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Andrew D. Seidman

Current status of dose-dense chemotherapy for breast cancer

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Abstract In an effort to improve the effectiveness of chemotherapy for breast cancer, examination of the impact of dose intensity, dose density, and treatment duration may have as much relevance as the specific antineoplastic agents utilized. After several years of pilot feasibility studies of dose-dense chemotherapy regimens, whose delivery has been made safe and feasible by the use of hematopoietic growth factor support (in particular, filgrastim), we now have phase III data demonstrating the advantages of this approach in the adjuvant treatment of breast cancer.

Keywords Breast cancer · Adjuvant chemotherapy · Dose density

Introduction

Despite the judicious use of "state-of-the-art" adjuvant chemotherapy regimens for early-stage breast cancer, the prognosis for patients presenting with extensive axillary lymph node involvement remains poor [4, 15]. Nevertheless, systemic adjuvant chemotherapy remains a critical component in the eradication of occult micrometastases and cure. In an attempt to improve efficacy of existing chemotherapy, a phase III intergroup trial led by the Cancer and Leukemia Group B (CALGB 9741) [2] (Fig. 1) was designed to test a mathematical model of tumor growth based on the Norton–Simon hypothesis [14]. This hypothesis, developed about 3 decades ago, and the kinetic model derived from it formed the basis for the concepts of dose-density and sequential therapy, both tested in CALGB 9741. This large, prospective, randomized study convincingly demonstrated that shortening the time interval between each chemotherapy cycle while maintaining the same dose size results in significant improvement of disease-free survival (DFS) and overall survival (OS) in patients with node-positive breast cancer without increasing toxicity. This result is highly relevant, has immediate practical implication, and changes the standard practice of breast cancer treatment in the adjuvant setting. Should we be surprised? This article outlines the theoretical framework for dose-dense chemotherapy in breast cancer and critically reviews recent clinical trials that address this concept and approach to breast cancer treatment.

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A. D. Seidman
Breast Cancer Medicine Service,
Division of Solid Tumor Oncology, Department of Medicine,
Memorial Sloan-Kettering Cancer Center, 1275 York Avenue,
New York, NY 10021, USA
E-mail: seidmana@MSKCC.ORG
Tel.: +1-212-6395875
Fax: +1-212-7173619

Growth kinetics of human cancers

When considering the role of dose density, it is useful to revisit the concept of dose intensity. Dose intensity describes body size-adjusted dose (mg/m^2) divided by time in weeks [9]. The most widely used method of increasing dose intensity is dose escalation (increase of dose size), which has been shown to be modestly successful for certain drugs in selected diseases, and over some dose ranges [20] (Fig. 2). The total impact of therapy relates to the log cell kill for each dose, periodicity of drug administration, and rate of tumor re-growth between each treatment. Thus a fixed cell kill achieved at shorter time intervals should improve the overall impact of therapy, since this allows less time and opportunity for the emergence and proliferation of surviving, drug-resistant cell clones. This concept is termed as dose density [14].

Another strategy to improve efficacy of chemotherapy employs sequential non-cross-resistant regimens to optimize cytotoxicity in a heterogeneous group of tumor

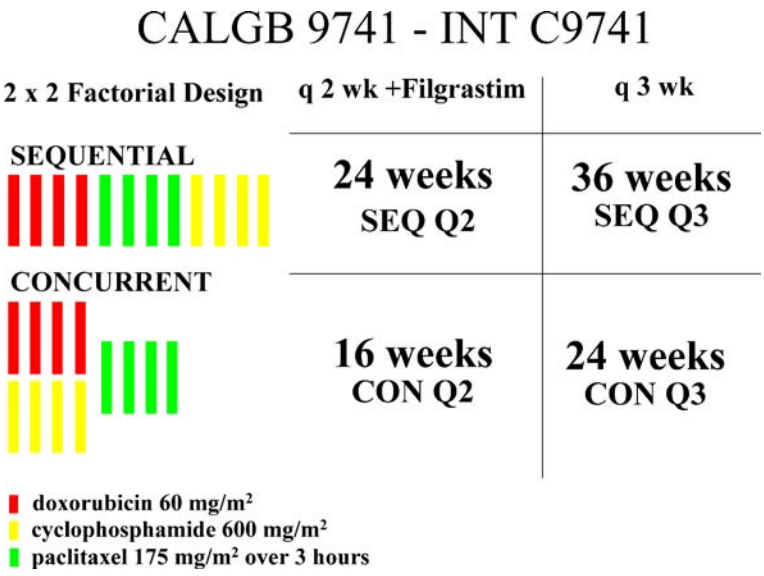

Fig. 1 Schema for Cancer and Leukemia Group B Adjuvant Trial 9741

cells. An understanding of the importance of sequential therapy requires re-examination of tumor cell growth kinetics. Human solid tumors do not exhibit exponential but rather Gompertzian growth pattern in which doubling time is not constant but increases with increasing tumor size up to a certain mass/volume [13]. Thus, surviving tumor cell re-growth after suboptimal therapy may be quite rapid after each cycle of therapy and complete eradication of disease difficult to achieve [8] (Fig. 3). The Skipper–Schabel–Wilcox model, also termed the log-kill model, was the first significant proliferation model in clinical oncology [16]. By this model, enough cycles of sufficient drugs at high enough individual doses should be able to kill a high percentage, if not all, of the cells. Unfortunately, this has not been clinically proven for breast cancer. Since most tumors possess significant cellular heterogeneity, some components are likely to be indolent clones that are resistant to drugs used. An alternative model, the Norton–Simon model, predicts that the best way to cure this heterogeneous mix of cells is to eradicate the numerically-dominant, faster-growing cells first, followed by eradication of the more slowly-growing, resistant cells [14]. This is termed as sequential therapy and has been proven to be clinically superior to alternating therapy [1].

Lessons from adjuvant chemotherapy trial CALGB 9741/INT C9741

CALGB 9741 was constructed to examine the concepts of dose-density and sequential therapy. In this trial, in which 2,005 women with node-positive breast cancer enrolled, patients were randomized to one of four treatment arms: (I) sequential doxorubicin (A) $\times$ 4 + paclitaxel (P) $\times$ 4 + cyclophosphamide (C) $\times$ 4 conventionally every 3 weeks; (II) sequential A $\times$ 4 + P $\times$ 4 + C $\times$ 4 every 2 weeks with filgrastim; (III) AC $\times$ 4 + P $\times$ 4 every 3 weeks; and (IV) AC $\times$ 4 + P $\times$ 4 every 2 weeks with filgrastim. This trial used a 2 $\times$ 2 factorial design (Fig. 1) to answer two questions: (1) is dose-dense superior to conventional chemotherapy? (2) is sequential superior to concurrent combination chemotherapy? This study was powered to detect a 33%

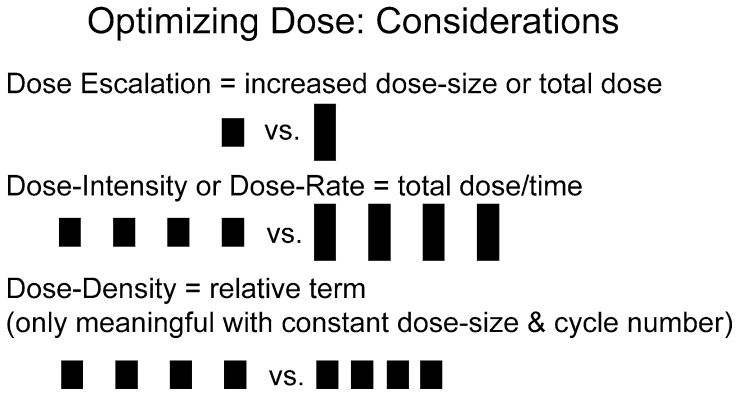

Fig. 2 Optimizing chemotherapy dose considerations

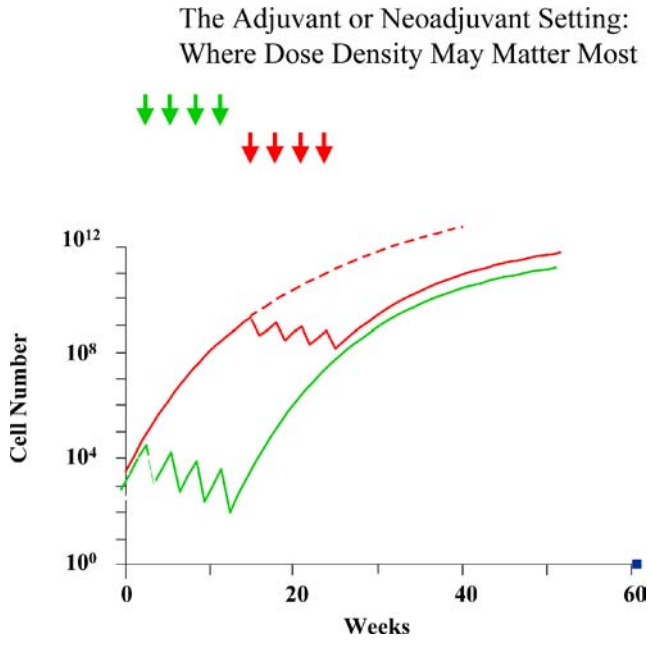

Fig. 3 Cytokinetic considerations based on the Norton–Simon hypothesis in the timing of adjuvant chemotherapy administration

difference in either DFS or OS. At a median follow-up of 36 months, 351 patients had relapsed or died compared with 515 expected treatment failures. DFS and OS were significantly prolonged in the dose-dense arms (II and IV) compared with the conventional arms (I and III; risk ratio [RR] = 0.74, $P = 0.010$ and RR = 0.69, $P = 0.013$, respectively). Four-year DFS was 82% for dose-dense regimens and 75% for conventional regimens (95% CI, 73.7–76.2%). Three-year OS was 92% (95% CI, 91.7–92.3%) in dose-dense arms and 90% in conventional arms (95% CI, 89.6–90.4%). The differences between dose-dense and conventional regimens are expected to increase over time. There was no difference in either DFS or OS between sequential and concurrent chemotherapy schedules. There was no interaction between dose-density and sequence. There was less frequent severe grade 4 granulocytopenia in patients on dose-dense regimens versus conventional regimens (6 vs. 33%; $P < 0.0001$). Overall, only 3% of patients were hospitalized for febrile neutropenia. Grade 3–4 emesis was more frequent in concurrent regimens than for sequential regimens (7 vs. 3%; $P = 0.0002$). About 13% of patients on dose-dense AC + P had at least one red blood cell transfusion versus none in conventional, sequential A + P + C and <4% in the other two arms ($P = 0.0002$). Only a small percentage of patients required dose delay or reductions. Three-year incidence of acute myelogenous leukemia or myelodysplasia was 0.18%, and the incidence of leukemia was not influenced by filgrastim. A provocative and unexpected finding was that dose-dense regimens were associated with significantly reduced incidence of contralateral breast cancer (0.3 vs. 1.5%; $P = 0.0004$). Overall, all treatments were well tolerated [2].

The design of this trial allows one to draw strong conceptual conclusions. All patients received the same number of drugs at the same cumulative doses. The results are consistent with the mathematical predictions that dose-dense chemotherapy should result in superior survival over conventional regimens. Also, sequential therapy that preserves dose density maintains efficacy; there was no adverse impact of uncoupling A from C (nor any benefit). This trial does not stand alone in support of the notion that dose-dense therapy is "ready for prime time".

Evidence from other trials examining dose density

Green et al. [7] recently reported comparative efficacy of dose-dense weekly versus every 3-weekly paclitaxel as neoadjuvant therapy (followed by fluorouracil/doxorubicin/cyclophosphamide postoperatively) in operable breast cancer at the MD Anderson Cancer Center. In this study the rate of pathologic complete response (pCR) of weekly dose-dense paclitaxel was more than double that of 3-weekly paclitaxel (28.8 vs. 13.6%; $P < 0.01$). Untch et al. [19] demonstrated the superiority of neoadjuvant dose-dense, sequential epirubicin (E) + Taxol (paclitaxel) (T) every 2 weeks with filgrastim to conventional 3-weekly ET in terms of pCR and breast conservation rate. However, in this trial the concepts of dose intensity and dose density were blurred, since the dose-dense arm received higher cumulative doses of chemotherapy than the 3-weekly arm. Hence, it is not clear whether bi-weekly treatment in this study was superior based on dose density alone.

Not all "dose-dense trials" have been viewed as confirmatory; however, on closer inspection not all trials cited as "dose-dense trials" actually test the concept of dose-density. Therasse et al. [17] reported the results of a randomized phase III trial by the European Organization

for Research and Treatment of Cancer (EORTC)/National Cancer Institute of Canada/Swiss Group for Clinical and Epidemiological Cancer Research. The trial compared standard C + E + 5-fluouracil (F) × 6 (oral C days 1–14, E and F on days 1 and 8, every 28 days) to dose-intensified bi-weekly EC × 6 with filgrastim (i.e., without F) as primary chemotherapy in locally-advanced breast cancer. This trial did not show therapeutic benefit of dose-dense EC over conventional CEF. However, the interpretability of this trial as comparison of dose intensity versus density is confounded by the design, since the two arms were not equal in terms of the number of different drugs given (i.e., fluorouracil in only one arm) or even schedule and route of drug administration (i.e., cyclophosphamide). One can view this study with optimism in that similar efficacy was achieved with both regimens but duration of treatment was half as long with dose-dense EC without additional significant toxicity. Jackisch et al. [12] reported the results of the Geparduo study of preoperative chemotherapy comparing sequential 3-weekly AC × 4 + docetaxel (D) × 4 versus bi-weekly AD × 4. In this trial AC + D was superior to dose-dense AD in terms of clinical response rate, pCR, pathologic node-negativity rate, and breast conservation rate. However, this again was not a pure test of dose density, given that patients taking AC + D received one additional drug (cyclophosphamide) and that the cumulative doses of A and D were higher than that of the AD arm.

We await the results of multiple ongoing trials currently testing the concept of dose-density. The Eastern Cooperative Group Adjuvant Trial 1199 is a large, four-arm, phase III study of 3-weekly AC × 4 + 3-weekly P × 4 versus weekly P × 12, AC × 4 → 3-weekly D × 4 versus weekly D × 12. This study completed accrual in January 2002, and is designed to answer the question as to whether dose-dense weekly taxane is superior to conventionally administered taxane. CALGB 9840 ($n = 585$), which completed accrual in November 2003 and was reported at the American Society of Clinical Oncology meeting in 2004, addressed this same question for paclitaxel in patients with metastatic disease. Of note, in this trial the weekly arms were both more dense and intense, although the results of CALGB 9342 suggest no advantage for paclitaxel dose intensity, at least with every 3-week dosing. Finally, the National Cancer Institute of Canada MA.21 is currently comparing standard CEF × 6 versus AC × 4 + P × 4 versus bi-weekly EC × 6 + 3-weekly P × 4 [18]. Interestingly, only EC is dose-dense and the results should reveal whether there is any therapeutic benefit in accelerating part of a regimen.

Future directions

Dose-dense trials have demonstrated that filgrastim-facilitated bi-weekly chemotherapy is feasible [5, 10, 11]. Based on the landmark results of CALGB 9741, many groups have adopted this strategy as a new standard of care. However, appropriate caution should be applied in extrapolating these data to any/all regimens outside a clinical trial setting, since unanticipated toxicities may emerge. At Memorial Sloan-Kettering Cancer Center (MSKCC) and elsewhere, feasibility trials are either planned or under way exploring dose-dense regimens containing other agents (e.g., docetaxel).

It is intuitive that patients may be willing to endure the minor inconvenience of filgrastim administration to shorten duration of treatment and to gain therapeutically. Cost-effectiveness analysis for the addition of filgrastim might be useful. With the availability of pegylated (PEG) filgrastim (Neulasta, Amgen, Inc., Thousand Oaks, CA, USA), a novel formulation that provides once-per-cycle dosing as opposed to daily injection, it might be important to explore its usage in bi-weekly regimens. At MSKCC, we evaluated a regimen of dose-dense bi-weekly FEC100 × 6 + weekly alternating D and P × 18 in high-risk (≥4 positive node) breast cancer patients, and found that this particular approach was not feasible due to nonhematologic toxicity [3]. We have explored the feasibility of recycling optimal doses of EC and P at 10–11-day (“denser”) intervals with filgrastim support (Fig. 4) [6].

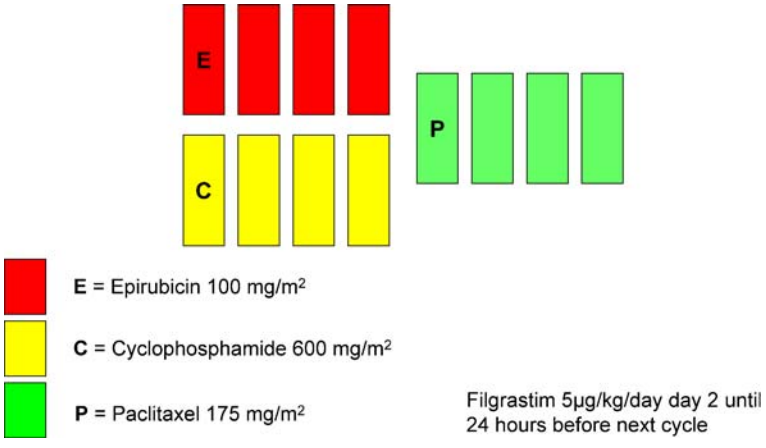

Fig. 4 Memorial Sloan-Kettering Cancer Center IRB protocol 03-092: dose-dense administration of chemotherapy components every 10–11 days, with filgrastim support

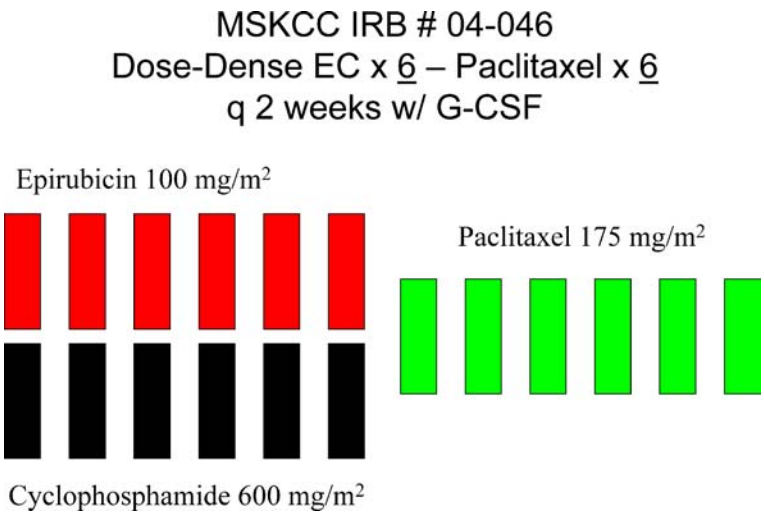

Fig. 5 Memorial Sloan-Kettering Cancer Center (MSKCC) IRB protocol 04-046: feasibility study of six cycles of dose-dense adjuvant epirubicin and cyclophosphamide chemotherapy followed by paclitaxel for six cycles administered every 14 days with filgrastim support

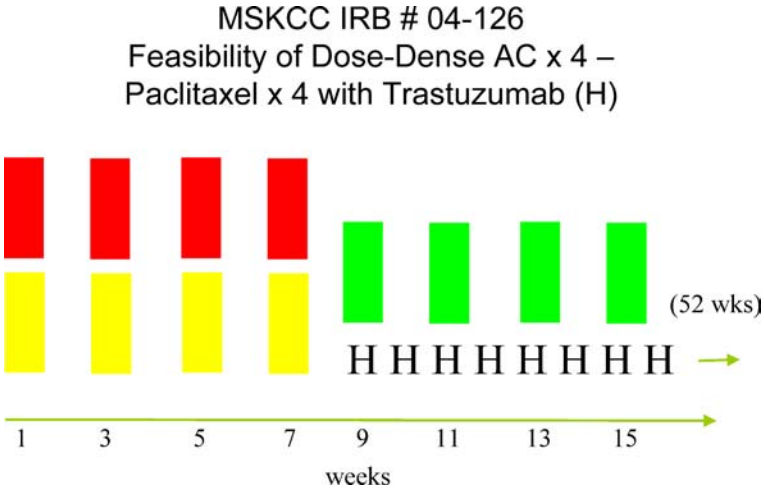

Fig. 6 Memorial Sloan-Kettering Cancer Center (MSKCC) IRB protocol 04-126: feasibility and cardiac safety of dose-dense administration of doxorubicin and cyclophosphamide followed by paclitaxel in a "CALGB 9741 format", with trastuzumab

Given the current controversy regarding the optimal cumulative anthracycline dose in adjuvant breast cancer chemotherapy, we are currently examining the feasibility of a longer dose-dense sequential regimen where six cycles of epirubicin plus cyclophosphamide after administered every 2 weeks, followed by paclitaxel for six cycles every 2 weeks (Fig. 5).

In the current era of emerging rationally targeted therapeutics, combinations of "biologic therapy" with dose-dense regimens to further improve efficacy of adjuvant treatment are ongoing (e.g., NCCTG 9831) or planned. It seems prudent to allow the dose-dense use of AC in these trials (vide supra) given the survival benefit observed in CALGB 9741. An ongoing pilot study at MSKCC examines the cardiac safety and feasibility for the incorporation of trastuzumab in the dose-dense regiment described in CALGB 9741 (Fig. 6).

Is dose-dense application of chemotherapy "ready for prime time"? Clearly the answer is yes. For all drugs in all diseases? No. Does "the buck stop here"? Hardly. There is every expectation that integration of targeted biologic therapies with optimally dosed and scheduled cytotoxic chemotherapy will lead to further incremental improvement in the adjuvant therapy of breast cancer. Most immediately, ongoing trials offer promise that this may be realized with agents such as trastuzumab and bevacizumab (Genentech, Inc., South San Francisco, CA, USA). A new chapter has begun; one that seems to hold greater promise than the chapter of dose-intensity in breast cancer. Ultimately, both the discovery of new agents and clarification of optimal scheduling and dosing must serve the interests of patients with breast cancer maximally.

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