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USING MATHEMATICAL MODELING AS A RESOURCE IN CLINICAL TRIALS

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Abstract. In light of recent clinical developments, the importance of mathematical modeling in cancer prevention and treatment is discussed. An existing model of cancer chemotherapy is reintroduced and placed within current investigative frameworks regarding approaches to treatment optimization. Areas of commonality between the model predictions and the clinical findings are investigated as a way of further validating the model predictions and also establishing mathematical foundations for the clinical studies. The model predictions are used to propose additional ways that treatment optimization could enhance the clinical processes. Arising out of these, an expanded model of cancer is proposed and a treatment model is subsequently obtained. These models predict that malignant cells in the marrow and peripheral blood exhibit the tendency to evolve toward population levels that enable them to replace normal cells in these compartments in the untreated case. In the case of dose-dense treatment along with recombinant hematopoietic growth factors, the models predict a situation in which normal and abnormal cells in the marrow and peripheral blood are obliterated by drug action, while the normal cells regain their growth capabilities through growth-factor stimulation.

1. **Introduction.** In 1997, Citron et al. [1] of Intergroup Trial C9741/Cancer and Leukemia Group B Trial 9741 (INT C9741) launched studies to test two propositions. These propositions were based on hypotheses arising from mathematical models of tumor cell growth kinetics introduced by Norton and Simon [2] in 1986. The INT C9741 studies looked at dose densification of chemotherapy and also addressed the issue of heterogeneous drug sensitivity through the use of sequential dose-dense, non-cross-resistant single agents or regimens. Pfreundschuh et al. [3, 4] of the German High-Grade Non-Hodgkin's Lymphoma Study Group (DSHNHL), in a different setting, have also studied the effects of dose densification on young and elderly patients with findings that are in some respects similar to and different from those of Citron et al. [1]. Other studies have come to similar or varying conclusions regarding the concept of dose densification in different situations [5, 6, 7]. Dose densification involves the delivery of chemotherapy at reduced intervals with the aim of maximizing the chances of eradicating a tumor. The use of mathematical models to better understand how chemotherapy might affect the kinetics of mammary tumor cells can be credited to Skipper [8], who in 1971 introduced the idea of log cell kill, in which a given dose of cytotoxic chemotherapy kills a constant fraction of the tumor. This idea derived from murine experiments. It was revisited by Norton and Simon [2] and later refined by Norton [9] to match data

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generated by clinical trials of adjuvant chemotherapy conducted in the last two decades. Growth curves that fit those data best were of the Gompertzian type, and the ensuing simulations showed that manipulations that compress the conventional schedule of drug administration could result in greater treatment efficacy through the minimization of tumor cell regrowth in between treatment cycles.

The work of Norton and Simon using mathematical models and clinical testing of those models by Citron et al. [1] shows the importance of mathematical modeling as a resource in clinical trials involving cancer chemotherapy. Chemotherapy is the single most effective kind of treatment against cancer, and this makes it imperative for clinicians to investigate various strategies that may be optimally efficient in carrying out cancer treatment in ways that maximize success and prolong the life of the patient. As the battle against cancer continues questions that will remain unanswered for a long time to come concern the best strategies for achieving remissions and laying the necessary foundations for a cure. As clinicians face the future challenges of ethical questions related to experiments involving animals and humans, mathematical models may provide initial important insights into treatment issues that, even though they may hold the key to breakthroughs in the clinic, could be considered dangerous in human clinical trials.

Clinical testing of the Norton-Simon hypothesis [2] is an indication that the biomedical community is welcoming and opening another significant front in the fight against cancer and other diseases. Piccart-Gebhart [10] points out that it took about 15 years to test the concept of dose densification in the clinic partly because of concerns about the safety of such an approach. He also explains that much of the energy of the oncology community in the last two decades has been driven by specific drug questions, to the neglect of most of the other key variables of chemotherapy that might turn out to be of utmost importance. These include the timing of chemotherapy in relation to tumor resection and initiation of endocrine therapy, the duration of chemotherapy, and the schedule of drug administration. Linch [11] raised other questions that combined with issues raised by Piccart-Gebhart in [10], suggest looking at cancer treatment as a formal optimization problem in which mathematical modeling plays a significant role. We must point out here that the significance of our work lies in the realization that more mathematical models will be needed in the future to gain useful insights on which investigations of biomedical phenomena can be based, as has been done by Citron and his co-workers. This article is written in that context.

Using the aforementioned points as a background, this article highlights the importance of mathematical modeling to the clinic. Consequently, this article is laid out as follows. In section 2, we briefly discuss the work of Citron et al. [1] and Pfreundschuh et al. [3, 4] and follow it up by reintroducing and placing in context an existing model [12] that employs the treatment-optimization approach. The aim is to further validate the predictions of that model based on the findings of Citron et al. [1] and Pfreundschuh et al. [3, 4] and consequently to seek model improvements that could aid in further clinical trials. In section 3, some models are introduced that serve as improvements of the model discussed in section 2; simulations of this model are discussed. Discussions and concluding remarks appear in section 4.

2. **The work of INT C9741, DSHNHL, and mathematical modeling.**

Citron and his co-workers [1] studied adjuvant chemotherapy for women with axillary node-positive breast cancer to compare sequential doxorubicin (A), paclitaxel

(T), and cyclophosphamide (C) with concurrent doxorubicin and cyclophosphamide (AC) followed by paclitaxel (T) for disease-free survival and overall survival. Their aim was to determine whether dose density of the cytotoxic agents improved disease-free survival and overall survival, and also to compare toxicities.

Subjects in the INT C9741 study were randomly divided into four groups and received regimens based either on the sequential or the concurrent modes of administration mentioned earlier. Among the two groups receiving sequential treatment, one group received filgrastim, a growth factor, with treatment carried out every two weeks, and the other group received no filgrastim and was treated every three weeks. A similar approach was adopted for the two groups receiving concurrent treatment. Specifically in this study, a total of 2,005 female patients were randomly assigned to receive one of the following regimens in a 2×2 factorial design:

- sequential A $\times$ 4 (doses) $\rightarrow$ T $\times$ 4 $\rightarrow$ C $\times$ 4, with doses every 3 weeks
- sequential A $\times$ 4 $\rightarrow$ T $\times$ 4 $\rightarrow$ C $\times$ 4 every 2 weeks with filgrastim
- concurrent AC $\times$ 4 $\rightarrow$ T $\times$ 4 every 3 weeks
- concurrent AC $\times$ 4 $\rightarrow$ T $\times$ 4 every 2 weeks with filgrastim

From the studies, Citron et al. [1] concluded that dose densification over a shorter treatment period of 2 weeks instead of 3 weeks improves clinical outcomes significantly, despite the lower-than-expected number of events at this time. They also reported that sequential chemotherapy is as effective as concurrent chemotherapy.

In one DSHNHL study [3], randomized groups of patients between ages 18 and 60 years with good-prognosis aggressive lymphoma were given combinations of cyclophosphamide, doxorubicin, vincristine, and prednisone or combinations of cyclophosphamide, doxorubicin, vincristine, prednisone, and etoposide every two or three weeks, respectively. These were classified as CHOP-21 or CHOP-14 (chemotherapy without etoposide carried out over 3 weeks or 2 weeks) and CHOEP-21 or CHOEP-14 (chemotherapy with etoposide carried out over 3 weeks or 2 weeks). In this study, 710 patients were randomized to 6 cycles of CHOP-21, CHOP-14, CHOEP-21, or CHOEP-14 in a 2×2 factorial study design. Patients in the biweekly regimens additionally received granulocyte colony-stimulating factor (G-CSF). The aim was to determine whether treatment over 2-week periods could produce better results than treatment over the standard 3-week period. Despite limitations of the study, certain aspects of the trial showed that the administration of combinations of cyclophosphamide, doxorubicin, vincristine, and prednisone provided better results in the 2-week treatment case than in the 3-week case with respect to survival. It was found that the regimen including combinations of cyclophosphamide, doxorubicin, vincristine, prednisone, and etoposide delivered 3 weeks improved only event-free survival, whereas the same regimen delivered every 2 weeks along with G-CSF significantly improved complete remission rates, reduced progressions under therapy, and improved event-free survival and overall survival. Even though this 2-week dosing strategy was observed to be more toxic, it was recommended for younger patients with good prognosis.

In another DSHNHL trial [4] that studied treatment of elderly patients between ages 61 to 75 years, 689 randomized groups of patients with aggressive lymphoma received the same types of regimens described above over respective 2- or 3-week cycles. The study concluded that administration of combinations of cyclophosphamide, doxorubicin, vincristine, and prednisone along with G-CSF given in 2-week cycles instead of 3-week cycles should be considered as the new standard chemotherapy regimen for patients age 60 or older.

The studies by Citron et al. [1], Pfreundschuh et al. [3, 4], and others uncover and suggest strategically viable options provided by the concept of dose densification within a growth factor enhanced treatment environment. However, more investigations are advocated [1, 3, 4, 10, 11] as a way to build enough confirmatory evidence in favor of such approaches. In the pursuit of further investigations we believe that mathematical models could give some insights to clinicians about how to optimize treatment so as to lessen the additional cost offered by addition of growth factors to the treatment regimens, for example. Among a number of questions relating to the treatment strategies are the following: How optimal is the reduction of the standard treatment time interval from three weeks to two weeks considering the various constraining factors on treatment? Are there other time intervals that could yield treatment optimality in terms of improving event-free and overall survival, and lessening myelosuppression? Should a rest period be factored into the overall treatment interval, and how long should this rest period be before another treatment cycle begins?

In addressing such questions and relating our work to the clinical studies, we reintroduce the treatment model proposed in [12]. At the time the model was proposed, it was difficult to find work in the medical literature that could be used to compare and validate the findings it engendered with regard to dose densification as hypothesized by Norton and Simon [2]. We therefore used the work of Yamasaki et al. [13], which even though did not investigate the concept of dose densification, fell to some extent within our investigative framework of probing the effects of growth factors in treatment. Recent work by Citron et al. [1] has made it possible and imperative to revisit this model and place it in current relevant context. We now reintroduce the treatment model based on the following assumptions:

1. Combinations of cytotoxic agents are delivered continuously to a patient whose diagnosis indicates the existence of a rapidly expanding malignant population with a certain level of cell loss and a dominated normal cell population.
2. The normal and abnormal cells exist side-by-side and obey the processes of Gompertzian growth. However, the malignant population interferes with and inhibits the growth of the normal cell population.
3. The recovery of the normal cell population is stimulated with the infusion of recombinant hematopoietic growth factors during the application of the cytotoxic agents.
4. The regrowth rate of the normal cells due to the infusion and action of growth factors is directly proportional to the quantity of normal cells available.
5. To limit damage to normal tissues from the drug insult, constraints are placed on the concentration of drugs.
6. The cost of treatment that should be minimized is taken to be proportional to the time interval of treatment. This cost involves the length of exposure to cytotoxic agents and the period of hospitalization.

These assumptions engender a treatment-optimization model that considers cancer treatment as a formal optimization problem. This model derives from superimposing a chemotherapeutic regimen on a model that describes cancer and normal cell growth kinetics in an environment in which account is taken of interactions among the cells. Such interactions give rise to normal cell inhibition by an expanding malignant population [14]. The model is as follows. Minimize

$$J = \int_0^R q dt \tag{1}$$

subject to

$$\frac{dL}{dt} = g\left(\log\frac{L_A}{L}\right)L - fL - ku(t)L, \tag{2}$$

$$\frac{dN}{dt} = a\left(\log\frac{N_A}{N}\right)N - bN - cNL - hu(t)N + G(t), \tag{3}$$

$$N(0) = N_0, L(0) = L_0, \tag{4}$$

with

$$u_{min} \leq u(t) \leq u_{max} \tag{5}$$

and

$$\begin{bmatrix} L(R) \\ N(R) \end{bmatrix} = \begin{bmatrix} \hat{L} \\ \hat{N} \end{bmatrix}, \tag{6}$$

where the quantity $L(t)$ represents the population of malignant cells at time t, the quantity $N(t)$ represents the population of normal cells at time t, the parameter g is the fractional growth rate of the abnormal cells, f is their fractional death rate, a is the fractional growth rate of the normal cells, b is their death rate, and c is the degree of inhibition exercised by the malignant cells over the normal cells. The quantities L_A and N_A are the carrying capacities of the abnormal and normal cell populations, respectively. The constants L_0 and N_0 are the respective populations of the malignant and normal cells at detection. Quantity $u(t)$ is an attribute or a measure of the lethality and toxicity of the concentration of drugs per unit time, $G(t)$ is the regrowth rate of the normal cells due to the infusion and action of recombinant hemopoietic growth factors and is represented in this case as $G(t) = rN$, where r is a constant defined as the recovery rate per unit time of normal cells due to the infusion of recombinant hematopoeitic growth factors. The parameter k is the fraction of malignant cells that are killed by the drug insult and h is the fraction of normal cells that are destroyed with the assumption that $k >> h$. The quantity R denotes the final time of treatment, $[0, R]$ denotes the chemotherapeutic time interval, and the parameter q is a constant of proportionality that can be defined as a penalizing factor if the treatment time is prolonged. Quantities $\hat{L}$ and $\hat{N}$ denote the final populations of abnormal and normal cells, respectively, at the end of treatment. It is expected that $\hat{L}$ will be small or negligible and $\hat{N}$ will be large enough to guarantee and facilitate normal cell regrowth after treatment is discontinued. The full details describing how this model is transformed and analyzed, along with numerical estimates of the model parameters, can be found in [12]. Here, with the objective of minimizing the treatment time interval described by equation (1) in the spirit of the dose densification concept, a Hamiltonian function is constructed and analyzed by adjoining a transformed version of equation (1) to transformed versions of equations (2) and (3) to obtain the results described in section 2.1.

2.1. **Model predictions and clinical trials.** Our aim at this juncture is to investigate the usefulness and relevance of the results generated by model system (1)–(6) to the clinical verifications of the concept of dose densification [1, 3, 4], with the goal of further validating the model predictions in this context and also suggesting ways in which the clinical trials could be enhanced through treatment optimization. From the analyses and simulations described in Figures 1, 2, and 3, the model predictions and their resulting implications are as follows:

1. It is possible to achieve significant reductions in malignant cell numbers through intensive treatment at reduced time intervals with high drug concentrations and addition of growth factors. This supports the conclusions about dose densification in [1, 3, 4].
2. The treatment outcomes when growth factors are used in intensive dose-dense therapies (shown in Fig. 1) appear to have an edge over outcomes that employ dose-dense treatments without growth factors (shown in Fig. 2). In Figure 1, normal cell recovery takes place during the active treatment period, while in Figure 2 the recovery takes place toward the end of the patient's period of rest.
3. Dose-dense treatment with growth factors enhances a better cell count differential that favors normal cells over the malignant ones toward the end of the treatment cycle. Figure 1 demonstrates a larger differential in cell counts of normal over abnormal cells than Figure 2 does, toward the end of the treatment cycle.
4. An optimal treatment cycle produces two separate periods–an active dose-dense treatment period and a rest period in which the patient is made to rest before another course of therapy is admistered. The calculations yielded 35 nondimensional time units (approximately 27 days) for a single treatment cycle in the case where growth factors are applied, where one nondimensional time unit is equivalent to 0.772 days. Within this treatment interval, the period of active dose-dense treatment was 22.42 nondimensional time units (about 17.3 days). The rest period was 12.58 nondimensional time units (about 9.7 days). Therefore, considering all things being equal to a first approximation, a 2-week treatment period will consist of about 9 days of active dose-dense treatment and a rest period of 5 days. In this same vein, a 3-week treatment cycle will consist of about 13.5 days of active dose-dense therapy and a rest period of 7.5 days.
5. The simulations shown in Figure 3 indicate a situation in which the abnormal cell population stays below a certain threshold beyond the rest period while the normal population increases beyond this threshold, possibly due to the effect of the growth factors on the normal population on one hand and to the effect of dose-dense treatment on the malignant population on the other.

In specifically comparing and contrasting the clinical studies [1, 3, 4] to the model design, predictions, and implications, assuming all things to be equal, the following observations can be made:

1. Combinations of drugs are employed in the clinical studies, while in model system (1)–(6) the drug combinations are essentially represented by the model quantity $u(t)$.
2. The growth factors (filgrastim and G-CSF) that are used in the clinical investigations find their expression through $G(t)$ in model system (1)–(6).
3. The growth factors applied in the clinical work are aimed at enhancing and stimulating normal cell recovery, and this is captured by the presence of $G(t)$ in model equation (3). Even though growth factors are thought to stimulate the growth of abnormal cells and recruit them into active cycle, existing supporting evidence for the presence of $G(t)$ only in model equation (3) [15] indicates that such cytokines may not necessarily cause this kind of malignant stimulation.

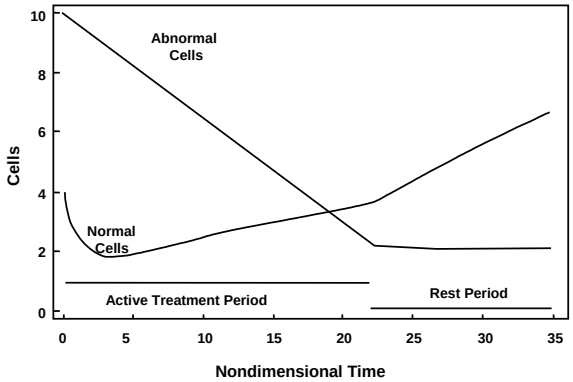

FIGURE 1. Intensive dose-dense treatment with infusions of growth factors. The normal and abnormal cells go through a process of decline during the period of active therapy. However, normal cell recovery begins during this period, leading to a domination of the abnormal population during this active treatment period and lasting through the rest period. In this simulation scheme growth-factor support was started 2.5 nondimensional time units after treatment began. The abscissa is measured in nondimensional time units, and the ordinate represents the cell populations measured on a log_{10} scale.

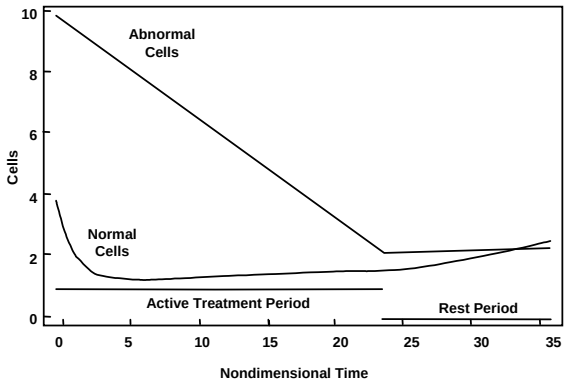

FIGURE 2. Intensive dose-dense treatment without infusions of recombinant hematopoietic growth factors. The normal and abnormal cells go through a process of decline during the period of active treatment, but even though the normal population begins to recover, it remains dominated by the abnormal population. The eventual domination gained by the normal cells over the abnormal population takes place only toward the end of the rest period and involves a relatively small advantageous differential. The abscissa is measured in nondimensional time units, and the ordinate represents the cell populations measured on a log_{10} scale.

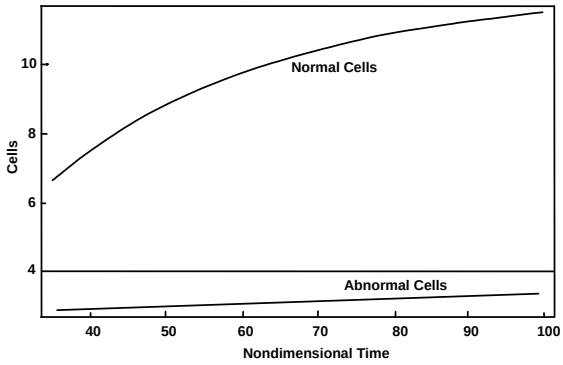

FIGURE 3. Growth of the normal and abnormal cell populations beyond the treatment cycle that involved the use of recombinant hemopoietic growth factors. The normal cells evolve toward their normal population level, while the abnormal cell population remains below a certain threshold. The abscissa is measured in nondimensional time units, and the ordinate represents the cell populations measured on a log_{10} scale.

4. Indications of the effects of the studies were measured by considering improvements in disease-free survival and overall survival among patients, while the model measured the effects of the treatment by looking at system dynamics in the presence or absence of growth factors and system behavior beyond the model-predicted treatment period. Improvements arising from the model came from observing differentials in the normal and malignant populations that were advantageous to normal cells.
5. By studying outcomes related to disease-free survival and overall survival among patients, the clinical investigations recommended dose-dense treatment over an arbitrarily chosen 2-week period instead of the standard 3-week period. With the objective of minimizing the treatment period based on constraining system kinetics, the model predicted a specified time interval over which to carry out dose-dense therapy.
6. Thus, from calculations, the model stipulates the division of the entire treatment interval into a calculated period of active dose-dense therapy and a period of rest before another treatment cycle is started. This is not considered in the clinical studies.
7. Consequently, as mentioned earlier, to a first approximation, a 2-week dose dense treatment period as recommended by the clinical studies could be shortened further through a model-predicted active dose dense therapy period of 9 days followed by a 5-day rest period.

Basically, the main findings of the clinical trials [1, 3, 4] were that the two-week dose-dense approach could be considered as a viable treatment strategy for either younger or older patients, compared to the standard treatment period of three weeks. These suggest that treatment be carried out in shorter time intervals with heavy doses of drugs in addition to growth factors. Thus, the clinical findings support the model predictions and their implications in a broad sense. In this context, the modeling approach situates and positions the clinical trials within a

formal optimization framework in which a number of calculations and estimations can be carried out before active treatment begins.

Comparing and relating the results of the clinical trials and the model, in regard to the items listed above, the following points highlight predictions of model system (1)–(6) that do not necessarily match the design and postulations of the clinical studies but may be insightful and relevant to integrating such studies with mathematical modeling techniques even before treatment begins.

1. The model suggests that the length of the entire treatment period that includes the time interval of active dose-dense treatment and the rest period could be calculated granted that patient data on parameters such as growth and death rates of the cell populations are known.
2. Determination of an approximate time to discontinue treatment when the entire time course of treatment is estimated.
3. Knowledge of the time interval of neutropenia that can be estimated from the time when the normal population begins to decrease because of drug insult until the time point when it starts to rise, as can be observed from Figure 1.
4. A threshold below which the abnormal population could be kept for some period of time to guarantee regrowth of the normal population, possibly before another course of therapy, if necessary, is administered.
5. An interval of time beyond the rest period over which to wait before carrying out any treatment of minimal residual disease.
6. Specification of the final populations of normal and abnormal cells to be reached by the end of the rest period to ensure count recovery.
7. Knowledge of the cost of treatment.

Essentially, it is instructive to note from the clinical trials that dose-densification protocols, as predicted by mathematical models [2, 12], may be advantageous to cancer patients. Quite possibly, such protocols may gain superiority over others and achieve wider applicability if carried out within a formal optimization setting, as the modeling approaches suggest. Within such a framework, estimations of time intervals for active dose-dense treatments and rest periods could be made in circumstances where it is necessary to determine whether to carry out treatments either over 2-week or 3-week cycles. It is safe to say at this juncture that the inherent nature of cancer chemotherapy tends to point to conclusions of dose densification over shorter treatment cycles. However, the underlying kinetic behavior of the interacting cells, which serves as a constraint on treatment, needs to be continuously understood. Therefore, it is imperative for us to keep improving our models as we seek to make them more insightful and relevant to clinical investigations. To this end, we introduce some new and expanded models of cell kinetic behavior in section 3.

3. **Expanded models.** In section 2, we related the clinical investigations [1, 3, 4] to an existing model of cancer chemotherapy and used those studies to further validate the predictions of the existing model. In the process, we also showed how the clinical findings could benefit from a formal optimization approach. Obviously, like any other models, the above model has certain limitations. One limitation is the lumping together of all normal and malignant cells into single populations of cells in the study of their kinetic behavior; this could blur some insights that might arise if cell kinetics were studied in the various compartments and organs participating in normal and abnormal hemopoiesis. In this section, we offer a way to begin

addressing some of the model limitations by considering cell kinetic behavior in the marrow and peripheral blood in an environment of malignancy in untreated and treated cases. The proposed new model in the untreated case is as follows:

$$\frac{dL_m}{dt} = aL_m \log\left(\frac{L_A}{L_m}\right) - (b + c)\, L_m, \tag{7}$$

$$\frac{dL_b}{dt} = cL_m - kL_b, \tag{8}$$

$$\frac{dN_m}{dt} = fN_m \log\left(\frac{N_A}{N_m}\right) - (g + h + jL_m)\, N_m, \tag{9}$$

$$\frac{dN_b}{dt} = hN_m - (l + nL_b)\, N_b, \tag{10}$$

$$L_m(0) = L_{m0},\ L_b(0) = L_{b0},\ N_m(0) = N_{m0},\ N_b(0) = N_{b0}. \tag{11}$$

In the case of treatment, we introduce a chemotherapeutic regimen into model system (7)–(11) to obtain the following model:

$$\frac{dL_m}{dt} = aL_m \log\left(\frac{L_A}{L_m}\right) - (b + c)\, L_m - pUL_m, \tag{12}$$

$$\frac{dL_b}{dt} = cL_m - kL_b - qUL_b, \tag{13}$$

$$\frac{dN_m}{dt} = fN_m \log\left(\frac{N_A}{N_m}\right) - (g + h + jL_m)\, N_m - rUN_m + G(t), \tag{14}$$

$$\frac{dN_b}{dt} = \gamma hN_m - (l + nL_b)\, N_b - sUN_b, \tag{15}$$

$$\frac{dU}{dt} = v(t) - \lambda U, \tag{16}$$

$$L_m(0) = L_{m0},\ L_b(0) = L_{b0},\ N_m(0) = N_{m0},\ N_b(0) = N_{b0}, U(0) = U_0\,. \tag{17}$$

In model systems (7)–(11) and (12)–(17), L_m is the population of abnormal cells in the bone marrow (BM) at time t, L_A is the asymptotic bound on the population of malignant cells in the marrow, L_b is the population of abnormal cells in the peripheral blood (PB) at time t, N_m is the population of normal cells in the BM, N_A is the asymptotic bound on the normal cell population in the BM, and N_b is the population of normal cells in the PB. The quantity $G(t)$ represents the infusion rate of recombinant hematopoietic growth factors at time t, and $U(t)$ represents the concentration of a combination of cytotoxic drugs. It can also represent the lethality or toxicity of cytotoxic drugs to normal and abnormal cells. Quantity $v(t)$ represents the infusion rate of the combinations of drugs. In the BM, parameters a and f are the respective growth speeds of abnormal and normal cells, b and g are respective loss rates of malignant and normal cells, c and h are respective release rates of abnormal and normal cells from the BM to the PB, j is the degree of inhibition suffered by the normal cells due to their interaction with abnormal cells, p is the fraction of abnormal cells that are killed because of drug action, and r is the fraction of normal cells destroyed by the drug insult. In the PB, parameters e and l are the respective loss rates of abnormal and normal cells, n is the degree of inhibition suffered by the normal cells due to their interaction with abnormal cells, q is the fraction of abnormal cells destroyed by drug action, and s is the fraction of normal cells that are killed because of drug toxicity. The quantity γ is an activation factor arising from the growth factor stimulation. Parameter λ represents the rate of decay of drug concentration.

Model systems (7)–(11) and (12)–(17) are new models that we have proposed in an attempt to gain a deeper understanding of the cell kinetics and are predicated on the following assumptions:

1. A process of hematopoiesis exists in the bone marrow that supports and maintains the homeostatic level of cells in the peripheral blood.
2. A malignant population of cells emerges in the marrow and peripheral blood.
3. The malignant population interacts with and interferes with the normal population in the BM and PB.
4. Growth of normal and malignant cells in the BM follows a Gompertzian process.
5. The PB does not experience cell growth but benefits from the release of normal and malignant cells to it from the BM.
6. Cell loss takes place from the BM and PB.
7. Infusion of recombinant hemopoietic growth factors takes place at rates that are proportional to the normal population in the bone marrow.
8. Stimulation of the BM by growth factors activates the rate at which normal BM cells enter the PB.
9. Infusions of combinations of drugs take place continuously during the period of active therapy.

3.1. **Analytical results, parameter estimates, and simulations.** An investigation of the steady-state properties of the new model system (7)–(11) reveals that it has four critical points. These are as follows:

I. $\overline{L}_m = 0, \overline{L}_b = 0, \overline{N}_m = 0, \overline{N}_b = 0$

II. $\overline{L}_m = 0, \overline{L}_b = 0, \overline{N}_m = N_A e^{-\alpha}, \overline{N}_b = (hN_A/l)e^{-\alpha}$ where $\alpha = \frac{g+h}{f}$

III. $\overline{L}_m = L_A e^{-\beta}, \overline{L}_b = (cL_A/k)e^{-\beta}, \overline{N}_m = N_A e^{-(g+h+jL_A)/f}$, $\overline{N}_b = \frac{hkN_A e^{\beta-(g+h+jL_A)/f}}{cnL_A + kle^{\beta}}$ where $\beta = \frac{b+c}{a}$

IV. $\overline{L}_m = L_A e^{-\beta}, \overline{L}_b = (cL_A/k)e^{-\beta}, \overline{N}_m = 0, \overline{N}_b = 0$

Among these critical points, steady states (III) and (IV) are stable to small perturbations. Stability of equilibrium point (III) comes directly from the analysis while that of point (IV) is determined from our work with data below. With these, and considering the difficulties entailed in obtaining parameter values in this area, we continue our studies by obtaining and inferring estimates of the model parameters from existing work [12, 14, 16], which deals with the modeling of cancer and its treatment under circumstances that are relevant to the investigations in this work. The parameter and other values along with associated correction factors used in this work are summarized as follows:

$a = 0.00396 \pm 0.05$	$b = 0.01925 \pm 0.05$	$c = 0.286 \pm 0.05$	$f = 0.03333 \pm 0.05$
$g = 0.0715 \pm 0.05$	$h = 0.477 \pm 0.05$	$k = .012 \pm 0.05$	$l = .086 \pm 0.05$
$p = 0.4 \pm 0.2$	$q = 0.4 \pm 0.2$	$r = 0.1 \pm 0.05$	$s = 0.1 \pm 0.05$
$j = 5 \times 10^{-6}$	$n = 5 \times 10^{-6}$	$L_A = 3.0 \times 10^{12}$	$N_A = 1.4 \times 10^{12}$

Parameters a, b, c, f, g, h, k, and l are measured per hour, and parameters j and n, which are chosen to be the same, are measured per 1,000 cells per hour. Since negative values of the parameters are unrealistic, we must point out that the range of values of the various parameters with the correction factor of 0.05 would have lower limits of zero. Using the parameter estimates above, we computed the numerical values of the steady states in (II)–(IV) above to obtain

b′. $\overline{L}_m = 0, \overline{L}_b = 0, \overline{N}_m = 5.83866 \times 10^8, \overline{N}_b = 2.26248 \times 10^9$

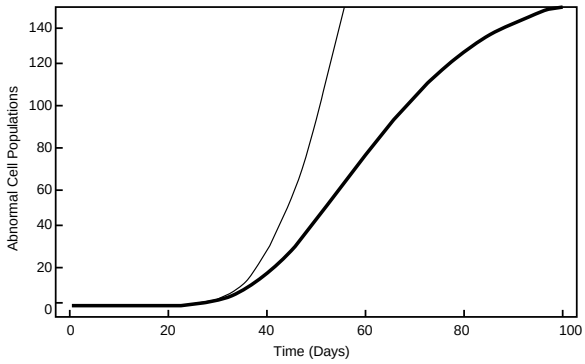

FIGURE 4. Time evolution of the abnormal marrow and peripheral blood cells. Upon emergence in the marrow and blood, these cells increase their population in those compartments of the body so as to dominate the normal marrow and peripheral blood cells. The thick curve represents the abnormal marrow cells, and the thin curve represents the abnormal peripheral blood cells. The abscissa is measured in days, and the ordinate is multiplied by 10^7 cells.

c′. $\overline{L}_m = 1.64243 \times 10^9$, $\overline{L}_b = 8.90089 \times 10^9$, $\overline{N}_m = 9.26383 \times 10^{-35}$, $\overline{N}_b = 1.09364 \times 10^{-36}$

d′. $\overline{L}_m = 1.64243 \times 10^9$, $\overline{L}_b = 8.90089 \times 10^9$, $\overline{N}_m = 0$, $\overline{N}_b = 0$.

It can be observed clearly from (c′) and (d′) that the numerical values coincide. Therefore, the stable steady state that arises in the untreated case is one in which there are almost no normal cells in the BM and PB. This means that these cells are ultimately replaced by the abnormal ones, and this situation may become fatal if left untreated. Steady state (I) is unstable and shows that a situation where there are no cells is impossible. Steady state (II) or (b′) breaks down and is unstable showing the dominance of abnormal cells in the disease state. We carried out simulations of the untreated case by investigating the evolutionary dynamics of the normal and abnormal BM and PB cells, respectively, as shown in Figures 4 and 5.

Figure 4 shows the increasing population of the abnormal cells in the BM and PB in the untreated case, while Figure 5 shows the diminishing population of normal BM and PB cells after some point in time. In Figure 5, the normal cells increase in population over time so as to maintain a semblance of normal hemopoiesis, but this increase is brought in check as the abnormal cells interfere with the development of the normal BM and PB population of cells. Following the analysis and simulations of the untreated case, we proceeded to study the simulations of model system (9)–(14). The simulations were based on predictions from model system (1)–(6) and results from the clinical studies of [1, 3, 4]. We investigated cell behavior in the marrow and peripheral blood in an active treatment environment over a formal period of 17 days by assuming various possible control strategies arising from work with model system (1)–(6). Thus, specification of an explicitly defined objective function adjoined to model system (9)–(14) was found to be unnecessary in the face of the kinetics playing an important role in system evolution.

In studying dose densification in this context, it was assumed that at an intensive level of treatment, $U(t)$ could be taken to measure the maximum level of drug

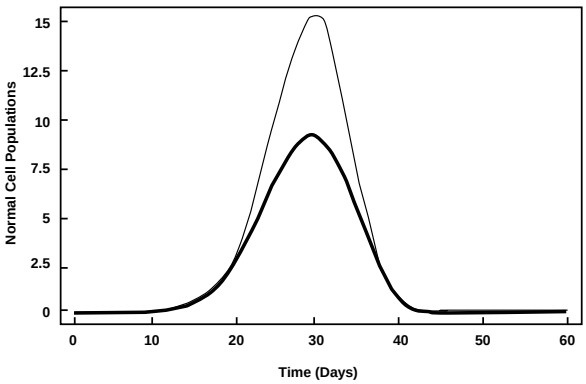

FIGURE 5. Evolutionary dynamics of the normal marrow cells (represented by the thick curve) and peripheral blood cells (represented by the thin curve) in the untreated case. To maintain a semblance of normal hemopoiesis when abnormal cells emerge, the normal cells increase in their numbers but start to decrease after some point, when the malignant populations in the marrow and peripheral blood exercise appreciable interference in their growth. The abscissa is measured in days, and the ordinate is multiplied by 10^7 cells.

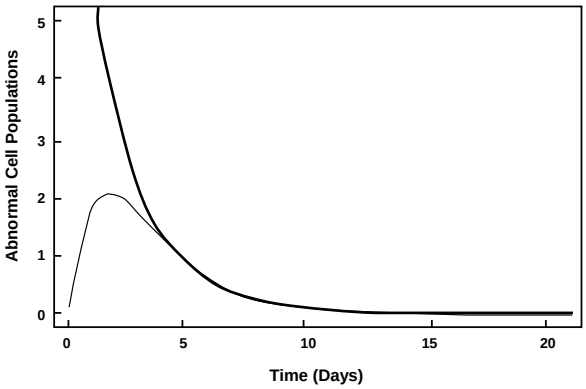

FIGURE 6. Time evolution of malignant marrow and peripheral blood cells upon introduction of dose-dense treatment. When drugs are applied, the abnormal cells in the marrow (represented by the thick curve) begin to decrease immediately toward low levels, but the abnormal cells in the peripheral blood (represented by the thin curve) temporarily experience a rise in their population level because of enhancements they obtain from marrow cells still entering the peripheral blood. This rise aborts when drug action on the marrow and peripheral blood takes hold, leading to an eventual decrease in these two cell populations. The abscissa is measured in days, and the ordinate is multiplied by 10^8 cells.

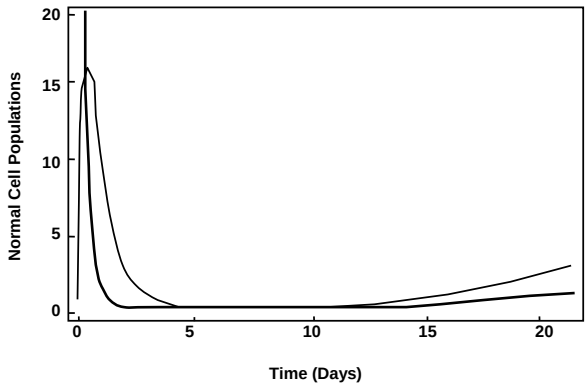

FIGURE 7. Evolutionary dynamics of normal marrow and peripheral blood cells in the dose-dense treatment case with growth factors. When dose-dense treatment is introduced, the normal marrow cells (represented by the thick curve) begin an instantaneous process of decline to a low level, but their population starts to rise toward the end of the treatment period because of the stimulation they receive from growth factors. The normal peripheral blood cells (represented by the thin curve) initially witness an increase in their population because of the enhancements they get from marrow cells entering this compartment. However, they go through a decline after the point when drug action takes hold. Toward the end of the treatment period, their population starts to rise because of growth-factor stimulation. The abscissa is measured in days, and the ordinate is multiplied by 10^8 cells.

lethality or toxicity. Thus, $U(t)$ was set equal to one. Simulations that yielded the evolutionary dynamics of the BM and PB cells in the dose-dense treatment case are shown in Figures 6 and 7. In Figure 6, we observe that upon introduction of dose-dense treatment, the abnormal cells in the marrow (represented by the thick curve) begin to decrease immediately toward low levels, but the abnormal cells in the peripheral blood (represented by the thin curve) temporarily experience a rise in their population level because of enhancements they obtain from marrow cells that are still entering the peripheral blood. This rise becomes truncated when drug action on the marrow and peripheral blood takes hold, leading to an eventual decrease in these two cell populations. This decrease does not show any tendency of recovery towards the end of the treatment period. The decrease down to a low level happens around day 12, that is, before day 17.

In Figure 7, upon introduction of dose-dense treatment, the normal marrow cells (represented by the thick curve) begin an instantaneous process of decline toward a low level, but their population starts to rise toward the end of the treatment period because of the stimulation they receive from growth factors. On the other hand, the normal peripheral blood cells (represented by the thin curve) initially witness an increase in their population because of the enhancements they get from marrow cells entering this compartment. However, they go through a decline after the point when drug action takes effect. Toward the end of the treatment period, their population starts to rise because of growth-factor stimulation.

4. **Discussion and concluding remarks.** As the search for the best treatment strategies in cancer treatment continue, it is important to note that the work of Citron et al. [1] shows that mathematical models have a significant role to play in confronting the nagging and seemingly intractable problems posed by cancer as a disease. It took a relatively long time for the postulates of Norton and Simon [2] to be verified in the clinic. Nonetheless, by basing their clinical studies entirely on the postulates of a mathematical model, Citron and his co-workers gave further credibility to an area of scientific endeavor that holds enormous potential for maximizing the benefits that would accrue from multidisciplinary collaboration involving clinicians, biologists, mathematical biologists, and other scientists.

In this article, we found commonality between specific predictions of model system (1)–(6) and the clinical findings of [1, 3, 4] and went on to enumerate other model predictions that could be investigated in the clinic as part of the process of placing the strategy of dose densification on firm theoretical and experimental grounds as a viable strategy in the fight against cancer. We used the model and its predictions to show that reduction of the treatment time from 3 weeks to 2 weeks could proceed along optimization lines in which 2 subintervals of treatment could be estimated, should the entire treatment time be either 2 or 3 weeks. The 2 subintervals comprise an active treatment time interval and a rest period. In the active treatment subinterval, the patient would receive combinations of drugs in addition to growth factors, and the patient would rest during the inactive period before another possible course of treatment. The simulations show that such a strategy could provide beneficial outcomes to the patient and clinician.

Since the search for the best treatment strategies continues and given the recommendations that testing of the clinical findings should continue to establish irrefutable evidence in favor of dose densification and other strategies, it is imperative to keep improving mathematical models alongside the clinical investigations to provide further predictive insights. Therefore, we sought improvements to model system (1)–(6) by introducing models that studied cell kinetic behavior in the marrow and peripheral blood in the untreated and treated cases. It is important to point out that knowledge of cell kinetic behavior in cancer is essential to designing and implementing treatment protocols. In analyzing model system (7)–(11), the model predicted that there was essentially one stable steady-state set in which abnormal cells populate and replace normal cells in the marrow, leading to a situation where no normal cells remained in the marrow and peripheral blood in the untreated case. Simulations of the model supported this analytical prediction. The simulations showed that normal cells may evolve toward levels aimed at presenting a semblance of hematopoietic normality but decline because of the presence of malignant cells in these compartments of the body. The investigation of the dose-dense treatment case with simulations of model system (12)–(17) over a formal treatment period of 17 days showed that the bone marrow and peripheral blood compartments could experience considerable depletions in normal and malignant cell levels within a time span of about 10 days of aggressive treatment. However, normal cell recovery in the BM and PB, at the expense of malignant cells, could be guaranteed through stimulation by growth factors.

We must mention that many other important questions will be investigated with our models in a sequel to this article, including, for example, the investigation of system behavior when certain types of growth factors trigger dormant or resting malignant cells into active cycle. One of our main aims in this discourse has been

to further demonstrate the roles mathematical models can play in clinical trials, and we hope to build on this through further model improvements. We believe that mathematical models could be positioned at locations before, during, and after treatment, when estimates of cell kinetic behavior, treatment times, drug concentrations, and other quantifiable entities need to be obtained so as to inform the treatment process.

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