Optimizing Adjuvant Chemotherapy: Recent Trial Results

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Phase III randomized trials have demonstrated that taxane-containing adjuvant regimens enhance relapse-free and overall survival. BCIRG 001 compared TAC (docetaxel, doxorubicin and cyclophosphamide) to FAC, and CALGB-9741 evaluated a dose-dense regimen of AC and paclitaxel administered with growth factor support. GEICAM 9805 demonstrated that the incidence of febrile neutropenia associated with TAC could be reduced with the use of filgrastim. In a Phase III randomized trial, pegfilgrastim was also found to reduce the incidence of febrile neutropenia associated with docetaxel. Additional trials have evaluated growth factor support with pegfilgrastim in patients receiving dose-dense chemotherapy.

PHASE III TRIAL OF ADJUVANT TAC VERSUS FAC

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

Eligibility	Stage T1-3, N1, M0; 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

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

Disease-free survival N = 1,491	Hazard ratio* TAC/FAC (95% CI)
ITT, adjusted for nodal status	0.72 (0.59-0.88)
1-3 nodes (n = 926)	0.61 (0.46-0.82)
≥4 nodes (n = 565)	0.83 (0.63-1.08)
Hormone receptor-positive (n = 1,132)	0.72 (0.56-0.92)
Hormone receptor-negative (n = 359)	0.69 (0.49-0.97)
Overall survival	
Adjusted for nodal status	0.70 (0.53-0.91)

ITT = intention to treat

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

SOURCE: Martin M et al. *N Engl J Med* 2005;352(22):2302-13.

DISEASE-FREE SURVIVAL IN THREE TRIALS EVALUATING DOSE-DENSE CHEMOTHERAPY: CALGB-N9741 AND THE SEATTLE TRIALS

	CALGB dose-dense trial	Seattle pilot trials	
	N9741[1] (N = 2,005)	(F)AC + G[2] (N = 52)	AC + G/T[3] (N = 54)
Median positive nodes	3	4	5
ER- and/or PR-positive	65%	65%	80%
HER2-positive	—	42%	22%
3y disease-free survival	81-85%	86%	90%

G = filgrastim; T = paclitaxel

SOURCES: [1] Citron ML et al. *J Clin Oncol* 2003;21(8):1431-9; [2] Ellis GK et al. *J Clin Oncol* 2002;20(17):3637-43; [3] Ellis GK et al. *Proc ASCO* 2005;Abstract 628.

EFFECTS OF IMPROVEMENTS IN ADJUVANT CHEMOTHERAPY IN NODE-POSITIVE BREAST CANCER: 20-YEAR EXPERIENCE OF CALGB AND UNITED STATES BREAST INTERGROUP

		Average hazard reduction (confidence interval)			
Trial comparison		CALGB-8541 dose of CAF low → high	CALGB-9344 paclitaxel without → with	CALGB-9741 Rx interval 21d → 14d	Overall low → 14d
DFS	ER-neg	36% (15-52%)	25% (11-36%)	23% (0-42%)	63% (43-76%)
	ER-pos	14% (-18-37%)	12% (-4-25%)	10% (-19-33%)	32% (-7-56%)
OS	ER-neg	29% (3-48%)	25% (11-37%)	22% (-5-43%)	59% (34-74%)
	ER-pos	8% (-27-36%)	10% (-10-26%)	1% (-44-32%)	18% (-41-52%)

Adjusted for positive nodes, tumor size, menopausal status
DFS = disease-free survival; OS = overall survival

SOURCE: Berry DA et al. Presentation. San Antonio Breast Cancer Symposium 2004;Abstract 29.

PHASE III TRIAL OF ADJUVANT TAC VERSUS 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

After enrollment of 224 patients, a protocol amendment mandated the use of prophylactic G-CSF for all subsequent patients receiving TAC. An interim safety analysis assessed the impact of G-CSF on the incidence of febrile neutropenia (fever ≥ Grade II with Grade IV neutropenia) and other Grade III/IV toxicities.

INTERIM SAFETY ANALYSIS

	TAC		FAC	
	Without mandatory G-CSF*	With G-CSF*	Before protocol amendment*	After protocol amendment*
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.

PHASE III STUDY OF PEGFILGRASTIM VERSUS PLACEBO IN PATIENTS RECEIVING DOCETAXEL

Accrual: 928 (Closed)

Eligibility	Breast cancer, ECOG performance of 0-2 ≥18 years of age
ARM 1	Docetaxel 100 mg/m^2 + pegfilgrastim*
ARM 2	Docetaxel 100 mg/m^2 + placebo*

* Patients on either arm experiencing febrile neutropenia entered an open-label phase in which they received docetaxel with pegfilgrastim.

EFFICACY DATA

Parameter	Placebo† (n = 465)	Pegfilgrastim† (n = 463)	*p*-value
Febrile neutropenia (FN)	17%	1%	<0.001
FN-related hospitalizations	14%	1%	<0.001
FN-related IV anti-infective use	10%	2%	<0.001
Chemotherapy planned dose on time (cycles 2-4)‡	78%	80%	Not reported

† 62 percent of patients had metastatic disease.
‡ Placebo arm included patients receiving open-label pegfilgrastim.

Conclusions:

- Pegfilgrastim was well tolerated.
- Early intervention with pegfilgrastim prevents FN by 94 percent and further prevents hospitalizations and use of IV anti-infectives by 80 percent.
- 67 percent of FN occurred during the first cycle in the placebo group.

SOURCE: Vogel CL et al. *J Clin Oncol* 2005;23(6):1178-84.

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.

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

Martin M et al. **Adjuvant docetaxel for node-positive breast cancer.** *N Engl J Med* 2005;352(22):2302-13.

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.

BCIRG 001: ADJUVANT TAC VERSUS FAC

In our first study, BCIRG 001, 1,500 women from 21 countries were randomly assigned to six cycles of adjuvant TAC or FAC. The women enrolled in the trial had node-positive disease. We now have mature results with five years of follow-up. The trial demonstrated that adjuvant TAC significantly improved disease-free survival by 28 percent in relative terms ($p = 0.001$). Overall survival was also strikingly improved; the trial demonstrated a 30 percent relative reduction in mortality with adjuvant TAC, which was an absolute six percent improvement in overall survival. This would be a perfect story if an increase in side effects did not occur. In fact, TAC was associated with a high rate of febrile neutropenia. Approximately 25 percent of the women receiving TAC experienced an episode of febrile neutropenia, which was not unexpected because primary prophylaxis with G-CSF was not allowed. We now know that if we were to do the study again and administer TAC with G-CSF, we would see a febrile neutropenia rate, on a per-patient basis, of about three to six percent.

— *John Mackey, MD.* Breast Cancer Update *2005 (1)*

DEVELOPMENTS IN ADJUVANT CHEMOTHERAPY

The development of the dose-dense approach has marked a recent step in the progressive improvement of prospects for women with node-positive primary breast cancer, especially HR-negative cases. Other stages on the way have been the benefits achieved by increasing the doses of cyclophosphamide, doxorubicin, and 5-fluorouracil used in CAF and the advent of the taxanes. Further improvements may stem from current research aimed at: (A) reducing the interval between cycles from 14 days to 10 or 11 days; (B) extending the period for which anthracyclines and taxanes can be given; (C) adding noncytotoxic agents such as the humanized anti-HER2 antibody trastuzumab to chemotherapy in HER2-positive cases; and (D) adding antiangiogenesis agents, eg bevacizumab.

— *Larry Norton, MD.* Oncologist *2005;10(6):370-81.*

TRIAL OF PEGFILGRASTIM VERSUS PLACEBO

The objective of this study was to determine if pegfilgrastim significantly reduces febrile neutropenia in patients receiving a chemotherapy regimen associated with an expected rate of approximately 20 percent. Patients were eligible for the trial whether they were receiving docetaxel in the adjuvant or the metastatic setting. In this double-blind, randomized trial, patients received docetaxel with pegfilgrastim versus a placebo. If patients developed febrile neutropenia, they were able to subsequently receive pegfilgrastim. Febrile neutropenia, related hospitalizations and intravenous anti-infective use were all significantly reduced by pegfilgrastim. While the difference in the rates of patients receiving their planned chemotherapy dose on time doesn't look impressive, all the placebo patients who developed febrile neutropenia received pegfilgrastim. Consequently, both groups experienced delivery of the planned dose on time.

— *Charles L Vogel, MD.* Breast Cancer Update *Think Tank, August 2004*

This study provides compelling evidence that administering pegfilgrastim in the first and subsequent cycles of moderately myelosuppressive chemotherapy can significantly reduce the risk of potentially life-threatening infections that can result in hospitalizations and require intravenous antibiotics. Approximately 600,000 chemotherapy patients are at risk of developing neutropenia, which has traditionally been treated reactively. Doctors usually reserve proactive use of pegfilgrastim for only those patients considered at very high risk of developing chemotherapy-induced neutropenia. This study may give physicians the evidence they need to help protect cancer patients from chemotherapy-induced neutropenic complications beginning in the first cycle of chemotherapy treatment.

— *Lee Schwartzberg, MD. Interview, Multinational Association of Supportive Care in Cancer 2004 Annual Meeting*