Dose-Dense Adjuvant Chemotherapy

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

PHASE III ADJUVANT TRIAL OF STANDARD VERSUS ACCELERATED FEC

Protocol ID: GOGO-9901
Accrual: 2,124 (Closed)

Eligibility
Non-positive or high-risk node-negative operable breast cancer

ARM 1
FEC21 q2w (500/500/500 mg/m²) x 6

ARM 2
FEC21 q2w (500/500/500 mg/m²) x 6 + filgrastim

Change in hazard of death with FEC21 q2w compared to FEC21 q2w


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

Protocol ID: AGO
Accrual: 1,208 (Closed)

Eligibility
High-risk breast cancer (3-5 positive nodes, age >65)

ARM 1
E (150 mg/m²) x 5 (225 mg/m²) x 4 + G-CSF + Epo

ARM 2
E (150 mg/m²) x 5 (225 mg/m²) x 4 + G-CSF + IFP + paclitaxel


A THREE-RANDOMIZED STUDY OF DOSE DENSE versus CONVENTIONAL SCHEDULING AND SEQUENTIAL VERSUS CONVENTIONAL CHEMOTHERAPY

Protocol IDs: CALGB-9344, E-2197, NSC-57417, SWOG-9617 (Closed)

ARM 1
A (400 mg/m²) x 4 (225 mg/m²) x 4

ARM 2
A (400 mg/m²) x 4 (225 mg/m²) x 4 + T q2wk

ARM 3
A (400 mg/m²) x 4 (225 mg/m²) x 4 + T q2wk + G-CSF + Epo

ARM 4
A (400 mg/m²) x 4 (225 mg/m²) x 4 + T q2wk + G-CSF + Epo


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.

DOSAGE SCHEDULE OF FEC

Three of the four regimens were dose dense. FEC21 q2w was 1-6 cycles of 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 others for the approach that is 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 positive.

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

SELECT PUBLICATIONS


Vogel CL et al. The role of growth factor support following neutropenic events in early stage breast cancer: A retrospective study with adjuvant docetaxel, doxorubicin, and cyclophosphamide (TAC). J Clin Oncol. 2006;24(56):30-35.
