Dose Density in Breast Cancer: A Simple Message?

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“Everything should be made as simple as possible, but not one bit simpler.”

—Albert Einstein

In the 1970s, Norton and Simon (1), applying Gompertzian principles to cancer cell growth, hypothesized that maximal chemotherapy effectiveness could be achieved by scheduling the interval of chemotherapy to correspond to the period of most rapid tumor growth. As an outgrowth of this initial work, several pilot trials and two large randomized trials were conducted to test the feasibility and effectiveness of what has come to be called dose-dense chemotherapy. The Cancer and Leukemia Group B (CALGB) trial 9741, which was conducted in the North American Intergroup (2), provided support to Norton and Simon’s hypothesis by demonstrating that a change in the interval of anthracycline- and taxane-based chemotherapy, from every 3 weeks to every 2 weeks, improved disease-free and overall survival in women with lymph node–positive, early-stage breast cancer.

In this issue of the Journal, Venturini et al. (3) report the results of a multicenter phase III study, led by the Gruppo Oncologico Nord Ovest-Mammella InterGruppo (GONO-MIG), comparing fluorouracil, epirubicin, and cyclophosphamide administered every 3 weeks (FEC21) versus the same regimen administered every 2 weeks with filgrastim support (FEC14) in patients with lymph node–positive or high-risk lymph node–negative breast cancer. They reported that FEC14 was both feasible and safe: Patients achieved an actual 48% increase in dose density, and no incident cases of acute myelogenous leukemia or myelodysplastic syndrome were observed. Only one case (0.2%) of grade 2 cardiac toxicity was reported on each arm. In contrast to the CALGB/Intergroup trial, however, the difference between the two arms did not reach traditional criteria for statistical significance for either recurrence (hazard ratio [HR] = 0.88, 95% confidence interval [CI] = 0.71 to 1.08) or death (HR = 0.87, 95% CI = 0.67 to 1.13).

Overall, the study was thoughtfully designed, and the results are mature. The treatment arms were balanced in terms of patient and disease characteristics. The investigators recorded the incidence of treatment-related amenorrhea and found no difference between the two arms. As in the CALGB/Intergroup trial, the chemotherapy dose per cycle and total number of cycles were held constant, and only the interval between doses varied. Thus, the study is only one of two trials specifically designed to test the concept of dose density in the context of adjuvant breast cancer treatment.

How should clinicians, researchers, and patients integrate the results of the present study into the overall body of evidence evaluating dose-dense treatment for breast cancer? Is dose density a unifying concept that should be applied whenever adjuvant chemotherapy is administered, or is it specific to a particular chemotherapeutic regimen or tumor subtype? How does toxicity vary according to schedule, and in whom do the additional benefits of dose-dense chemotherapy outweigh the potential risks?

On the surface, the conclusions from CALGB/Intergroup trial and the Venturini study appear to be discordant. There are several possible explanations, including subtle differences in the patient populations, differences in the chemotherapy regimens, and the play of chance. Of these possibilities, the absence of a taxane in the Italian study is the most compelling. A body of literature (4,5) in both the metastatic and preoperative settings suggests that more frequent paclitaxel scheduling can lead to meaningful differences in disease control. By extension, some researchers have hypothesized that most if not all of the benefit attributed to dose density in the CALGB 9741 trial could be related to the optimization of taxane scheduling.

Several studies, however, argue against a specific effect of taxane scheduling. More than two decades ago, Bonadonna et al. (6) conducted a landmark study comparing four cycles of doxorubicin followed by eight cycles of cyclophosphamide, methotrexate, and fluorouracil (CMF) with one cycle of doxorubicin alternating with two cycles of CMF, for a total of 12 cycles of therapy. The trial was originally designed to ask whether alternating non–cross-resistant regimens would improve outcomes in women with lymph node–positive breast cancer, but, if viewed in a different light, it could be considered a trial evaluating dose density of both CMF and doxorubicin. At a medium follow-up of 9 years, there was a highly statistically significant difference in survival (58% versus 44%, difference = 14%; $P = .002$) in favor of the sequential arm. More recently, albeit in a very different setting, a German group (7) demonstrated that delivering cyclophosphamide, doxorubicin, vincristine, and prednisone every 2 weeks, compared with every 3 weeks, statistically significantly improved survival in elderly patients with aggressive lymphomas (relative risk reduction = 0.58, 95% CI = 0.43 to 0.79; $P < .001$). The results of each of these trials suggest that the benefits of a dose-dense treatment approach are not specific to a single class of drugs (i.e., taxanes).

Despite the non–statistically significant results observed in the GONO-MIG trial, on closer examination, the findings are not entirely inconsistent with results of the CALGB/Intergroup study. There was a trend toward improved event-free and overall survival for women who received the every-14-day regimen.
(i.e., FEC14). The GONO-MIG trial observed a higher actuarial 10-year survival (78%, 95% CI = 74% to 82%) in the control group than was expected, but the number of total events and total deaths (and hence the power) in the GONO-MIG trial were similar to those in the CALGB/Intergroup trial. The GONO-MIG study actually had 80% power to detect a true 26% relative reduction in the risk of recurrence and a true 32% relative reduction in the risk of death, which are similar to the observed differences in the initial report of the CALGB study at a median follow-up of approximately 3 years. Using an exponential assumption, we estimated hazard ratios for event-free survival and overall survival from the GONO-MIG trial at a median follow-up of 3 years; the ratios for both event-free survival and overall survival appear to be within approximately 1% of those reported in the CALGB/Intergroup study. At 3 years, the GONO-MIG study had far fewer recurrences than did the CALGB trial. If a formal statistical analysis had been performed at that time, it is unlikely that a statistically significant difference would have been detected in spite of the similar hazard ratios. With additional follow-up, the average risk reductions in the CALGB trial are somewhat smaller than in their first report, a phenomenon that is often observed in clinical trials, because the impact of chemotherapy is greatest on early recurrences. From a practical standpoint, many clinicians and patients would still consider a smaller risk reduction to be meaningful, particularly with a regimen that involves the same drugs and identical doses.

As with most other large adjuvant trials, the present study included women with lymph node–positive disease regardless of tumor subtype. Women with lymph node–negative tumors were included if they were young or if they had tumors that were hormone receptor negative or of high grade. Subgroup analyses were underpowered to determine whether increasing dose density resulted in similar benefits across tumor subtypes, but predictable trends did emerge. The qualitative differences in outcomes according to estrogen receptor status were striking and remarkably consistent with a retrospective analysis of the benefits of more intensive chemotherapy in three sequential CALGB studies, including 9741 (8). Venturini et al. also examined disease outcomes among the 103 patients with HER2-positive tumors on the study and observed improved 10-year event-free survival in the arm receiving dose-dense therapy, compared with the arm receiving standard therapy (72% [95% CI = 58% to 85%] vs. 44% [95% CI = 27% to 61%]; P = .03 and $P_{interaction} = .043$). In this context, it is of interest that the benefit of anthracycline-based chemotherapy regimens appears strongest for HER2-positive tumors (9,10). Although all of these subgroup analyses should be viewed as hypothesis generating, they contribute to the mounting evidence that the relative and absolute benefits of chemotherapy are strongly influenced by the hormone receptor status and the HER2 status of the tumor, as well as other biologic factors that are yet to be defined (11,12). Data from multiple preoperative studies also support the hypothesis that tumor subtype and proliferative markers influence the probability of response to chemotherapy (13–16). If, indeed, increasing dose density improves outcomes by killing more cancer cells as the cancer cells regrow after the previous cycle of therapy, then it would be reasonable to hypothesize that the interval between cycles of chemotherapy may be most critical in high-grade rapidly proliferating tumors.

In our view, the totality of evidence supports the concept that dose density has a modest impact on the outcome of unselected patients with early-stage breast cancer. Furthermore, there is compelling reason to believe that the benefits of dose-dense therapy will be greater in specific subsets of women with breast cancer.

From the standpoint of tolerability, although 93% of patients were able to complete protocol-specified therapy, the FEC14 regimen was associated with more toxicity than the FEC21 regimen. Consistent with results of the CALGB 9741 trial, a reduction in the interval between cycles to 2 weeks was associated with a greater incidence of anemia. FEC14 was also associated with statistically significantly increases in asthenia, bone pain, and psychologic distress than FEC21 (17). These toxicities were largely transient, and the overall duration of therapy was reduced by one-third, which is an advantage in and of itself for some patients.

What lessons can be learned from the trial reported by Venturini et al.? First, despite the failure of the overall results to reach statistical significance, there is still solid evidence, in the context of other trial data, that using a dose-dense approach can decrease the risk of disease recurrence and improve overall survival. Second, the difference in actual versus predicted outcome in the reference arm has been observed in nearly every large, cooperative group study, and in planning future trials, we need to account for this eventuality or risk conducting long, resource-intensive studies that are underpowered for the primary study question. Third, in light of the provocative data suggesting differential benefit of chemotherapy by tumor subtype, it is imperative that we incorporate what is known about breast cancer biology prospectively into the design of clinical trials. The optimal approach to adjuvant chemotherapy for a woman newly diagnosed with breast cancer almost certainly differs according to tumor subtype. If we attempt to apply a single treatment approach across all patients and tumor subtypes, we risk missing a large benefit among a small subset of patients. Conversely, we may falsely conclude that we are improving outcomes for all patients, when, in fact, we may be exposing many patients to more toxicity, without additional benefit. The challenge is now upon us to design innovative, adequately powered clinical trials that test therapeutic principles in the major biologic subtypes of breast cancer.

**References**


