

EDITORIAL

Mathematics and Oncology: A Match for Life?

INTERGROUP TRIAL 9741, reported in this issue of the *Journal of Clinical Oncology* by Citron et al,¹ was launched in 1997 to test two novel concepts based on mathematical models of tumor cell growth kinetics that were articulated by Norton² 15 years ago. The first concept implies that dose densification of chemotherapy—delivering chemotherapy at reduced intervals—will maximize the chances of eradicating the tumor. The second concept addresses heterogeneous drug sensitivity through the use of sequential dose-dense, non-cross-resistant single agents or regimens. It is truly fascinating to witness this elegant mathematical model materializing, at least in part, in the positive results of a randomized clinical trial.

The credit for using mathematics as a way to better understand how chemotherapy might affect the kinetics of mammary tumor cell growth is given to Skipper,³ who in 1971 introduced the important concept of log cell kill, in which a given dose of cytotoxic chemotherapy kills a constant fraction of the tumor. This theory, derived from murine experiments, was revisited by Norton and Simon² and later refined by Norton⁴ to match the data generated by clinical trials of adjuvant chemotherapy conducted in the last two decades. The growth curves that best fit these data had a sigmoid (Gompertzian) shape, and simulations of chemotherapy effects predicted that the simple manipulation of compressing the conventional schedule of drug administration would achieve considerably greater efficacy by minimizing the regrowth of tumor cells between treatment cycles.

The very first question that arises is why it took 15 years to bring this interesting concept to the clinic. Certainly, the safety of the dose-dense chemotherapy approach was an issue, and it prompted a number of pilot feasibility studies that greatly benefited from the introduction of granulocyte colony-stimulating factors into the clinic. With the use of such growth factors, it became possible to deliver chemotherapy on time, with a low rate of febrile neutropenia.⁵⁻¹¹ At the same time, much of the energy of the oncology community in the last two decades has been driven by specific drug questions, neglecting most of the other key variables of chemotherapy that might turn out to be of utmost importance, including the timing of chemotherapy in relation to tumor resection and

initiation of endocrine therapy, the duration of chemotherapy, and finally, the schedule of drug administration.

WHAT ARE THE STRENGTHS OF INT 9741 BESIDES ITS MATHEMATICAL RATIONALE?

Its design leaves little to criticize: Careful attention has been paid to control all four arms of the trial for the types of agents given (doxorubicin, cyclophosphamide, and paclitaxel) as well as the cumulative doses administered, leaving for analysis solely the variables of interest to the investigators. Possible interactions between chemotherapy and radiation therapy or adjuvant tamoxifen have been eliminated by postponing these other treatment modalities until after the completion of the chemotherapy program. The trial used a 2×2 factorial design, which allows us to answer two questions simultaneously, provided that no interaction exists between the treatment arms. The study was adequately powered to detect a 33% difference in hazard for either main effect: disease-free survival or overall survival.

The conduct of the trial was quite satisfactory. Fewer than 2% of the randomized patients did not receive protocol therapy; they were excluded from the analysis, which is not usually done according to the intent-to-treat principle. It is unlikely, however, that the inclusion of these patients would have generated different results. Finally, according to a detailed toxicity analysis on a subset of the trial population, only a small percentage of the patients required dose reduction or dose delay of one or more of their prescribed drugs.

DOES THE CURRENT REPORT OF INT 9741 SUFFER FROM WEAKNESSES?

The answer is yes. The reported data should still be viewed as immature, both in terms of efficacy and safety. Although the results for the first 2 years after randomization are stable, the risk ratio (RR) for both relapse (RR = 0.74; $P = .010$) and death (RR = 0.69; $P = .013$) are likely to change as substantially more events are observed during long-term follow-up.

The study was clearly not powered for individual comparisons of the four treatment arms, and such comparisons should be avoided or taken with extreme caution. It is, however, of some concern that the sequential every-3-weeks regimen seems to

perform less well than the current American standard arm of doxorubicin (A) plus cyclophosphamide (C) followed by paclitaxel (T) every 3 weeks (AC → T), raising the possibility that the therapeutic benefit achieved by switching from this current standard to either one of the dose-dense regimens might be smaller than suggested by the 2 × 2 main effects analysis.

So far, the toxicity data are rather reassuring: There is no suggestion of an increased incidence of cardiotoxicity or secondary leukemia with the dose-dense schedules. However, the definitive evaluation of the leukemia rate might require additional years of follow-up, and long-term follow-up in excess of 5 years might be more suitable for a clear assessment of cardiac risk.

One may regret the lack of quality-of-life evaluation in a subset of patients enrolled on INT 9741; these data might have added value to the traditional way of reporting treatment side effects, strengthened the concept that women in the dose-dense arms do better overall, and perhaps highlighted subtle differences between the dose-dense single-agent sequential arm and the dose-dense combination arm.

Because INT 9741 is a positive trial as far as its first question is concerned—namely, the superiority of accelerated over conventionally timed chemotherapy—a cost-effectiveness analysis would also provide useful information to the medical community. Although there are obvious concerns about the added cost of growth factors, a detailed cost/benefit analysis might alleviate these concerns by balancing higher drug costs against the reduced costs of toxicity management and loss of productivity.

Perhaps the most relevant criticism of INT 9741 relates to the lack of prospective stratification for estrogen receptor (ER) status. Clinical investigations in recent years have drawn our attention to the fact that the magnitude of the adjuvant chemotherapy effect may vary substantially in subgroups of patients with ER-positive or ER-negative tumors and may be confounded by its indirect endocrine effects. Two striking examples are the lack of a significant benefit from AC → T in the ER-positive subpopulation of Cancer and Leukemia Group B (CALGB) Trial 9344^{12,13} and the extremely poor results of adjuvant cyclophosphamide/methotrexate plus fluorouracil (CMF) in very young women with ER-positive disease who do not experience ovarian ablation through this treatment modality, in contrast to older premenopausal women.¹³ The reported lack of an interaction between ER status and treatment in INT 9741 does not preclude the existence of potential confounding variables in the ER-positive subpopulation, such as a more efficient and more rapid induction of menopause in young women receiving accelerated chemotherapy. Half of the women in INT 9741 were younger than 50 years of age, and two thirds had ER-positive disease. It will be interesting to see the relapse-free and overall survival rates relative to the induction of menopause in a more mature report of this trial.

As we progressively leave the era of empirical medicine and enter one of molecular medicine, it is becoming increasingly more obvious that the one-shoe-fits-all theory will find ever fewer supporters. Recent gene-profiling studies have nicely confirmed that ER-positive and ER-negative breast cancer are essentially two different diseases.^{14,15} Moreover, a further analysis of the ER-negative subset reveals the existence of at least two subtypes: an *HER-2* overexpressing subset and a basal-like

one. Among the latter, a further subgroup can be delineated with the overexpression of several key genes involved in cellular proliferation (Sotiriou C, Neo S-Y, McShane L, et al, manuscript submitted for publication). It is extremely tempting to speculate that this subset could be the one that derives the greatest benefit from a chemotherapy dose-densification approach. Unfortunately, INT 9741 has not been adequately powered for subgroup analyses, and these analyses may be important to better understand how to maximize the clinical utility of chemotherapy in general and of expensive dose-dense regimens in particular.

DOES INT 9741 STAND ALONE IN A MISTY LANDSCAPE OF CHEMOTHERAPY DOSE-DENSIFICATION ATTEMPTS?

In the era before taxanes, most investigations of chemotherapy dose densification for breast cancer treatment generated negative results, but they have all suffered from severe design limitations. These include insufficient power, asymmetry between arms with respect to types of drugs administered, use of suboptimal doses of drugs, or manipulation of drug density and cumulative doses at the same time as drug dose, thereby confusing the interpretation of the results.^{16,17} Trials of densified regimens in advanced breast cancer have been disappointingly small and negative with regard to progression-free survival and overall survival, although trends of improved responses have been reported occasionally.

In locally advanced breast cancer, a relatively small 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 failed to show an improvement over the 6-month Canadian cyclophosphamide, epirubicin, and fluorouracil regimen for a 3-month dose-intensified and dose-dense epirubicin-cyclophosphamide (EC) combination given with filgrastim support. An optimistic view of this trial emphasizes the similar efficacy of a short course of therapy when compared with a prolonged one, and with a 5-year follow-up, no increased rate of cardiotoxicity or acute myeloid leukemia has been observed with the dose-dense strategy.¹⁸

In early breast cancer, a small (N = 183) and clearly underpowered trial targeting a high-risk subset of women with ≥ 10 positive nodes or extracapsular invasion showed similar results for dose-dense EC and conventionally timed EC → CMF.¹⁹ At the same time, a somewhat larger Eastern Cooperative Oncology Group (ECOG) trial (N = 646) showed a trend for improved disease-free survival with a dose-dense and metronomic regimen using continuous oral cyclophosphamide and a biweekly regimen of doxorubicin, vincristine, and fluorouracil alternating with biweekly fluorouracil as opposed to standard American cyclophosphamide, doxorubicin, and fluorouracil.²⁰

The ECOG trial highlights a potential challenge to the dose-densification concept: Is it possible that chemotherapy administered at relatively low doses but according to a frequent, metronomic schedule might be superior to an accelerated, biweekly schedule? Metronomic chemotherapy is receiving increasing attention in view of preclinical studies showing that it optimizes the antiangiogenic effects of cytotoxic agents²¹⁻²⁴ and in view of clear-cut antitumor efficacy in advanced breast cancer.^{25,26} A metronomic AC regimen given over 15 weeks has been successfully piloted by the Southwest Oncology Group (SWOG)²⁷ and will

be soon incorporated into an elegant prospective randomized trial designed to challenge the dose-dense concept.

More provocative data have been generated by dose-densification strategies since taxanes have been introduced. Although we are still anxiously waiting for the results of important trials directly comparing 3-weekly to weekly taxane administration in advanced and early breast cancer, interesting results have been generated in trials of preoperative chemotherapy, suggesting the potential clinical superiority of dose-dense paclitaxel. In an M.D. Anderson Cancer Center trial,²⁸ the rate of pathologic complete response for patients receiving dose-dense weekly paclitaxel was nearly double that of patients receiving the standard 3-weekly regimen of paclitaxel (25% v 15%; $P = .01$). This observation raises another important question: Will weekly paclitaxel be as good as or even better than biweekly paclitaxel with granulocyte colony-stimulating factor support? Fortunately, the previously mentioned, innovative SWOG-Intergroup trial comparing the relative merits of dose-dense and metronomic chemotherapy will also address this important question.

Another study from the German group found dose-dense, sequential epirubicin and paclitaxel to be superior to the combination of these agents given according to a standard, 3-weekly schedule. Unfortunately, however, this trial combined both dose-intensity and dose density and did not control for total cumulative doses, which were higher in the dose-dense arm.²⁹

Last among the taxane trials, the reasonably large study ($N = 913$) by Jackisch et al,³⁰ recently presented at the San Antonio Breast Cancer Conference, conveys the important message that not all dose-dense regimens will improve patient outcome and that extrapolation of the INT 9741 results to other drugs or combinations is potentially hazardous. In the study by Jackisch et al, a dose-dense doxorubicin-docetaxel regimen given for four cycles was found to be inferior to a more conventional regimen of sequential AC → docetaxel preoperative chemotherapy in terms of complete and pathologically complete responses, as well as in rates of breast conservation.

One interesting trial currently recruiting patients might shed light on the still controversial issue of anthracycline dose-intensity: National Cancer Institute of Canada MA21 compares six cycles of Canadian cyclophosphamide, epirubicin, and fluorouracil with both AC → T (as given in CALGB 9344) and a sequence of dose-dense EC (as given in the previously described locally advanced breast cancer trial coordinated by the EORTC) followed by 3-weekly paclitaxel. The dissociation between dose-dense EC and a conventionally timed taxane might tell us whether there is any merit to accelerated anthracycline/cyclophosphamide administration in a more favorable operable breast cancer population than the one targeted by the EORTC trial.³¹

It is unclear at this point in time whether dose densification of docetaxel will be of any value, but dose-dense, sequential doxorubicin/docetaxel at full doses has been found to be associated with an excessive rate of severe skin toxicity.³²

Collectively, the current data indicate that the superiority of a sequential dose-dense approach might be specific to paclitaxel; the data on docetaxel are too scarce and suboptimal in nature, and the data on anthracyclines are not convincing.

SEQUENTIAL SINGLE AGENTS OR COMBINATION THERAPY?

The second question posed by INT 9741—namely, the potential superiority of sequential single agents over their combined use—has received a negative answer thus far. This does not mean that the concept is wrong: INT 9741 is by today's standards a relatively small trial, and it may have missed a small, but still significant, clinical benefit. It is quite likely that ongoing or recently closed adjuvant trials of the taxane era will be able to provide a definitive answer to this question after a meta-analysis. Indeed, close to 10,000 women have been enrolled onto such trials, highlighting the strong interest of oncologists in this question.³³ Furthermore, the fact that the sequential regimens seem to yield a similar efficacy with a more favorable toxicity profile is also an important message to retain from INT 9741. It should, however, be noted that in the pretaxane era, SWOG 0137 failed to show the expected 30% increase in disease-free survival with sequential, increased doses of doxorubicin/cyclophosphamide over their combined administration, and the sequential treatment course was more toxic.³⁴ In the taxane era and in advanced disease, an ECOG trial showed similar survival for sequential paclitaxel/doxorubicin (or the reverse sequence) and for the combined use of the drugs.³⁵

WHAT ARE THE IMPORTANT MESSAGES FROM INT 9741 FOR THE ONCOLOGY COMMUNITY?

For oncologists involved in clinical research, the message is that choice of which chemotherapy drugs to use is not the only way forward: The schedule of drug administration is an important variable, in addition to the timing and duration of chemotherapy, which might also play a role but have been poorly investigated to date. Now it is our task to confirm these data independently with a much larger trial that will allow identification of subgroups that derive substantial benefit from the dose-densification approach.

On the basis of a single trial of 2,000 women, it would not be wise for clinicians in practice to routinely adopt accelerated chemotherapy for all patients with high-risk breast cancer. Nevertheless, while waiting for the confirmatory evidence, the individualized use of these dose-dense regimens as given in INT 9741 for high-risk women—particularly for those who cannot count on beneficial effects of adjuvant endocrine therapy—is not unreasonable, provided that the women are informed about the uncertainties regarding the risk/benefit ratio of dose-dense therapies. A last, but certainly no less important, message is that it might be dangerous and harmful to extrapolate the results of INT 9741 to other drugs or combinations.

Overall, Citron and his colleagues must be congratulated for what could well be a landmark adjuvant trial in breast cancer. This study symbolizes the marriage between mathematics and breast cancer chemotherapy after a 15-year romance. The future will tell us if this is a life-long relationship.

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