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The concept of mathematically optimised dose-scheduling as applied to the adjuvant chemotherapy of primary breast cancer: theory and recent results

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ABSTRACT

Theoretical analyses and theory-motivated laboratory experiments have confirmed that for anti-mitotic drugs administered by bolus the inter-treatment interval is a critical determinant of ultimate success. Maximum cell kill is best achieved by using the optimal (not necessarily the maximum tolerated) dose level as often as feasible considering the impact of the drug on host toxicity. This approach has been termed 'dose density', which captures the concept of optimally frequent administration. The feasibility and non-comparative efficacy of the application of this concept was developed in a series of clinical trials at Memorial Sloan-Kettering Cancer Center, New York, USA. These results were used to design an objective, prospectively randomised trial in the Cancer and Leukemia Group B and the North American Breast Intergroup: Study CALGB 9741 involved over 2000 volunteer female patients with node-positive operable primary breast cancer. In a 2 × 2 design, this study asked if – holding dose level and dose density constant – how simultaneous combination chemotherapy compared with purely sequential treatment, and – holding dose-level and combination or sequential use constant – how dose-density influenced disease-free and overall survival in the post-operative adjuvant setting for node-positive disease. Specifically, the study examined sequential doxorubicin, paclitaxel and cyclophosphamide compared with concurrent doxorubicin and cyclophosphamide followed by paclitaxel, and also dose-dense (every 2 week administration) compared with conventional (every 3 week administration) scheduling. The results, with long-term follow-up, confirm the predictions of the model. Not only is the shortened inter-treatment interval of chemotherapy better in terms of disease-free and overall survival, but it is less toxic as well. Combination chemotherapy (doxorubicin plus simultaneous cyclophosphamide) offers no advantage over sequential chemotherapy (doxorubicin followed later by cyclophosphamide) if dose level and dose density are the same, except that combinations shorten overall treatment duration and are thus more convenient. These results define a more effective, less toxic conceptual approach to the adjuvant chemotherapy of breast cancer, which should apply to all chemotherapy drugs given in the intravenous bolus format, even when biological agents are added. Further development of the principles and methods established by CALGB 9741 are currently underway.

1. Introduction

In cancer chemotherapy, as in most areas of internal medicine, the availability of active agents is necessary but

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not sufficient for their optimal use in restoring or preserving health. Drugs need to be applied in optimal dose schedules, which takes into account the pharmacology of the individual agents, their interactions (if any), and the characteristics of the disease states that they are used to perturb. We are all aware of the fact that anticancer agents are very effective in making advanced cancers shrink in size, but cure of advanced disease is rare. Hence, the surrogate endpoint – the likelihood of tumour volume regression, called 'response rate' – is poor, in that it has not moved us rapidly toward our ultimate aspiration: cancer cures. Of course, a smaller tumour takes longer to grow to a lethal size than a larger tumour, all else being equal, so it is not surprising that when our anticancer drugs are used against subclinical disease, as in the postoperative adjuvant setting, it takes longer for cancers to grow to appreciable sizes (i.e. improved disease-free survival) and lethal sizes (improved overall survival). Just because more patients are alive at specified time points after surgery if they are given chemotherapy does not mean that we are curing disease. Hence, there is much to be learned and applied if we are truly to make a difference in the management of primary breast cancer. One issue to be addressed is: are we using our drugs optimally? If not, how can we improve, and what would that tell us about the nature of neoplasia?

In 1825, the British mathematician Benjamin Gompertz invented an equation that described a growth curve that has since been shown to apply to a large number of situations in biology, including human cancers, such as breast cancers. The Gompertzian curve is in reality an exponential curve that is "exponentially decremented," meaning that as it grows bigger it deviates faster and faster from simple exponential growth. In practical terms, this means that the overall shape of the curve is like the letter S: the early portion of the curve sweeps upward, as in exponential growth, but then the curve clearly bends over so that eventually the growth rate is so slow that it appears to be at a plateau, or steady state. How does such a growth curve respond to growth-perturbing bolus therapy? The key observation in this regard is that the rate of shrinkage of the mass is always proportional to the rate of growth.[1] Therapeutic concepts derived from this observation have been applied to two forms of administration of anticancer therapy: (1) daily administration on a continuous or intermittent basis and (2) bolus administration, the most commonly used to date and hence the most studied. So-called 'metronomic' therapy, in which frequent low-dose administration of cytotoxic agents with the intention of targeting endothelial cells, rather than cancer cells directly, may be regarded as a variant on the former dose-scheduling pattern.[2]

For bolus therapy (as in the intravenous administration of cytotoxic chemotherapy given intermittently, with doses usually separated by at least 1 – and usually 3 – weeks), there is an acute effect on the perturbation of the growth curve that wears off quickly in the interval between treatments. Repeated cycles continue this pattern, with the ultimate benefit dependent on two factors. The first is obviously the amount of growth perturbation caused by each dose of chemotherapy, which is related to the actual dose administered, but not in a linear or even strictly rising way (i.e. the degree of perturbation rises with increasing dose to a point, but after that point, increasing dose level does not cause appreciable increases in growth perturbation, perhaps because receptor sites on targets or transporting molecules are already saturated). The second factor is the amount of regrowth between cycles of therapy, which is itself a function of the rapidity with which the effects of the therapy wear off and the intrinsic growth kinetics of the cancer.[3]

For these reasons, one of the most robust (i.e. applicable to most circumstances) ways of maximising the impact of bolus cytotoxic chemotherapy is to administer the optimally effective dose level as often as feasible considering the toxicity of such treatment to normal organs. 'Optimally effective' does not mean 'maximum tolerated', for the reason previously mentioned. 'As often as feasible' does not imply that dosage levels should be reduced below optimally effective just so that the frequency of administration can be increased. Therefore, the best way of using bolus cytotoxic therapy involves a balance between dose level and frequent administration, a concept that has been termed 'dose density' to distinguish it from 'dose intensity': an approach more wedded to the escalation of dose levels.

The idea of increasing dose density is appropriately linked to the concept that human cancer cells grow by non-exponential Gompertzian kinetics, but it is also commonly described with reference to the term 'log kill', popularised by Howard Skipper and colleagues.[4] This body of work was summarised in a model that expressed the impact of chemotherapy as the fraction of cells killed by a treatment. Moreover, the fraction was expressed in logarithmic terms, such that if 90% of cells are killed (say from 10^5 cells to 10^4), the log kill would be 1. If 99% of cells were killed, the log kill would be 2, and so on. For tumours that grow by simple exponential kinetics, the log kill caused by a given dose level of chemotherapy is independent of the number of cells being treated. However, for Gompertzian tumours, where the effect of therapy is linked to the unperturbed growth rate, the log kill changes as a function of tumour size. In addition, the Norton-Simon model focuses more on perturbation of growth rate than the killing of cancer cells. Certainly, killing cells is one way of impeding growth, but it is not the only way. As our scientific sophistication increases, we realise that growth and regression are complex processes, involving not just mitosis, but also apoptosis, necrosis, other means of cell death, vascularity or the lack thereof, matrix molecules and even elements of tissue geometry, influenced by adhesion molecules and stromal structure.[5] The advantage of a phenomenological model like the Norton-Simon model is that it is assumption free, just describing phenomena in such a way (in this case mathematically) that experiments can be designed and interpreted without dependence on hidden conjectures.

For practical applications in the treatment of solid tumours like breast cancer, there are two easily accomplished manipulations that should, by theory, significantly increase the efficacy of therapy.[6] The first is sequential treatment, the use of one agent or properly designed combination followed by another, rather than a forced combination of all of the agents that necessitates reductions of dose levels below the optimal ones. Let us imagine that the best dose level of drug

1 is A, of drug 2 is C, and of drug 3 is T. Drug 1 and 2 can be given together at full dose AC, but to combine these with T would required dose-level modifications of all three drugs. Hence, it would be better to treat with AC for an arbitrary (say four) cycles every X weeks, followed by T for four cycles every X weeks, than to give A/2 together with C/2 and T/2 in a simultaneous combination for eight cycles every X weeks. Moreover, were one to give Ax4 followed by Tx4 followed by Cx4 (each administration every X weeks), there would be no disadvantage to this approach. The reason is that the 'dose density' of each agent is maintained in ACx4 followed by Tx4 as compared with Ax4 followed by Tx4 then Cx4. However, (ATC)/2 for eight X-week cycles reduces the density by lowering the dose level of each agent below its optimum. Sequential chemotherapy, therefore, should be understood as a method of increasing dose density.

It should be emphasised that the use of several non cross-resistant agents and/or combinations in one overall regimen is a necessary step were we to address the issue of heterogeneity in drug sensitivity in any one cancer. Hence, finding the optimal way of combining regimens is a necessary step in our quest for tumour eradication.[7] The landmark study of Bonadonna *et al.*, in which sequential chemotherapy was superior to a strict alternation of doxorubicin with the cyclophosphamide, methotrexate, 5-fluorouracil (CMF) combination, must therefore be accorded due respect.[8]

The other approach towards increasing dose density is to reduce the interval between dose administrations from the conventional 3 weeks to 2 weeks, which has been proven practical by a long series of clinical trials.[9] By keeping dose levels the same, but reducing the interval between administrations, the density is obviously increased. Hence, if ACx4 every 3 weeks is followed by Tx4 every 3 weeks (X = 3 in the previous paragraph), this should, in theory, be inferior to the same regimen given with X = 2 weeks. Of course, the reason that 3 weeks between administrations became conventional is that this is the time it usually takes for the normal human body to recover from haematopoietic toxicity of much commonly employed anticancer chemotherapy. Chemotherapy-induced neutropenia has long been known to be a dose-limiting toxicity in cancer treatment. The discovery that, by the use of granulocyte colony-stimulating factor (G-CSF), bolus chemotherapy could be given safely in 2-week intervals was, therefore, a critical advance in the application of dose density. The term 'safety', in this regard, originally referred to neutropenia (and hence neutropenia-related infections), but further experience has happily indicated that other toxicities could be ameliorated as well.[7]

A potential third approach, still under development, may be to decrease regrowth rates between cycles of therapy with biological agents that are not strictly cytotoxic. The danger here of course, is that those agents might also reduce the ability of the bolus chemotherapy to perturb the cancer's growth curve. The ideal agent would slow the regrowth of the tumour and also augment the anticancer effect of the cytotoxic agent. In trastuzumab, we might already have such an agent, a possibility that will be discussed further below.

The successful application of these concepts may be illustrated with data from several bolus-type chemotherapy trials in patients with operable primary breast cancer.

2. BIG 02-98 trial: sequential versus concurrent therapy

Although Bondonna's experiment tested alternating versus sequential doxorubicin and CMF,[8] and several studies demonstrated the advantages of sequential therapy (using taxanes) over regimens not including taxanes,[10–12] only recently was combination chemotherapy as it is traditionally employed compared with sequential therapy. The Breast International Group (BIG) 02-98 trial investigated docetaxel in sequence, rather than in combination with doxorubicin as adjuvant chemotherapy, in patients with node-positive breast cancer.[13] A total of 2887 patients aged 18–70 years were randomised to be treated with one of four treatment regimens, each followed by CMF at a conventional schedule for three cycles. In one arm, the sequential treatment, patients received doxorubicin for three cycles followed by docetaxel for three cycles. Another used doxorubicin in combination with docetaxel for four cycles, but – as required to manage toxicity – at reduced dose levels. Two arms that did not contain the taxane could be regarded as controls: one was doxorubicin every 3 weeks for four cycles and the other was doxorubicin combined with cyclophosphamide for four cycles.

After about 5 years, median follow-up events were observed in 732 patients (25% of study population). In terms of event-free survival (EFS), docetaxel-containing regimens were superior to non-docetaxel regimens at a borderline level of statistical significance. However, the more meaningful result is that EFS was clearly superior in the group receiving sequential chemotherapy (doxorubicin followed by docetaxel) compared with the group receiving the same agents given concurrently.[13] There was a strong suggestion of a survival benefit as well. Viewing all arms of the study, sequential, but not concurrent, adjuvant chemotherapy with docetaxel was superior to the non-docetaxel regimens.

3. Intergroup/CALGB 9741 trial: the role of dose density and concurrent versus sequential therapy at equivalent dose levels

In 1997, following a long sequence of preliminary pilot studies,[9] and based on CALGB 9344,[10] the Cancer and Leukemia Group B and The North American Breast Intergroup began accrual to a trial designed to address two issues motivated by the theoretical discussion above.[6] Previous research had determined the optimal bolus dose levels of the three effective anticancer drugs: doxorubicin (A at 60 mg/m^2), cyclophosphamide (C at 600 mg/m^2), and paclitaxel (T at 175 mg/m^2).[10,14,15] But how should these drugs be combined? Specifically, how would ACx4 cycles followed by Tx4 cycles compare with Ax4, then Tx4, then Cx4? According to theory, there should be no difference in efficacy between these approaches since the dose levels, density, and numbers of cycles are all identical. Yet, were both of these treatment plans densified by using a 2-week cycle instead of the conventional 3-week cycle length, theory would predict greater efficacy.

The CALGB 9741 trial used a 2 × 2 factorial design, the

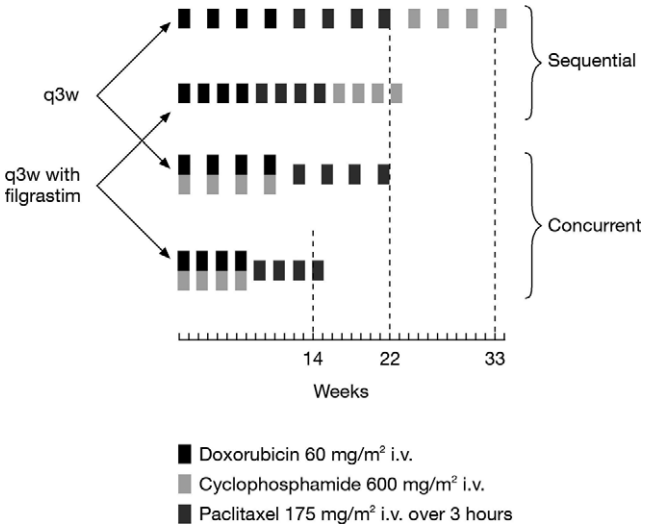

Fig. 1 – Treatment regimens in the Cancer and Leukaemia Group B 9741 (CALGB 9741) trial.[6,16]

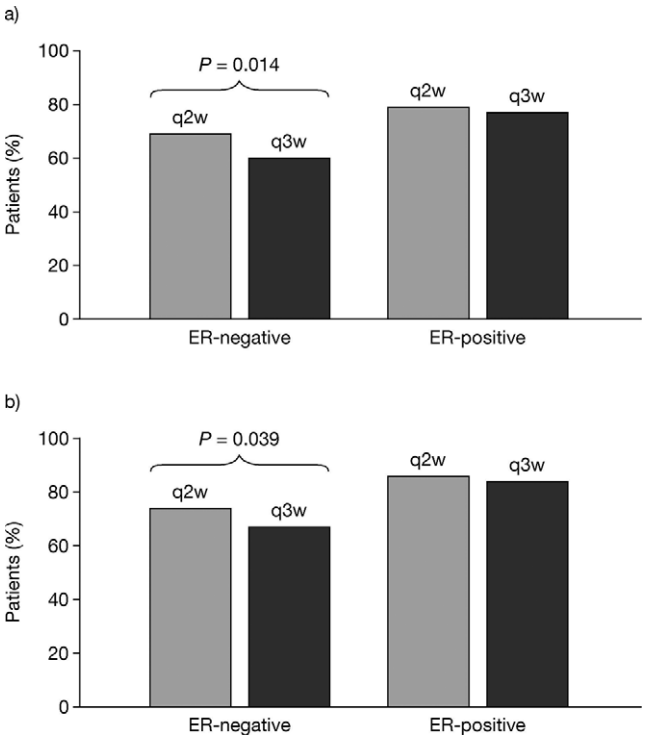

Fig. 2 – Disease-free survival (a) and overall survival (b) by oestrogen receptor (ER) status and dose density (every 3 weeks [q3W] versus every 2 weeks [q2W]) in the Cancer and Leukemia Group B 9741 (CALGB 9741) trial.[16,17]

two factors being sequential (A→T→C) versus dose level-preserved concurrent chemotherapy administration (AC→T) and a conventional 3-week dosing interval versus a 2-week, dose-dense interval (Fig. 1). The dose-dense regimen required the use of seven doses of G-CSF (filgrastim) on days 3–10 of each cycle. The A→T→C every 3 weeks was the longest treatment regimen at 36 weeks. In contrast, the AC→T every 2 weeks was delivered over only 16 weeks. Tamoxifen was recommended to be used for 5 years after the completion of chemotherapy in all premenopausal patients with hormone receptor-positive cancers, and in all postmenopausal patients regardless of their tumours' receptor status.

The study closed to accrual at 2005 female patients with operated node-positive primary breast cancer.[6,16] The study participants had a median age of 50 years, and 65% had oestrogen receptor (ER)-positive tumours. They had a median of three involved lymph nodes, and 12% had 10 or more involved lymph nodes. Hence, this was a representative sample of primary node-positive stage II–IIIA breast cancer as one would find in the community.

A total of 1972 of the 2005 patients were treated and were evaluable for endpoints of toxicity and efficacy. As predicted by theory, there were no significant differences in outcome between the A→T→C approach and AC→T. However, after a median follow-up of 69 months (range 0.2–87 months), the use of bolus chemotherapy in a dose-dense fashion significantly improved disease-free survival (DFS) (hazard ratio [HR] = 0.80, 95% confidence interval [CI] 0.67, 0.96, $P = 0.018$), with a trend of similar magnitude for overall survival (OS) (HR 0.85, 95% CI 0.68, 1.05, $P = 0.12$).[16] There was no apparent interaction between density and sequence.

On the other hand, there was a strong indication of an interaction between density and the hormone receptor status of the primary tumours. An unplanned analysis demonstrated markedly greater benefit in those patients who had ER-negative disease compared with those who had ER-positive disease.[17] For DFS, hazard reductions were 29% for ER-negative cases versus 10% for ER-positive cases, with the advantage in both settings for the denser regimens. For OS, the respective hazard reductions were 32% and 11%. The advantages of dose density were statistically significant for both DFS and OS in the patients with ER-negative breast cancer (Fig. 2).[16,18]

The fact that dose density interacts with hormone receptor status is consistent with the statement that hormone receptor status is a surrogate maker for tumour growth rate. Since hormone receptor-negative cancers tend to be faster growing, it is expected, by the theory described above, that they should be more perturbed by chemotherapy, and hence more sensitive – at least early on – to manipulations in bolus chemotherapy scheduling.[3] It is of note in this regard, that the major impact of dose density is seen in the first 3 years of follow-up. However, this does not mean that density will not eventually prove to be a superior strategy in ER-positive cases: it might just take longer to see the advantages in this slower-growing group. This is especially likely when one realises that the ER-positive cases are receiving additional treatment in the form of hormonal manipulation (tamoxifen) for 5 years after the end of chemotherapy.

Therefore, the therapeutic results of CALGB 9741 are entirely consistent with theory. What was not predicted, is that the efficacy advantages observed with dose-dense chemotherapy were not accompanied by increased toxicity.[6] The incidence of acute myelogenous leukaemia and myelodysplastic syndrome were similar in all treatment regimens. Hence, the incidence of leukaemia was not influenced by the use of filgrastim in the dose-dense arms. This observation

was consistent with the results of CALGB 9344, which used filgrastim in the highest dose level doxorubicin arm with no adverse effect on leukemogenesis.[10] But of course, there was a decreased rate of hospitalisation for febrile neutropenia with the use of filgrastim in the dose-dense regimens compared with the 3-weekly schedules, which did not routinely use G-CSF. Neuropathy and cardiac toxicity were also not increased by the application of dose density. In addition, patients on dose-dense treatment returned to their normal lives sooner than patients on standard treatment, since the regimens were completed one-third faster. It was also observed that there were fewer cases of contralateral breast cancer in patients treated with dose-dense chemotherapy, although causality cannot be attributed in the absence of independent confirmatory data. Yet, the more rapid recovery to normal activity, together with improved efficacy regarding cancer recurrence and survival in the ER-negative cases and the decreased rate of hospitalisation for febrile neutropenia in all cases, argues for the possible cost effectiveness of administering chemotherapy every 2 weeks instead of every 3 weeks in node-positive primary breast cancer. This might well be a productive topic for formal health economic evaluation.

A kinetic way of explaining the reduced non-haematological toxicity of dose-dense chemotherapy may relate to the fact that normal tissues as well as malignant ones follow Gompertzian kinetics. The difference, of course, is that normal tissues are in their plateau phase of growth under normal conditions. When normal tissues are transiently perturbed such that they are reduced in cell population size they tend to recover at a rate appropriate for the degree of perturbation. That is, if pushed lower on their Gompertzian curves they would re-grow faster than if they are perturbed to a lesser degree. It can be shown mathematically that tissues during the plateau phase of growth are more perturbed by duration of therapy than by dose density.[1] Cancerous tissues, in contrast, are already low on their Gompertzian curves, being that they are far from plateau sizes, so they are more sensitive to the density of the chemotherapy than the duration.

The above is a hypothesis, of course, that would benefit from more experimental study. Nevertheless, there are no arguments in favour of chemotherapy regimens in the adjuvant setting that are longer than necessary to achieve a desired reduction of the cancer cell population. Hence, even if dose-dense regimens and conventionally-timed regimens achieved the same degree of cancer cell killing, the dose-dense approach would still be preferable to conventionally-timed ones. Nor are these concepts necessarily limited to the drugs so far employed. For example, the use of pegfilgrastim to support a two-weekly CMF chemotherapy program (which is a more dose-dense use of these drugs than the conventional three-week cycle length) is now starting to be studied at Memorial Sloan-Kettering Cancer Center. The bolus cyclophosphamide is used for only the first four of the eight cycles, since the results of CALGB 9741 indicate the lack of excess leukaemia with this number of administrations.

4. Intergroup/NCCTG N9831 Trial: biological therapy as an approach to increasing dose density

For the last several years, popular culture in organised oncology has identified targeted therapy, with the antibody trastuzumab of the human epidermal growth factor receptor 2 (HER2), as one of the most promising advances. One important study in this regard is the North Central Cancer Treatment Group (NCCTG) N9831 Intergroup adjuvant trial, which examined the impact of a year of trastuzumab, started either concurrently with 12 cycles of weekly paclitaxel in patients with HER2-overexpressing breast cancer, or following such paclitaxel.[19,20] This randomised, phase III trial compared three regimens. All three began, after local surgery for primary disease, with a standard doxorubicin plus cyclophosphamide combination every 3 weeks for four cycles. This was followed, in the control arm, by weekly paclitaxel alone. Another arm gave weekly paclitaxel for 12 weeks, then weekly trastuzumab for 52 weeks. The third arm gave weekly paclitaxel plus weekly trastuzumab for 12 weeks, then weekly trastuzumab for 40 weeks.

After 4 years of follow-up, no statistically significant differences in DFS were noted between the group receiving paclitaxel and the group receiving paclitaxel followed by trastuzumab (number of events = 117 versus 103, respectively, HR = 0.87, stratified log rank 2P = 0.2936). However, the concurrent treatment of trastuzumab plus paclitaxel was shown to significantly improve DFS compared with sequential treatment of trastuzumab plus paclitaxel (number of events = 53 versus 84, respectively, HR = 0.64, stratified log rank 2P = 0.0114).[20] Of course, it is too early to conclude that the sequential paclitaxel-trastuzumab is ineffective, especially in light of positive results with sequential trastuzumab following chemotherapy in the European HERA trial.[21] However, there is a clear indication from this trial that the combination of trastuzumab plus paclitaxel is more effective that their sequential use.

Could these results have a kinetic basis? It is known from experimental animal data and from human trials that trastuzumab has relatively weak activity as a single agent, as measured by tumour volume regression.[22,23] However, it has a real impact in slowing tumour growth. Therefore, it should inhibit the regrowth of HER2-dependent breast cancer following bolus cytotoxic chemotherapy. The result of inhibiting regrowth is that the tumour volume at the time of next chemotherapy bolus would be smaller. By Gompertzian kinetics, the impact of that next cytotoxic treatment would be greater if the presence of the trastuzumab does not interfere with the cytotoxicity of the chemotherapy. Experimental evidence supports such a lack of interference, lending credence to this hypothesis.[22] Hence, the Norton-Simon Model might explain the seeming synergy between chemotherapy and trastuzumab.

Can dose-dense chemotherapy be given with simultaneous trastuzumab for HER2-overexpressing breast cancer? This would seem to be the perfect marriage of the two applications of Gompertzian theory. At Memorial Sloan-Kettering Cancer Center, we have recently completed accrual to a phase II trial, currently in follow-up, which indicates no increased cardiac toxicity of this approach in the adjuvant

setting as assessed by the measurement of cardiac ejection fraction.[24] With further follow-up, and after, these results might be regarded as defining a new standard of care for node-positive cases of operated or neo-adjuvant HER2-dominant primary breast cancer.

It is certainly possible that other means of slowing the regrowth of cancers between dose-dense cycles of bolus chemotherapy could find clinical utility. The observation so far, that most anticancer biological agents – bevacizumab, for example – work best when combined with chemotherapy, is supportive of this concept. A notable exception is hormonal therapy, which slows regrowth but also impairs the cytotoxicity of many chemotherapy agents.[25] Therefore, meticulous experimentation and the proper choice of agents to be tested will be required to develop this idea.

5. Beyond Gompertz, beyond bolus chemotherapy

One of the pressing scientific issues looming over all of this work is the molecular aetiology of Gompertzian growth. Recent observations and mathematical reasoning have coalesced into a new theory of tumour growth called 'self-seeding'.[5] This theory conceptualises tumour growth as a weed bed rather than a single large weed. That is, a weed bed grows and destroys a garden by two mechanisms: the first is the growth of each weed plant by the process of mitosis; the second is the seeding of new weed plants at the periphery of the weed bed. Since seeding of the weed bed itself requires mobility of the seeds, the process is closely related to the seeding of adjacent gardens (invasion) and even gardens at a distance (metastasis). The key mathematical observation here is that growth by seeding concentrates new events at the periphery of any collection of weeds. Since a periphery is proportional to the diameter of a bed, while the area of the bed is proportional to the diameter squared, growth would seem to slow down as the bed's diameter increases. A self-seeded tumour – being a three-dimensional object in most cases – would grow at a rate proportional to its surface area divided by its volume, which would also decrease as the diameter of the mass increases. It has been shown mathematically that this process would explain Gompertzian growth.[5] The new equation expressive of this idea is starting to be used in the modelling of anticancer drug effects.

Another new application of growth kinetics is intermittent continuous therapy rather than just bolus chemotherapy. For example, capecitabine has been used as 14 days of daily oral administration with 1 week breaks between cycles with no biological rationale. The drug is effective, but has the dose level-limiting toxicity of erythema and even desquamation of the palms and soles. This toxicity, rather than lack of anticancer efficacy, often limits the total duration of therapy. We have recently applied mathematical modelling to discover that the major anticancer impact of capecitabine (as assessed by the perturbation of the growth kinetics of experimental tumours) is seen in the first week of administration, with rapidly-developing tachyphylaxis thereafter.[26] Hence, we have designed and tested, in a phase I–II clinical trial, a 7-day schedule of daily administration of the drug, with 7-day breaks between cycles. This has allowed us to increase the dose level of the agent safely.[27] Integration of this schedule with various biological agents is underway.[28]

6. Conclusion

These brief remarks are intended to illustrate that a simple but sophisticated way of looking at tumour growth mathematically has led to some clinical innovations that have already improved clinical practice. The clearest example to date is the dose-dense bolus use of doxorubicin, cyclophosphamide, and paclitaxel in the adjuvant chemotherapy of operable breast cancer, especially in hormone-independent cases. However, biological therapies like trastuzumab and bevacizumab may also be examined in this context, perhaps explaining why the simultaneous use of these agents with cytotoxic therapy is particularly advantageous.

It deserves emphasis that Intergroup/CALGB 9741 used dose levels, determined by much prior research to be optimal, that were well below the maximum tolerated dose levels. The use of filgrastim in this study markedly reduced the haematopoietic toxicity of the chemotherapy. While this was expected, the lack of – and perhaps reduction in – other toxicities was unanticipated, but rewarding. Furthermore, the best regimens in this trial were the shorter ones, allowing patients to resume their normal lives more quickly. Therefore, on the basis of increased therapeutic benefit, greater tolerability and quality of life (if not economic) issues, the principles established by the CALGB 9741 trial may justify the application of dose density more universally for bolus chemotherapy.

Newer mathematical models, extension of these concepts to continuous chemotherapy, intermittent chemotherapy and biological therapy, and the inclusion of fresh agents are all interesting novel avenues for further development. It is possible that even with existing agents, the application of these ideas will significantly improve cancer therapy or, at the least, improve efficacy/toxicity ratios. Hence, dose-density should not be regarded as the end of a research pathway, but rather its beginning, even if it has already achieved some important milestones.

7. Conflict of interest statement

Larry Norton has no potential conflict of interest to declare.

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