$ or metaanaly$ or systematic review$ or pooled analys?s or statistical pooling or mathematical pooling or statistical summar$ or mathematical summar$).tw.	64524
42	(systematic adj (review$1 or overview$1)).tw.	28436
43	(cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or cinhal or science citation index or scisearch of bids or sigle or cancerlit).ab.	24710
44	(reference list$ or bibliograph$ or hand-search$ or relevant journals or manual search$).ab.	18963
45	(selection criteria or data extraction).ab. and (review.pt. or exp Review Literature as Topic/)	13859
46	(clinical trial, phase III or clinical trial, phase IV or randomized controlled trial).pt.	160833
47	exp Clinical Trials, Phase III as Topic/ or exp Clinical Trials, Phase IV as Topic/	3142
48	exp Randomized Controlled Trials as Topic/	47202
49	(randomi$ control$ trial? or phase III or phase IV or phase 3 or phase 4).tw.	81088
50	random allocation/ or double blind method/ or single blind method/	168129
51	((single$ or double$ or treb$ or tripl$) adj (blind$3 or mask$3 or dummy)).tw.	102274
52	placebos/ or placebo$.tw.	175765
53	randomly allocated.tw.	12786
54	(allocated adj2 random).tw.	317
55	41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54	524651
56	(clinical trial or clinical trial, phase II or controlled clinical trial).pt.	252459
57	exp Clinical Trials as topic/	111419
58	(phase 2 or phase II).tw.	42036
59	(clinic$ adj trial?).tw.	172859
60	(56 or 57 or 58 or 59) and random$.tw.	159343
61	55 or 60	547971
62	exp chemotherapy, adjuvant/	19822
63	exp neoadjuvant therapy/	33147
64	(adjuvant or neoadjuvant or neo adjuvant or post operativ$ or postoperativ$ or pre operativ$ or preoperativ$ or following surgery or after surgery or post surgery or before surgery or prior to surgery or pre surgery or early breast or primary breast or operable).tw.	502110
65	62 or 63 or 64	518428
66	exp taxoids/	13859

67	(taxane? or paclitaxel or docetaxel or taxol or taxotere or taxoid?).tw.	33659
68	exp paclitaxel/	38418
69	66 or 67 or 68	49505
70	40 and 61 and 65 and 69	874
71	limit 70 to humans	869
72	limit 70 to english	793
73	72 not (comment or letter or editorial or news or newspaper article or patient education handout).pt.	775
74	37 or 73	1023
75	remove duplicates from 74	800

Inclusion Criteria

Articles and abstracts were selected for inclusion in the systematic review if they were published English-language reports involving human participants, of Phase II or III randomized controlled trials (RCTs) comparing concurrent cyclophosphamide plus docetaxel with another agent and/or placebo, particularly concurrent doxorubicin plus cyclophosphamide, in women with early, operable breast cancer. Outcomes of interest are described above.

Exclusion Criteria

Letters, editorials, notes, retrospective studies, case studies, and non-systematic reviews were not eligible. Non-English articles were excluded because translation capabilities were not available.

Synthesizing the Evidence

As there was only one trial included in this report, no statistical summarization of the evidence was required.

CONFLICT OF INTEREST

The authors wish to state no conflicts of interest at this time.

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