Dose-dense Adjuvant Chemotherapy

25TH ANNUAL SAN ANTONIO BREAST CANCER SYMPOSIUM 15

A number of randomized trials — including NSABP B-22 and other studies using autologous stem cell support — have failed to demonstrate an advantage to dose-intensive chemotherapy. A dose-dense chemotherapy regimen involves a strategy where closer than normal dosing intervals are utilized, often facilitated by hemotopoietic growth factor support, i.e. filgrastim. Several Phase II trials have assessed different dose-dense regimens as adjuvant therapy in women with node-positive breast cancer. As a result, two major Phase III randomized trials are evaluating the role of dose-dense adjuvant chemotherapy. CALGB 9741 is closed to accrual, and initial results will be reported at this meeting, suggesting a disease-free and survival advantage in the dose-dense randomization arm. CAN-NCIC-MA21 is actively accruing patients.

PHASE III RANDOMIZED STUDY OF SEQUENTIAL CHEMOTHERAPY USING DOXORUBICIN, PACLITAXEL, AND CYCLOPHOSPHAMIDE OR CONCURRENT DOXORUBICIN AND CYCLOPHOSPHAMIDE FOLLOWED BY PACLITAXEL AT 14- AND 21-DAY INTERVALS IN WOMEN WITH NODE-POSITIVE STAGE II OR IIIA BREAST CANCER — Closed Protocol

Protocol IDs: CLB-9741, E-C9741, NCCTG-C9741, SWOG-C9741

Projected Accrual: 2,000 patients

Eligibility:	Operable, stage II or IIIA adenocarcinoma of the breast (T0-3, N1-2, and M0) surgically treated by either a modified radical mastectomy or a segmental mastectomy plus axillary node dissection
ARM 1	A q3w x 4 → T q3w x 4 → C q3w x 4
ARM 2	A q2w x 4 → T q2w x 4 → C q2w x 4 G-CSF days 3-10 after each dose of chemotherapy.
ARM 3	AC q3w x 4 → T q3w x 4
ARM 4	AC q2w x 4 → T q2w x 4 G-CSF days 3-10 after each dose of chemotherapy.

A= doxorubicin; T = paclitaxel; C= cyclophosphamide
After completion of all chemotherapy, patients receive tamoxifen x 5 years and undergo radiotherapy. Patients are followed q 6 months x 5 years, then annually until death.

Source: NCI Physician Data Query, October 2002

PHASE III RANDOMIZED STUDY OF ADJUVANT CYCLOPHOSPHAMIDE, EPIRUBICIN AND FLUOROURACIL VERSUS CYCLOPHOSPHAMIDE, EPIRUBICIN, FILGRASTIM (G-CSF), AND EPOETIN ALFA FOLLOWED BY PACLITAXEL VERSUS CYCLOPHOSPHAMIDE AND DOXORUBICIN FOLLOWED BY PACLITAXEL IN PREMENOPAUSAL OR EARLY POSTMENOPAUSAL WOMEN WITH PREVIOUSLY RESECTED NODE-POSITIVE OR HIGH-RISK NODE-NEGATIVE STAGE I-IIIA BREAST CANCER — Open Protocol

Protocol IDs: AMGEN-CAN-NCIC-MA21, BMS-CAN-NCIC-MA21, CAN-NCIC-MA21, JANSSEN-CAN-NCIC-MA21, NCCTG-CAN-NCIC-MA21, P-UPJOHN-CAN-NCIC-MA21

Projected Accrual: 1,500 patients

Eligibility:	Node-positive or high-risk node-negative breast cancer
ARM 1	FEC q4w x 6
ARM 2	EC q2w x 6 (+ G-CSF + epoetin) → paclitaxel (G-CSF + epoetin) x 4
ARM 3	AC q3w x 4 → paclitaxel x 4

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Source: NCI Physician Data Query, October 2002

SELECT PHASE II DOSE-DENSE ADJUVANT CHEMOTHERAPY TRIALS

Reference	Eligibility	Number of Patients	Chemotherapy Regimen	Results
Hudis 1999	≥4 positive lymph nodes	71	A q 21 days x 4 → C q 14 days x 3 + (filgrastim days 3-10 of each cycle)	5 years: 52% DFS, 60% OS
Hudis 1999	≥4 positive lymph nodes	42	A q 14 days x 3 → T q 14 days x 3 → C q 14 days x 3 (filgrastim days 3-10 of each cycle)	4 years: 78% DFS
Fountzilas 2001	T1-T3; ≥10 positive lymph nodes	49	E q 2 wks x 3 → T q 2 wks x 3 → CMF q 2 wks x 3 (filgrastim days 2-10 of each cycle)	3 years: 72% DFS, 90% OS
Ellis 2002	Node+ and HER2+ or ER/PR - or ≥4 positive lymph nodes	52	[A ± F q wk] x 20-24 wks + C qd x 20 wks + filgrastim each day of treatment with C	5 years: 85% DFS, 86% OS

A = doxorubicin; T = paclitaxel; C = cyclophosphamide; E = epirubicin; M = methotrexate; F = 5-fluorouracil; DFS = disease-free survival; OS = overall survival

SELECT PUBLICATIONS

Ellis GK et al. **Dose-dense anthracycline-based chemotherapy for node-positive breast cancer.** *J Clin Oncol* 2002;20(17):3637-3643.

Fornier MN et al. **Doxorubicin followed by sequential paclitaxel and cyclophosphamide versus concurrent paclitaxel and cyclophosphamide: 5-year results of a phase II randomized trial of adjuvant dose-dense chemotherapy for women with node-positive breast carcinoma.** *Clin Cancer Res* 2001;7(12):3934-3941.

Fountzilas G et al. **Dose-dense adjuvant chemotherapy with epirubicin monotherapy in patients with operable breast cancer and ≥10 positive axillary lymph nodes. A feasibility study.** *Oncology* 1998;55(6):508-512.

Fountzilas G et al. **Dose-dense sequential adjuvant chemotherapy with epirubicin, paclitaxel and CMF in high-risk breast cancer.** *Oncology* 2001;60(3):214-220.

Hudis C et al. **5-year results of dose-intensive sequential adjuvant chemotherapy for women with high-risk node-positive breast cancer: A phase II study.** *J Clin Oncol* 1999;17(4):1118-1126.

Hudis C et al. **Sequential dose-dense doxorubicin, paclitaxel, and cyclophosphamide for resectable high-risk breast cancer: Feasibility and efficacy.** *J Clin Oncol* 1999;17(1):93-100.

Razis E et al. **Dose-dense sequential chemotherapy with epirubicin and paclitaxel in advanced breast cancer.** *Cancer Invest* 2001;19(2):137-144.

Trudeau ME. **Optimizing adjuvant breast cancer chemotherapy: Rationale for the MA.21 study.** *Oncology (Huntingt)* 2001;15(5 Suppl 7):7-13.

Untch M et al. **Dose-dense and sequential strategies in adjuvant breast cancer therapy.** *Oncology (Huntingt)* 2001;15(5 Suppl 7):14-20.

DEFINITION OF DOSE-DENSE CHEMOTHERAPY

"The delivery of multiple cycles of chemotherapy using the shortest possible intervals is therefore hypothesized to minimize tumor regrowth between one cycle and the next. This is called 'dose-dense' chemotherapy, herein an increase in dose-intensity is obtained by shortening the intervals between treatments and not, as has been done previously, by simply increasing dose levels."

—Hudis C et al. J Clin Oncol 1999;17:1118-1126.

"The concept of 'dose intensity' (DI) in the management of breast cancer has been widely explored by medical oncologists during the last decade… DI can be increased either by dose escalation or by reducing the interval between cycles, a concept termed 'dose density.' The administration of drugs at an adequate dosing at shorter time intervals, i.e. every 2 weeks, became feasible with the introduction of hemopoietic growth factors into the clinical practice…Sequential chemotherapy and dose-dense chemotherapy are two concepts that greatly influenced the design of adjuvant clinical trials in breast cancer during the last decade. The design of such trials was mostly empirical although it was based on mathematical and experimental evidence stressing the superiority of dose-dense sequential chemotherapy over conventional chemotherapy."

—Fountzilas G et al. Oncology 2001;60:214-220.

ADJUVANT A → C

"Our pilot study of doxorubicin followed by cyclophosphamide demonstrates the safety and feasibility of the sequential dose-dense plan. Long-term follow-up, although noncomparative, is promising…Because the sequential plan can decrease overlapping toxicities, it is an appropriate platform for the addition of newer active agents, such as taxanes or monoclonal antibodies."

—Hudis C et al. J Clin Oncol 1999;17:1118-1126.

ADJUVANT E → T → CMF

"The E-T-CMF regimen is well tolerated, as adjuvant treatment, in patients with operable breast cancer with promising activity and deserves further evaluation in phase III studies."

—Fountzilas G et al. Oncology 2001;60:214-220.

ADJUVANT WEEKLY AC

"Continuous dose-dense chemotherapy with G-CSF support produced encouraging results, which seem to be superior to those expected with 'standard' doxorubicin and cyclophosphamide chemotherapy. It deserves a test in the form of a randomized trial where this approach to anthracycline-based treatment is compared with intermittent administration."

—Ellis GK et al. J Clin Oncol 2002;20:3637-3643.

BIOLOGIC RATIONALE FOR DOSE-DENSE CHEMOTHERAPY

"The application of log-kill principles to the sigmoid growth curve characteristic of human cancers suggests that the chances of eradicating tumor will be increased by dose-dense schedules. If the tumor is composed of several cell lines with different sensitivities, the optimum therapy is likely to consist of several drugs given in sequence at a good dose and on a dense schedule. Such sequential chemotherapy, rather than the use of drugs given in combination at longer intervals, should maximize log-kill at the same time as minimizing tumor regrowth."

—Norton L. Semin Oncol 1999;26(1 Suppl 3):1-4.