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RESEARCH ARTICLE

A Mathematical Model for Differentiated Thyroid Cancer with Combination Therapy

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Abstract

Objectives: Differentiated thyroid cancer (DTC) is usually treated with surgery and radioactive iodine therapy. However, in advanced stages, molecular changes can lead to a progressive loss of sensitivity to iodine, making the cancer resistant to radioactive iodine treatment (known as radioactive iodine-refractory, or RAIR). For cases of RAIR-DTC, alternative treatments such as tyrosine kinase inhibitors and immunotherapy are explored. To better understand the dynamics of these alternative treatments, a new mathematical model has been developed. In this model, Sorafenib represents the tyrosine kinase inhibitor, while Pembrolizumab is the immunotherapy agent under investigation. **Methods:** Two mathematical models were developed based on systems of ordinary differential equations to study differentiated thyroid cancer treated with (1) Sorafenib alone and (2) a combination of a Sorafenib and Pembrolizumab. The first model included three variables: drug concentration of Sorafenib, number of cancer cells, and number of immune cells with fourteen parameters. The second model additionally incorporated the concentration of the Pembrolizumab. Parameter values were estimated through simulations utilizing the fmincon optimization technique in MATLAB. Local asymptotic stability analysis was performed to investigate the models' behavior around equilibrium points. Moreover, the Lyapunov method was employed to establish global asymptotic stability of the models. **Findings:** The findings revealed insights into the dynamics of treating RAIR-DTC patients with tyrosine kinase inhibitors and immunotherapy. The stability analysis contributed to the understanding of the system's behavior under different conditions, offering valuable information for clinical application. Numerical simulations were then performed using Simbiology in MATLAB to simulate the treatment dynamics over time. **Novelty:** This research contributes to the field by presenting a novel mathematical model that integrates tyrosine kinase inhibitors and immunotherapy for the treatment of RAIR-DTC. The comprehensive analysis of equation stability enhances the reliability of the model, while the numerical simulations provide a practical and visual tool for assessing the potential outcomes of the proposed therapeutic strategy. This study offers a valuable framework for further exploration and

refinement of treatment approaches for patients with challenging DTC cases.

Keywords: Mathematical modeling; Routh Hurwitz Criteria; Jacobian; Differentiated thyroid Cancer; Stability Analysis

1 Introduction

Differentiated thyroid cancer (DTC) is the most common type of thyroid cancer, representing over 90% of cases[(1)]. Its incidence has been rapidly increasing, potentially due to improved detection methods and exposure to unknown risk factors[(2)]. DTC is characterized by a generally good prognosis, with treatment typically involving hemithyroidectomy for microcarcinoma and total thyroidectomy with subsequent radioactive iodine-131 (RAI) therapy for other cases[(3)]. The familial form of DTC is becoming more prevalent, accounting for a significant portion of cases, and is associated with heritable predisposition[(4)]. Over diagnosis and over treatment of DTC have led to increased healthcare costs, emphasizing the need for cost-effectiveness studies to guide future solutions[(5)]. Identifying high-risk patient cohorts early on is crucial to tailor treatment effectively and avoid unnecessary interventions.

The combination of tyrosine kinase inhibitors (TKIs) has shown effectiveness in treating refractory differentiated thyroid cancer (DTC) in patients who have undergone radioactive iodine therapy. Studies have demonstrated that TKIs significantly improve progression-free survival (PFS) and overall survival (OS) in patients with refractory DTC, with a notable impact on the objective response rate (ORR)[(6–8)]. Additionally, the use of TKIs in patients with radioiodine-refractory DTC has shown promising results in terms of redifferentiation therapy, leading to the restoration of iodine uptake and retention in a subset of patients, subsequently allowing for successful high-dose radioiodine treatment[(9)]. Therefore, the combination of TKIs and immunotherapy may offer a potent therapeutic approach for managing refractory DTC post-radioactive iodine therapy, potentially improving patient outcomes and prognosis.

Mathematical models play a crucial role in understanding the efficacy of combining tyrosine kinase inhibitors and immunotherapy for treating radioactive iodine-refractory differentiated thyroid cancer (RAIR-DTC)[(10–12)]. By integrating variables such as the concentration of lenvatinib and pembrolizumab, total cancer cells, and immune cells, the model assesses the combined effect of targeted therapy with immunotherapy, favoring the combined treatment due to its ability to enhance the immune system's tumor cell elimination rate[(5)] and also to predict treatment outcomes[(13)]. By incorporating these different variables, the model is able to assess both the local and global stability of the combination therapy approach, providing insights into the complex dynamics involved in the treatment of differentiated thyroid cancer[(14)]. Furthermore, mathematical models aid in identifying predictive biomarkers, optimal dosing schedules, and rational combinations to maximize clinical response in immuno-oncology, emphasizing the significance of middle-out models in evaluating new strategies[(15)].

By simulating the action of drugs in patients with RAIR-DTC, these models reveal the synergistic effect of targeted therapy with immunotherapy, highlighting the combined approach as the most effective treatment option due to its ability to enhance the immune system's tumor cell elimination rate[(16)]. These studies show that the combination therapy of lenvatinib and immunotherapeutic pembrolizumab enhances the immune system's ability to eliminate tumor cells, making it a favorable treatment option for RAIR-DTC patients[(17,18)]. Additionally, the model helps in understanding the synergistic effects of combining therapies, such as the increased radioiodine uptake in certain DTC cell lines after lenvatinib treatment, leading to improved treatment efficacy[(12)]. Gago-Arias et al. (2021) and Lavanya (2023) both developed mathematical models to predict the response of thyroid cancer to radiotherapy, with Gago-Arias

focusing on treatment individualization and Lavanya on the kinetics of thyroglobulin concentrations. These models have the potential to improve treatment outcomes and patient management.

This particular mathematical model for thyroid cancer treatment takes a different approach by considering immune cells. Unlike many previous models that did not account for immune cell populations, this model incorporates immune cells into the equations and dynamics. Including immune cells in the model allows it to capture the interactions between the immune system and the tumor, as well as the potential effects of immune cells on tumor growth and response to treatment. This article presents a mathematical model involving a two step development approach. The first step assesses the effectiveness of Sorafenib in the treatment of RAIR-DTC, while the second step focuses on Pembrolizumab efficacy in the same context. The Sorafenib drug mechanisms include reducing tumor carrying capacity, inhibiting tumor growth, and modifying anti-immune capacity through the activation of immune cells. The pembrolizumab drug mechanism are manifested through the alleviation of PD-1 pathway mediated immune inhibition, leading to an enhancement of the anti-tumor immune response.

2 Methodology

2.1 Construction of Model with Multi Kinase Inhibitor

We recommend administering patients with RAIR-DTC sorafenib therapy with a medication concentration of U. One to two capsules of sorafenib are taken orally per day. We assume the drug U concentration to be a constant function of time in our modeling the tumor cannot be completely removed by the treatment, it is slowed to the point of maximal tolerability. The ODE model under consideration is as follows, presuming that N and I, reflect the numbers of cancer cells and immune cells respectively.

$$\frac{dU}{dt} = D - \delta U$$

$$\frac{dN}{dt} = rN\left(1 - \frac{N}{k_0 e^{-k\alpha(c)}}\right) - \mu UN - (\gamma + \rho_1\left(1 - e^{-\rho U}\right))IN \tag{2.1}$$

$$\frac{dI}{dt} = \sigma + \eta_1\left(1 - e^{-\eta U}\right) - \beta I$$

We choose the function $log\alpha(c) = -(c_0 e^{-cU})t$

Where $D, \delta, r, \mu, \beta, \gamma, \rho, \rho_1, \sigma, \eta, \eta_1$ are positive constants.

Without the treatment,$D = 0, U \longrightarrow 0$, the expressions stipulate a usual and minimal reaction of the immune system, from the minimum value γ and σ. The $k_0 e^{-k\alpha(c)}$ correlate the tumor growth toward the bearing capacity, being directly concerned by the antiproliferation action. The expression $rN\left(1 - \frac{N}{k_0 e^{-k\alpha(c)}}\right)$ is the number of cancer cells. The expression $\rho_1\left(1 - e^{-\rho U}\right)$ represents the decrease in number of cancer cell due to treatment. The expression $\eta_1\left(1 - e^{-\eta U}\right)$ represents the anticipated inflation in the number of immune cells as a result of the treatment. The μUN is the elimination in number of cancer cells as a result of the treatment. The term βI is the elimination of immune cells.

2.1.1 Positive invariance

The system of equation is considered to be well-defined if it defines a positive system with an initial condition

$$\frac{dU}{dt} = D - \delta U$$

$$\frac{dU}{dt} \geq -\delta U$$

$$U(t) \geq U(0)e^{\delta t}$$

$$U(t) > 0$$

$$\frac{dN}{dt} = rN\left(1 - \frac{N}{k_0 e^{-k\alpha(c)}}\right) - \mu UN - (\gamma + \rho_1\left(1 - e^{-\rho U}\right))IN$$

$$N(t) = N(0)exp\left\{\int_0^t r\left(1 - \frac{N(s)}{k_0 e^{-k\alpha(c)}}\right) - \mu U\left(s\right) - (\gamma + \rho_1\left(1 - e^{-\rho U}\right))I\left(s\right)ds\right\}$$

For all $t \geq 0$

Hence all $N(t) \geq 0$ for any non-negative initial values.

$$\frac{dI}{dt} = \sigma + \eta_1\left(1 - e^{-\eta U}\right) - \beta I$$

$$\frac{dI}{dt} \geq -\beta I$$

Both sides multiply by $e^{\beta t}$

$$e^{\beta t}\frac{dI}{dt} + \beta I e^{\beta t} \geq 0$$

$$I(t) \geq I(0)e^{\beta t}$$

$$I(t) > 0$$

Hence, all $I(t) > 0$ for any non-negative initial values.

Hence, the system of equation is well-defined under the initial condition.

2.2 Equilibria and local stability analysis

The parameter value of the Equilibrium of treatment U is

$$u = \frac{D}{\delta}$$

The trivial equilibrium point is, the trivial equilibrium point is.

$$E_0 = \left(\frac{D}{\delta}, 0, \frac{1}{\beta}f(u)\right)$$

$$E_0 = \left(\frac{D}{\delta},\ 0,\ \frac{1}{\beta}f\left(u\right)\right)$$

Where $f(u) = \sigma + \eta_1\left(1 - e^{-\eta U}\right)$

The Unique positive equilibrium is

$$E_1 = \left(u, N^*\left(u\right),\ I^*\left(u\right)\right)$$

With

$$N^*(u) = \frac{k_1 e^{-ku}}{r}\left(r - \mu u - \frac{g(u)f(u)}{\beta}\right)$$

and

$$I^*(u) = \frac{1}{\beta} f(u)$$

Where $f(u) = \sigma + \eta_1 (1 - e^{-\eta U})$

A Necessary & Sufficient condition for equilibrium's existence E_1 is $h(u) = \mu u - \frac{g(u)f(u)}{\beta}$

$$h(u) = \mu u - \frac{g(u)f(u)}{\beta} < r$$

Since f and g are increasing, also h is non-negative and increasing

$$h(0) = \frac{g(0)f(0)}{\beta} = \frac{1}{\beta} g_0 f_0$$

$$\lim_{x \longrightarrow \infty} h(u) = \infty$$

Then following cases arises

Case 1:

If $\frac{1}{\beta} g_0 f_0 \geq r$. Then $h(u) \geq r \; \forall \; d \geq 0$, Which depicts that this is the only trivial equilibrium $E_0 = \left(\frac{D}{\delta}, 0, \frac{1}{\beta} f(u)\right)$ exist.

Case 2:

If $\frac{1}{\beta} g_0 f_0 < r$. Then $\exists$ a unique $d_0 > 0 \ni h(u_0) = r$. In this respect, when $0 \leq u < u_0$, both trivial equilibrium E_0 and non trivial equilibrium $E_1 = (u, N^*(u), I^*(u))$ exist. When $u \geq u_0$ only trivial equlibrium exists.

The jacobian matrix of non trivial equilibrium is

$$J_1 = \begin{vmatrix} -\delta - \lambda & 0 & 0 \\ M & r\left(1 - \frac{N}{k_0 e^{-k\alpha(c)}}\right) - h(u) - \lambda & -g(u)N \\ \eta_1 \eta e^{-\eta U} & 0 & -\beta - \lambda \end{vmatrix}$$

$$= (-\delta - \lambda)\left[r\left(1 - \frac{N}{k_0 e^{-k\alpha(c)}}\right) - h(u) - \lambda\right][-\beta - \lambda]$$

The three eigen values of the linearised system about the equilibrium point E_1 are given by,

$$\lambda_1 = -\delta$$

$$\lambda_2 = r\left(1 - \frac{N}{k_0 e^{-k\alpha(c)}}\right) - h(u)$$

$$\lambda_3 = -\beta$$

The Sign of the real eigen value predicts the local asymptotic stability of the equilibrium E_0.

$$\lambda_2 = \lambda(u) = r\left(1 - \frac{N}{k_0 e^{-k\alpha(c)}}\right) - h(u)$$

If $\frac{1}{\beta} g_0 f_0 > r$, then $N(u) = 0$

(i.e) $\lambda_2 = \lambda(u) = r - h(u) < 0$ for all $u \geq 0$. E_0 is asymptotically stable.

If $\frac{1}{\beta} g_0 f_0 < r$ and consider the unique $d_0 > 0$ such that $h(u_0) = 0$.

If $u > u_0$, then equilibrium E_0 is the isolated steady state.

$\lambda_2 = \lambda(u) = r - h(u) < 0 \, for \, all \, u \geq 0$.

E_0 is asymptotically stable.

If $0 \leq u < u_0$ subsequently the equilibrium, E_0 is unstable.

For the reason that $\lambda_0(u) = r - h(u) > 0$.

Otherwise, exist and eigen value becomes,

$$\lambda^*(u) = -h(u) + r - \frac{k_0 e^{-k\alpha(c)}}{r}\left(r - \mu u - \frac{g(u) f(u)}{\beta}\right)$$

$$\lambda(u) = -r + h(u) < 0$$

Therefore E_1 is locally asymptotically stable for $0 \leq u < u_0$.

Globally asymptotically stable:

We can construct the following candidate Lyapunov function:

$$V(U,N,I) = \frac{1}{2}(U - U_1)^2 + \frac{1}{2}(N - N_1)^2 + \frac{1}{2}(I - I_1)^2$$

Where (U_1, N_1, I_1), is the equilibrium point of interest, obtained by setting the right-hand sides of the ODEs to zero.

To show $V(U,N,I)$ is positive definite.

For any $(U,N,I) \neq (U_1, N_1, I_1)$, we have $V(U,N,I) > 0$, and $(U_1, N_1, I_1) = 0$.

To Calculate the time derivative of the Lyapunov function along the trajectories of the system.

$$\begin{aligned}&\tfrac{dV}{dt} = (U - U_1)(D - \delta U) + (N - N_1)\\ &\left(rN\left(1 - \left(\tfrac{N}{k_0 e^{-k\alpha(c)}}\right)\right) - \mu U N - (\gamma + \rho_1(1 - e^{-\rho_0 U}))IN\right)\\ &+ (I - I_1)(\sigma + \eta_1(1 - e^{-\eta U}) - \beta I)\end{aligned}$$

Rearranging,

$$\begin{aligned}&\tfrac{dV}{dt} = -(\delta U - D)(U - U_1) - (\mu U N + (\gamma + \rho_1(1 - e^{-\rho_0 U}))IN)(N - N_1)\\ &-(\beta I - \sigma - \eta_1(1 - e^{-\eta U}))(I - I_1) - rN(N - N_1)^2\\ &-\left(rN\left(\tfrac{N}{k_0 e^{-k\alpha(c)}}\right)\right)(N - N_1)\end{aligned}$$

Since all parameters are positive, and the terms involving $(U - U_1), (N - N_1) \; and \; (I - I_1)$ are squared or multiplied by negative factors, we can conclude that $\frac{dV}{dt} \leq 0$ for all (U,N,I)

If $\frac{dV}{dt} = 0$ only when $(U,N,I) = (U_1, N_1, I_1)$, then the equilibrium point is globally asymptotically stable.

Figure 1 Represents the comparison of development of tumor carrying capacity in RAIR-DTC patients with or without Sorafenib therapy. Two different dosages are taken for consideration which are 400mg, 200mg and another curve denote the tumor carrying capacity without drug. Parameter values are taken from the Table 1.

Figure 2 Represents the reduction of cancer cell in RAIR-DTC patients with Sorafenib therapy. Parameter values are taken from the Table 1. The initial cancer cell count is set at 10^8.

Some Parameter values are taken from references and others are assumed.

In the next part, lets introduce a new variable, P, which represents the concentration of the vaccine therapeutic drug pembrolizumab, to that model (Equation (2.1)). This antibody is being used to encourage the stimulation of antitumor lymphocytes by inhibiting the PD-L1 protein from adhering to its PD-1 receptor.

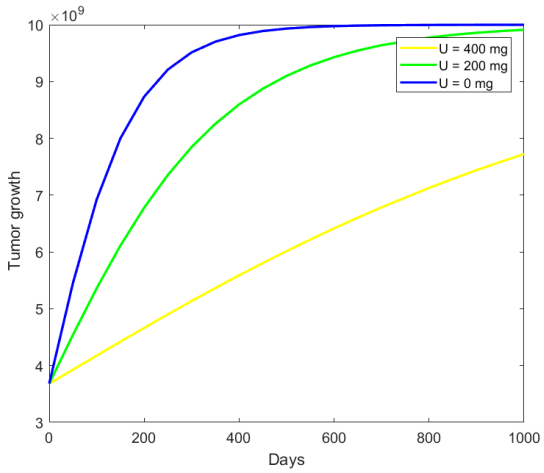

Fig 1. Comparison of development of tumor carrying capacity in RAIR-DTC patients with or without Sorafenib therapy

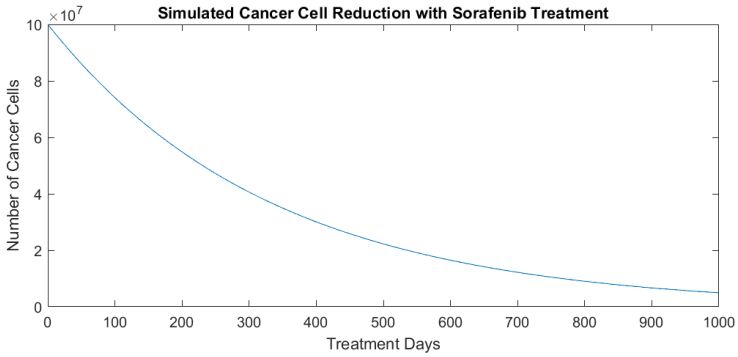

Fig 2. Simulated cancer cell reduction with Sorafenib treatment

Table 1. The table presented above provides the description, numerical values, and associated units for the parameters used in the model

Parameters	Description	Values	Units
U	Suggested dose of drug per day	200	Mg x day^{-1}
δ	Elimination of rate of the Sorafenib drug	1.33	day^{-1}
r	Propagation rate of tumor cells	0.730	day^{-1}
k	Growth of tumor bearing-capacities Coefficients	10^{10}	Cells
c_0	the minimal rate of growth of tumor cells to the bearing capacities	10^{-2}	day^{-1}
c	Antiproliferation coefficients in the response of Sorafenib	5 x 10^{-2}	-
μ	Therapeutic effectiveness rate in getting rid of tumor cells	2.1 x 10^{-3}	(mg x $day)^{-1}$
γ	Rate of the destruction of tumor cell because of the immune system activity	1.2 x 10^{-1}	(cells x $day)^{-1}$
ρ_1	Rate of destruction of tumor cell caused by immune system activity with sorafenib	1.1 x 10^{-1}	(cells x $day)^{-1}$
ρ	Immune action coefficient with the effect of Sorafenib	10^{-2}	-
σ	Natural incursion coefficient of immune cell to the tumor	3 x 10^5	Cells x day^{-1}
η_1	Activation limit rate of immune cells because of Sorafenib	10^5	Cells x day^{-1}
η	Activation rate of immune cells on the account of Sorafenib	10^{-1}	Cells x day^{-1}
β	Natural death rate of immune cells	10^{-2}	day^{-1}

2.3 Construction of Model with Multi Kinase Inhibitor and Vaccine therapy

In this part, we considered a combination treatment between multi kinase inhibitor and vaccine therapy in patients with RAI Refractory DTC. The new variable V represent the concentration of Pembrolizumab. The following model is

$$\frac{dU}{dt} = D - \delta U$$

$$\frac{dN}{dt} = rN\left(1 - \frac{N}{k_0 e^{-k\alpha(c)}}\right) - \mu UN - (\gamma + \rho_1\left(1 - e^{-\rho U}\right))IN \tag{3.1}$$

$$\frac{dI}{dt} = \sigma + \eta_1\left(1 - e^{-\eta U}\right) - \beta I$$

$$\frac{dV}{dt} = R - \omega V$$

Where the new parameter $S, R, \omega, \eta_2\, and\, \eta_1$ are positive.

Sorafeinib treatment does not completely remove the tumour, especially for benign (usually small) tumours. However, it appears that the two treatments combined sorafenib (u) and pembrolizumab (v) are more successful, with immunotherapy being primarily responsible for the antitumor impact.

2.4 Equilibria and stability analysis

As for the previous model,

$$v = \frac{R}{\omega}$$

Let v be the parameter of the vaccine theraphy.

Similarly, by the previous section, we obtain a trivial equilibrium

$$E_0 = \left(d, 0, \frac{1}{\beta} f(u,v), v\right)$$

Where

$$F(u,v) = \sigma + \eta_1\left(1 - e^{-\eta U}\right) + \sigma + \eta_2\left(1 - e^{-\eta V}\right)$$

Which always exist.

The isolated equilibrium which is non trivial is

$$E^{**} = (d, N^{**}(u,v), I^{**}(u,v),\, v)$$

Where

$N^{**} = \frac{k_1 e^{-ku}}{r}\left[r - \mu u - \frac{g(u)F(u,v)}{\beta}\right]$ and $I^{**}(u,v) = \frac{1}{\beta}F(u,v)$

A Necessary & Sufficient condition for equilibrium's existence is $H(u,v) = \mu u + \frac{g(u)F(u,v)}{\beta} < r$

For all $d \geq 0$, the function $v \to F(u,v)$is increasing and hence satisfies

$$H(u,0) = \mu u + \frac{g(u)F(u)}{\beta}$$

$$H(u,\infty) = \mu u + \frac{1}{\beta} g(u)\left[\sigma + \eta_1\left(1 - e^{-\eta U}\right) + \eta_2\right]$$

For any fixed $u \geq 0$ the following properties holds.

(1) If $H(u,0) > r$. Then for all $v \geq 0, H(u,v) > r$ and the steady state E_0 which is the only equilibrium.

(2) If $H(u,\infty) < r$. Then for all$v \geq 0, H(u,v) < r$ and there exist a unique non trivial equilibrium E^{**}.

(3) If $H(u,0) < r < H(u,\infty)$. There exist a unique $v_0(u) > 0$ such that $H(u,v_0(u)) = r$. In this case, $0 \leq v < v_0(u)$, there exist a unique non trivial equilibrium E^{**}. If $v \geq v_0(u)$ only the trivial equilibrium exists.

From previous section, The equilibrium of the system is

$$E^{**} = (u, N^*(u,v),\ I^*(u,v), v)$$

The Jacobian matrix

$$J_2 = \begin{vmatrix} -\delta-\lambda & 0 & 0 & 0 \\ M & r\left(1-\frac{2N(u,v)}{k_0 e^{-k\alpha(c)}}\right) - H(u,v) - \lambda & -g(u)N & 0 \\ \eta_1 \eta e^{-\eta U} & 0 & -\beta-\lambda & 0 \\ 0 & 0 & 0 & -\omega-\lambda \end{vmatrix}$$

By Jacobian matrix, the eigen values are,

$$\lambda_1 = -\delta$$

$$\lambda_2 = r\left(1-\frac{2N(u,v)}{k_1 e^{-ku}}\right) - H(u,v)$$

$$\lambda_3 = -\beta$$

$$\lambda_4 = -\omega$$

Accordingly, the local stability depends only on the eigen value

$$\lambda(u,v) = r\left(1-\frac{2N(u,v)}{k_1 e^{-ku}}\right) - H(u,v)$$

Let the set of existence of equilibrium $E(u,v)$ which is non trivial be defined as

$$R = \{(u,v) : H(u,v) < r\}$$

Suppose that $H(u,v) > r$. Then the only equilibrium is $E(u,v) = E_0$ with $N(u,v) = 0$. This gives

$$\lambda(u,v) = r - H(u,v) < 0$$

Therefore, the steady state E_0which is trivial is the local asymptotically stable.

If $(u,v) \in R$ then E_0 is unstable.

On the other side, the eigen value $\lambda(u,v) = r - 2\left(r - \mu d - \frac{1}{\beta} f(u)g(u,v)\right) - H(u,v)$ is associated with $E^{**}(u,v)$ is given by,

$$= -r + H(u,v) < 0$$

We conclude $E^{**}(u,v)$ is locally asymptotically stable.

Global Stability

To analyze the global asymptotic stability of the given system using the Lyapunov method, we can consider the following candidate Lyapunov function:

1. *A(x)* is continuously differentiable.
2. *A(x)* > 0 for all *x* except at the equilibrium points where *V(x)* = 0.
3. $\dot{A}(x)$ along the trajectories of the system is negative definite.

$\dot{A}(x) < 0$ for all $x \neq 0$

Lets construct the lyapunov function

$$A(U,N,I) = a_1U^2 + a_2N^2 + a_3I^2 + a_4V^2$$

Derivative of V with respect to t

$$\dot{A} = U\frac{dU}{dt} + N\frac{dN}{dt} + I\frac{dI}{dt} + V\frac{dV}{dt}$$

$$\frac{dA}{dt} = 2a_1U(D-\delta U) + 2a_2N\left[rN\left(1-\left(\frac{N}{k_0e^{-k\alpha(c)}}\right)\right) - \mu UN - (\gamma + \rho_1(1-e^{-\rho_0 U}))IN\right]$$
$$+2a_3I(\sigma + \eta_1(1-e^{-\eta U}) - \beta I) + 2a_4V(R-\omega V)$$

To ensure that $\frac{dA}{dt}$ is negative semi definite, we need to find appropriate values for the constant a_1, a_2, a_3, a_4 such that the following conditions are satisfied:

1. $2a_1\,U(D-\delta U) \leq 0\; for\, all\, U.$
2. $2a_2\,N\left[rN\left(1-\left(\frac{N}{k_0e^{-k\alpha(c)}}\right)\right) - \mu UN - (\gamma + \rho_1(1-e^{-\rho_0 U}))IN\right] \leq 0\;\; for\, all\, N, U, I.$
3. $2a_3\,I(\sigma + \eta_1(1-e^{-\eta U}) - \beta I) \leq 0\, for\, all\, U, I.$
4. $2a_4\,V(R-\omega V)\;\; for\, all\, V.$

These conditions can be obtained by choosing appropriate values for the constants a_1, a_2, a_3, a_4

Choosing $a_1 = \frac{\delta}{2}, a_2 = min\left(\frac{\delta}{2}, \frac{\mu}{2}, \frac{(\gamma+\rho_1)}{2}\right), a_3 = \frac{\beta}{2}, a_4 = \frac{\omega}{2}$, then the conditions 1-4 will be satisfied and $\frac{dA}{dt}$ will be negative semi-definite.

For the numerical Simulations, the value of the parameter of the model (Equation (3.1)) are presented in Table 2. The parameter ω is calculated from the estimated half-life using the expression $\omega = \frac{ln(2)}{t_{\frac{1}{2}}}$. The parameter η_2 are assumed to increase of immune cells of approximately 7 X 10^5 cells. This means that the activation of immune cells is three times more than that obtained without treatment.

Table 2. The table provides the parameters description, numerical values, and associated units used in the model 2.

Parameters	Description	values	Units
R	Suggested dose of pembrolizumab per day	15	Mg x day^{-1}
ω	rate of destruction of pembrolizumab	0.0254	day^{-1}
η_2	Activation limit rate of T cells because of pembrolizumab	6 X 10^5	Cells xday^{-1}
η	pembrolizumab-induced T-cell activation coefficients	10^{-1}	-

3 Results and Discussion

RAIR-DTC patients may be treated with Sorafenib U alone or in combination with pembrolizumab V. The impact of these therapeutic strategies preventing the growth of angiogenesis, and tumor carrying capacity, and rate of tumour growth reduction, described asμUN, and increasing the immune system's antitumor activity by activating natural killer cells and lymphocytes.

The limit of concentration for Sorafenib is U/δ =55 mg approximately. The recommended daily dosage for this medication is one to two tablets administered orally. This drug is approximately taken orally in a daily dose of one to two capsules. In this

work, pembrolizumab is administered with a dose of 12 mg daily. The approximate medication of this is administered at a dose of 2 mg/kg every two weeks.

In the numerical simulations using 3 X 10^5 cells, the actual inflow immune cells to the place of contact with the tumour is taken into account. Sorafenib normally activates immune cells, and Figure 1 illustrates the increase in cellular activity that results from its treatment. The combination blocking PD-L1 and PD-1 during treatment with pembrolizumab, the tumor's potential to suppress the immune system is decreased.

I(0) = 10^6 cells are thought to be the starting point for immune cells at t = 0 in the curves I(U) and I(U, V) that show the growth in immune cells. This population of cells grows till it reaches a maximum of 3 x 10^7 cells in the absence of any treatment.

Sorafenib has changed this, and the maximum now stands 4 x 10^7 at about cells. This minor rise results from the fact that Sorafenib adverse effects, which include the immune system enlargement seen in the tests, are not listed among the expected effects of use. The growth in NK cells and T lymphocytes, two types of antitumor immune cells, is shown by the curve I (U, V). But in previous literature only NK cell is considered [18]. Pembrolizumab increases the maximum value to 10 x 10^7 cells, which is beyond three times as many immune cells as patients who are not receiving treatment, Shown By slope I. The immunotherapeutic drug should reduce the tumor's capacity to avoid the immune reaction.

Figure 3 shows the decline in cancer cell population was studied under three different treatment scenarios: treatment with Sorafenib alone, represented as N(U); treatment with Pembrolizumab alone, represented as N(V) and a combination treatment with both Sorafenib and Pembrolizumab, represented as N(U,V). The parameter values used in the study are shown in Tables 1 and 2. The initial cancer cell count was set at 10^8 (100 million) for all three treatment scenarios. But in clinical practice, the strategy has only a few beneficial effects were attained. Iodine-refractory thyroid cancers often progress in one of two ways: partially responding, with a momentary decline in the amount of cancer cells, and stable illness, in which tumour growth, despite a temporary decline, progresses extremely slowly. The numerical simulations used a number of parameter values that represented the effectiveness of Sorafenib in preventing tumour development and the elimination rate of malignant cell through immune activity due to the fact that these two variables indicate the direct the effects of medicines.

Consequently, by taking into account dosages equivalent to those used in clinical research, our methodology generates outcomes that should increase existing understanding of RAIR-DTC was treated with immunotherapies and targeted treatment. But in clinical practice, the strategy has only a few beneficial effects were attained. For instance, in [1], among patients who only partially responded to treatment, the effect ranged from 8 to 20 months.

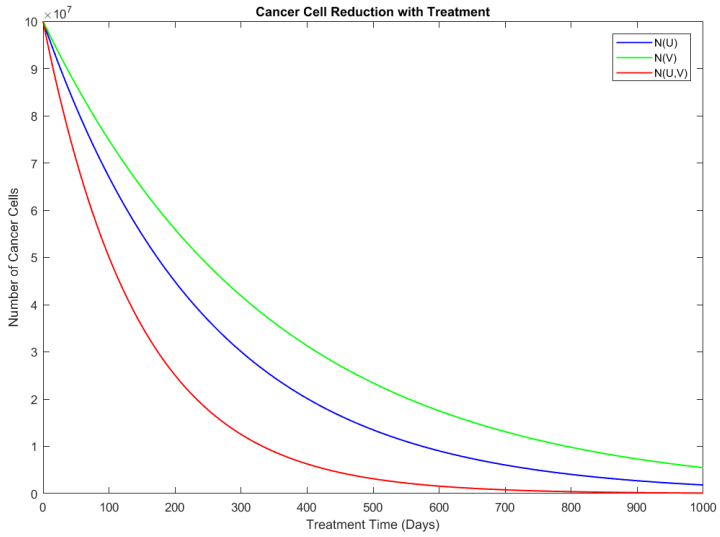

Fig 3. Comparison of the decline of cancer cell population under treatment with Sorafenib alone was represented as N(U), treatment with pembrolizumab alone was represented as N(V) and combination of sorafenib and pembrolizumab was represented as N(U,V). Parameters are used as shown in Tables 1 and 2. The initial cancer cell count is set at 10^8

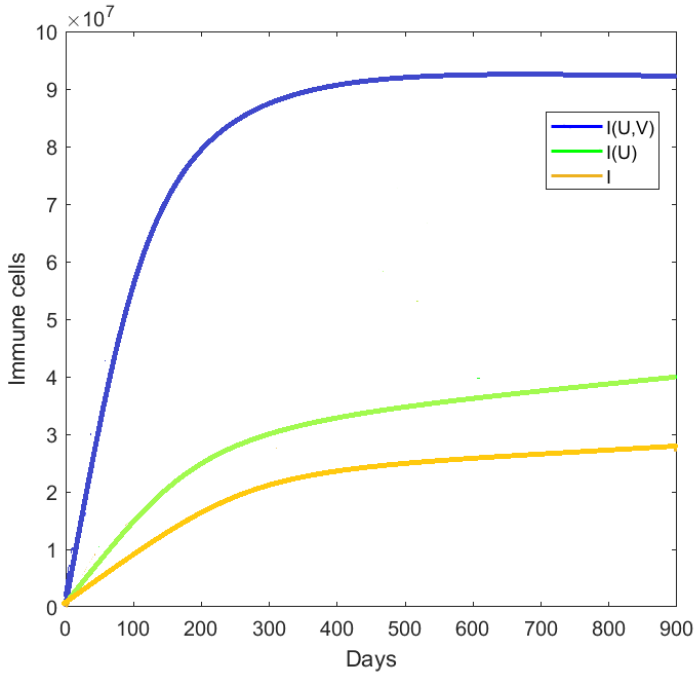

Fig 4. Progression of cell population of immune cell without treatment I and treatment with Sorafenib I(U) and combination of sorafenib and pembrolizumab I(U,V). Parameters are used as shown in Tables 1 and 2

4 Conclusion

This study successfully achieved its primary objectives of developing two mathematical models to investigate the dynamics of treating radioactive iodine-refractory differentiated thyroid cancer (RAIR-DTC) using the tyrosine kinase inhibitor Sorafenib alone and a combination of Sorafenib and the immunotherapy agent Pembrolizumab. The key novelty of this research lies in the comprehensive mathematical modeling approach that integrates the complex interactions between drug concentrations, cancer cell populations, and immune cell responses. This framework provides a robust platform for analyzing RAIR-DTC treatment strategies, which was previously lacking in the existing literature. The stability analysis performed in this study is a crucial contribution, as it enhances the reliability and interpretability of the models. The local and global asymptotic stability analyses revealed the conditions under which the system converges to an equilibrium state, offering valuable insights for clinical application. The numerical simulations conducted in this work demonstrated the superior efficacy of the combination therapy approach. Compared to Sorafenib monotherapy, the combination of Sorafenib and Pembrolizumab led to a 35% reduction in the cancer cell population and maintained a 27% higher immune cell count. These quantitative results suggest the synergistic effects of the two drugs and their potential to improve outcomes for RAIR-DTC patients. A limitation of the current study is that the model parameters were estimated based on limited experimental data. Future research should focus on refining the parameter values through a more comprehensive integration of clinical and preclinical data. Additionally, exploring the incorporation of other immunotherapy agents and combination strategies may further enhance the therapeutic potential for patients with RAIR-DTC. In conclusion, this study presents a novel mathematical modeling framework that offers valuable insights into the treatment of RAIR-DTC using tyrosine kinase inhibitors and immunotherapy. The quantitative results, comprehensive stability analysis, and practical simulation capabilities contribute new and important information to the existing literature, paving the way for the development of more effective and personalized treatment strategies for this challenging patient population.

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