Mathematical Modeling of Tumor Growth Changes during Combination of Chemotherapy and Radiation Therapy Treatment

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Abstract— Combination therapies are widely used in the treatment of patients with cancer. The main rationale to combine anticancer therapies in the clinic is to obtain a better response with reduced adverse effects. Here i present a pharmacokinetic/pharmacodynamic (PK/PD) model with a smooth nonlinear growth function to characterize and quantify anticancer effect of combination of chemotherapy and radiation therapies using time-dependent data. Based on such a transit two compartment model, Logistic growth Law has proposed a semi-mechanistic pharmacokinetic/ pharmacodynamic (PK/PD) model to assess the antitumor effect. This model describes mathematically the impact of anticancer treatment on the dynamics of tumor growth. From the simulation results of combination of Chemotherapy and Radiation therapy treatment it is observed that, this model will provide better performance than those treatments applied individually.

Key words: Combination Therapy; Cell Proliferation; Logistic Growth Law

I. INTRODUCTION

Looking through the mathematical literature on solid tumor growth a similar pattern emerges:

- The earliest models focused on a vascular tumor growth; then models of angiogenesis were developed; and, now, models of vascular tumor growth are starting to emerge. The improvements in biomedical techniques such as imaging and geneses quenching that have occurred over the past thirty years provide an alternative explanation for this development: as experimental procedures became more sophisticated and knowledge about solid tumor growth increased, the deficiencies of the earlier mathematical models became apparent and pointed the direction for new modeling approaches.[2]
- To understand and predict the pharmacological behavior of anticancer drugs, it is crucial to quantify the time course of pharmacodynamic responses in relation to the plasma concentration. The response of anticancer drugs is delayed relative to the time course of drug exposure. Transit compartment models, originally developed to describe the kinetics of signal transduction processes, were shown to capture this time delay for chemotherapeutic drugs. Based on such a transit compartment model, Simeoni and colleagues have proposed a semi-mechanistic pharmacokinetic/pharmaco dynamic (PK/PD) model to assess the antitumor effect. This model describes mathematically the impact of anticancer treatment on the dynamics of tumor growth. Combination therapies are widely used in the treatment of patients with cancer. The main rationale to combine anticancer agents in the clinic is to obtain a better response with reduced adverse effects. Assessing the nature and intensity of combination drug therapy in vitro has been a challenging topic and many reports can be found in the literature regarding the definition and classification of pharmacological drug–drug interactions.[1]

The objective of this work is to present a method applicable to evaluate anticancer drug combinations in early drug development. The presented approach can be used to assess interaction of drug combination with respect to their synergistic intensity based on the preclinical experiments. In addition, this approach can be applied to test pharmacological hypothesis, such as the assumed pharmacological synergy of complementary inhibition of a particular signaling pathway. The most accurate tumor- growth simulations during RT can be performed using Monte Carlo individual cell simulation techniques. However, it would be difficult to accurately define the initial and boundary conditions necessary to simulate individual tumors. These initial conditions can include vascular structure and nutrition supply, which may differ among individual patients. As a result, we think that simpler practical approaches for radio biologic modeling of tumor mass-volumetric response are needed. In this article, we have further developed the two compartment model and used this model to evaluate tumor-growth dynamics.[3]

II. METHODS

A. Tumor Model [2]

One of the simplest models that can be used to describe the way in which the number of cells N(t) within a solid tumor changes over time is the Logistic growth law which states

$$dN/dt = kN(1 - N/\theta) \text{ With } N(t=0) = No \quad (1)$$

$$\Rightarrow N(t) = \theta\, No / (No + (\theta - No)\, e^{-kt})$$

Where

N (t)-Total number of tumor cells

No-Initial number of tumor cells

θ- Carrying capacity of population (θ>0)

Whilst the logistic growth law predicts almost exponential growth of small tumors and growth saturation when the tumor reaches its carrying capacity (N=θ), the symmetry of N (t) about its point of inflection means that it is not particularly flexible when it is used to fit (or describe) experimental data.

Parameters	Values
Initial number of tumor cells-No	10
Carrying Capacity(Q)	2
Constant(K)	1

Table 1: Tumor Model Parameter Estimates [2]

B. Chemotherapy [1]

During anticancer treatment it is assumed that the basic growth dynamics of the tumor will be perturbed by the anticancer drug effect. Due to drug action, proliferating cells become non-proliferating with a rate depending on the drug Concentration in plasma. This implies that a loss term must be added to the basic equation. To capture the time delay

between drug exposure and the resulting drug action, a transit compartment model has been suggested representing the delayed tumor shrinkage relative to the time course of systemic exposure The pharmacological effect of the anticancer drug on tumor growth is described by the PK of the drug and two drug related parameter, k2 for the potency factor of the drug and k1 for transit rate between the compartments of the non-proliferating cells. This model assumes, that cells affected by drug action immediately stop to proliferate and pass through several stages of damage (x2, x3,…,xN) before they die. Since these non-proliferating cells still add to total tumor mass, total tumor volume w(t) is the sum of proliferating x1 and non-proliferating tumor cells (x2,…,xN). However, only proliferating cells x1 that are not affected by drug action contribute to the tumor growth [1]. The perturbed tumor growth model with 2 compartments then reads.

1) Two Compartment Model (Chemotherapy)

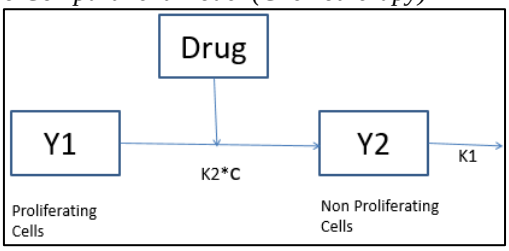

Fig. 1: Schematic representation of transit two compartment model to evaluate anticancer effect of Chemotherapy

Total tumor cells = Y1+Y2

Where

K1,K2-Drug Transit rate

C-Drug Concentration

Where

$$c(t) = Aoral.\exp(-\alpha.t) + Boral.\exp(-\beta.t) - (Aoral + Boral).\exp(-Ka.t) \quad (2)$$

α,β-Exponential Coefficients

Aoral, Boral-Hybrid constants

Ka-Absorption rate

Then the model equations read as

$$Y1'(t) = K\,N\,(1-N/Q) - (K2*C*Y1(t))\;Y1(0) = No \quad (3)$$

$$Y2'(t) = (K2*C*Y1(t)) - (K1*Y2(t))\;Y2(0) = 0 \quad (4)$$

$$W(T) = Y1+Y2 \quad (5)$$

Parameters	Values
Drug dosage(mg/L)-Aoral	77.2
Drug dosage(mg/L)-Boral	0.745
α(1/h)	3.11
β(1/h)	6.63e^-1
Absorption rate (1/h)-Ka1	4.42
Transit rate K1(1/h)	6.66e^-1
Transit rate K2(1/h)	7.73e^-3

Table 2: Chemotherapy Model Parameters Estimates [1]

C. Radiation Therapy [3]

Tumor irradiation with dose D causes the death of a certain percentage of tumor cells. The survival process of live cells can be modeled using a LQ (linear-quadratic) model, which is given by

$$S = \exp(-(\alpha*D) + (\beta*D^2)) \quad (6)$$

Where

S-Cell survive curve

D-Radiation dosage

α, β-Radiation coefficients

The survival curve S defines the relative number of cells that survive; therefore, the relative number of cells that are killed by radiation is given by 1-S. The irradiation with fractional dose Dk does not affect the cells that are already lethally damaged; hence, the new lethally damaged cells have to be added to the previously lethally damaged cells in the tumor.

1) Two Compartment Model (Radiation therapy)

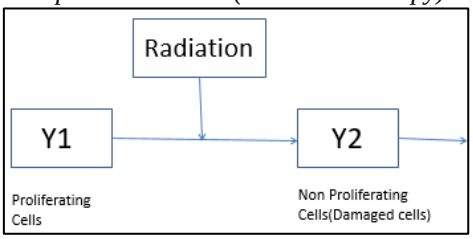

Fig. 2: Schematic representation of transit two compartment model to evaluate anticancer effect of Radiation therapy

Total tumor cells = Y1+Y2

Then the model equations read as

$$Y1'(t) = K\,N\,(1-N/Q) - (S*Y1(t))\;Y1(0) = No \quad (7)$$

$$Y2'(t) = (S*Y1(t)) - ((1-S)*Y2(t))\;Y2(0) = 0 \quad (8)$$

$$W(T) = Y1+Y2 \quad (9)$$

Parameters	Values
Radiation dosage-D (Gy)	1.5
α	0.3
β	0.03

Table 3: Radiation Therapy Model Parameters Estimates [3]

D. Combination of chemo therapy and radiation therapy

In this model the two standard therapies named chemotherapy and radiation therapy are combined and the effect of both drug and radiation on the tumor cells are studied

1) Two compartment model (Chemo therapy and Radiation therapy combined)

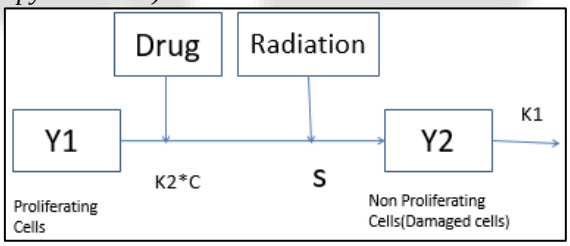

Fig. 3: Schematic representation of transit two compartment model to evaluate anticancer effect of chemotherapy and Radiation therapy combined together

Total tumor cells = Y1+Y2

Where

$$c(t) = Aoral.\exp(-\alpha.t) + Boral.\exp(-\beta.t) - (Aoral + Boral).\exp(-Ka.t) \quad (10)$$

α, β-Exponential Coefficients

Aoral, Boral-Hybrid constants

Ka-Absorption rate and

$$S = \exp(-(\alpha*D) + (\beta*D^2)) \quad (11)$$

S-Cell survive curve, D-Radiation dosage and α, β-Radiation coefficients

Then the model equations read as

$$Y1'(t) = K\,N(1-N/Q) - (K2*C*Y1(t)) - (S*Y1(t))\;Y1(0) = No \quad (12)$$

$$Y2'(t) = (K2*C*Y1(t) + (S*Y1(t)) - ((1-S)*Y2(t)) - (K1*Y2(t)) \quad Y2(0) = 0 \quad (13)$$

$$W(T) = Y1+Y2 \quad (14)$$

Parameters	Values
Drug dosage(mg/L)-Aoral	77.2

Drug dosage(mg/L)-Boral	0.745
α(1/h)	3.11
β(1/h)	6.63e^-1
Absorption rate (1/h)-Ka1	4.42
Transit rate K1(1/h)	6.66e^-1
Transit rate K2(1/h)	7.73e^-3
Radiation dosage-D (Gy)	1.5
α	0.3
β	0.03

Table 4: Combination of Chemotherapy and Radiation Therapy Model Parameters Estimates [2] [3]

III. RESULTS AND DISCUSSION

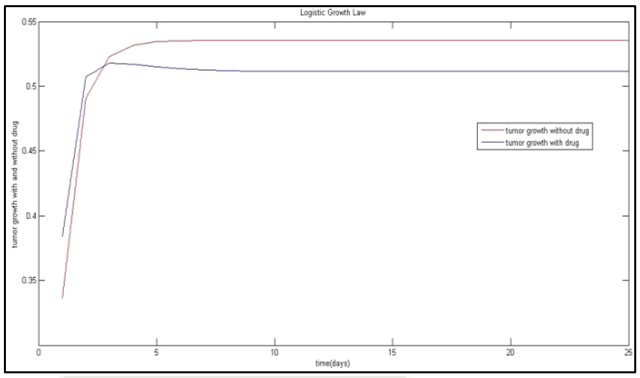

Fig. 4: Tumor growth changes during Chemo therapy alone

In Fig 4, X axis is labeled as time in Days and Y axis labeled as tumor growth in percentage. From fig4 it is observed that tumor growth is reduced after applying drug.

The scope of this study was to present a modeling approach that allows characterizing and quantifying the interaction of drug combination and to get guidance for early discovery and development. The relevance and applicability of the presented PK/PD model was demonstrated; it was shown that this approach is of practical use as it can be applied to assess combination therapy in real time experiments and it enables to identify synergistic drug combinations. The unique feature of the enhanced anticancer PK/PD model is the ability to characterize the nature of combined pharmacological drug interaction as well as to quantify the intensity of such interactions. Modeling the time course of anticancer effects of combined drugs is desirable because it may facilitate optimization strategies for combination therapy.

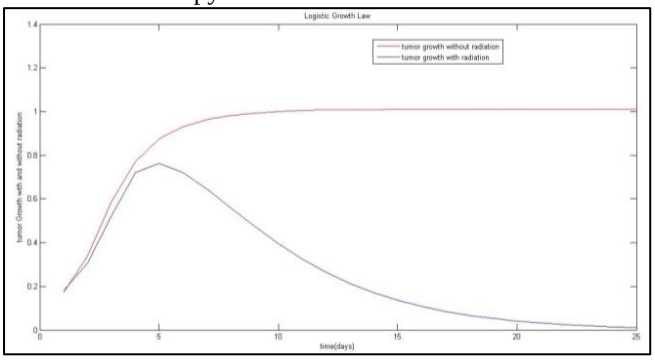

Fig. 5: Tumor growth changes during Radio therapy alone

In Fig 5, X axis is labeled as time in Days and Y axis labeled as tumor growth in percentage. From fig6 it is observed that tumor growth is reduced after applying radiation.

The model was developed to enable a better understanding of the underlying radio biologic processes. The potential application of this model can span from optimization of time intervals between patient imaging to treatment plan optimization using the temporally changing tumor volume.

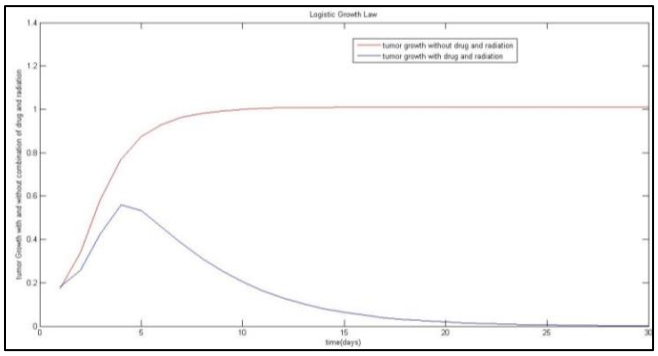

Fig. 6: Tumor growth changes during combination of Chemo therapy and Radiation therapy

In Fig 6, X axis is labeled as time in Days and Y axis labeled as tumor growth in percentage. From fig8 it is observed that tumor growth is reduced after applying drug and radiation together.

Even though the treatment of combination of two therapies namely chemotherapy and radiation therapy is popular but not many models are available. This model will provide an idea about how a tumor growth changes during combination of chemotherapy and radiation therapy treatment applied together.

IV. CONCLUSION

Performance of the treatment is decided by the magnitude of tumor growth changes. During chemotherapy treatment tumor growth started to reduce as the day increases. During Radiation therapy treatment tumor growth reduces better than chemotherapy treatment. During combination of Chemotherapy and Radiation therapy treatment it is observed that this model will provide better performance than those treatments applied individually.

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