Optimizing Adjuvant Chemotherapy: Recent Trial Results

27TH ANNUAL
San Antonio Breast Cancer Symposium
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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 was 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 the dose-dense every two-week scheduling is related to the AC portion of the regimen or paclitaxel scheduling.

PHASE III RANDOMIZED TRIAL COMPARING ADJUVANT TAC TO FAC

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

Eligibility	Operable, high-risk breast cancer Node-negative, age 18 to 70 years; KPS* ≥80%
ARM 1	TAC (75/50/500 mg/m²) q3wk x 6
ARM 2	FAC (500/50/500 mg/m²) q3wk x 6

* Karnofsky performance status
T = docetaxel

Of the first 224 patients enrolled, those experiencing febrile neutropenia (≥ Grade 2 fever with Grade 4 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.

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

ADJUVANT TAC VERSUS FAC (GEICAM-9805): 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 toxities	50.4%	20%	27%	26.5%

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

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

SECONDARY PROPHYLAXIS WITH G-CSF AND INCIDENCE OF FEBRILE NEUTROPENIA PER CYCLE OF TAC OR FAC: A RETROSPECTIVE SUBGROUP ANALYSIS FROM BCIRG-001

	TAC (n=4,278)		FAC (n=4,348)	
Cycles administered with G-CSF as secondary prophylaxis	18.7%		2.9%	
Febrile neutropenia per cycle	–G-CSF 6.0%	+G-CSF 3.1%	–G-CSF 0.5%	+G-CSF 0.3%

n = number of cycles; –G-CSF = without granulocyte colony-stimulating factor; +G-CSF = with granulocyte colony-stimulating factor

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

PHASE III TRIAL COMPARING DOCETAXEL IN COMBINATION WITH DOXORUBICIN AND CYCLOPHOSPHAMIDE (TAC) VERSUS 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/m²) q3wk x 6
ARM 2	FAC (500/50/500 mg/m²) q3wk x 6

* Karnofsky performance status
T = docetaxel

SOURCES: http://www.bcirg.org/Internet/Studies/BCIRG+001.htm, February 2004. Vogel CL et al. *Proc ASCO* 2004;Abstract 677.

ADJUVANT TAC VERSUS FAC: DISEASE-FREE SURVIVAL (DFS) AND OVERALL SURVIVAL (OS) AFTER A MEDIAN FOLLOW-UP OF 55 MONTHS (BCIRG-001)

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

* Hazard ratios less than one indicate values in favor of TAC.
CI = confidence interval

SOURCE: Martin M et al. Presentation. SABCS, 2003;Abstract 43.

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)

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

RR = relative reduction or risk reduction

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

SELECT PUBLICATIONS

Budman DR et al; **The Cancer and Leukemia Group B. Dose and dose intensity as determinants of outcome in the adjuvant treatment of breast cancer.** *J Natl Cancer Inst* 1998;90(16):1205-11.

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. *Epub* 2003 Feb 13. Erratum in: *J Clin Oncol* 2003;21(11):2226.

Ellis GK et al. **Dose-dense anthracycline-based chemotherapy for node-positive breast cancer.** *J Clin Oncol* 2002;20(17):3637-43.

Henderson IC et al. **Improved disease-free (DFS) and overall survival (OS) from the addition of sequential paclitaxel (T) but not from the escalation of doxorubicin (A) dose level in the adjuvant chemotherapy of patients (PTS) with node-positive primary breast cancer (BC).** *Proc ASCO* 1998;Abstract 390.

Henderson IC et al. **Improved outcomes from adding sequential paclitaxel but not from escalating doxorubicin dose in an adjuvant chemotherapy regimen for patients with node-positive primary breast cancer.** *J Clin Oncol* 2003;21(6):976-83.

Kaufman PA et al. **Randomized double-blind phase 2 study evaluating same-day vs next-day administration of pegfilgrastim with docetaxel, doxorubicin, and cyclophosphamide (TAC) in women with early stage and advanced breast cancer.** Presentation. SABCS, 2004;Abstract 1054.

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. SABCS, 2003;Abstract 43.

Venturini M et al. **Phase III adjuvant trial comparing standard versus accelerated FEC regimen in early breast cancer patients: Results from GONO — MIG1 study.** *Breast Cancer Res Treat* 2003;Abstract 12.

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 schedules. This trial, which accrued over 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, and it has a solid basis.

— Larry Norton, MD

Unlike some other trials, analysis of CALGB-9741 was time-driven, not event-driven. I'm glad we didn't have an event trigger because we'd still be waiting for this important data, and results are only relevant for a certain period of time. The study stipulated an analysis at 36 months and, consistent with trends in adjuvant therapy in general and adjuvant therapy trials in particular, the actual number of events at 36 months was far less than expected — 315 events for event-free survival rather than the expected 515 events. The data revealed a statistically significant advantage to every two-week versus every three-week therapy but no difference between sequential versus concurrent AC.

— Clifford A Hudis, MD

I believe the dose-dense approach is an advance in treatment. It's amazing that chemotherapy every two weeks rather than every three weeks can be less toxic, but that's been my experience. With dose-dense therapy, dose delays do not occur, the patients feel fine and are thrilled to finish therapy earlier, and neutropenic fever is rare. The one toxicity that concerns me is neurotoxicity because it's less objective. We can harm patients by continuing paclitaxel when significant neurotoxicity is present.

— Melody A Cobleigh, MD

Currently, the weight of the evidence supports dose-dense AC followed by paclitaxel regimen, but TAC may be as efficacious. Data from the TAC/FAC adjuvant study have been updated and demonstrate a survival benefit when 5-FU is replaced with a taxane. AC followed by docetaxel in a sequential manner is probably tolerated better and may be just as efficacious, but, we only have surgical data from NSABP-B-27, not long-term results.

— Julie R Gralow, MD

USE OF ADJUVANT TAC

Taxanes clearly offer benefit in the adjuvant setting, and 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

My first choice for treatment of younger patients with node-positive disease is TAC, which most of my patients choose. My second choice is the dose-dense regimen because the Phase III data shows a benefit, but I am concerned about the reported 13 percent incidence of blood transfusions. I've spoken with physicians who say it's not that high in actual practice, so it may not be a real effect, rather just a result of limited data.

My third choice is AC followed by docetaxel, because in NSABP B-27 we saw a higher pathologic complete response rate, although not a survival benefit. I don't use anthracycline-based regimens like FEC or CAF because I prefer a regimen that includes a taxane. Although data support using these regimens in the pre- or postmenopausal patient, I'm convinced the taxanes provide an additive benefit.

— Sandra Swain, MD