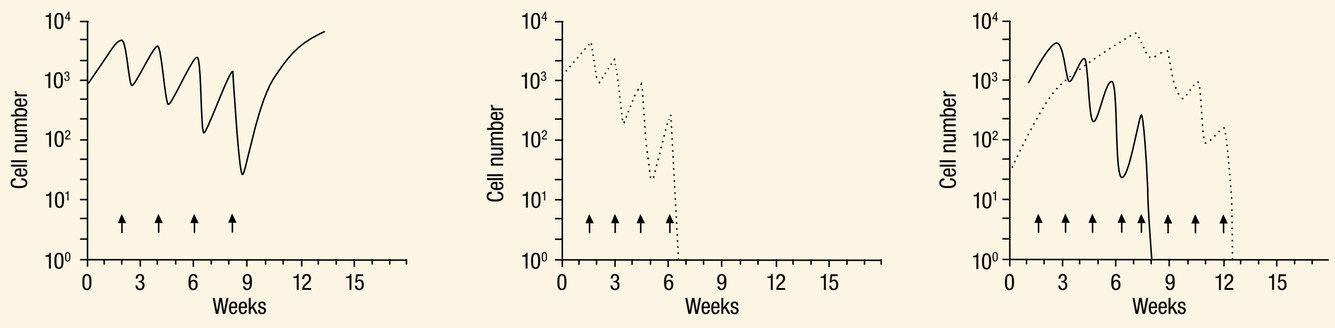
Dose-Dense Adjuvant Chemotherapy

27TH ANNUAL
San Antonio Breast Cancer Symposium 14

A number of randomized trials have failed to demonstrate an advantage to dose-intensive chemotherapy. Dose-dense chemotherapy involves the use of shorter dosing intervals, facilitated by hematopoietic growth factor support (ie, filgrastim, pegfilgrastim). This strategy is based on theoretical mathematical modeling by Norton and others, suggesting a potential benefit to retreatment before tumor regrowth occurs. In December 2002, results of CALGB-9741 were reported at the San Antonio Breast Cancer Symposium, demonstrating a disease-free and overall survival advantage to two dose-dense chemotherapeutic regimens involving doxorubicin, cyclophosphamide and paclitaxel given every two weeks with filgrastim support. A number of ongoing randomized trials are incorporating the dose-dense strategy and also are evaluating the role of pegfilgrastim.

LOG CELL KILL IN GOMPERTZIAN GROWTH NEEDED FOR IMPACT OF ADJUVANT CHEMOTHERAPY



SOURCE: Reproduced with permission from Norton L. **Theoretical concepts and the emerging role of taxanes in adjuvant therapy**. *The Oncologist* 2001;6(56):30-35.

PHASE III ADJUVANT TRIAL OF STANDARD VERSUS ACCELERATED FEC

Protocol ID: GONO-MIG1
Accrual: 1,214 (Closed)

Eligibility	Node-positive or high-risk node-negative operable breast cancer
ARM 1	FEC21 q3wk (600/60/600 mg/m²) x 6
ARM 2	FEC14 q2wk (600/60/600 mg/m²) x 6 + filgrastim

Change in hazard of death with FEC14 q2wk compared to FEC21 q3wk

	FEC14 q2wk	Hazard ratio (HR)
Overall population	-18%	HR = 0.82 (95% CI = 0.6-1.12), p = 0.22
<50 years	-49%	HR = 0.51 (95% CI = 0.27-0.94)
50-59 years	-29%	HR = 0.71 (95% CI = 0.40-1.25)
>60 years	+48%	HR = 1.48 (95% CI = 0.80-2.75)

SOURCE: Venturini M et al. *Breast Cancer Res Treat* 2003;Abstract 12.

PHASE III ADJUVANT TRIAL OF DOSE DENSE SEQUENTIAL CHEMOTHERAPY VERSUS CONVENTIONALLY DOSED CHEMOTHERAPY

Protocol ID: AGO
Accrual: 1,284 (Closed)

Eligibility	High-risk breast cancer (>4 positive nodes), age <65
ARM 1	E (150 mg/m²) → T (225 mg/m²) → C (2500 mg/m²) q2wk + G-CSF
ARM 2	E (150 mg/m²) → T (225 mg/m²) → C (2500 mg/m²) q2wk + G-CSF + Epo
ARM 3	EC (90/600 mg/m²) x 4 → T (175 mg/m²) q3wk

E = epirubicin; T = paclitaxel; C = cyclophosphamide; Epo = epoetin alpha

Endpoint	E → T → C* (n=599)	EC → T (n=570)	p-value
Relapse or death	94 (15.7%)	127 (22.3%)	0.0009
Death	43 (7.2%)	60 (10.5%)	0.03

* Epo arm resulted in less transfusion but similar survival

SOURCE: Mobus VJ. Presentation. ASCO, 2004;Abstract 513.

A PHASE III RANDOMIZED STUDY OF DOSE-DENSE VERSUS CONVENTIONAL SCHEDULING AND SEQUENTIAL VERSUS COMBINATION ADJUVANT CHEMOTHERAPY

Protocol IDs: CLB-9741, E-C9741, NCCTG-C9741, SWOG-C9741 (Closed)

ARM 1	A q3wk x 4 → T q3wk x 4 → C q3wk x 4
ARM 2	A q2wk x 4 → T q2wk x 4 → C q2wk x 4*
ARM 3	AC q3wk x 4 → T q3wk x 4
ARM 4	AC q2wk x 4 → T q2wk x 4*

* Filgrastim (G-CSF) is administered on days 3-10 after each dose of doxorubicin, paclitaxel and cyclophosphamide.

A = doxorubicin; T = paclitaxel; C = cyclophosphamide

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

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

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

Martin M et al. **Advanced Search - Breast 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.

Mobus VJ et al. **Dose-dense sequential chemotherapy with epirubicin(E), paclitaxel (T) and cyclophosphamide (C) (ETC) is superior to conventional dosed chemotherapy in high-risk breast cancer patients (≥ 4 +LN). First results of an AGO-trial.** *Proc ASCO* 2004;Abstract 513.

Rodriguez-Lescure A et al. **Multicenter, randomized phase III study of adjuvant chemotherapy for axillary positive breast cancer (APBC) comparing 6 cycles (cy) of FEC vs 4 cy of FEC followed by 8 weekly paclitaxel (T) administrations: Safety analysis of GEICAM 9906 trial.** *Proc ASCO* 2004;Abstract 596.

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: DOSE-DENSE CHEMOTHERAPY

At a median follow-up of three years, dose-dense treatment was associated with a 26 percent proportional reduction in relapse and a 31 percent proportional reduction in mortality. We had expected 515 relapses based on CALGB-8541, the CAF dose-intensive trial; however, only 315 patients had a recurrence. The four-year disease-free survival was 82 percent for dose-dense therapy and 75 percent for the every three-week regimens. I was surprised by the magnitude of the difference — seven percent at four years is significant. We'll have to see whether the survival benefit is lost or confirmed with further follow-up. Most patients received the optimal doses of their drugs in all arms, which may be related to the low ANC requirement and the fact that less than eight percent of treatment cycles were delayed. This assured us that the benefits of dose density could not be attributed to a lower dose or further dose delays in the conventional regimens — the arms were balanced in that regard.

— Marc Citron, MD

HAZARD RATES OF RECURRENCES

Some criticize the data from CALGB-9741 because the magnitude of benefit over time may not be as large as it is now. That's fair, because it could fluctuate, but the positivity won't go away. We saw the same phenomenon in CALGB-9344. If you plot the hazard function and compare paclitaxel to no paclitaxel, sometimes the curves are close together and sometimes the curves are further apart, but the aggregate benefit is clear and consistent.

— Clifford A Hudis, MD

DOSE-DENSE THERAPY TARGETS INHIBITION OF REGROWTH

A paper in *Seminars in Oncology* in the mid-1980s indicated that the primary problem in Gompertzian growth is not cell kill, but rather regrowth between cycles. While therapy gets us closer to the cure limits, you have to get below a small number of cells to prevent regrowth, and you regrow faster away from that limit. There's a rebound effect, and the key is to inhibit that regrowth.

One of the simplest ways to address regrowth is to move the doses of therapy close enough together to have less regrowth between cycles. This is extremely powerful in Gompertzian kinetics, as long as you can drive the tumor toward that cure limit. In the adjuvant setting, when you're probably close to the cure limit, you can have dramatic benefits by giving the doses closer together in time.

— Larry Norton, MD

DOSE-DENSE STUDY OF FEC

At the 2003 San Antonio Breast Cancer Symposium, Venturini et al presented data from a trial comparing FEC every two weeks versus every three weeks. It's one of the few studies that, like CALGB-9741, truly tested dose density because every patient received the same doses of the same drugs for the same number of cycles and the only variable was the interval between treatments. I commend Venturini and his colleagues because that approach is the key to demonstrating the value of dose-dense therapy.

We hoped Venturini's trial would confirm CALGB-9741 as a general principle, but their event rate was lower than expected and the study lost its power. In CALGB-9741, we also had fewer events than expected. Fortunately, our trial was large enough to demonstrate the benefit of dose density at 36 months. They presented the data showing a trend in favor of the dose-dense therapy, stating that while the trial was not positive, the range of possibilities included positivity.

Consistent with CALGB-9741, they were able to show that dose-dense therapy was faster with fewer episodes of febrile neutropenia. Although I was disappointed that their study didn't have the power to confirm the CALGB data, I'm confident that their data was consistent with ours.

— Clifford A Hudis, MD