Optimizing Adjuvant Chemotherapy: Ongoing Trials and Recent Results

Two taxane-containing regimens have demonstrated improved efficacy in recent studies — dose-dense, every two-week AC → paclitaxel with growth factor support, and TAC (docetaxel, doxorubicin and cyclophosphamide). Because of the relatively high rate of febrile neutropenia, growth factor support is required for the TAC regimen. Indirect comparison of these databases suggests similar efficacy and tolerability, and both have demonstrated an overall survival advantage in randomized trials. Another taxane-containing regimen — AC followed by docetaxel — is commonly utilized in the adjuvant setting but has only been reported in a major randomized trial in the neoadjuvant setting. While the benefits in terms of disease-free and overall survival observed in CALGB-9741 are clear, it is unclear whether the advantage observed from dose-dense scheduling is related to the AC portion of the regimen or paclitaxel scheduling.

PHASE III TRIAL OF ADJUVANT TAC VS FAC

Protocol ID: GEICAM-9805
Accrual: 448 (Closed)

Eligibility	Operable, high-risk breast cancer; node-negative; age 18 to 70; KPS ≥80%
ARM 1	TAC (75/50/500 mg/m^2) q3wk x 6
ARM 2	FAC (500/50/500 mg/m^2) q3wk x 6

KPS = Karnofsky performance status; T = docetaxel

Of the first 224 patients enrolled, those experiencing febrile neutropenia (≥Grade II fever with Grade IV neutropenia) were treated with granulocyte colony stimulating factor (G-CSF) in all subsequent cycles. In the following 224 patients enrolled, a protocol amendment mandated the use of prophylactic G-CSF for those receiving TAC.

INTERIM SAFETY ANALYSIS

	TAC		FAC	
	Before protocol amendment* (n=109)	After protocol amendment* (n=115)	Before protocol amendment* (n=111)	After protocol amendment* (n=113)
Febrile neutropenia	23.8%	3.5%	0.9%	1.7%
Other Grade III/IV toxicities	50.4%	20%	27%	26.5%

* Protocol amendment mandated the use of prophylactic G-CSF for patients receiving TAC.

SOURCE: Martin M et al. *Proc ASCO* 2004;Abstract 620.

THREE-YEAR RESULTS OF CALGB-9741

Parameters	Dose-dense scheduling	Conventional scheduling	Response rate (*p*-value)
Disease-free survival	85%	81%	0.74 (0.010)
Overall survival	92%	90%	0.69 (0.013)

SOURCE: Citron ML et al. *J Clin Oncol* 2003;21(8):1431-9.

PHASE III TRIAL OF ADJUVANT TAC VS FAC

Protocol ID: BCIRG-001
Accrual: 1,491 (Closed)

Eligibility	Stage T1-3, N1, M0; age ≤70; KPS ≥80%
ARM 1	TAC (75/50/500 mg/m^2) q3wk x 6
ARM 2	FAC (500/50/500 mg/m^2) q3wk x 6

KPS = Karnofsky performance status; T = docetaxel

DISEASE-FREE SURVIVAL AND OVERALL SURVIVAL (MEDIAN FOLLOW-UP 55 MONTHS)

N=1,491	Hazard ratio* TAC/FAC (95% CI)	*p*-value
Disease-free survival		
Adjusted for nodal status	0.72 (0.59-0.88)	0.0010
1-3 nodes (n=923)	0.61 (0.46-0.82)	0.0009
≥4 nodes (n=568)	0.82 (0.63-1.08)	0.1629
Hormone receptor-positive	0.73 (0.57-0.94)	0.0132
Hormone receptor-negative	0.66 (0.47-0.93)	0.0163
Overall survival		
Adjusted for nodal status	0.70 (0.53-0.91)	0.0080

* Hazard ratios less than one indicate values in favor of TAC.

SOURCES: Martin M et al. Presentation. San Antonio Breast Cancer Symposium, 2003;Abstract 43.

www.bcirg.org/Internet/Studies/BCIRG+001.htm, January 2005.

Vogel CL et al. *Proc ASCO* 2004;Abstract 677.

THREE-YEAR RESULTS OF CALGB-9741

Complications during treatment	Dose-dense scheduling	Conventional scheduling
Patients with dose delay	37.5%	39.0%
Patients transfused	7.8%	1.9%
Patients hospitalized for febrile neutropenia	2.0%	4.3%

SOURCE: Citron ML et al. *J Clin Oncol* 2003;21(8):1431-9.

ONGOING PHASE III TRIALS OF ADJUVANT CHEMOTHERAPY

Protocol ID	Target accrual	Eligibility	Randomization
US Oncology 01-062	1,810	Node-positive or high-risk node-negative	AC x 4 → docetaxel x 4 AC x 4 → (docetaxel + capecitabine) x 4
SWOG-S0221	4,500	Node-positive or high-risk node-negative	[AC + PEG-G (d2)] q2wk x 6 → [paclitaxel + PEG-G (d2)] q2wk x 6 [A + C_{oral} (d1-7) + G (d2-7)] qwk x 15 → [paclitaxel + PEG-G (d2)] q2wk x 6 [AC + PEG-G (d2)] q2wk x 6 → paclitaxel qwk x 12 [A + C_{oral} (d1-7) + G (d2-7)] qwk x 15 → paclitaxel qwk x 12
NSABP-B-38	4,800	Node-positive	TAC q3wk x 6 AC q2wk x 4 → paclitaxel q2wk x 4 AC q2wk x 4 → paclitaxel/gemcitabine q2wk x 4
CAN-NCIC-MA21	1,500	Node-positive or high-risk node-negative	[E + 5-FU (d1-8) + C_{oral} (d1-14)] q4wk x 6 [EC + G (d2-13)*] q2wk x 6 → [paclitaxel + G (d2-13)*] q3wk x 4 AC q3wk x 4 → [paclitaxel + G (d2-13)*] q3wk x 4
CALGB-40101	4,646	High-risk node-negative	AC q2wk x 4 AC q2wk x 6 Paclitaxel q2wk x 4 Paclitaxel q2wk x 6

A = doxorubicin; C_{oral} = oral cyclophosphamide; C = cyclophosphamide; E = epirubicin; G = filgrastim; PEG-G = pegfilgrastim
* Epoetin alpha is administered weekly in patients with a hemoglobin <13 g/dL.

SOURCES: NCI Physician Data Query, September 2004; Protocol Summaries, NSABP Group Meeting, June 2004; US Oncology Protocol 01-062, June 2002.

SELECT PUBLICATIONS

Citron ML et al. **Randomized trial of dose-dense versus conventionally scheduled and sequential versus concurrent combination chemotherapy as postoperative adjuvant treatment of node-positive primary breast cancer: First report of Intergroup Trial C9741/Cancer and Leukemia Group B Trial 9741.** *J Clin Oncol* 2003;21(8):1431-9. Erratum in *J Clin Oncol* 2003;21(11):2226.

Martin M et al. **Prophylactic growth factor (GF) support with adjuvant docetaxel, doxorubicin, and cyclophosphamide (TAC) for node-negative breast cancer (BC): An interim safety analysis of the GEICAM 9805 study.** *Proc ASCO* 2004;Abstract 620.

Martin M et al. **TAC improves disease free survival and overall survival over FAC in node positive early breast cancer patients, BCIRG 001: 55 months follow-up.** Presentation. San Antonio Breast Cancer Symposium, 2003;Abstract 43.

Vogel CL et al. **The role of growth factor support following neutropenic events in early stage breast cancer (BC) patients treated with adjuvant docetaxel, doxorubicin, and cyclophosphamide (TAC): A sub-analysis of BCIRG 001.** *Proc ASCO* 2004;Abstract 677.

CALGB-9741: ADJUVANT DOSE-DENSE CHEMOTHERAPY

This study, designed with input from all members of the Breast Intergroup and coordinated by the CALGB, had a two-by-two factorial design. The two parameters were dose density — giving drugs every two weeks with G-CSF instead of every three weeks — and combination versus sequential therapy. The doses were derived from previous clinical trial experience. The only difference was the schedule.

This trial, which accrued more than 2,000 patients, shows improved efficacy, decreased death rates and reduced toxicity. I believe in dose-dense therapy because I've seen its evolution in the laboratory and the clinic for 25 years. It has a solid basis.

— Larry Norton, MD

SWOG-S0221: DOSE-DENSE VERSUS CONTINUOUS CHEMOTHERAPY

In this study, AC is administered in either a dose-dense manner with pegfilgrastim or what might be described as a metronomic schedule with filgrastim. Both schedules are then followed by paclitaxel. We chose six cycles of AC and paclitaxel in the control arms for several reasons. By imposing similar durations of treatment in all arms, we avoid wondering later whether an inferior outcome in any arm reflected the duration of treatment.

Data suggest six cycles is superior, although this is still controversial. This more continuous schedule may provide a good chemotherapy base upon which to add other antiangiogenic approaches. Evidence suggests that with the maximum tolerated dose schedule a burst of vasculogenesis occurs between cycles. Hematopoietic growth factors possibly augment that, but it is unclear whether that occurs with weekly doxorubicin and daily cyclophosphamide.

— G Thomas Budd, MD

USE OF ADJUVANT TAC

Taxanes clearly offer benefit in the adjuvant setting. I typically utilize the six-cycle TAC regimen. The disease-free and overall survival of dose-dense therapy and TAC are similar. Growth factor support, used in conjunction with TAC, reduces the rate of febrile neutropenia to that seen in CALGB-9741.

— Denise A Yardley, MD

INTEGRATING DOSE DENSITY INTO CLINICAL TRIALS

CALGB-40101 incorporates the every two-week schedule comparing paclitaxel to AC in patients with high-risk, node-negative breast cancer. It also compares four cycles versus six, and although many clinicians think they already know which is better, this is the first point-on testament. It's not so difficult to believe that therapy every two weeks is better than every three weeks. One may question whether it's worth the effort, but because treatment is completed faster and it lowers the risk of neutropenic fever, I believe it's worth it.

— Clifford Hudis, MD

NSABP TRIAL B-38

NSABP-B-38 will compare two anthracycline/taxane regimens with a new combination in the paclitaxel phase. It's a good trial design because in addition to determining whether one of the two standard combinations is superior, it examines an agent new to the adjuvant setting — gemcitabine. At the 2004 ASCO meeting, Kathy Albain reported results from a trial in metastatic breast cancer that showed an advantage for gemcitabine/paclitaxel versus paclitaxel alone. While the every two-week schedule is a bit of a leap, it was necessary to make it comparable to the dose-dense paclitaxel schedule.

— G Thomas Budd, MD

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