Chemotherapy for Breast Cancer
Why this regimen?

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CancerCare Manitoba
Disclosures

• none
Outline

- Background
- Evidence
  - Adjuvant
  - Metastatic
- Cases
Background

• Always a case of risk:benefit
• Risk of disease
• Risk of treatment
• Benefit of treatment
Background

• Clinical Situation
  – Adjuvant
    • Node positive
    • Node negative
    • Other tumour characteristics (Grade, LVI)
  – Metastatic
Background

• Age
• Comorbidity
• Previous treatments
• Molecular markers
  – ER, PR, HER2, Oncotype
• Histology
Evidence

ADJUVANT
Assessment of Risk

• Adjuvant! Online
• Classic pathological markers
  – Histological type – ductal, lobular
  – Histological grade
  – Lymphovascular invasion
  – Tumour size
  – ER PR HER2

• OncotypeDx
Adjuvant! Online

Adjuvant! for Breast Cancer (Version 8.0)

**Patient Information**
- **Age:** 73
- **Comorbidity:** Average for Age
- **ER Status:** Negative
- **Tumor Grade:** Grade 3
- **Tumor Size:** 3.1 - 5.0 cm
- **Positive Nodes:** 4 - 9
- **Calculate For:** Mortality
- **10 Year Risk:** 66

**Adjuvant Therapy Effectiveness**
- **Horm:** Tam for 2-3 yrs then AI for 2-3 yrs
- **Chemo:** 3rd Generation Regimens

**No additional therapy:**
- 22.3 alive in 10 years.
- 59.5 die of cancer.
- 18.2 die of other causes.

**With hormonal therapy:** Benefit = 0.0 alive.

**With chemotherapy:** Benefit = 14.9 alive.

**With combined therapy:** Benefit = 14.9 alive.

Buttons:
- Print Results PDF
- Access Help and Clinical Evidence
- Images for Consultations
OncotypeDx

• Node negative, ER/PR+

• Tumour specimen sent to California

• 21-gene assay done

• Risk score...
  – Low risk – hormone therapy only
  – Intermediate risk - ?chemo plus hormone therapy
  – High risk – chemo plus hormone therapy
OncotypeDX Clinical Validation: Recurrence Score as Continuous Predictor

My RS is 30. What is the chance of recurrence within 10 years?

Distant Recurrence at 10 Years

0% 5% 10% 15% 20% 25% 30% 35% 40%

Recurrence Score

95% CI
Taxotere
Cyclophosphamide
Herceptin

Cycle 1
Cycle 2
Cycle 3
Cycle 4

Radiation Therapy
Hormonal Therapy (ER/PR+)
Herceptin (HER2+)

5y
1y

Exercise
Docetaxel With Cyclophosphamide Is Associated With an Overall Survival Benefit Compared With Doxorubicin and Cyclophosphamide: 7-Year Follow-Up of US Oncology Research Trial 9735


ABSTRACT

Purpose
We previously reported that four cycles of docetaxel/cyclophosphamide (TC) produced superior disease-free survival (DFS) compared with four cycles of doxorubicin/cyclophosphamide (AC) in early breast cancer. Older women are under-represented in adjuvant chemotherapy trials. In our trial 16% of patients were ≥ 65 years. We now report 7-year results for DFS and overall survival (OS) as well as the impact of age, hormone receptor status, and HER2 status on outcome and toxicity.

Patients and Methods
Patients were randomly assigned to receive either four cycles of standard-dose AC (60/600 mg/m²; n = 510), or TC (75/600 mg/m²; n = 506), administered by intravenous infusion every 3 weeks.

Results
The median age in women younger than 65, was 50 years (range, 27 to 64) and for women ≥ 65 was 69 years (range, 65 to 77). Baseline characteristics in the two age subgroups were generally well matched, except that older women tended to have more lymph node involvement. At a median of 7 years follow-up, the difference in DFS between TC and AC was significant (81% TC v 75% AC; P = .033; hazard ratio [HR], 0.74; 95% CI 0.56 to 0.98) as was OS (87% TC v 82% AC; P = .032; HR, 0.69; 95% CI, 0.50 to 0.97). TC was superior in older patients as well as younger patients. There was no interaction of hormone-receptor status or HER-2 status and treatment. Older women experienced more febrile neutropenia with TC and more anemia with AC.

Conclusion
With longer follow-up, four cycles of TC was superior to standard AC (DFS and OS) and was a tolerable regimen in both older and younger patients.
Disease-Free Survival (proportion)

- TC
- AC

95% CI: 0.56 to 0.98

P = 0.033
HR = 0.74

No. at risk
TC
- 506
- 481
- 442
- 410
- 378
- 349
- 320
- 195

AC
- 510
- 483
- 449
- 405
- 372
- 343
- 303
- 194

Time (months)
Overall Survival (proportion)

- TC
- AC

95% CI: 0.50 to 0.97

P = 0.032
HR = 0.69

No. at risk

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**5FU, Epirubicin, Cyclophosphamide**

**Taxotere**

**Herceptin**

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**Cycle 1**
- FEC

**Cycle 2**
- FEC

**Cycle 3**
- FEC

**Cycle 4**
- T

**Cycle 5**
- T

**Cycle 6**
- T

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**Radiation Therapy**

**Hormonal Therapy (ER/PR+)**

**Herceptin (HER2+)**

**Exercise**

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**FEC-D**
Sequential Adjuvant Epirubicin-Based and Docetaxel Chemotherapy for Node-Positive Breast Cancer Patients: The FNCLCC PACS 01 Trial

Henri Roché, Pierre Fumoleau, Marc Spielmann, Jean-Luc Canon, Thierry Delozier, Daniel Serin, Michel Symann, Pierre Kerbrat, Patrick Soulié, François Eichler, Patrice Viens, Alain Monnier, Anita Vindevoghel, Mario Campone, Marie-Josèphe Goudier, Jacques Bonneterre, Jean-Marc Ferrero, Anne-Laure Martin, Jean Genève, and Bernard Asselain

ABSTRACT

Purpose
The PACS 01 trial compared six cycles of fluorouracil, epirubicin, and cyclophosphamide (FEC) with a sequential regimen of three cycles of FEC followed by three cycles of docetaxel (FEC-D) as adjuvant treatment for women with node-positive early breast cancer.

Patients and Methods
Between June 1997 and March 2000, 1,999 patients with operable node-positive breast cancer were randomly assigned to either FEC every 21 days for six cycles, or three cycles of FEC followed by three cycles of docetaxel, both given every 21 days. Hormone-receptor–positive patients received tamoxifen for 5 years after chemotherapy. The primary end point was 5-year disease-free survival (DFS).

Results
Median follow-up was 60 months. Five-year DFS rates were 73.2% with FEC and 78.4% with FEC-D (unadjusted $P = .011$; adjusted $P = .012$). Multivariate analysis adjusted for prognostic factors showed an 18% reduction in the relative risk of relapse with FEC-D. Five-year overall survival rates were 90.7% with FEC and 95.0% with FEC-D, demonstrating a 27% reduction in the relative risk of death (unadjusted $P = .014$; adjusted $P = .017$). The incidence of grade 3 to 4 neutropenia, the need for hematopoietic growth factor, and incidence of nausea/vomiting were higher with FEC. Docetaxel was associated with more febrile neutropenia in the fourth cycle, stomatitis, edema, and nail disorders. Though rare overall, there were fewer cardiac events after FEC-D ($P = .03$), attributable mainly to the lower anthracycline cumulative dose.

Conclusion
Sequential adjuvant chemotherapy with FEC followed by docetaxel significantly improves disease-free and overall survival in node-positive breast cancer patients and has a favorable safety profile.
Overall Survival (probability)

Survival Time (years)

No. at risk:

FEC-D  1,003  997  966  936  876  427  106  1  0
FEC     996  987  958  913  835  397  116  2  0

HR = 0.73; 95% CI, 0.56 to 0.94
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Controversies

• Adjuvant hormonal therapy
  – tamoxifen versus aromatase inhibitors
  – Which aromatase inhibitor?
  – Ovarian suppression plus tamoxifen and AI

• Adjuvant bisphosphonates
  – ? Anti-cancer effect
  – Improved Disease-Free Survival (NEJM 2009)
Hazard ratio for disease progression, 0.64 (95% CI, 0.46–0.91)
P=0.01, Wald test
P=0.01, log-rank test

No. of events

Months since Randomization

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Evidence

METASTATIC DISEASE
Principles

• Molecular Characteristics

• Location of Metastatic Disease
  – Visceral
  – Bone-only
Choice of Chemo

• Combination chemotherapy may have a better response rate
• No survival advantage to combination chemo
Common first line

• Anthracyclines
• Taxanes
• Capecitabine
Other common regimens

- Vinorelbine
- Cis/Carbo & Gemcitabine
- Abraxane
- Cyclophosphamide
- methotrexate
New drugs

- Eribulin
- Ixabepilone
- TDM1
- Pertuzumab
CHEMOTHERAPY REGIMENS FOR RECURRENT OR METASTATIC BREAST CANCER

Preferred Single Agents

**Anthracyclines**
- Doxorubicin
- Epirubicin
- Pegylated liposomal doxorubicin

**Taxanes**
- Paclitaxel
- Docetaxel
- Albumin-bound paclitaxel

**Anti-metabolites**
- Capecitabine
- Gemcitabine

**Other microtubule inhibitors**
- Vinorelbine
- Eribulin

Other Single Agents

- Cyclophosphamide
- Mitoxantrone
- Cisplatin
- Etoposide (po) (category 2B)
- Vinblastine
- Fluorouracil CI
- Ixabepilone

Preferred Chemotherapy Combinations

- CAF/FAC (cyclophosphamide/doxorubicin/fluorouracil)
- FEC (fluorouracil/epirubicin/cyclophosphamide)
- AC (doxorubicin/cyclophosphamide)
- EC (epirubicin/cyclophosphamide)
- AT (doxorubicin/docetaxel; doxorubicin/paclitaxel)
- CMF (cyclophosphamide/methotrexate/fluorouracil)
- Docetaxel/capecitabine
- GT (gemcitabine/paclitaxel)

Other Combinations

- Ixabepilone + capecitabine (category 2B)

Preferred First-line Agents For HER2-positive Disease

- Pertuzumab + trastuzumab + docetaxel (category 1)
- Pertuzumab + trastuzumab + paclitaxel

Other First-line Agents For HER2-positive Disease

*Trastuzumab with:*

- Paclitaxel ± carboplatin
- Docetaxel
- Vinorelbine
- Capecitabine

Agents For Trastuzumab-exposed HER2-positive Disease

- Lapatinib + capecitabine
- Trastuzumab + capecitabine
- Trastuzumab + lapatinib (without cytotoxic therapy)
- Trastuzumab + other agents

Preferred Agents With Bevacizumab

- Paclitaxel
Chemotherapy Regimens for Recurrent or Metastatic Breast Cancer

Preferred Chemotherapy Combinations

CAF chemotherapy\(^1\)
- Cyclophosphamide 100 mg/m\(^2\) PO days 1-14
- Doxorubicin 30 mg/m\(^2\) IV days 1 & 8
- 5-Fluorouracil 500 mg/m\(^2\) IV days 1 & 8
Cycled every 28 days.

FAC chemotherapy\(^2\)
- 5-Fluorouracil 500 mg/m\(^2\) IV days 1 & 8 or days 1 & 4
- Doxorubicin 50 mg/m\(^2\) IV day 1
- Cyclophosphamide 500 mg/m\(^2\) IV day 1
Cycled every 21 days.

FEC chemotherapy\(^3\)
- Cyclophosphamide 400 mg/m\(^2\) IV days 1 & 8
- Epirubicin 50 mg/m\(^2\) IV days 1 & 8
- 5-Fluorouracil 500 mg/m\(^2\) IV days 1 & 8
Cycled every 28 days.

AC chemotherapy\(^4\)
- Doxorubicin 60 mg/m\(^2\) IV day 1
- Cyclophosphamide 600 mg/m\(^2\) IV day 1
Cycled every 21 days.

EC chemotherapy\(^5\)
- Epirubicin 75 mg/m\(^2\) IV day 1
- Cyclophosphamide 600 mg/m\(^2\) IV day 1
Cycled every 21 days

AT chemotherapy\(^6\)
- Doxorubicin 60 mg/m\(^2\) IV day 1
- Paclitaxel 125-200 mg/m\(^2\) IV day 1
Cycled every 21 days

AT chemotherapy\(^7\)
- Doxorubicin 50 mg/m\(^2\) IV day 1
- Docetaxel 75 mg/m\(^2\) IV day 1
Cycled every 21 days

CMF chemotherapy\(^8\)
- Cyclophosphamide 100 mg/m\(^2\) PO days 1-14
- Methotrexate 40 mg/m\(^2\) IV days 1 & 8
- 5-Fluorouracil 600 mg/m\(^2\) IV days 1 & 8
Cycled every 28 days.

Docetaxel/capecitabine chemotherapy\(^9\)
- Docetaxel 75 mg/m\(^2\) IV day 1
- Capecitabine 950 mg/m\(^2\) PO twice daily days 1-14
Cycled every 21 days.

GT chemotherapy\(^10\)
- Paclitaxel 175 mg/m\(^2\) IV day 1
- Gemcitabine 1250 mg/m\(^2\) IV days 1 & 8 (following paclitaxel on day 1)
Cycled every 21 days.

Other Combinations
- Ixabepilone/capecitabine (category 2B)
  - Ixabepilone 40 mg/m\(^2\) IV day 1
  - Capecitabine 2000 mg/m\(^2\) PO days 1-14
  Cycled every 21 days.
Preferred Single Agents

Anthracyclines:
- Doxorubicin
  - 60-75 mg/m² IV day 1, cycled every 21 days\textsuperscript{11}
  - or
  - 20 mg/m² IV weekly\textsuperscript{12}
- Epirubicin 60-90 mg/m² IV day 1, cycled every 21 days.\textsuperscript{13}
- Pegylated liposomal encapsulated doxorubicin 50 mg/m² IV day 1, cycled every 28 days.\textsuperscript{14}

Taxanes:
- Paclitaxel
  - 175 mg/m² IV day 1, cycled every 21 days.\textsuperscript{15}
  - or
  - 80 mg/m² IV weekly\textsuperscript{16}
- Docetaxel
  - 60-100 mg/m² IV day 1, cycled every 21 days.\textsuperscript{17,18}
  - or
  - 40 mg/m² IV weekly for 6 wks followed by a 2 week rest, then repeat\textsuperscript{19}
- Albumin-bound paclitaxel
  - 100 mg/m² or 150 mg/m² IV days 1, 8, and 15, cycled every 28 days.\textsuperscript{20,21}
  - or
  - 260 mg/m² IV, cycled every 21 days.\textsuperscript{20}

Anti-metabolites:
- Capecitabine 1000-1250 mg/m² PO twice daily days 1-14, cycled every 21 days.\textsuperscript{22}
- Gemcitabine 800-1200 mg/m² IV days 1, 8 & 15, cycled every 28 days.\textsuperscript{23}

Other microtubule inhibitors:
- Vinorelbine 25 mg/m² IV weekly\textsuperscript{24}
- Eribulin 1.4 mg/m² IV weekly for 1 and 8, cycled every 21 days.\textsuperscript{25}

Other Single Agents
- Cyclophosphamide
- Mitoxantrone
- Cisplatin
- Etoposide (PO) (category 2B)
- Vinblastine
- Fluorouracil CI
- Irinotecan CI

Preferred Agents With Bevacizumab
- Paclitaxel plus bevacizumab\textsuperscript{26}
  - Paclitaxel 90 mg/m² by 1 h IV days 1, 8 & 15
  - Bevacizumab 10 mg/kg IV days 1 & 15
  - Cycled every 28 days.
Preferred First-line Agents For HER2-Positive Disease

Pertuzumab + Trastuzumab + Docetaxel
- Pertuzumab 840 mg IV day 1 followed by 420 mg IV
d- Trastuzumab 8 mg/kg IV day 1 followed by 6 mg/kg IV
d- Docetaxel 75-100 mg/m² IV day 1
Cycled every 21 days.

Pertuzumab + Trastuzumab + Weekly Paclitaxel
- Pertuzumab 840 mg IV day 1 followed by 420 mg IV cycled every 21 days
- Trastuzumab
  - 4 mg/kg IV day 1 followed by 2 mg/kg IV weekly
    or
  - 8 mg/kg IV day 1 followed by 6 mg/kg IV cycled every 21 days
- Paclitaxel 80 mg/m² IV day 1 weekly.

Other First-line Agents For HER2-Positive Disease

TCH chemotherapy
- Carboplatin AUC of 6 IV day 1
- Paclitaxel 175 mg/m² IV day 1
Cycled every 21 days.
- Trastuzumab
  - 4 mg/kg IV day 1 followed by 2 mg/kg IV weekly
    or
  - 8 mg/kg IV day 1 followed by 6 mg/kg IV every 21 days

Weekly TCH chemotherapy
- Paclitaxel 80 mg/m² IV days 1, 8 & 15
- Carboplatin AUC of 2 IV days 1, 8 & 15
Cycled every 28 days.
- Trastuzumab
  - 4 mg/kg IV day 1 followed by 2 mg/kg IV weekly
    or
  - 8 mg/kg IV day 1 followed by 6 mg/kg IV every 21 days

Trastuzumab + Paclitaxel
- Paclitaxel
  - 175 mg/m² IV day 1 cycled every 21 days
  or
  - 80-90 mg/m² IV day 1 weekly
- Trastuzumab
  - 4 mg/kg IV day 1 followed by 2 mg/kg IV weekly
    or
  - 8 mg/kg IV day 1 followed by 6 mg/kg IV every 21 days

Trastuzumab + Docetaxel
- Docetaxel
  - 80 - 100 mg/m² IV day 1 cycled every 21 days
  or
  - 35 mg/m² IV day 1 weekly
- Trastuzumab
  - 4 mg/kg IV day 1 followed by 2 mg/kg IV weekly
    or
  - 8 mg/kg IV day 1 followed by 6 mg/kg IV every 21 days

Trastuzumab + Vinorelbine
- Vinorelbine 25 mg/m² IV day 1 weekly
- Trastuzumab
  - 4 mg/kg IV day 1 followed by 2 mg/kg IV weekly
    or
  - 8 mg/kg IV day 1 followed by 6 mg/kg IV every 21 days

Trastuzumab + Capecitabine
- Capecitabine 1000-1250 mg/m² PO twice daily days 1-14 cycled every 21 days
- Trastuzumab
  - 4 mg/kg IV day 1 followed by 2 mg/kg IV weekly
    or
  - 8 mg/kg IV day 1 followed by 6 mg/kg IV every 21 days
Agents For Trastuzumab-exposed HER2-positive Disease

Capecitabine plus lapatinib\textsuperscript{39}
- Capecitabine 1000 mg/m\textsuperscript{2} PO twice daily days 1 - 14
- Lapatinib 1250 mg PO daily days 1-21
Cycled every 21 days

Capecitabine + Trastuzumab\textsuperscript{40}
- Capecitabine 1000-1250 mg/m\textsuperscript{2} PO twice daily days 1-14, cycled every 21 days
- Trastuzumab
  - 4 mg/kg IV day 1 followed by 2 mg/kg IV weekly\textsuperscript{32,38}
  - or
  - 8 mg/kg IV day 1 followed by 6 mg/kg IV every 21 days

Lapatinib + Trastuzumab\textsuperscript{41}
- Lapatinib 1000 mg PO daily
- Trastuzumab
  - 4 mg/kg IV day 1 followed by 2 mg/kg IV weekly
  - or
  - 8 mg/kg IV day 1 followed by 6 mg/kg IV every 21 days\textsuperscript{30}
CASES
Case 1

- 35 year old female
- 1.2 cm IDC  mSBR 9/9
- Nodes 0/3
- ER neg PR neg
- HER2 pending
Case 2

- 58 year old female
- ER pos  PR pos  HER2 neg
- FECD in 2009 for 23/28 + nodes
- Now metastatic to liver & lungs
Case 3

- 67 year old female
- Diabetic, previous MI
- 3.6cm grade II
- 3/12 + nodes
- ER neg  PR neg  HER2 pos