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Evidence-based Series #1-7: Section 1

Adjuvant Taxane Therapy for Women with Early-stage, Invasive Breast Cancer: A Clinical Practice Guideline

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Section 1: Clinical Practice Guideline
Section 2: Systematic Review
Section 3: Guideline Development and External Review – Methods and Results

Guideline Questions

1. Compared with a standard anthracycline-based regimen (e.g., doxorubicin and cyclophosphamide [AC], 5-fluorouracil, doxorubicin, and cyclophosphamide [FAC], 5-fluorouracil, epirubicin, and cyclophosphamide [500/100/500mg/m^2] [FEC-100], or cyclophosphamide, epirubicin, 5-fluorouracil [75/60/100mg/m^2] [CEF]), does a concurrent taxane-anthracycline regimen improve clinically meaningful outcomes (disease-free and overall survival)?
2. Compared with an anthracycline-based regimen, does a sequential taxane–anthracycline regimen improve clinically meaningful outcomes?
3. Compared with a standard (three-weekly) anthracycline–taxane regimen, does a dose-dense (two-weekly) regimen improve clinically meaningful outcomes?
4. Compared with an anthracycline-based regimen, does a non-anthracycline taxane regimen improve clinically meaningful outcomes?
5. What are the harms associated with adjuvant taxane regimens?

Target Population

Women with T 1-3, operable, node-positive breast cancer.

Recommendations and Key Evidence

SUMMARY RECOMMENDATION

The following taxane-containing regimens are considered reasonable treatment options for the target population:

- **Six cycles of three-weekly docetaxel, doxorubicin, and cyclophosphamide (DAC) (75/50/500 mg/m^2)**
- **Four cycles of doxorubicin and cyclophosphamide (AC) (60/600 mg/m^2) followed by four cycles of paclitaxel (175 mg/m^2 or 225 mg/m^2 every three weeks or 175 mg/m^2 every two weeks with granulocyte colony-stimulating factor [G-CSF]).**
- **Three cycles of FEC-100 followed by three cycles of docetaxel (100 mg/m^2).**

These regimens are recommended over their non–taxane-containing counterparts (six cycles of FAC, four cycles of AC, or six cycles of FEC-100), as they have been shown to be superior in efficacy.

Qualifying Statements

- Taxane-containing counterparts to other commonly used non-taxane anthracycline regimens (e.g., CEF) have not yet been evaluated by randomized clinical trials. However, these non–taxane-containing regimens remain reasonable treatment options.

Six cycles of three-weekly DAC (75/50/500 mg/m^2) is recommended over six-cycles of three-weekly FAC (500/50/500 mg/m^2).

- In the analysis of the Breast Cancer International Research Group (BCIRG) 001 trial (1), (n=1,491) women receiving six cycles of three-weekly DAC experienced improved disease-free survival (DFS) (hazard ratio [HR] 0.72, 95% confidence interval [CI] 0.59 to 0.88, absolute difference at five years 7%, p<0.001) and overall survival (OS) (HR 0.70, 95% CI 0.53 to 0.91, absolute difference at five years 6%, p=0.0080) at a median follow-up of 55 months compared with women receiving six cycles of three-weekly FAC.

Qualifying Statements

- There are no data comparing epirubicin-based regimens such as FEC-100 or CEF to their epirubicin-containing and taxane-containing counterparts. There is also no evidence directly comparing 1) doxorubicin, cyclophosphamide, and a taxane to FEC-100 or CEF or 2) FAC to FEC-100 or CEF. Therefore, there are no grounds on which to base a recommendation as to which of FEC-100, CEF, or DAC may be preferable. However, in the case of FEC-100, see the recommendations for sequential anthracycline–taxane regimens below.
- Data is available from the European Cooperative Trial in Operable Breast Cancer (ECTO) in abstract form (2,3). This trial reported a significant benefit for the combination of doxorubicin and paclitaxel followed by CMF compared to doxorubicin alone followed by CMF. As neither of these regimens is commonly used in Ontario, no specific recommendation is made based on this trial.
- A meta-analysis of DSF and OS was conducted on five trials (1-8) of concurrent anthracycline–taxane regimens compared to their non-taxane containing counterparts. For DFS, the estimated summary HR was 0.82 (95% CI 0.71 to 0.94), with little statistical heterogeneity (χ^2 test for heterogeneity p=0.16, I^2=39.1%). For OS, the estimated summary HR was 0.84 (95% CI 0.66 to 1.08), with evidence of statistical heterogeneity (χ^2 test for heterogeneity p=0.02, I^2=65.1%). Based on the pattern of greater toxicity found in the studied concurrent regimens and the lack of a consistent OS benefit, no specific statement regarding the general value of using a taxane concurrently with an anthracycline-based regimen can be made at this time.

The inclusion of a taxane in sequence with an anthracycline-based regimen should be considered. The following regimens have been specifically studied in comparison to their non–anthracycline-containing counterparts and are recommended.

- **Four cycles of three-weekly AC (60/600 mg/m^2) followed by four cycles of three-weekly paclitaxel (175 mg/m^2 or 225 mg/m^2) is recommended over four cycles of three-weekly AC alone (60/600 mg/m^2).**
- **Three cycles of FEC-100 followed by three cycles of docetaxel (100 mg/m^2) is recommended over six cycles of FEC-100 alone.**

- A meta-analysis of DFS and OS was conducted on six trials (7-15) of sequential anthracycline–taxane regimens compared to their non–taxane-containing counterparts. For DFS, the estimated summary HR was 0.80 (95% CI 0.75 to 0.86), and for OS, it was 0.83 (95% CI 0.76 to 0.91). There was no statistical heterogeneity in either estimate (I^2=0% for both estimates).
- At median follow-ups of 69 and approximately 64.6 months, DFS was improved in both the Cancer and Leukemia Group B (CALGB) 9344 trial (9) (n=3,170) (HR 0.83, 95% CI 0.73 to 0.94, absolute difference at five years 5%, p=0.0023) and the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-28 (13) (n=3,060) (HR 0.83, 95% CI 0.72 to 0.95, absolute difference at five years 4%, p=0.006) trial with the addition of four cycles of three-weekly paclitaxel (175mg/m^2 or 225mg/m^2) following AC (60-90/600mg/m^2). The CALGB 9344 trial detected improved OS (HR 0.82, 95% CI 0.71 to 0.95, absolute difference at five years 3%, p=0.0064) with the addition of paclitaxel, whereas the NSABP B-28 trial did not (HR 0.93, 95% CI 0.78 to 1.12, absolute difference at five years 0%, p=0.46). In unplanned subgroup analyses of the CALGB 9344 trial, the DFS benefit was most pronounced among women whose tumours were hormone receptor-negative, whereas in the NSABP B-28 trial, the opposite was true.
- In the Programmes d'Actions Concertées Sein (PACS) 01 trial (14,15) (n=1999), after a planned median follow-up of 60 months, five-year DFS was improved with a three-cycle FEC-100, three-cycle docetaxel regimen as opposed to a six-cycle FEC-100 regimen (absolute difference 5.1%; p=0.014).

Qualifying Statements

- The El Grupo Español de Investigación en Cáncer de Mama (GEICAM) 9906 trial (10,11) interim analysis published abstract reported a significant DFS benefit for FEC followed by paclitaxel compared to FEC alone. As these results are from an interim analysis, and the trial was not reported to have stopped early due to effect, no recommendation is made regarding this regimen at this time.
- The Breast International Group (BIG) 2-98 trial primary analysis published abstract reported a significant DFS benefit for doxorubicin followed by docetaxel followed by CMF compared to doxorubicin alone followed by CMF. As neither of these regimens is commonly used in Ontario, no specific recommendation is made based on this trial.
- Four cycles of three-weekly paclitaxel (250mg/m^2) followed by four cycles of three- weekly to four-weekly FAC (500/50/500 mg/m^2) (taxane [T]→FAC) may not be different from eight cycles of three- weekly to four-weekly FAC; however, data are only available from one small randomized trial (n=524) for which only the DFS was reported. In the M.D. Anderson Cancer Center (MDACC) trial (12) (n=524), there was a trend towards improved DFS (absolute difference, 3%; p=0.09) with four cycles of paclitaxel followed by four cycles of FAC versus eight cycles of FAC at a median follow-up of 60 months. OS was not reported.

Women in the target population should be considered for dose-dense therapy with doxorubicin and cyclophosphamide followed by paclitaxel. In practice, four cycles of two-weekly AC (60/600 mg/m^2) followed by four cycles of two-weekly paclitaxel (175 mg/m^2) (AC→T) is more commonly used due to a shorter duration of treatment.
G-CSF (days three to 10 of each cycle [a total of seven doses] at 5 µg/kg rounded to either 300 µg or 480 µg total dose) should be given in combination with four cycles of two-weekly AC→T to prevent neutropenia.
• In the Intergroup (INT) C9741 trial (16-18) (n=1,973), DFS was significantly improved in women who received G-CSF and four cycles of two-weekly A→T→C or AC→T compared with women who received the same regimens every three weeks at a median follow-up of 69 months (HR 0.80, 95% CI 0.62 to 0.96, p=0.018). At a median follow-up of 36 months, the absolute difference in four-year DFS was 7% (p=0.010).

Qualifying Statements

- To date no trial has investigated the relative efficacy of dose-dense AC→T with either standard anthracycline-based regimens (i.e., FEC-100, CEF), taxane-containing counterparts to those regimens, or other dose-dense regimens. Therefore, there are no grounds on which to base a recommendation as to which of these various regimens should be preferred.

Four cycles of three-weekly docetaxel and cyclophosphamide (75/600 mg/m^2) (DC) is recommended over four cycles of three-weekly AC (60/600 mg/m^2).
• In the U.S. Oncology (USON) 9735 trial (19-21), DFS was significantly improved in women treated with DC versus those treated with AC (HR 0.67, absolute difference at five years 6%, p=0.015). No significant difference was reported in OS (HR 0.76, absolute difference at five years 3%, p=0.131).

Qualifying Statements

- To date, no trial has compared a taxane-only regimen to either a concurrent or sequential anthracycline/taxane regimen, so there are no grounds on which to base a recommendation preferring one of these options.

Prophylactic G-CSF should be considered in patients receiving concurrent anthracycline/taxane regimens.
Women receiving an adjuvant anthracycline–taxane regimen should be closely monitored for febrile neutropenia. In those who experience febrile neutropenia while receiving DAC, G-CSF should be administered with subsequent docetaxel infusions. Alternatively, a dose reduction should be considered.
The Breast Cancer DSG considers the following G-CSF regimen to be reasonable for either prophylaxis for or treatment of febrile neutropenia: day three to ten of each cycle (a total of seven doses) at 5 µg/kg rounded to either 300 µg or 480 µg total dose.
Women receiving a taxane regimen should also be monitored for other toxicities, including diarrhea, stomatitis, amenorrhea, asthenia, myalgia, paresthesia, and leukopenia.
• Among trials of concurrent taxane-anthracycline therapy versus non-taxane anthracycline therapy, hematologic toxicity, particularly febrile neutropenia, was considerably higher on the taxane-containing arm. Rates of febrile neutropenia on the taxane-containing arm ranged from 24.6% to 40.8%, while, on the non–taxane-containing arm, they ranged from 2.5 to 10%. In the BCIRG 001 trial (1) of DAC versus FAC, grade 3+ neutropenia (65.5% versus [vs.] 49.3%, p<0.001), grade 3+ anemia (4.3% vs. 1.6%, p=0.003), and febrile

neutropenia (24.7% vs. 2.5%, p<0.001) were all significantly more frequent with DAC therapy. With regard to non-hematologic toxicity, grade 3+ nausea and vomiting were generally more frequent in the non–taxane-containing arm, while stomatitis/mucositis, diarrhea, and myalgia/arthralgia were more frequent in the taxane-containing arm.

- Among trials of sequential taxane-anthracycline therapy versus non-taxane anthracycline therapy, hematologic toxicity was mixed. The GEICAM 9906 trial (10-11) of FEC→T versus FEC found significantly less frequent grade 3+ neutropenia (20.5% vs. 30%, p=significant), grade 3+ leucopenia (7.4% vs. 10.6%, p=significant), and febrile neutropenia (5.1% vs. 9.3%, p=0.004) in patients receiving FEC→T. In contrast, the PACS 01 trial (14,15) of FEC→D versus FEC found more frequent febrile neutropenia on the taxane arm (4.6% vs. 1%, p=0.001). The CALGB 9344 trial (9) reported fewer occurrences of hematologic toxicity during the paclitaxel cycles of the AC→T arm than during the equivalent cycles of AC in the AC-only arm. With regard to grade 3+ non-hematologic toxicity, only the GEICAM 9906 trial (10-11) reported a significant difference, with the rate of mucositis being significantly higher in patients receiving FEC→T compared to FEC (3% vs. 5.4%, p=significant). Additionally, the MDACC trial (12) reported a higher rate of grade 3+ myalgia in patients treated with T→FAC compared to patients treated with FAC (1.5% vs. 12.5%), but a significance test was not reported. The PACS 01 trial (14-15) reported significantly more moderate to severe edema (4.8% vs. 0.3%, p<0.001) and moderate to severe nail disorders (10.3% vs. 1.0%, p<0.001) during the docetaxel cycles of the FEC→D regimen than in the equivalent cycles of the FEC-alone regimen.
- The INT C9741 trial (16-18) of dose-dense versus standard sequential doxorubicin and paclitaxel therapy reported a lower rate of grade 3+ neutropenia (5.9% vs. 12%, significance test not reported) with dose-dense AC→T versus standard AC→T. Also, grade 2+ anemia was significantly higher in patients receiving dose-dense AC→T (23%, p<0.0001) compared to patients receiving standard AC→T (8%). It is important to note that patients receiving dose-dense therapy in this trial received G-CSF prophylaxis.
- In the USON 9735 trial (19-21) of DC versus AC, docetaxel-related side effects, such as paresthesia, edema, weight gain, rash, and arthralgia, were more common with DC, whereas more anemia, vomiting, and stomatitis were associated with AC. Grade 3 and 4 leukopenia, infections, asthenia, and hair loss were similar. Febrile neutropenia was significantly more common among patients treated with DC compared to those treated with AC (6% vs. 3%, p=0.03).

Qualifying Statement

- It is the expert opinion of the Breast Cancer DSG that pegylated G-CSF may be a reasonable alternative to G-CSF in conjunction with non–dose-dense chemotherapy. If used, an appropriate dose is 6 mg, given once 24 hours after completion of chemotherapy.

Related Topics

Practice guidelines published by the PEBC on related topics (available at: http://www.cancercare.on.ca/index_breastCancerGuidelines.htm):

- PG #1-8: *Adjuvant Systemic Therapy for Node-Negative Breast Cancer.*
- PG #1-20 *The Role of Taxanes in Neoadjuvant Chemotherapy for Women with Non-metastatic Breast Cancer*.

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