Chemotherapy Drug Scheduling for the Induction Treatment of Patients With Acute Myeloid Leukemia

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Abstract—Leukemia is an immediately life-threatening cancer wherein immature blood cells are overproduced, accumulate in the bone marrow (BM) and blood and causes immune and blood system failure. Treatment with chemotherapy can be intensive or nonintensive and can also be life-threatening since only relatively few patient-specific and leukemia-specific factors are considered in current protocols. We have already presented a mathematical model for one intensive chemotherapy cycle with intravenous (IV) daunorubicin (DNR), and cytarabine (Ara-C) [1]. This model is now extended to nonintensive subcutaneous (SC) Ara-C and for a standard intensive chemotherapy course (four cycles), consistent with clinical practice. Model parameters mainly consist of physiological patient data, indicators of tumor burden and characteristics of cell cycle kinetics. A sensitivity analysis problem is solved and cell cycle parameters are identified to control treatment outcome. Simulation results using published cell cycle data from two acute myeloid leukemia patients [2] are presented for a course of standard treatment using intensive and nonintensive protocols. The aim of remission–induction therapy is to debulk the tumor and achieve normal BM function; by treatment completion, the total leukemic population should be reduced to at most 10^9 cells, at which point BM hypoplasia is achieved. The normal cell number should be higher than that of the leukemic, and a 3-log reduction is the maximum permissible level of population reduction. This optimization problem is formulated and solved for the two patient case studies. The results clearly present the benefits from the use of optimization as an advisory tool for treatment design.

Index Terms—Cell cycle models, chemotherapy optimization, mathematical modelling, pharmacodynamics, pharmacokinetics.

I. INTRODUCTION

ACUTE myeloid leukemia (AML) is a cancer of the bone marrow (BM) and blood wherein blood cells are unable to develop or function normally, are overproduced at an immature stage of development and overtake any normal elements remaining in the BM and blood. This uncontrolled growth compounds the morbidity and mortality due to the disease by inhibiting development of healthy blood and immune cells through multiple mechanisms [3], [4].

The main aim of treatment for AML is to reduce the leukemia burden in the BM to the point of being undetectable which, if maintained, is defined as cure. Treatment for AML in a fit patient is usually intensive chemotherapy. The first stage of treatment is induction chemotherapy which aims to achieve the rapid restoration of normal BM function by reducing the total body leukemic cell burden by 3-logs, during therapy at which point BM hypoplasia will be achieved (total 10^9 leukemic cells). The desired hypoplastic marrow will be characterized by a smaller and weaker leukemic population and a higher proportion of normal BM cells normally functioning to support blood production and the immune system. It is generally assumed, however, that after completion of induction treatment, a substantial burden of leukemia cells will remain undetected (minimal residual disease). In order to consolidate the remission and instigate cure, postremission therapy is directed toward further reduction of residual leukemia, which may be as high as 10^8 to 10^9 cells when the disease is considered to be in complete morphologic remission [5]. The elimination of these residual leukemic cells may be accomplished by either cytotoxic chemotherapy, causing significant myelosuppression or by replacement of a patient's stem cells through allogeneic transplantation, a procedure combining myeloablation and immunotherapy [5].

Chemotherapy treatment itself can be life-threatening since only relatively few patient-specific and leukemia-specific factors are considered in current protocols; choice of chemotherapy, intensity and duration often depends on either the availability of a clinical trial, the treating physician's experience or the collective experience of the treating center, with significant international protocol variability. There is, therefore, a need to optimize current treatment schedules for cancers such as AML in order to limit toxicities, improve clinical trial pathways for new drugs, and to enable personalized healthcare. Toward this end various system engineering approaches have been developed for the automation of chemotherapy as treatment [6]–[10]. Various mathematical models have been developed for different cancer types in an attempt to describe disease dynamics during chemotherapy and thereafter to propose the optimal treatment design in a hypothetical average patient case study. Due to the hypothetical design, these models do not include patient- and disease-specific characteristics as parameters in the model, but rather use mean values derived from a number of patient/volunteers studied. To
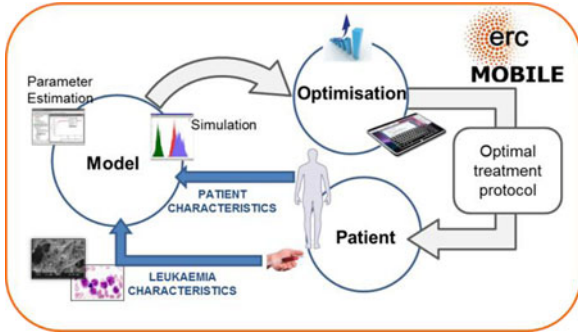
Fig. 1.   Schematic representation of the closed-loop system for the design of optimal personalized chemotherapy protocols.

TABLE I
BRIEF GUIDE TO MODEL EQUATIONS

Model Part	Equations	
PK	$\inf low_{,j} = \dfrac{u_{,j}}{duration_{,j}}$	(eq. 1)
	$V_B \cdot \dfrac{dC_{B,j}}{dt} = \sum\limits_{i:H,Li,M,Le,K} Q_i \cdot C_{i,j} - Q_B \cdot C_{B,j} + \inf low_{,j}$	(eq 2)
	$V_i \cdot \dfrac{dC_{i,j}}{dt} = Q_i \cdot C_{B,j} - Q_i \cdot C_{i,j} - k_{k,j} \cdot C_{B,j} - k_{L,j} \cdot C_{i,j} \cdot V_{iT}$	(eq. 3)
SC	$\dfrac{dS}{dt} = Inflow - k_a \cdot k_b \cdot S$	(eq. 2a)
	$V_B \cdot \dfrac{dC_B}{dt} = \sum\limits_{i:H,Li,M,Le,K} Q_i \cdot C_{i,j} - Q_B \cdot C_{B,j} + k_a \cdot k_b \cdot S$	(eq. 2b)
PD	$effect_{,j} = \dfrac{E_{\max,j} \cdot C_{M,j}^{slope,j}}{E_{50,j}^{slope,j} + C_{M,j}^{slope,j}}$	(eq. 4)
Cell Cycle	$\dfrac{dP_y}{dt} = k_{y-1} \cdot P_{y-1} - k_y \cdot P_y - effect_{,j} \cdot P_y$	(eq. 5)

our knowledge, there is a lack of models that include personalized patient and disease information and which use optimization methods in order to design optimal personalized chemotherapy protocols.

In this paper, a closed-loop system is proposed and presented for the design of optimal personalized chemotherapy protocols (see Fig. 1). A mathematical model is presented that captures AML disease dynamics under the treatment effect of two antileukemic agents: cytarabine (Ara-C) and daunorubicin (DNR). The chemotherapy protocols followed are consistent with standard clinical practice [11] and consist of 1) DNR and Ara-C used via the intravenous (IV) route (DA protocol) and 2) low dose Ara-C administered via the subcutaneous (SC) route (LD Ara-C protocol). Both DNR and Ara-C are considered cell-cycle specific agents. Specifically, Ara-C acts on the proliferation phase of the cell cycle (S-phase) [12] and DNR acts on the S-phase and the growth phase of the cell cycle (G1-phase) [13]. The action of these drugs defines cell cycle as a critical factor within the proposed mathematical model together with the pharmacology aspects of pharmacokinetics (PK) and pharmacodynamics (PD) that provide the complete description of drug diffusion and action after administration.

Sensitivity analysis method is applied on the developed model that uses the model parameters and their assigned interpatient variability ranges to identify the most crucial parameters that control the treatment outcome. Published cell cycle data for two patient case studies [2] are used for the simulation of AML behavior and treatment outcomes for the patients under the two studied treatment protocols. Moreover, the optimization scheduling problem of chemotherapy treatment as an application is presented. The developed and presented optimization algorithm is afterward applied to the studied patients and the results demonstrate the potential benefit of treatment design from the use of mathematical modeling and optimization methods (see Fig. 1).

II. DESCRIPTION OF THE MATHEMATICAL MODEL

The need for more personalized treatment design has been previously discussed [14]–[16]; the main sources of inter- and intra-patient variability are in the cellular kinetics of the tumor and normal cell populations and in the kinetics of the anti-cancer agents when administered to patients. Thus, the desired

mathematical model for the simulation of patient behavior and tumor response during chemotherapy should consist of three parts: 1) the cell cycle model, which is the target of drug action, 2) PK, and 3) PD aspects that provide the complete description of drug diffusion and action after administration.

A mathematical model for the treatment of AML using IV DA protocol has already been developed and presented for the first chemotherapy cycle of induction treatment [1]. This model is extended in this paper to cover both IV and SC doses for the full-length course of chemotherapy treatment (four successive chemotherapy cycles) under DA and LD Ara-C protocols.

A brief guide of the proposed model is available in Table I. Initially, drug dose $(u_{,j})$ of antileukemic agent j is injected into the patient IV over $duration_{,j}$ [see (1)]. The inflow rate of drug j is then transmitted by direct injection into the blood [see (2)] and is circulated to the whole body. This inflow is the main input for the calculation of drug concentration in the blood $(C_{B,j})$ taking into account patient-specific parameters such as the total patient blood volume (V_B), the blood flow in organs [Q_i i: heart (H), liver (Li), BM (M), Le (lean muscle), K (kidneys)] and $C_{i,j}$ is the concentration of drug j in organs i. The drug is transmitted via the blood to the organs and the general mass balance in the organs is represented in (3), that includes the elimination rate of the drug in the liver $(k_{,L,j})$. After drug elimination and action, the drug is excreted through the urine with clearance rate $(k_{k,j})$ from the kidneys.

The PD model is used for the calculation of drug effect, which is the percentage of dead cells due to drug action. The main input for PD is the drug concentration in the location of the tumor which, for AML is the concentration of drug in the BM $(C_{M,j})$ as is calculated by the PK model. $E_{\max,j}, E_{50,j}$ and slope are the PD parameters that depend on the drug, j. Slope parameter has physical meaning only for DNR and thus for this drug the PD model will be used in its current formulation as a sigmoid Emax model [see (4)]. For Ara-C, slope equals unity and if it is replaced in the PD formulation in (4) it will convert the expression to an E-max PD model. The effect, j, calculated by the PD model is the percentage of cells which react with the drug j and are killed. This effect is multiplied by the number

TABLE II
CHEMOTHERAPY OPTIMIZATION ALGORITHM

Objective Function	
Equality Constraints	$Cells_{nor,n,j} = f(effect_{n,j})$
	$Cells_{leuk,n,j} = f(effect_{n,j})$
	$effect_{n,j} = f(C_{M,n,j})$
	$C_{M,n,j} = f(\inf low_{n,j})$
	$Inflow_{n,j} = \sum_{n=1}^{n=NA} \dfrac{u_{n,j}}{t_{n,j}} \cdot (t_{n,j} - \tau_n)$
Inequality Constraints	$Cells_{nor}\big|_{n=NA} \geq Cells_{leuk}\big|_{n=NA}$
	$Cells_{nor} \geq 3 - \log reduction$

TABLE III
PK, PD, AND CELL CYCLE PARAMETERS AND INTERINDIVIDUAL RANGES
USED FOR MODEL SENSITIVITY ANALYSIS AND SI RESULTS

	Symbol	Default Value	Deviation	Sensitivity Index
PK	$k_{l,Ara-C}$	0.069	0.067-0.07	0.0007
	$k_{k,DNR}$	1.5	0.036-1.7	0.017
	$k_{l,DNR}$	0.015	0.014-0.017	0.000085
PD	$E_{max,Ara-C}$	0.83	0.79-0.86	0.0003
	$E_{50,Ara-C}$	0.29	0.25-0.33	0.0049
	$E_{max,DNR}$	0.91	0.88-0.93	0.00925
	$E_{50,DNR}$	0.09	0.076-0.1	0.0928
	$slope_{DNR}$	1.23	1.06-1.4	0.000468
Cell Cycle	T_s	15	6-43	**0.2705**
	T_C	60	18-211	**0.604**

*$k_{l,Ara-C}$ is the Ara-C liver elimination rate (min⁻¹) ; $k_{k,DNR}$ DNR clearance rate by the kidneys ($\frac{lt}{min}$); $k_{l,DNR}$ is the DNR elimination rate in liver (min⁻¹); $E_{max,Ara-C}$ is the Ara-C maximum drug effect; $E_{50,Ara-C}$ is the Ara-C concentration at half drug effect ($\frac{mg}{lt}$); $E_{max,DNR}$ is the DNR maximum drug effect ; $E_{50,DNR}$ is the DNR concentration at half drug effect ($\frac{mg}{lt}$); $slope_{DNR}$ is the slope scaling factor for DNR kinetics; T_s is the S-phase duration (hr); T_C is the Total cell cycle duration (hr).

of cells reacting with drug in order to calculate the number of cells dead due to treatment and the cells which remain after drug action. The mass balance is in (5), where, y is the cell cycle phase (y: G1, S, G2M), P_y is the cell population in phase y and k is the transition rate of cells from one phase to its proceeding phase, i.e., k_{y-1} is the transition rate from phase $y-1$ to phase y.

The SC route is an alternative route of drug delivery wherein the chemotherapy is injected directly into the patient's subcutaneous tissue (S). In this type of drug administration, the drug inflow reaches the systemic circulation with a certain time delay (absorption rate) and in a decreased amount (bioavailability) as some of the initial drug given is bound during absorption through to the blood compartment. For the model of the SC route, (2) will be replaced by (2a) and (2b) which account for drug bioavailability (k_b) and absorption delay (k_a).

III. OPTIMIZATION ALGORITHM FOR CHEMOTHERAPY SCHEDULING

The aim of remission-induction therapy is to debulk the tumor and restore normal BM function. By the end of treatment, the leukemic population should be reduced to a level of at most approximately 10^9 cells, at which point BM hypoplasia is achieved. Moreover, the normal cell population should be higher than that of the leukemic and a 3-log reduction is set as the maximum permissible level of population reduction. Treatment design will be mainly based on the control of four schedule parameters, i.e., the drug used, the dose load, the dose duration, and the number of dose applications. The optimization algorithm is presented in Table II.

The objective function is the minimization of the leukemic cells ($Cells_{leuk}$) subjected to the treatment schedule that is defined by the drug used (j), the dose load ($u_{n,j}$), the dose duration ($t_{n,j}$) the number of applications (NA) and the interval period between two succeeding dose applications (τ_n). The four first parameters are the optimization schedule variables, whereas, the interval period between two doses is a design variable defined by preclinical drug testing and/or by treating clinicians.

The feasible optimization solutions are defined by the set of the equality and inequality constraints. Equality constraints consist of the expressions used to calculate the number of leukemic and normal ($Cells_{nor}$) cells throughout the treatment. Both cell populations are functions of the drug PD effect ($effect_n$) that is defined by the drug concentration profile at the tumor site, i.e., the BM ($C_{M,n,j}$). The drug concentration profile is determined by the treatment inflow, a variable calculated by the schedule and design parameters. Moreover, the inequality constraints consist of constraints on the number of normal cells with a maximum population reduction set to 3-log throughout the treatment (path-constraint) and by treatment completion they will have to be higher than that of the number of leukemic cells (end-point constraint).

IV. RESULTS

A. Sensitivity Analysis

To gain a further understanding of the model and the crucial parameters affecting treatment outcome, i.e., the level of leukemic cells, a global sensitivity analysis and quasi-Monte Carlo-based high-dimensional model representation using Sobol's indices was performed using the GUI-HDMR software [17]. The output of interest is the number of leukemic cells and the parameters checked are for the cell cycle times, PK and PD (see Table III).

Specifically, drug elimination rates in the liver were included for the studied drugs as interpatient variability has been previously reported [18], [19]. Patient variability for DNR renal clearance is well-documented; however, there is no measured

Physiological Patient Characteristics				
	Sex	Age (yrs)	Height (m)	Weight (kg)
Patient 1	F	61	1.60	70
Patient 2	F	68	1.60	70
AML Population Characteristics				
	Tumor burden (blasts/kg)	G_1-phase duration (hrs)	S-phase duration (hrs)	G_2M-phase duration (hrs)
Patient 1	$1.82 \cdot 10^{11}$	61	19	3.62
Patient 2	$1.12 \cdot 10^{11}$	24	22	3.47

variability for renal excretion of Ara-C at the proposed doses and this parameter is not included in the sensitivity analysis. For analysis of interpatient PD variability, previously reported parameters [20] have been used which include analysis of PD action of DNR and Ara-C on BM samples of 179 patients with AML.

For the calculation of parameters sensitivity index (SI), 40 000 simulations were run of all the possible combinations of the tested parameters within their assigned ranges. The SI results are presented in Table III.

The SA results clearly indicate that the duration of the cell cycle phases is the most crucial parameter where the whole cell cycle duration (T_c) has an effect of 60.4% and the DNA replication, S-phase (T_s), has 27.05% effect on the treatment outcome. Of note, the limit for a parameter to be considered crucial for the measured variable is at least 10%.

B. Simulation Results

The presented model is used for the simulation analysis of two different chemotherapy protocols, the LD Ara-C and DA protocols, consistent with current standard clinical practice [11]. LD Ara-C consists of (SC) Ara-C doses of 20 mg administered every 12 h for 10 days, whereas, DA consists of DNR 60 mg/m^2 infused for 1 h IV on days 1, 3, and 5 with Ara-C 100 mg/m^2 injected IV every 12 h for 10 days, also starting on day 1 of the protocol. The two protocols (LD Ara-C and DA) are simulated for two patient case studies using previously published AML- and patient-specific data [2]. Table IV lists the cell population and physiological characteristics of the two patient case studies. For the normal cell population, published data from the work of [21] are used and for the PK and PD information of the two drugs, parameters in Table III are set to their nominal values.

In clinical practice, AML treatment usually consists of four chemotherapy cycles of either the nonintensive LD Ara-C or the intensive DA protocol with interval recovery periods between chemotherapy cycles of approximately 25 days when no drug is supplied. During this period, frequent blood tests take place to monitor patient blood and immune system recovery, i.e.,
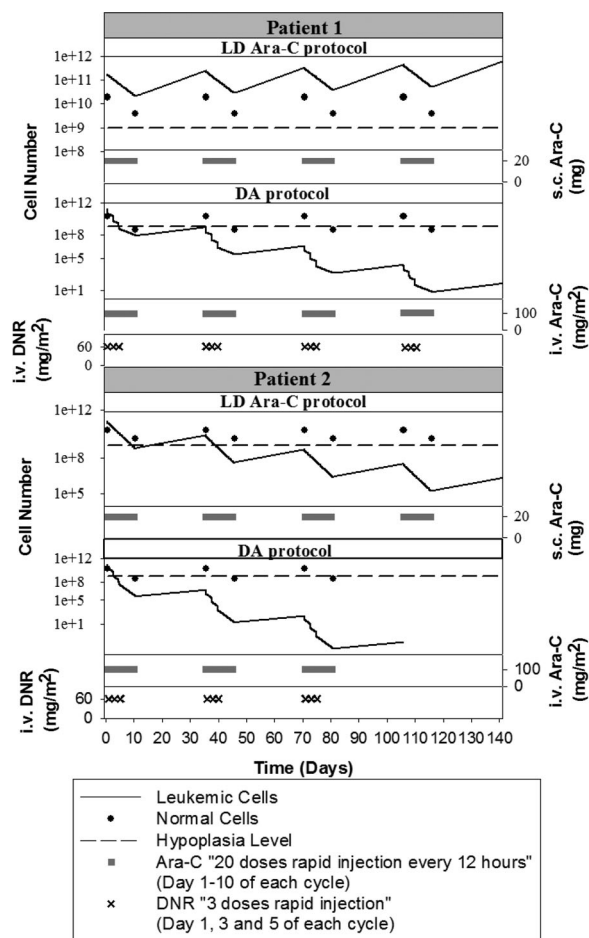

Fig. 2. Simulation results for the full treatment course using LD Ara-C and DA protocols for patients 1 and 2.

the recovery of the level of leukocytes, platelets, and erythrocytes. Practical limitations restrict the acquisition of recurrent data-points for the number of leukemic/blast cells throughout treatment; the number of BM aspirations is limited for patient safety and ethical reasons. This "black box" period increases the uncertainty for the analysis of clinical data as the behavior of leukemic cells is unknown.

Based on clinical experience over this period, recovery of normal populations will be achieved with a risk of disease relapse. A 1-log leukemic cell increase is assumed in our model that is expressed by cell cycle times T_s and T_c equal to 40 and 211 h, respectively [22] assuming a slower attrition rate. We have assumed slower cell expansion as chemotherapy administration causing BM hypoplasia will also alter the BM microenvironment and initially limit the previously permissive effects enabling rapid leukemic cell growth.

The disease behavior of the two patients presented in Table IV is simulated for the full course of treatment using DA and LD Ara-C. The calculated normal and leukemic populations for each chemotherapy cycle of the two patients are shown in Fig. 2.

Patient 1 shows resistance to LD Ara-C from the first cycle of treatment as tumor debulking is suboptimal, to a level of less than

1-log reduction. At the start of the second cycle, the AML cell number is $2.44 \cdot 10^{11}$ (see Fig. 2), higher than the initial tumor load of $1.82 \cdot 10^{11}$ cells (see Fig. 2). This pattern is kept throughout treatment and, at completion of the four cycle course, AML disease burden is maintained at $5.89 \cdot 10^{11}$ cells, indicating that this protocol may not by adequate to induce a remission for this case study as indicated by model simulation; the leukemic population is consistently higher than that of the normal for the entire course of nonintensive treatment. In contrast, the DA protocol simulation clearly demonstrates effectiveness for Patient 1. The leukemic burden decreases to $<10^9$ cells and BM hypoplasia is achieved from the first chemotherapy cycle. Moreover, even with the first cycle of DA, the leukemic population is debulked to a level enabling a relative excess of normal cells (see Fig. 2), achieving one of the major objectives of remission-induction for AML.

For Patient 2, both protocols are effective at reducing the leukemic burden to less than that required to achieve hypoplasia, i.e., 10^9 cells. However, with DA, the leukemic population is undetectable from completion of the third cycle, whereas residual disease ($1.9 \cdot 10^6$ cells) remains after completion of LD Ara-C, although still at a level compatible with the standard definitions of complete morphologic remission, i.e., total AML burden of $<10^9$ cells.

This difference in the level of leukemic burden throughout the treatment course of Patient 2 is due to the increased toxicity of DA that results in a decreased number of normal cells as well. The calculated normal population reduction is 1-log after LD Ara-C and 2-log after DA. Moreover, for both chemotherapy protocols, the leukemic population of Patient 2 is decreased from the very first chemotherapy cycle to a level at which the normal population is higher. That is an important objective for treatment with chemotherapy as it will allow for normal cells to reconstitute the BM resulting in improved recovery.

Based on the current model, the treatment outcome of AML depends on the initial tumor burden and on leukemia population kinetics. As illustrated by simulation results, Patient 1 is a more difficult clinical challenge compared with Patient 2. Patient 1 is resistant to LD Ara-C, whereas, DA affords better results—regardless, leukemic disease burden is worse compared with that of Patient 2. Patient 2 responds to both protocols (by definition achieving morphologic complete remission), although DA is superior since AML cells are undetectable after the third cycle of simulated intensive treatment.

The difference in treatment outcomes is possibly due to the difference in cell population kinetics between the two patients (see Table IV). The initial leukemic burden of Patient 1 is slightly higher compared with that of Patient 2. Moreover, Patient 1 has higher duration of the G_1-phase, that is the cell cycle phase unaffected by the actions of Ara-C and on which DNR is active. This population is the nonproliferating leukemic population that causes a time delay from the formation of a newly formed cell until its duplication through S-phase. The longer the G_1-phase, the more resistant the cell population to standard chemotherapy since the cells untouched by DNR will continue into S-phase and proliferate once treatment ceases. Moreover, Patient 1 also has a lower duration of S-phase, indicating a high proliferation

rate and faster disease expansion. These three characteristics, long G_1-phase, short S-phase, and high proliferation rate are indicative features of more resistant disease.

According to the current presented results, one would suggest DA for the treatment of both patients. However, consideration of AML population kinetics only is not sufficient for the selection of treatment type or schedule for treatment of individual patients. In clinical practice, choice of chemotherapy type and regimen is determined by the treating clinician by combining personal experience in treating the condition with patient-specific parameters such as age, physiologic state as determined by liver, heart, pulmonary and kidney function, past medical history and potential tolerance (performance status) to the expected toxicities of chemotherapy. For this reason, the purpose of this paper is not to compare the two studied protocols but to optimize and analyze them separately for each patient.

C. Optimization Results

The optimization algorithm presented in Section III is solved for the two patients undergoing simulated treatment with the two studied protocols [11], [19]. For Ara-C in the DA protocol, the bounds of the total drug administration (sum of all applied doses) are set between 50 and 4000 mg/m^2 with dose duration between 1 min (rapid bolus dosing) to 24 h administration (continuous infusion). In contrast, because DNR has a lower threshold for potential toxic effects, the window for dose optimization is stricter with administration within 60 min on days 1, 3, and 5. The only independent variable for optimization of DNR is the dose load that can be within 30–90 mg/m^2 per dose. Moreover, for LD Ara-C, the maximum dose load per day is 40 mg and doses are permitted up to four daily rapid bolus doses or daily continuous doses applications for a maximum period of 20 days.

This optimization problem was formed and solved using gOPT [23] and the optimized treatment protocols for the two patient case studies are presented below.

1) Optimization of the DA Protocol: The purpose of induction chemotherapy is to reduce the leukemic population to a level below that represented in a hypoplasic BM (i.e., 10^9 cells) and below the level of normal cells remaining while permitting a maximum 3-log reduction in the number of normal cells. With these constraints, at the end of chemotherapy, a BM with a recovering normal population and a weakened or ideally undetectable leukemic cell population will be achieved. Simulation results reach the desired BM state for both patients analyzed with DA (see Fig. 2). For this reason, the aim of DA optimization in these patients would not be to increase dose load, i.e., treatment toxicity, but to use the same total dose and optimize for schedule. This optimization problem is solved for the two patients using DA. Standard DA uses DNR 60 mg/m^2 on days 1, 3, and 5 and Ara-C 100 mg/m^2 every 12 h for days 1–10. The optimized protocol suggests daily continuous doses of Ara-C at 200 mg/m^2/day whereas, the same schedule for DNR is maintained as the toxicity window of this drug does not allow for the flexibility of alternative optimization solutions. Fig. 3
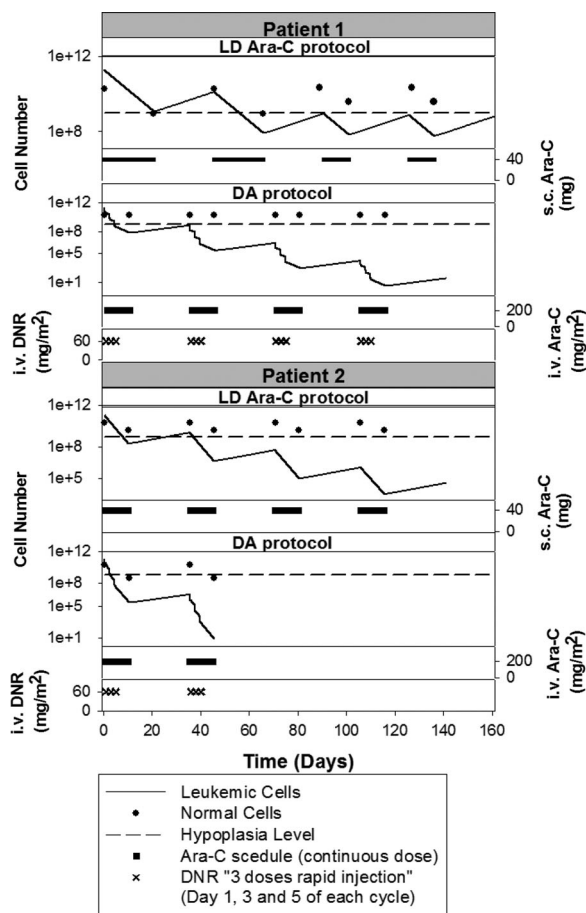
Fig. 3. Optimization results for the full treatment course using LD Ara-C and DA protocols for patients 1 and 2 bolus doses or daily continuous doses applications for a maximum period of 20 days.

summarizes the results using the optimized DA treatment protocol for both patients.

After completion of the first chemotherapy cycle with optimal DA for Patient 1, the leukemic burden is further reduced with a variance of $7.3 \cdot 10^6$ cells compared with that of unoptimized DA at the same time point. This reduction will successively affect the initial conditions of the following chemotherapy cycles resulting in further reduction of leukemic cell numbers and which eventually become undetectable at completion of optimal treatment.

Rapid tumor debulking with optimized DA occurs in Patient 2 where, after the first chemotherapy cycle, leukemic cells are further reduced by $1.2 \cdot 10^5$ cells compared with the same point after an optimized DA. This difference leads to a decreased number of the initial leukemic population for the second chemotherapy cycle, by the end of which AML cells are undetectable and there is no need for a third cycle. Moreover, the normal population is kept to the same order of magnitude for both the simulation and optimization DA protocols. This might be expected considering that normal BM compartments consist of proliferating cells susceptible to chemotherapy as well as a relatively stable supply (dependent on age) of quiescent stem and progenitor cells which are in reserve for the purposes of BM reconstitution

when needed, e.g., after hypoplastic crisis [23]. Since the transition rate of quiescent cells depends on population depletion, the population will be adjusted to the loss and the transition rate will be adapted to keep the population constant [1]. In the optimal protocol, since there is a constant infusion and fewer dosing intervals, it may enable a constant transition of quiescent cells to the proliferating state and result in more robust recovery of normal BM.

2) Optimization of the LD Ara-C Protocol: Standard LD Ara-C consists of 20 mg given SC every 12 h for 10 days on each cycle of treatment. Patient 1 showed resistance to standard LD Ara-C simulated treatment; leukemic burden decreased over each chemotherapy cycle, but over the entire course of treatment, the final leukemic population was higher than that at diagnosis. For this reason, the optimization protocol suggests that for the two first chemotherapy cycles, extended treatment duration to 20 days may be of benefit. For the first two cycles, a total dose increase of 400 mg is suggested (i.e., 800 mg total dose over the first two cycles), administered as continuous SC infusions. Debulking is more effective and, after the end of the second cycle, leukemic cell burden is below the desired hypoplasia level (see Fig. 3). For cycles 3 and 4, the total dose is kept to the same levels as for that of the simulation protocol, i.e., 400 mg but given as continuous daily SC infusions, as in cycles 1 and 2. At the end of optimal LD Ara-C treatment, there is a total 3-log reduction of leukemic cell burden ($6.4 \cdot 10^8$ cells; Fig. 3). This population is below the level defined by complete morphologic remission and below the level of remaining normal cells, meeting the treatment objective. The reduction of normal cells is higher over the first two chemotherapy cycles compared with that during the last two cycles (see Fig. 3) as is expected since the first cycles are of increased toxicity. Moreover, normal cell numbers are greater than that of leukemic onwards from the second chemotherapy cycle (see Fig. 3). The optimization objective is to achieve a higher normal population from the first chemotherapy cycle, but given the aggressiveness of the leukemic population of Patient 1, this constraint had to be relaxed for an optimal solution to be found. Therefore, for Patient 1, the required difference between the normal and leukemic population is relaxed over the first cycle to the maximum possible level and then over the second cycle, the normal population is higher indicating a healthier BM.

Patient 2 had a successful outcome with standard LD Ara-C simulated treatment—leukemic cells were lower than the defined level of complete remission and normal cells were in excess. For this patient, the optimization problem will be to keep the total dose constant, i.e., 400 mg total and determine if there is an ameliorated treatment schedule. This optimization problem is solved and the optimized protocol suggests daily continuous SC infusion of 40 mg/day for 10 days per cycle of treatment.

During the optimized protocol, a reduction of the leukemic burden is achieved, although the total dose is kept constant. This difference increases as chemotherapy continues, due to the lower initial tumor burden of each successive cycle, between cycles 2 to 4. By treatment completion, the leukemic population is further reduced with a variance of $1.86 \cdot 10^6$ cells compared with that of the simulated standard LD Ara-C protocol.

V. DISCUSSION

This paper focuses on the design and optimization of chemotherapy protocols for the treatment of AML. A mathematical model is developed and presented for the full course of treatment using two standard chemotherapy protocols, one intensive (DA) and the other nonintensive (LD Ara-C). The developed model has been created in the gPROMS environment [24] and consists of a model simulator and an optimizer. The required information input for both the simulator and the optimizer consist of patient, disease, and drug information. Sensitivity analysis takes place in this paper using collectible data from the open literature in order to define the parameter ranges for PK, PD, and cell cycle. The results show that cell cycle time is the crucial model parameter that highly affects disease treatment outcome. However, it should be noted that the current model described leukemic and normal population dynamics under the influence of two different chemotherapy protocols using two antileukemic agents. If this model were expanded to cover the comparison of different chemotherapy protocols with a variety of drugs, then the PK information would be equally important for the accurate estimation of treatment behavior. In this case, detailed patient-specific information affecting PK properties such as metabolism, excretion, and clearance rate would be required for the automation of treatment design.

Simulation results are presented over the two chemotherapy protocols for two patient cases [2]. Patient 1 is a more difficult case study in terms of establishing a successful treatment outcome, due to more aggressive leukemic cell population kinetics. Specifically, this patient shows a higher initial tumor burden together with a lower proliferation S-phase and a prolonged nonproliferation state of cells, with limited effect of chemotherapy. Simulation results of this patient show successful treatment outcome only for DA, not for LD Ara-C during which leukemic cells continue to increase. In contrast, Patient 2 displays a better simulated treatment outcome for both protocols. Of note, leukemic cells become undetectable for this patient under the simulated DA protocol.

The treatment objective is to reduce the leukemic population to a level of approximately 10^9 cells at which point BM hypoplasia is achieved and, in terms of leukemia burden, is defined as complete morphologic remission. Moreover, the normal cell population should be higher than that of the leukemic and a 3-log reduction is the maximum level of population reduction permitted per chemotherapy cycle. In this way normal BM reconstitution and function will be achieved and is one of the main aims of remission induction therapy in AML. This optimization problem is solved using gOPT [24] for the two patient case studies.

Overall, the optimization protocols are more efficient and effective in disease management than the simulated protocols applied in standard clinical practice. The common feature for both patients and for both protocols is that continuous infusions of Ara-C are preferred. Using these optimized protocols, BM hypoplasia within each cycle and complete morphologic remission is achieved for all patients with an excess of normal cells onward from the end of cycle 2. Continuous dosing is already performed in clinical practice in the U.S. for AML. Specifically, the DA 7+3 protocol includes Ara-C 100–200 mg/m^2 continuous IV infusion for seven days with standard infusion DNR 60–90 mg/m^2/day for three days. However, the constraints in dosing and duration in the optimization model are control variables that would be modified based on the physician's flexibility on treatment design and will be defined on a patient-by-patient basis, i.e., a stricter window for dose ranges would be preferred for patients with poorer performance status.

AML is a biologically and clinically heterogeneous disease with diverse morphologic, immunophenotypic, and cytogenetic characteristics. Numerous genetic and epigenetic abnormalities as well as changes in the microenvironment in the BM have been detected that lead to AML and, in current clinical practice, an attempt is being made to use some of these changes in the classification of disease, prognosis and treatment modifications toward the design of more specialized clinical protocols. However, in most patients, these factors are currently not useful in treatment design as there is no robust methodology which can apply the data to design of protocols in relation to outcome, nor which can model treatment toxicities in a disease-specific, patient-specific fashion. As most of these changes in AML relate to growth of the leukemic clone(s), we have therefore taken the first step in this work to use growth as related to cell cycle in addition to the PK and PD to model optimized treatment schedules and outcomes. This platform can now be verified in real time with datasets from actual patients who have undergone treatment. Moreover, further elaboration of the PK models of DNR and Ara-C used herein with inclusion of more compartments such as the central nervous system would be of interest in order to quantify other organ-specific drug toxicities. Inclusion of these toxic effects would pose a challenging optimization problem that would account for the patient-specific control of treatment toxicity in other organs at risk and not only that of the normal BM considered in this paper. However, with currently available datasets, it is unrealistic to derive a mathematical model which could accurately describe such an inclusive disease and treatment-response system. In this case, a great pool of parameters would have to be considered with no measured experimental values leading to increased uncertainty in the simulation results. The leading principle behind the current presented model is to include phenomena governed by parameters measured in clinical practice (patient physiological characteristics, treatment schedule, blast percentage in BM aspirate, BM cellularity) and parameters provided by pharmaceutical companies on drug properties (drug half-life, clearance rate) and the only parameters not measured routinely are the cell cycle duration times (a test which could be easily added into routine clinical practice at patient diagnosis using current technology). The ultimate purpose of this paper is to demonstrate the usefulness of mathematical modeling and optimization as advisory tools for treatment design. Further work is required before the findings of this tool are made useful and fit-for-purpose for use in treatment algorithms in clinical practice. The patient case studies and simulated treatment outcomes demonstrate that chemotherapy regimens can be improved by using the same total dose under an optimal

dosing treatment schedule. The derivation of such a system is fundamental for automation and systematic design of optimal personalized chemotherapy treatment protocols with improved effectiveness and outcomes yet limited toxicity.

REFERENCES

[1] E. Pefani, N. Panoskaltsis, A. Mantalaris, M. C. Georgiadis, and E. N. Pistikopoulos, "Design of optimal patient-specific chemotherapy protocols for the treatment of acute myeloid leukemia," *Comput. Chemical Eng. J.*, vol. 57, pp. 187–195, Oct. 2013.

[2] B. Clarkson, T. Ohkita, K. Ota, and J. Fried, "Studies of cellular proliferation in human leukemia. I. estimation of growth rates of leukemic and normal hematopoietic cells in two adults with acute leukemia given single injections of triatiated thymidine," *J. Clin. Invest.*, vol. 46, pp. 506–529, Dec. 1967.

[3] N. Panoskaltsis, C. D. L. Reid, and S. C. Knight, "Quantification and cytokine production of circulating lymphoid and myeloid cells in acute myelogenous leukemia," *Leukemia*, vol. 17, pp. 716–730, 2003.

[4] N. Panoskaltsis, "Dendritic cells in MDS and AML—Cause, effect or solution to the immune pathogenesis of disease?" *Leukemia*, vol. 19, pp. 354–357, 2005.

[5] W. J. Williams, E. Beutler, A. J. Erslev, and M. A. Lichtman, *Hematology*, 3rd ed.   New York, NY, USA: McGraw-Hill, 1983.

[6] P. Dua, V. Dua, and E. N. Pistikopoulos, "Optimal delivery of chemotherapeutic agents in cancer," *Comput. Chemical Eng.*, vol. 32, no. 1/2, pp. 99–107, Jan. 2008.

[7] M. M. Hadjiandreou and G. D. Mitsis, "Mathematical modeling of tumor growth, drug-resistance, toxicity, and optimal therapy design," *IEEE Trans. Biomed. Eng.*, vol. 61, no. 2, pp. 415–425, Sep. 6, 2013.

[8] M. R. Somayaji, M. Xenos, L. Zhang, M. Mekarski, and A. A. Linninger, "Systematic design of drug delivery therapies," *Comput. Chemical Eng.*, vol. 32, pp. 89–98, Jan. 2008.

[9] C. Hall, E. Lueshen, A. Mosat, and A. A. Linninger, "Interspecies scaling in pharmacokinetics: A novel whole-body physiologically based modeling framework to discover drug biodistribution mechanisms in vivo," *J. Pharm. Sci.*, vol. 101, pp. 1221–1241, Mar. 2012.

[10] Y. Hsu and A. A. Linninger, "Quantitative integration of biological, pharmacokinetic, and medical imaging data for organ-wide dose-response predictions," *IEEE Trans. Biomed. Eng.*, vol. 60, no. 3, pp. 625–632, Mar. 2013.

[11] D. W. Milligan, D. Grimwade, J. O. Cullis, L. Bond, D. Swirsky, C. Craddock, J. Kell, J. Homewood, K. Campbell, S. McGinley, K. Wheatley, and G. Jackson, "Guidelines on the management of acute myeloid leukemia in adults," *Brit. J. Haematol.*, vol. 135, pp. 470–474, 2006.

[12] D. Kufe, D. Spriggs, E. M. Egan, and D. Munroe, "Relationships among ara-CTP pools, formation of (Ara-C)DNA, and cytotoxicity of human leukemic cells," *Blood*, vol. 64, pp. 54–58, Jul. 1984.

[13] D. H. Huffman and N. R. Bachur, "Daunorubicin metabolism in acute myelocytic leukemia," *Blood*, vol. 39, pp. 637–643, May 1972.

[14] S. D. Undevia, C. G. Gomez-Abuin, and M. J. Ratain, "Pharmacokinetic variability of anticancer agents," *Nature Rev.*, vol. 5, pp. 447–458, Jun. 2005.

[15] S. Garattini, "Pharmacokinetics in cancer chemotherapy," *Eur. J. Cancer*, vol. 43, pp. 271–282, Jan. 2007.

[16] M. A. G. Essers and A. Trumpp, "Targeting leukemic stem cells by breaking their dormancy," *Mol. Oncol.*, vol. 4, no. 5, pp. 443–450, Oct. 2010.

[17] T. Zhien and A. S. Tomlin, "GUI–HDMR—A software tool for global sensitivity analysis of complex models," *Environ. Modelling Software*, vol. 24, pp. 775–785, Jul. 2009.

[18] UCLH - Dosage Adjustment for Cytotoxics in Renal Impairment (Version 3) (Jan. 2009). [Online]. Available: http://www.eastmidlandscancernetwork.nhs.uk/Library/RenalDosageAdjustments.pdf

[19] BC Cancer Agency. (2006). Cancer drug manual: Daunorubicin. [Online]. Available: http://www.bccancer.bc.ca/NR/rdonlyres/74387BC6-E514-4B BC-9D0F-7AD044B0D287/28818/Daunorubi-cinmonograph_14Apr08_ RW.pdf

[20] A. Quartino, M. Karlsson, A. Freijs, N. Jonsson, P. Nygren, J. Kristensen, E. Lindhagen, and R. Larsson, "Modeling of in vitro drug activity and prediction of clinical outcome in acute myeloid leukemia," *J. Clin. Pharmacol.*, vol. 47, pp. 1014–1021, Aug. 2007.

[21] L. K. Andersen and M. C. Mackey, "Resonance in periodic chemotherapy: A case study of acute myelogenous leukemia," *J. Theor. Biol.*, vol. 209, pp. 113–130, Mar. 2001.

[22] A. Raza, H. D. Preisler, R. Day, Z. Yasin, M. White, J. Lykins, C. Kukla, M. Barcos, J. Bennett, and G. Browman, "Direct relationship between remission duration in acute myeloid leukemia and cell cycle kinetics: A leukemia intergroup study," *Blood*, vol. 76, pp. 2191–2197, Sep. 1990.

[23] B. Lewin, L. Cassimeris, V. R. Lingappa, and G. Plopper, *Cells*, 2nd ed. Boston, MA, USA: Jones & Bartlett Publishers, 2007.

[24] gPROMS, Introductory user's guide, release 2.2, Process Systems Enterprise Limited, London, U.K., 2003.

Authors'photographs and biographies not available at the time of publication.