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Design and Analysis of Chemotherapy and Immunotherapy Drug Scheduling Model for Cancer Tumour Treatment

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Abstract

This paper presents an investigation into a mathematical model of cancer tumour growth and response with chemotherapy and immunotherapy treatments. d'Onofrio and co-workers[1-3]developed a model to predict and control cancer tumour growth based on cell functions and effects of chemotherapy and immunotherapy. Several design objectives and constraints were used to obtain optimal drug scheduling. These included (i) maximizing tumour cell killing, (ii) tolerable drug concentration, (iii) tolerable body temperature rise and (iv) normal increase of vasculature cell at the end of treatment regime [1]. This paper, initially, implements the model in a simulation environment and then analyzes it with several drug doses that maximize killing of cancerous cells and increase normal vasculature cells during and after treatment period. Then a number of doses have been designed heuristically to improve aforementioned treatment objectives and to analyze the effects of chemotherapy and immunotherapy further. The designed doses show significant improvement in terms of cancerous cell killing with a normal recovery of vasculature cell after the treatment period. This paper also presents an investigation into parameter sensitivity of the model that shows tumour response with different model parameters and drug doses.

Keywords: Chemotherapy, Drug scheduling, Immunotherapy, Malignant cell, Vasculature cell.

I Introduction

Cancer is one of the major diseases of humanity. Cancer arises from a mutation of genes which are responsible for the correct reproduction of cells. The final result is a malignancy, a tumor, which grows uncontrolled and invasive. Classic treatments contain the removal of the tumour by surgery, radiotherapy, immunotherapy and also chemotherapy, which means infusion of drugs that inhibits or stops the growth of tumor cells[4-5]. Chemotherapy, in general, affects non-tumor cells, a negative side effect, which has to be kept under control. Such therapies may be combined with additional therapies, like anti-angiogenesis, which has an effect on the blood vessel in the neighborhood of the tumor, or immunotherapy which aims at a stimulation of the patients' immune system[4-5]. Particularly for medical treatments such as chemotherapy, immunotherapy, anti-angiogenic therapy, and a combination of them, time and amount of drug infusion may be crucial, since the cell population undergo complex processes. As a result mathematical Modeling, simulation, and optimization have become an indispensable ingredient of research[3-9]. This paper presents an investigation into a mathematical model of cancer tumour growth and response with chemotherapy and immunotherapy treatments.

II. Cancer Chemotherapy Model

The cancer tumour model developed by d'Onofrio and co-workers[1-2] is modification of Hahnfeldt model[10].The model consists of two states, three control and eleven parameters in three parameter sets. It contains a combination of chemotherapy and immunotherapy. Model equations are stated below[3]:

$$X_o`(t) = -\epsilon x_o(t) \ln (x_o(t)/x_1(t)) - \phi x_o(t) u_{1,}(t) \text{-----} \quad (1)$$

$$X_1`(t) = b\, x_o(t) - \mu\, x_1(t) - d\, x_o(t)^{2/3} x_1(t) - \gamma \mu_0(t) -$$

$$x_1(t) - n\, \mu_1(t) x_1(t) \text{ ----------} \quad (2)$$

$$X_2`(t) = \mu_0(t) \text{ ----------} \quad (3)$$

$$X_3`(t) = \mu_1(t) \text{ ---------- --------} \quad (4)$$

Here, ϕ = cells killed per unit time per unit drug concentration, b = Vasculature cell carrying capacity, ϵ =Tumor growth rate, d =carrying capacity of tumour cells, μ = Vasculature cell growth factor, γ = The mutation rate of vasculature cells, n = drug decay, $\mu_{0=}$ immunotherapy dose and $\mu_{1=}$ chemotherapy dose.

Equation (1) represents tumour population x_0 after the treatment regime whereas volume of vasculature cell after treatment regime is expressed by equation (2). Equation (3) and (4) represent applied immunotherapy and chemotherapy doses. Parameter sets of the model are shown in Table 1.

Table. 1. Parameter sets[3]

Model parameters	Values
ϕ	0.1 day^{-1}
ϵ	0.084day^{-1}
b	0.17 day^{-1}
d	0.00873 day^{-1}
μ	0.02 day^{-1}
γ	0.15 day^{-1}
n	0.1 day^{-1}
y_{max}	350 Mg
z_{max}	450 Mg
u_{max}	75 Mg
v_{max}	75 Mg

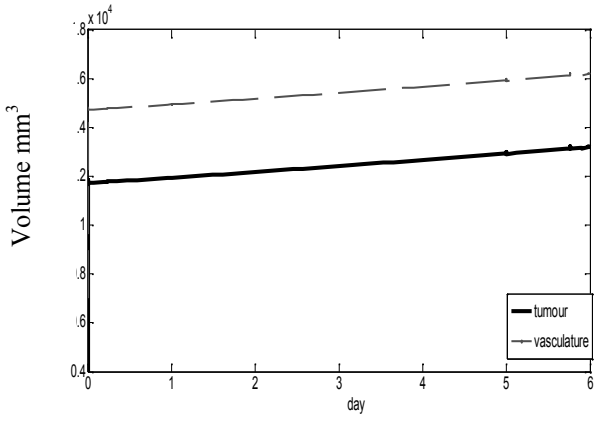
III. Implementation and Results

The whole model, as stated earlier, is implemented in Matlab/Simulink[11] environment where standard set of parameters, as indicated in Table 1 is used. Matlab/Simulink is chosen as it offers easier implementation and visualization of response of such system. It is to be noted that following constraints in relation to drug doses must be maintained while implementing the model.

Table. 2. Design constraint values[3]

Design constraint	**Accepted values**
Cumulative immunotherapy doses	≤ 350mg
Cumulative chemotherapy doses	≤ 450mg

Figure 1 shows the growth of vasculature and tumour cells when no therapy is applied. Both vasculature and tumour cells show gradual increase in course of time. Initial volume of tumour is 1.2×10^4 and it reaches to 1.3×10^4 after one week which is about 10% of the initial value. In case of vasculature cell, initial volume is 1.5×10^4 and it reaches to 1.62×10^4. When no therapy is used, both tumor cell and vasculature cell volume are maximum in number. In cancer treatment, chemotherapy works on tumour and immunotherapy affects the vasculature cells those help the cancerous cells to spread. So both the cells must be reduced initially. But at the end of treatment plan, it is targeted that tumour cells are in falling trend and affected vasculature cells are in the recovery phase. Several treatment cases are tested on the model and the cases listed below:



Time (day)

Fig. 1. Growth of vasculature and tumour cells without any therapy.

Case 1: High chemo dose between 4th and 5th day with some variations of immunotherapy.

Case 2: High chemo and immunotherapy dose for 2 & 4 days respectively.

Case 3: High chemo dose between after 1st day with some variations of immunotherapy.

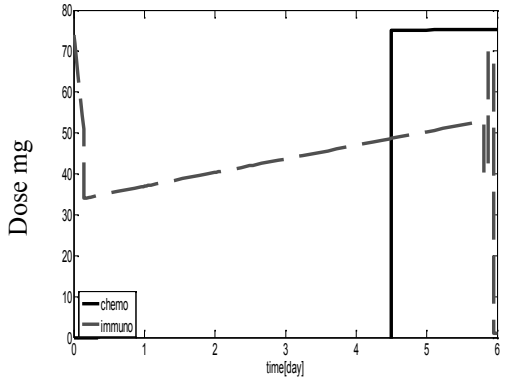
Case 4: High chemo dose between at the start of 4th day with gradual increase of immunotherapy.

Case 5: High chemo dose at the start of 2nd day with gradual increase of immunotherapy

Case 6: Maximum dose of chemotherapy is applied through the whole session.

Following sections will discuss response of each case and corresponding results.

Case 1: Figure 2 shows chemotherapy and immunotherapy drug doses and corresponding responses of tumour and vasculature cells with Case 1. Prior to treatment, volumes of tumour and vasculature cells were $12000mm^3$ and $14000mm^3$ respectively.



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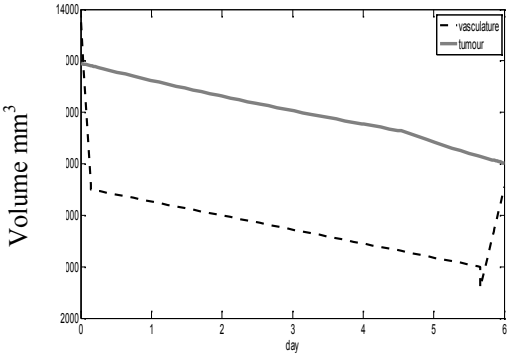

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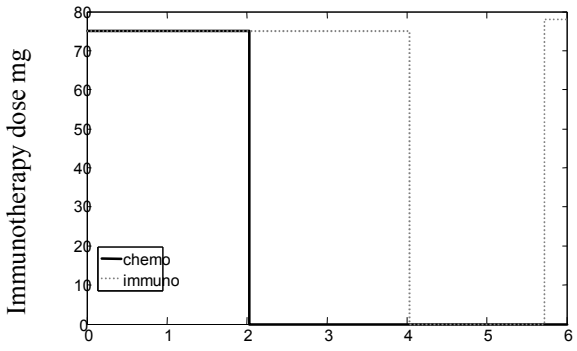
(b)

Fig. 2. (a) Chemotherapy and Immunotherapy drug doses, (b) Response of cells with Case 1 treatment plan

Maximum immunotherapy dose is applied at first, drug dose falls to 30mg. Then it is closely monitored and increased gradually to 60mg. Due to high dose of immunotherapy, vasculature cell volume falls drastically from $14000mm^3$ to

6000mm^3 and then gradually decreased to 4000mm^3. Due to rapid destruction of vasculature cells, tumour cells do not get the opportunity to grow. The volume also reduced to 10000mm^3 from 12000mm^3 without any chemo application. Between 4thand 5th day maximum dose of chemo is applied and continued till end. At last tumour volume is also reduced to 9000mm^3.

Case 2: Maximum amount of chemo & immunotherapy dose is applied at first, chemo dose is reduced to 0 after 2 days but immunotherapy is continued for 4 days. Figure 3 shows chemotherapy and immunotherapy drug doses and corresponding responses of tumour and vasculature cells with Case 2. Tumour cell volume is reduced rapidly to 75% within two days as an effect of chemotherapy and then gradually to 8000mm^3 due to continuation of immunotherapy. Vasculature cell volume reduces to 5000mm^3 from 14000mm^3 due to both high chemo and immune dose. Then due to absence of chemo dose vasculature cell goes to the recovery phase.



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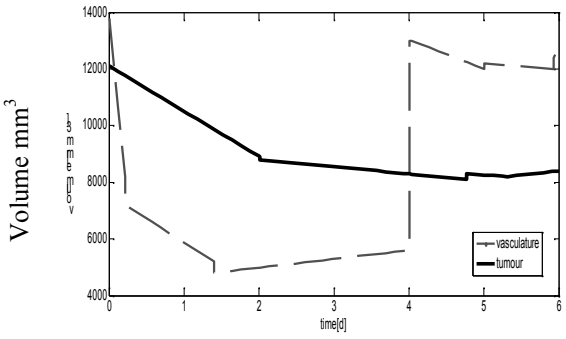
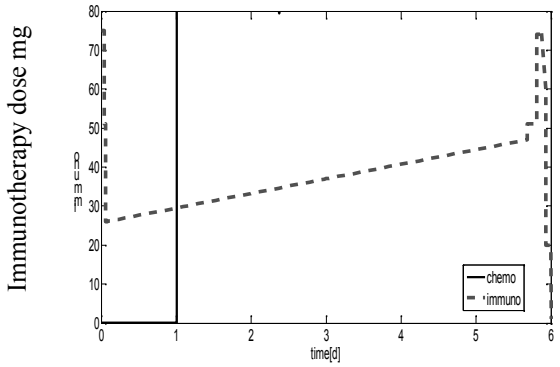


(b)

Fig. 3. (a) Chemotherapy and Immunotherapy drug doses, (b) Response of cells with Case 2 treatment plan

Case 3: Figure 4 shows chemotherapy and immunotherapy drug doses and corresponding responses of tumour and vasculature cells with Case 3. Vasculature cell volume is decreased from 14000mm^3 to 7500mm^3 i.e. about 50% of its initial value very rapidly and then gradually decreased more than 30%. Tumour cell volume also reduced slightly due to immuno therapy effect. When high dose of chemotherapy is applied there is a rapid reduction to 4000mm^3, about 67% reduction is achieved.



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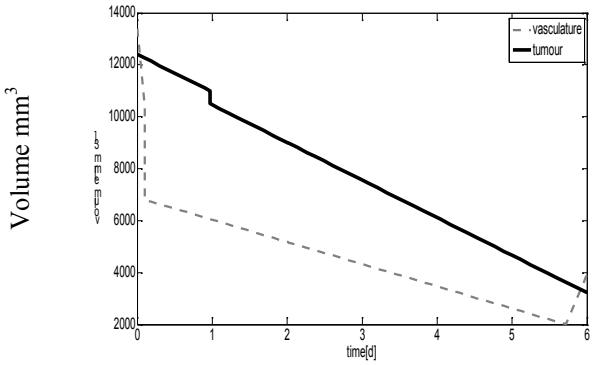

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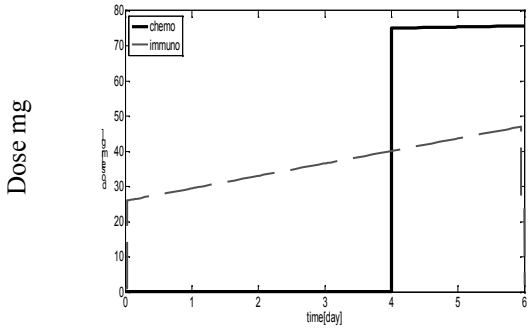
Fig. 4. (a) Chemotherapy and Immunotherapy drug doses, (b) Response of cells with Case 3 treatment plan

Case 4: Figure 5 shows chemotherapy and immunotherapy drug doses and corresponding responses of tumour and vasculature cells with Case 4 treatment plan. Immunotherapy dose is increased to 25mg at the very beginning of the treatment and then gradually increased up to 50mg. Prior to immunotherapy the vasculature cell volume is increased from 5000 mm^3 to 9000mm^3 and then decreased from 9000 mm^3 to 4000 mm^3 as the response of immunotherapy—reduction rate is 55%. Such a reduction of vasculature cell also causes the reduction of tumour cell volume from 14000mm^3 to 11000mm^3 i.e. 22% reduction without any chemotherapy. Then before 2 days of the cycle the maximum dose of chemotherapy is applied and cancerous cell volume reduces to 8000mm^3 which is 56% of the initial value. It means another 22% reduction in 2 days for maximum chemo dose. At the end

immunotherapy is decreased to zero to facilitate vasculature cell reproduction.



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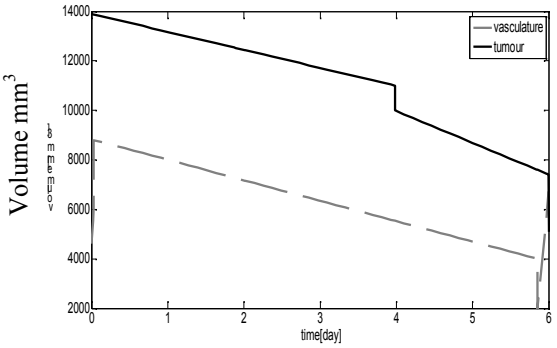
(a)



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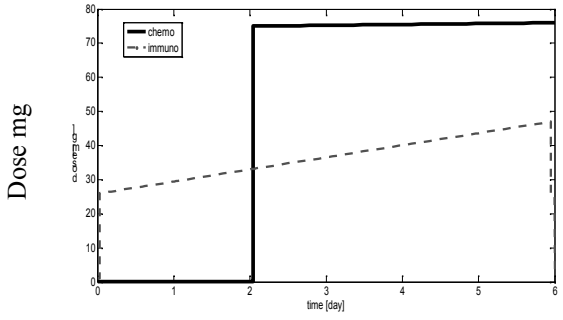
(b)

Fig. 5. (a) Chemotherapy and Immunotherapy drug doses, (b) Response of cells with Case 4 treatment plan.

Case 5: In this case, immunotherapy dose is increased to 25mg at the very beginning of the treatment and then gradually increased up to 50mg. Figure 6 shows chemotherapy and immunotherapy drug doses and corresponding responses of tumour and vasculature cells with Case 5.



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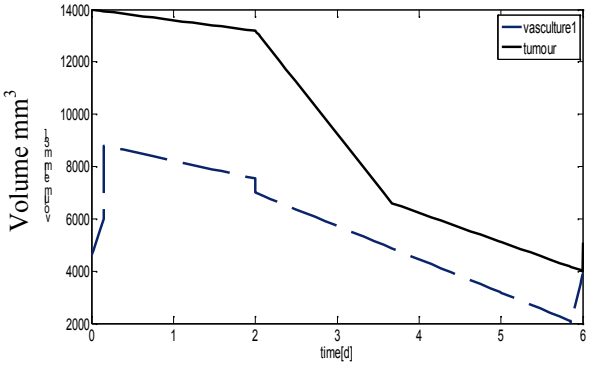

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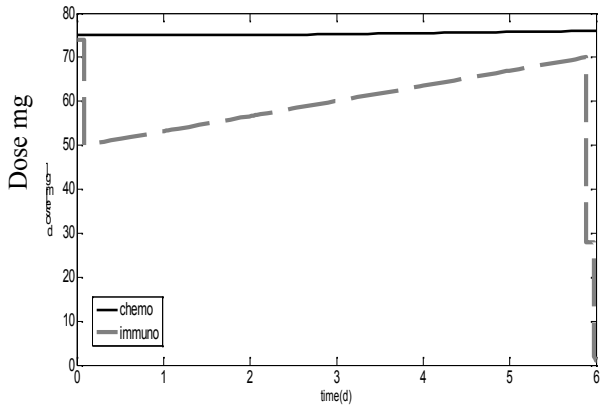
(b)

Fig. 6. (a) Chemotherapy and Immunotherapy drug doses, (b) Response of cells with Case 5 treatment plan.

The vasculature cell volume reduction is 77%. Then after 2 days the maximum dose of chemotherapy is applied and cancerous cell volume reduces to 4000 mm^3 which is 28% of the initial value. At the end immunotherapy is decreased to zero to facilitate vasculature cell recovery phase.

Case 6: Figure 6 shows chemotherapy and immunotherapy drug doses and corresponding responses of tumour and vasculature cells with Case 6. It is observed that, cancerous cell volume reduces from 12000 mm^3 to 4000mm^3, i.e. reduction is about 67%. Immunotherapy is decreased from 75mg to 50mg and then slowly increased up to 60mg. Due to the high dose of both the therapy vasculature cell volume decreased from 14000mm^3 to 6000mm^3 : reduction is 57% at the beginning and finally reaches to 2000 mm^3 i.e reduction is 87% from initial value. Such a reduction of vasculature cell also causes the rapid reduction of tumour cell volume. The end value of vasculature cell recovery is 4000mm^3. Performance measures of different treatment cases are summarized in Table 3.



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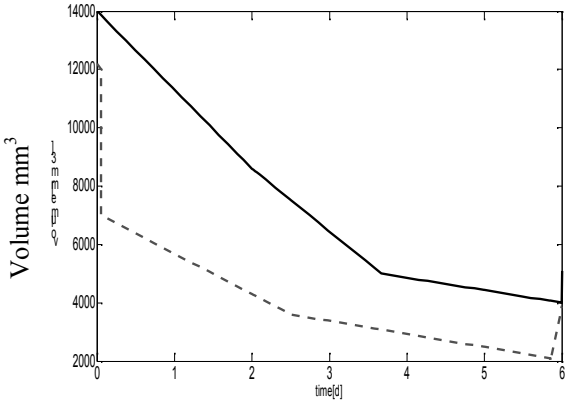


(b)

Fig. 7. (a) Chemotherapy and Immunotherapy drug doses, (b) Response of cells with Case 6 treatment plan

Remarks

In Case 3, there is a maximum reduction of tumour cell volume at the cost of high chemo dose. It also affects the vasculature cells to a great extent. Recovery to the normal state requires a long period. In case 4, although reduction is 43%, it requires 40% chemotherapy compared to Case 3. Vasculature cells are not too much and there is a normal increase of volume at the end compared to prior the treatment. So Case 4 can be considered most suitable to apply.

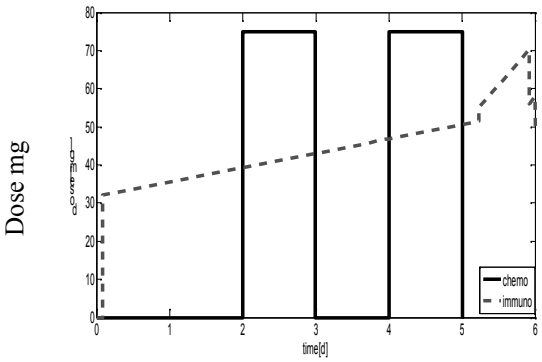
IV. Heuristically Design Drug Doses and Their Effects

Since Case 4 delivers the best results, the scheduling can be modified to achieve even better response. Several combinations are tested and two more cases, namely, Case 7 and Case 8, are presented in this section. In case 7, high dose of chemotherapy is applied between 2nd and 3rd day & then again between 4th and 5thday. For immunotherapy there is a gradual increase. In Case 7, cumulative chemotherapy and

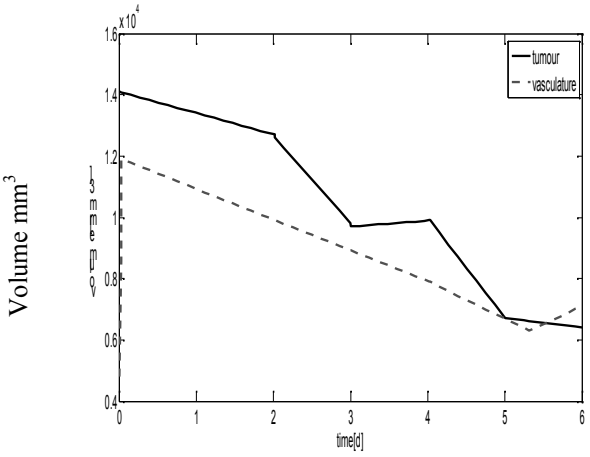
Table. 3. P**erformance measures of different treatment cases**

Cases	Cumulative dose of chemo (mg)	cumulative dose of immuno-therapy (mg)	Tumour cell volume Prior to treatment (mm^3)	Tumour cell volume after treat-ment (mm^3)	Percentage of the reduction	Vasculature cell volume Prior to treatment (mm^3)	Vasculature cell volume after treatment (mm^3)	Percentage of he change of vasculature cell
Case 1	112.5	137	12000	9000	42%	14000	8000	-42.85%
Case 2	150	400	12000	8000	34%	14000	12000	-14.28%
Case 3	375	139	12000	4000	67%	14000	4000	-72%
Case 4	**150**	**190**	**14000**	**8000**	**43%**	**5000**	**8000**	**+60%**
Case 5	300	210	14000	4000	43%	5000	4000	-20%
Case 6	450	365	12000	4000	67%	14000	4000	-72%

immunotherapy doses are 150mg and 313mg respectively. Figure 8 shows drug doses and response of model with Case 7. After the treatment period tumour volume decrease from 14000mm^3 to 6300mm^3.There is natural increase of vasculature cell volume from 6000mm^3 to 6500mm^3. It can be explained as, since there is a rest period of chemotherapy within the treatment schedule, it helps the antibody cells and vasculature cells to recovery from toxic effects of chemo medicine.



(a)

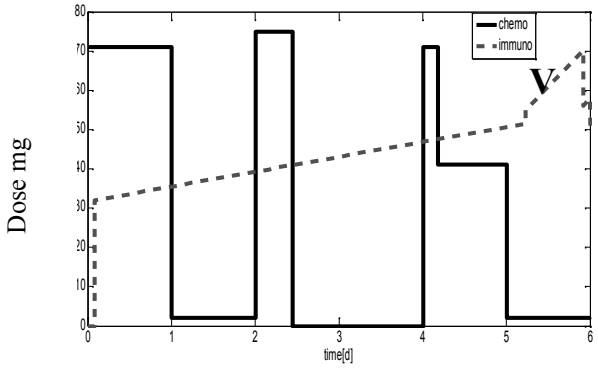


(b)

Fig. 8. (a) Chemotherapy and Immunotherapy drug doses, (b) Response of cells with Case 7 treatment plan.

Figure 9 shows drug doses and response of model with Case 8. Here high dose of chemotherapy is applied at first. Then there is a quick decrease between 1st and 2nd day. Then between 4th

and 5th day there is a step wise decrease to zero. For immunotherapy there is a gradual increase. Cumulative chemotherapy and immunotherapy doses are 155mg and 313mg respectively. After the treatment period tumour volume decrease from 14000mm^3 to 4000mm^3 and vasculature cell volume are reduced from 4000mm^3 to 7000mm^3. All results are shown in Table 4. From Table 4, it is observed that for a fixed immunotherapy by applying a well scheduled chemotherapy it is possible to obtain maximum amount of reduction of tumour volume with very little effect on normal body cell. In Case 8, chemotherapy is 40mg lower than the first case but tumour volume is reduced 18% more because of well scheduling. At the same time vasculature cell volume is in increasing trend by a well margin showing better recovery.



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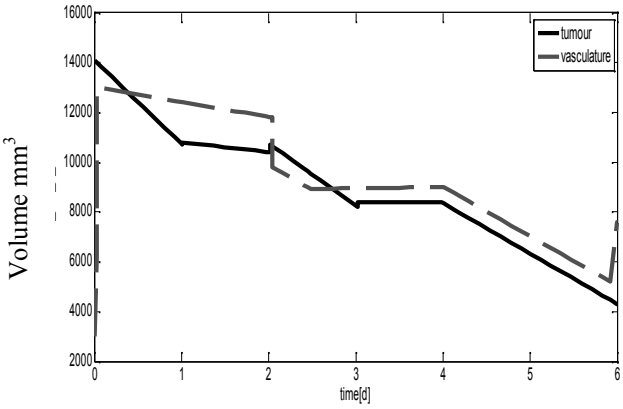

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Fig. 9. (a) Chemotherapy and Immunotherapy drug doses, (b) Response of cells with Case 8 treatment plan.

V. Parameter Sensitivity

In preceding sections, optimum values of three parameters; (i) growth speed of the cancer cells (ϵ), (ii) cells killed per unit time per unit drug concentration(ϕ), and (iii) carrying capacity of vasculature cells(b), as indicated in Table 1, are used. It is also noted that, values of parameters remained unchanged for the whole period to observe the effectiveness of drugs on cancer tumour. It may be mentioned that the predefined set of parameters correspond to a specific physiological condition and drug type under investigation.

Table. 4. Performance measures of different Cases

Cases	Cumulative dose of chemo (mg)	cumulative dose of immuno-therapy (mg)	Tumour cell volume prior to treatment (mm^3)	Tumour cell volume after treat-ment (mm^3)	Percenta ge of reduction	Vasculature cell volume prior to treatment (mm^3)	Vasculature cell volume after treatment (mm^3)	Percentage of change of vasculature cell
Case 7	150	313	14000	6300	55%	6000	6500	+10%
Case 8	155	313	14000	4000	71.43%	4000	7000	+75%

Further investigations are carried out in this section to analyze the sensitivity of the aforementioned three parameters of d'Onofrio et al. model. A particular treatment plan (Case 4) is administered on the tumour model with different values of parameters and output responses of the model, are recorded and analyzed.

At first, the parameter (ϵ), is varied within a range of [0.07,0.1] while setting the remaining parameters at optimum values and results are shown in Table 5. The maximum tumour cell reduction is obtained with 0.07 which is reduced from 15000mm^3 to 9000 mm^3 i.e. 40%. At the same time vasculature cell growth is also suppressed by tumour growth rate.

Table. 5. Effect of (ϵ) on tumour

Values of (ϵ)	upper value of tumour (mm^3)	lower value of tumour (mm^3)	Percentage of reduction
0.07	**15000**	**8000**	**47%**
0.08	15500	8500	45%
0.09	16000	9500	40%
1.0	16500	10000	39.4%

Secondly, the effect of model parameter: cells killed per unit time per unit drug concentration(ϕ) is analyzed in similar way. Here the parameter is varied within a range of [0.115, 0.085]

while setting the remaining three parameters at optimum values. Different performance of tumour model due to the drug scheduling Case 4 and results are shown in Table 6. It is noted that maximum cell reduction is obtained with $\emptyset$ = 0.115 where the volume of tumour remaining is 2000mm^3.

Table. 6. Effects of parameter ($\emptyset$) on tumour

values of($\emptyset$)	upper value of tumour (mm^3)	lower value of tumour (mm^3)	Percentage of reduction
0.115	**15000**	**2000**	**87%**
0.09	15000	4000	73%
0.085	150000	5000	66.6%
0.08	15000	6000	60%

Thirdly, the effect of model parameter: carrying capacity of vasculature cells(b) is also analyzed with treatment plan Case 4 where the parameter is varied in the range of [0.2, 0.145] and results are shown in Table 7. The maximum tumour cell reduction is obtained with b=0.2, for which final volume of tumour is 1500mm^3.

Table. 7. Effects of parameter (b) on tumour

Values of (b)	upper value of tumour (mm^3)	lower value of tumour (mm^3)	Percentage of reduction
0.155	13000	3000	77%
0.180	12000	2500	79%
0.2	11500	1500	87%

VI. Conclusion

This paper has presented a design and investigation into a mathematical model of cancer tumour response with chemotherapy and immunotherapy treatments. Optimal drug dosages and scheduling for chemotherapy and immunotherapy as designed by d'Onofrio and co-workers using several design objectives and constraints have been tested to observe the response of tumour during and after the treatment. Moreover, a number of dosages, both for chemotherapy and immunotherapy, have been designed based on heuristic method in the light of earlier dosages to improve the treatment further. It is observed that instead of applying a high dose for a long time, periodic application of high dose yields better results with regard to tumour volume reduction. The optimal treatment yields a tumour volume 71% smaller than the initial stage. In this paper an investigation into parameter sensitivity of the model has also been presented that helps to predict the effect of drugs on different types of cancer cell as well as effect of different types of drugs on tumour and vasculature cells.

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