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Chemotherapy and Imunotherapy Effect on the Population Dynamics of Cancer Cells.

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Abstract

In this paper we develop Mathematical models that describe population dynamics of cancer cells and its interaction with normal killer cells (NK), $CD8^+T$ cells, circulating lymphocytes, immunotherapy and chemotherapy with the goal of understanding the dynamics of cancer cells and its control by these immune cells. These mathematical models are system of differential equations. The equations describing cancer cell population dynamics response to chemotherapy and lmmunotherapy are fully studied, solved and analysed.

Keywords: Tumour, Population dynamics, Immune cells, Models, Control

Meaning of symbols used:

a = logistic tumour growth rate.
k = fractional tumour cell kill by chemotherapy.
$b = b^{-1}$ is the tumour carrying capacity.
d = saturation level of fractional tumour cell kill by $CD8^+T$ cells.
c = fractional rate of NK cell production by stems cell (stem cell measured by number of circulating lymph generation).
f = fractional death rate of Nk cells.
g = maximum KN cell recruitment rate of tumour cells.
K_N = fractional NK cell kill by chemotherapy.
h = steepness coeff of the $CD8^+T$ cell recruitment.
q = $CD8^+T$ cell inactivation rate of tumour cell.
r_1 =rate $CD8^+T$ cells are stimulated to be produced by tumour cells killed by circulating lymphocytes.
r_2 =
u = Regulatory function by NK cell on $CD8^+T$ cells.
p_i = maximum $CD8^+T$ cell recruitment rate.
q = $CD8^+T$ cells inactivation rate by tumour cells.
m = death rate of $CD8^+T$ cell.

$\propto$ = *constant source of circulating lymphocytes.*

β = *natural death and differentiation of circulating lymphocytes.*

γ = *rate of chemotherapy drug decay.*

μ_i = *rate of IL-2 drug decay.*

s = steepness coefficient of the tumour competition term.
g_i = *steepness coefficient of* $CD8^+$ *T cell recruitment curve by IL-2.*

K_T = *fractional Tumour cell kill by chemotherapy.*
K_L = *fractional* CD^+ *8 T reduction by chemotherapy.*
V_I =*human intervention by immunotherapy*
K_C = *fractional circulating lymphocytes cell kill by chemotherapy.*
V_M =*human intervention by chemotherapy*
e =recruitment rate of circulating lymphocytes

1.0 Introduction

Tumour arises by the exaggerated and abnormal proliferation of single cell or group of cells. Tumour can be defined as abnormal mass of tissue that are uncoordinated with that of normal tissue but persist in the same excessive manner after cessation of stimuli which evoked the change, [10]. Tumour can be either malignant or benign. A malignant or cancerous tumour acquires vascular system for blood supply, a period of angiogenesis. To ensure its sustained growth, tumour may secrete chemical compounds which cause neighbouring capillaries to form sprouts which then migrate towards it furnishing the tumour with an increased supply of nutrients.

2.0 Biological Background

The growth of tumour proceeds in two distinct phases, vascular and avascular phase. At early stage of primary tumour (Benign) formation, there is absence of a vascular network. At this stage it is very small. It does not have its own blood supply but takes in nutrients and expels waist products by diffusion alone. However, this mechanism limits the growth of tumour, [4]. As tumour grows, demand increases and nutrients diffusing through the surface of tumour are used up before they can reach to the centre. Cells at the middle of the tumour are starved and begin to die. At this stage tumour becomes dormant and growth will stop.

At this stage if the tumour which is just a few millimeters in size must grow, it no longer can rely on blood vessels of the host for supply of nutrients and so it needs to develop its own vascular system for blood supply. The tumour can overcome this deficiency by acquiring a blood supply and it does so by inducing neighboring blood vessels to grow towards tumour [6]. The formation of blood vessel is called angiogenesis. Tumour angiogenesis is initiated by the release of a number of chemicals collectively known as tumour angiogenic factor (TAF) into the surrounding tissue, [10]. These factors diffuse through the tissue space creating a chemical gradient between the tumour and any existing vasculature. There is a bi-directional signaling between the endothelial cells, which provide the lining for the newly forming vessels of the tumour and tumour cells stipulating growth. The vessels are stipulated to degrade their basement membrane to invade the surrounding stroma and to migrate towards the tumour. As cells migrate, the

endothelium begins to form sprouts which can then form loops and branches through which blood circulates. The endothelial cell produce growth factors that stimulate the proliferation of the tumour cell population. The whole process repeats forming a capillary network which eventually connects with the tumour, completing angiogenesis and supplying the tumour with the nutrients it needs to grow further.
One of the ways of controlling tumour from growing to cancer level is to look at how tumour is controlled by the system itself, i.e. body mechanism of fighting the tumour cells. Here, we consider development of certain cells that go around the body dividing the cells of the body so as to differentiate the self from non-self. These cells are known as HLA (Human Lococide Antigen). But these cells first develop on the bone marrow. i.e. Pre-T-lymphocyte and Pre-B-lymphocyte.

The Pre-T-lymphocytes eventually populate the gastro intestinal lymphoid tissue (Burser Fabricius equivalent) where they develop as B-lymphocytes. There are also those which do not have this maker and they are non – B, non – T – lymphocytes. These cells fight the invasion of the body by the cancer by process called cellular and humoral immunity. Cellular immunity are detected by antigen processing cells (APC) which present its T – cell which undergoes activation and proliferation and destroy the tumour cells. More so, the process also involves activation and proliferation of B – cells. T – cell implies cellular immunity and B – cell implies humoral immunity. The non – T, non – B lymphocytes in addition to other cellular mediators like cytokines all participates in the fight and defense of body when invaded by tumour.

Immunotherapy is currently under intensive investigation as one of the controlling factors of tumour progression model. The basic argument about immunotherapy is that by boosting the immune system in vitro, the

body can eradicate cancer on its own. Immune system can be boosted in the following ways; vaccine therapy, IL – 2 growth factor injections and the direct injection of highly activated specific immune cells such as $CD8^{+}T$ cells into the blood stream. The idea of boosting immune cells directly is to cultivate a large number of tumour primed $CD8^{+}T$ outside the body, and then inject them into the blood – stream. To boost the immune system, primed $CD8^{+}\ T$ - cells from a patient are cultured so that they have a chance to multiply, then are re-injected into the patient. This artificial increase on the strength of the immune response may give a patient the assistance needed to eradicate the cancer [14].

Chemotherapy is used to control cancer at a very high level. The drug is administered intravenously. The disadvantage in chemotherapy drug is that chemotherapy drug kills cells in the process of division. Secondly, high doses of drug can also damage other tissue or the body [7]. A way forward to this therapy is to combine several specific drugs that act on cells in different phases. This also helps counteract tumour population that is immuned to one type of drug and to ensure that no drug needs to be applied at levels toxic to the body, [12].

Other controls are Growth factor, Reduction, Hormonal Treatment, Specific Inhibitors, Biology response modifier, viral treatment, e.t.c. There is another natural way of fighting tumour (Cancer) by Environmental Protection, that is, by avoiding environmental inducers like Cigarette Smoking, Alcohol, Radiation, Proper Screening of blood to exclude HBV, HIV, e.t.c.

Natural killer (NK) cell which are the body's first line of defense against disease and are always present in healthy individuals also helps to control tumour attack. Natural killers travel through the blood stream and lymph system to the extra cellular fluids, where they find and destroy non-self cells that are toxic, [1].

It is observed that the early vascular stage and the subsequent stages of tumour growth are characterized by a chronic Inflammatory infiltration of neutrophils, eosinophils, basophils, monocytes/macrophages, T - lymphocytes, B – lymphocytes and Natural Killer (NK) cells [15]. These cells penetrate the interior of the tumour tissue with high locomotive ability of activated immune cells, [13]. It is discovered that during the avascular stage, tumour development can be effectively eliminated by tumour infiltrating cytotoxic lymphocytes (TICLs), [7]. TICLS may be cytotoxic lymphocytes $(CD8+CTLS)$, natural killer – like (NK-like) cells and/or lymphokine, activated killer (LAK) cells, [2].

3.0 The Model

Mathematical models for tumour growth in a human system as given by [16] are as follows:

$$\frac{dT}{dt} = aT(1-bT) - cNT - dD - k_T\left(1-e^{-m}\right)T \tag{3.1}$$

$$\frac{dN}{dt} = eC - fN + g\frac{T^2}{h+T^2}N - \rho NT - K_N\left(1-e^{-m}\right)N \tag{3.2}$$

$$\frac{dL}{dt} = -mL + j\frac{D^2}{k/d^2 + D^2}L - qLT + \left(r_1N + r_2C\right)T - \mu NL^2 - K_L\left(1-e^{-m}\right)L + \frac{p_iLI}{g_i + I} + V_L(t) \tag{3.3}$$

$$\frac{dC}{dt} = \alpha - \beta C - k_c\left(1-e^{-m}\right)c \tag{3.4}$$

where $$D = \frac{(L/T)^{eL}}{S + (L/T)^{eL}}T$$

$$\frac{dI}{dt} = -\mu I + V_I(t) \tag{3.6}$$

$$\frac{dm}{dt} = -\gamma M + V_m(t) \tag{3.5}$$

However, we will be interested in the case of fully grown tumour that have advanced to cancer stage . This therefore leads us to the modifications of these models in line with realistic situation that obtains at the cancer level of tumour growth in human system. Thus, we have the following modifications:

(a) $aT(I-bT) \Rightarrow$ Tumour grows logistically.

$bT \Rightarrow$ Tumour carrying capacity by the system.

If $bT > I$, tumour level reduces or dies.

$bT < I$, tumour growth increases.

$bT = I \Rightarrow \frac{dT}{dt} = 0$ which means no growth. We modify $aT(I-bT)$ to aT because here tumour is at a full cancerous stage. There is no more restriction in space and materials. There is no carrying capacity restrictions because it is cancerous already.

(b) We now consider the complex term NT describing the interaction of the natural killer and tumour cells. For the tumour to have developed to cancer, the presence of tumour cells must have dominated the effect of natural killer. In other words, the presence of the natural killer does little or no work in the control of the growth of cancer cells. Thus, we assume in this equation that the natural killer N is constant or dormant and therefore the complex N can be written as N_oT, where N_o is assumed constant.

(c) The tumour inactivation by $CD8^+T$ cells was given by

$F_i(T,L) = d\frac{(L/T)^{eL}}{s + (L/T)^{eL}}T$, where s and d are constants.

Now, this form is complex and has not been validated to be absolutely correct by, [16]. Even if it is, then for simplicity of the model, we can equally redefine this term. Thus, L stands for $CD8^+T$ cell effectiveness at time t. We know that when it eventually interacts with the tumour cells, it cannot produce 100% effectiveness in killing the tumour cells. *Tumour has advanced to cancerous level that* $CD8^+T$ *cells effectiveness must have reached its equilibrium state* and therefore can no longer vary.

$$\Rightarrow dD = \left(\frac{(L/T)^{eL}}{s + (L/T)^{eL}} \right) \approx \xi T$$

In other words, we can have some βL attack of the $CD8^{+}T$ cell on removing or killing the tumour cell, where $\beta L < L$. In such a case therefore we define $F_L(T,L) = \xi T$, where $\xi = (\beta L)^{\alpha} < L$, for $\alpha = 1, 2, \ldots\ldots\ldots$ and $\beta \angle 1$

(e) $eC - fN = G(N) \Rightarrow$ Growth of NK

$eC \Rightarrow$ Recruitment of circulating lymphocyte at the point of tumour cell attack.

$fN \Rightarrow$ fractional death rate of NK cells.

As lymphocytes cells are being recruited to attack the tumour, some of the NK cells will be killed and removed thereby reducing the effectiveness of natural killer.

(f) $g\dfrac{T^2}{h+T^2}N \Rightarrow$ This is also recruitment of Natural killer at the point of tumour attack, hence increasing the NK cells.

But $\dfrac{T^2}{h+T^2} \approx \dfrac{1}{\dfrac{h}{T^2}+1}$

Now if h is small (a constant) and T is large then $\dfrac{h}{T^2}$ can be neglected and so $\dfrac{T^2}{h+T^2} \approx 1$. If otherwise, i.e. h is still small and T not necessary large, then $0 < \dfrac{T^2}{h+T^2} < 1$. Hence, we approximate $\dfrac{T^2}{h+T^2}$ by $(1-at)$ where $0 \le a \le 1$.

$\therefore R_n(T,N) \approx g(1-at)N$ *where* g is a proportionality constant or rate of recruitment.

(g) $K_N\left(1-e^{-\gamma}\right)N \Rightarrow$ fractional cell kill as a result of chemotherapy drug effect on Natural killer,and this reduces the effectiveness of NK. $e^{-\gamma} \rightarrow$ rate of drug decay.

Considering $CD8^{+}T$ cells in the above models, the following were observed.

i. $CD8^{+}T$ cells is primed

ii. it increases in number by multiplying before going out to attack the tumour cells.

iii. when it has conquered the tumour cells, it becomes obsolete and must be removed by death.

iv. it attacks by forming a complex with the tumour cells.

Hence, in the model it was assumed that cell changes for $CD8^{+}T$ cells consists of only death rate since no $CD8^{+}T$ cells are assumed to be present in the absence of tumour cells. This is not true because $CD8^{+}T$ cells exist in the lymph nodes but in small quantity until it is primed. And as observed they then multiply in number before going out to fight the foreign body. The quantity that is released and continues to be released is usually like other cell reactions proportional to the amount of foreign body in the system. Hence, the statement that $G(L) = -iL$ is not acceptable. We therefore modify this as $G(L) = (\alpha - i)L$, where

$\alpha =$ multiplication rate

$i =$ death rate

(i) $j\frac{D^2}{k/d^2+D^2}L \Rightarrow$ Recruitment of $CD8^+T$ cells at the point of attack (Tumour cells) which increases the $CD8^+T$ cells in the system. D, k, d, j, L are all constant and therefore we can represent $j\frac{D^2}{k/d^2+D^2}$ as βL to make the model simpler.

(j) $K_L\left(1-e^{-\gamma}\right)L$ - fraction of $CD8^+T$ cells killed by chemotherapy

$e^{-\gamma}$ - rate of chemotherapy drug decay.

(N) $\frac{P_i LI}{g_i+I} \approx \beta e^{\alpha(1-L)t} I$.

where $0 \le L \le I$ and when $L=1$, then $\beta = 0$

$g_i =$ steepness coeff of $CD8^+T$ cell recruitment curve by L_2

$I =$ immunotherapy

$L =$ $CD8^+T$ cell

$P_i =$ maximum $CD8^+T$ cell recruitment rate.

The $CD8^+T$ release from the nodes is assumed exponential since it reacts like drug release from the interstitial cells.

When the L_2 is introduced, it stimulates the further release of the $CD8^+T$ depending on the effectiveness of the existing maximum level of the $CD8^+T$ in the system. Hence when $L << I$, we find that L_2 will stimulate the release of the $CD8^+$ and $L << I \Rightarrow$ very low efficiency or effectiveness of the available $CD8^+$.

(O) $\alpha - \beta c$ Growth of lymphocytes. The number of white blood cells, or circulating lymphocyte are not generated at constant rate as assumed here, but may be a function of the invading foreign body or bodies. If this is the case, then the model

$g(c) = \alpha - \beta c$ will not be acceptable, but will be

$G(c) = \lambda T - \beta c$ where

$T =$ Tumour cells

$c =$ circulating lymphocytes

$\lambda = \alpha =$ proportionality effect of T one

$\beta =$ removal rate of c

(P) $K_c\left(1-e^{-\gamma}\right)C$ - fraction of circulating lymphocytes cells killed by chemotherapy

(Q) $-yM =$ removal rate of chemotherapy. In the case of the chemotherapy, we have to note that when the drug is taken, it never enter the system whole at a time. It gradually enters into the blood stream (if taken or intramuscular) and equally decays generally. The clearance rate must be constant but the generation rate into the site of the interest is not generally constant. Hence, if not given intravenously the appropriate form of description of the drug intervention will be

$G(M) = \left\{a\left(1-e^{-kt}\right)-b\right\}M$ *or*

$= a\left(1-e^{-kt}\right)M - bM$

and not $g(M) = -\gamma M$

The immunotherapy has the form of chemotherapy since it is injected into the body. Hence, we have

$G(I) = S\left(1-e^{-\delta t}\right) - dI \text{ or } S\left(1-e^{-\delta t}\right) I - dt$

where δ is the multiplication rate once it has entered the body.

In general, drug intervention at the site of interest is not whole. We know that since the drug has life span, d also reduces in quantity/concentration at a rate dependent on the life span. Hence, we modify the above model equation by [16] as

$$\frac{dI}{dt} = aT - cN_oT - \xi T - K_T\left(1-e^{-\gamma}\right)T \tag{3.7}$$

$$\frac{dN}{dt} = eC - fN + g(1-at)N - cN_oT - K_N\left(1-e^{-\gamma}\right)N \tag{3.8}$$

$$\frac{dL}{dt} = (\alpha - i)L + \beta_i L - qLT + (\gamma_1 N + \gamma_2 C)T - \mu NL^2 - K_c\left(1-e^{-\gamma}\right)L + \beta_1 e^{\alpha(1-L)t_1} \tag{3.9}$$

$$\frac{dC}{dt} = \lambda T - \beta_i C - K_c\left(1-e^{-\gamma}\right)C \tag{3.10}$$

$$\frac{dM}{dt} = a\left(1-e^{-kt}\right)M - bM \tag{3.11}$$

$$\frac{dI}{dt} = s\left(1-e^{-\delta t}\right) - dI \tag{3.12}$$

4.0 Solution to the model equations

$$\frac{dT}{dt} = aT - cN_oT - \xi T - K_T\left(1-e^{-\gamma}\right)T \tag{4.1}$$

$$\frac{dT}{dt} = \left[a - cN_o - \xi - K_T\left(1-e^{-\gamma}\right)\right]T$$

Let $\left(a - cN_o - \xi - K_T\left(1-e^{-\gamma}\right)\right) = \phi = \text{constant}$

$$\frac{dT}{dt} = \phi T$$

$T = Ae^{\phi t}$ where $A = e^k$, k is a constant of integration.

Assuming $T = T_o$ when $t = 0$, we get $T = T_o e^{\phi t}$

$$T = T_o e^{\left(a - cNo - \xi - K_T\left(1-e^{-\gamma}\right)\right)t}$$

$$\frac{dN}{dt} = eC - fN + g(1-at)N - cN_oT_oe^{\phi t} - K_N\left(1-e^{-\gamma}\right)N \tag{4.2}$$

Putting $T = T_o e^{\phi t}$

i.e.

$$\frac{dN}{dt} = eC - fN + g(1-at)N - cN_oT_oe^{\phi t}$$

$$\frac{dN}{dt} + \left[fN - g(1-at)N + K_N\left(1-e^{-\gamma}\right)\right]N = eC - cN_oT_oe^{\phi t} \tag{4.3}$$

Solving equation (4.3) using integrating factor method yields

$$e^{\left[Ft - g\left(t - \frac{1}{2}at^2\right) + K_N\left(1-e^{-\gamma}\right)t\right]}\left[N(t) - N_o\right] = \int_o^t \left(eC - cN_oT_oe^{\phi t}\right) e^{\left[ft - g\left(t - \frac{1}{2}at^2\right) + K_N\left(1-e^{-\gamma}\right)t\right]}dt$$

$$eC\int_o^t e^{\left[ft-g\left(t-\frac{1}{2}at^2\right)+K_N\left(1-e^{-\gamma}\right)t\right]}dt - cN_oT_o\int_o^t e^{\left[\phi t+ft-g\left(t-\frac{1}{2}at^2+K_N\left(1-e^{-\gamma}\right)t\right)\right]dt}$$

$$= -\frac{\sqrt{\pi}}{\sqrt{-2ga}}e^{\left[\frac{\left(-f+g-K_N\left(1-e^{(-\gamma)}\right)\right)^2}{2ga}\right]}erf\left[\frac{gat-K_Ne^{(-\gamma)}+f-g+K_N}{\sqrt{-2ga}}\right]-$$

$$\frac{\sqrt{\pi}}{\sqrt{-2ga}}e\left[\frac{\left(-f+-K_N\left(1-e^{(-\gamma)}\right)\right)^2}{2ga}\right]erf\left[\frac{-f+g-K_N\left(1-e^{(-\gamma)}\right)}{\sqrt{-2ga}}\right]$$

Hence,

$$N = N_o - \frac{\frac{eC\sqrt{\pi}}{\sqrt{-2ga}}e\left[\frac{\left(-f+g-K_N\left(1-e^{-\gamma}\right)\right)^2}{2ga}\right]erf\left[\frac{gat-K_Ne^{-\gamma}+f-g+K_N}{\sqrt{-2ga}}\right]}{e^{\left[ft-g\left(t-\frac{1}{2}at^2\right)+K_N\left(1-e^{-\gamma}\right)t\right]}}$$

$$\frac{\frac{-ec\sqrt{\pi}}{\sqrt{-2ga}}e\left[\frac{\left(-f+g-K_N\left(1-e^{-\gamma}\right)\right)^2}{2ga}\right]erf\left[\frac{-f+g-K_N\left(1-e^{-\gamma}\right)}{\sqrt{-2ga}}\right]}{e^{\left[ft-g\left(t-\frac{1}{2}at^2\right)+K_N\left(1-e^{-\gamma}\right)t\right]}}+$$

$$\frac{\frac{cN_oT_o\sqrt{\pi}}{\sqrt{-2ga}}e\left[\frac{\left(-\phi-f+g-K_N\left(1-e^{-\gamma}\right)\right)^2}{2ga}\right]erf\left[\frac{gat-K_Ne^{-\gamma}+f-g+K_N+\phi}{\sqrt{-2ga}}\right]}{e^{\left[ft-g\left(t-\frac{1}{2}at^2\right)+K_N\left(1-e^{-\gamma}\right)t\right]}}$$

$$+\frac{\frac{cN_oT_o\sqrt{\pi}}{\sqrt{-2ga}}e\left[\frac{\left(-\phi-f+g-K_N\left(1-e^{-\gamma}\right)\right)^2}{2ga}\right]erf\left[\frac{-\phi-f+g-K_N\left(1-e^{-\gamma}\right)}{\sqrt{-2ga}}\right]}{e^{\left[ft-g\left(t-\frac{1}{2}at^2\right)+K_N\left(1-e^{-\gamma}\right)t\right]}}$$

$$\frac{dC}{dt} = \lambda T - \beta_i C - K_c\left(1-e^{-\gamma}\right)C, \text{ but } T = T_o = T_oe^{\phi t} \tag{4.4}$$

$$\Rightarrow \frac{dC}{dt} + \left[\beta_i + K_c\left(1-e^{-\gamma}\right)\right]C = \lambda T_oe^{\phi t}$$

Let $$\theta = \beta_i + K_c\left(1-e^{-\gamma}\right) \Rightarrow \frac{dC}{dt} + \theta C = \lambda T_oe^{\phi t}$$

Solving the first order differential equation, gives

$$Ce^{(\theta t)} = \frac{\lambda T_oe^{\left[(\theta+\phi)t\right]}}{(\theta+\phi)} + K$$

where K is a constant of integration which can be determined from the critical condition; $t = 0, c = c_o$. Therefore

$$c_o = \frac{\lambda T_o}{(\theta+\phi)} + k \;\Rightarrow\; k = c_o - \frac{\lambda T_o}{(\theta+\phi)}$$

$$C = C_o + \frac{\lambda T_o\left[e^{\left[\left(a-cN_o-\xi-K_T\left(1-e^{-\gamma}\right)\right)t\right]} - e^{\left[-\left(f+k_c\left(1-e^{-\gamma}\right)t\right)\right]}\right]}{-\beta - K_o\left(1-e^{-\gamma}\right) + a - cN_o - \xi - K_T\left(1-e^{-\gamma}\right)}$$

$$\frac{dM}{dt} = a\left(1-e^{-kt}\right)M - bM \tag{4.5}$$

This can be written as

$$\frac{dM}{dt} + \left[b - a\left(1-e^{-kt}\right)\right]M = 0$$

$$\frac{dM}{M} = -\left[b - a\left(1-e^{-kt}\right)\right]dt$$

$$\ln M = -\left[bt - a\left(t + \frac{1}{k}e^{-kt}\right)\right] + \phi$$

$$\therefore M = e^{\left[-\left(bt-a\left(t+{}^{1}/_{k}e^{-kt}\right)\right)\right]}e^{(\phi)}$$

$$M = M_o e^{\left(-\frac{a}{k}-bt+a\left(t+\frac{1}{k}.e^{-kt}\right)\right)}$$

$$\frac{dI}{dt} = S\left(1-e^{-\delta t}\right) - dI \tag{4.6}$$

$$\frac{dI}{dt} + dI = S\left(1-e^{-\delta t}\right)$$

$$\frac{d}{dt}\left(Ie^{dt}\right) = S\left(1-e^{-\delta t}\right)e^{dt}$$

$$Ie^{dt} = \int S\left(I - e^{-\delta t}\right)e^{dt}dt$$

$$Ie^{dt} = S\int\left(e^{dt} - e^{(d-\delta)t}\right)dt + \Delta$$

$$= S\left(\frac{I}{d} - \frac{I}{d-\delta}e^{-\delta t}\right) + \Delta e^{-dt}$$

$$I = S\left(\frac{I}{d} - \frac{e^{-\delta t}}{d-\delta}\right) + \left(I_o + \frac{\delta}{d(d-\delta)}S\right)e^{-dt}$$

5.0 Analysis of the Models

For the analysis of these mathematical models we use values that are set of human parameters that originated from the curve fits created by [13], human patients from clinical trials, [3] as well as from an additional and similar tumour models, [8]. For the malignant case, the values of the parameters were varied

in order to study the reaction of tumour to these variations. Hence the first step in the analysis of the model is the choice of values for the constants. Thus we have the values for the constants as:

$a = 0.43078,\quad b = 2.1686 \times 10^{-8}, c = 7.131 \times 10^{-10}, d = 8.165, e = 1.29 \times 10^{-3},\quad eL = 0.6566, f = 0.0412, g = 0.498, h = 2.019 \times 10^{7}, j = 0.996, k = 3.028 \times 10^{5}, m = 0.02, p = 1 \times 10^{-7}, q = 3.422 \times 10^{-10}, r_{1=} 1.1 \times 10^{-7}, r_{2=} 3 \times 10^{-11}, s = 0.6183, u = 1.8 \times 10^{-8}, k_T = 0.9, k_N = 0.9$

,

$k_L = 0.6, K_C = 0.6, \alpha = 1.21 \times 10^{5}, \beta = 0.012, \gamma = 0.9, \nu = 1.21 \times 10^{5}, z = 0.99, b_2 = 0.05, mu = 1.8 \times 10^{8}, ll = 0.01, b_3 = 0.012, k = 0.05, b_1 = 0.012, k = 0.05, l = 0.002, T = 1 \times 10^{6}, C = 3000, N = 12000, L = 50.0$

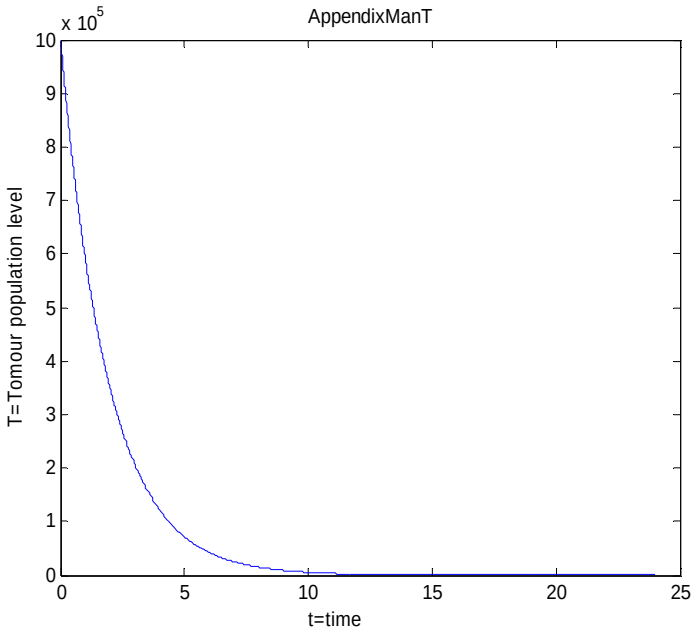
We discuss here the effect of chemotherapy on tumour as they interact with tumour. Since the Natural killer cannot control the tumour growth administration of external immunity is needed to boost the immunity of the system, to be able to conquer and destroy tumour cells. Thus the introduction of chemotherapy to over-power and control the tumour cells and this can be seen from the continuous decrease of tumour cells because of the presence of chemotherapy, (appendixmanT) .

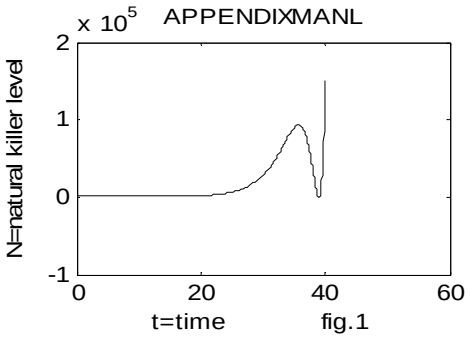
Also we consider the effect of $CD8^{+}T$ on malignant tumour cells. Because of the nature of the equation, the graph shows the interaction of the three immune populations i:e $CD8^{+}T$ effectiveness, natural killer, circulating lymphocytes level on tumour cells. We can see that because tumour is in its cancerous stage, the above immune system-(circulating Lymphocytes, natural killer, $CD8^{+}T$ effectiveness) could not control the tumour (Cancer). They could not control the rate of advancement. From the graph, natural killer, circulating lymphocytes and $CD8^{+}T$ effectiveness were at a steady state until at t=30. The very point where tumour began to increase was the point where natural killer, circulating lymphocytes began to increase to attack. We can see that even though Natural killer, Circulating lymphocytes were increasing they did not have much effect in controlling the growth of cancer. As a result of the ineffectiveness of the Natural killer and the circulating lymphocytes to control tumour growth, the Natural killer, Circulating lymphocytes were forced to decrease. The decrease of natural killer elicits the increase of $CD8^{+}T$ effectiveness. The $CD8^{+}T$ decreased initially because natural killer, circulating lymphocytes were in the increase. All of them cannot be on the increase, because effectiveness of $CD8^{+}T$ is noticed when natural killer and circulating lymphocytes have signaled $CD8^{+}T$ to attack tumour. $CD8^{+}T$effectiveness is a measure of the defense level by $CD8^{+}T$. Its main job is to, apart from alerting natural killer and circulating lymphocytes of an impending danger to the system, itself attacks the external body. It comes into attack when the natural killer, circulating lymphocytes could not attack tumour effectively. The change in the populations of the Tumour and the immune system are as shown in (appendixmanL).

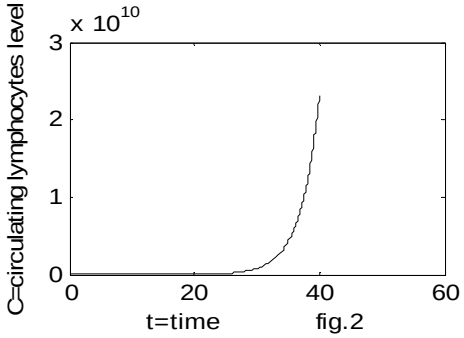
Here we discuss the reaction of five immune population on tumour. Considering appendixman10, we can see that natural killer, circulating lymphocytes, tumour were in steady state up to t=20. At the very point when tumour started increasing was the very point natural killer, circulating lymphocytes started increasing in order to attack tumour. We can see that even at that, natural killer , circulating lymphocytes could not control the growth of tumour. $CD8^{+}T$ effectiveness was in steady state up to a point at time t=40 before it started decreasing . It decreased because it was not effective enough to attack and control the growth of tumour, more so natural killer and circulating lymphocytes were increasing.

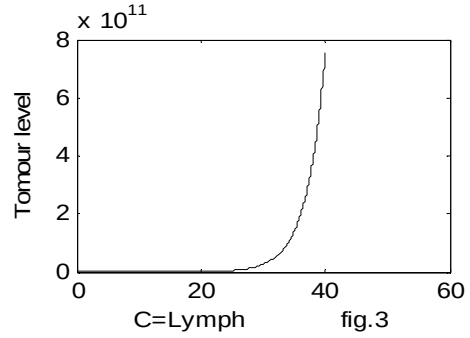
Here also immunotherapy increased very highly before it started decreasing gradually. The increase was as a result of boosting the immune system by administering vaccine therapy, $IL-2$ growth factor injections or the direct injection of highly activated specific immune cells such as $CD8^{+}T$ cells into the blood stream. As the immunotherapy is boosted it begins to attack tumour. As it attacks, it looses strength until it becomes ineffective and weak to attack tumour. We can see from the graph that immunotherapy is decreasing gradually.

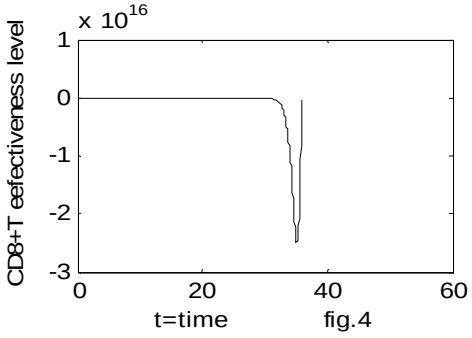
As immunotherapy is decreasing, the chemotherapy is increasing. This is because in case of chemotherapy, the more tumour continues to grow, the more chemotherapy treatment is applied. Chemotherapy treatment will continue to increase until the cancer is completely eradicated or reduced. We can see that from the graph. (see appendixman10)

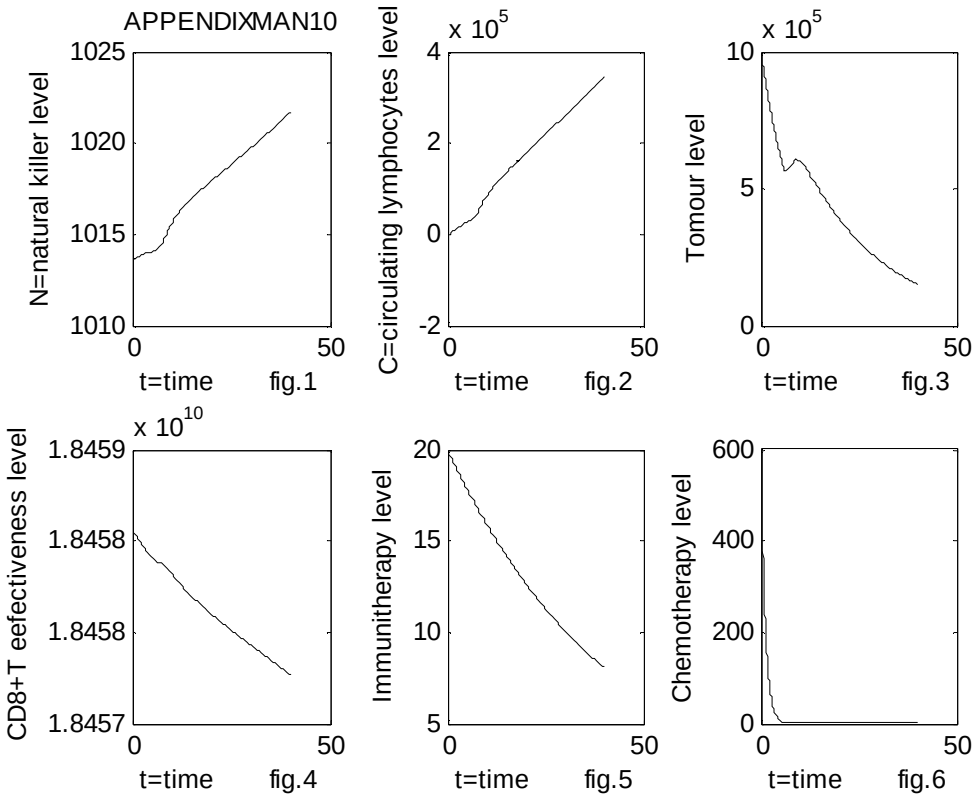

AppendixManT
x 10^5
T=Tomour population level
t=time


APPENDIXMANL
x 10^5
N=natural killer level
t=time
fig.1


x 10^10
C=circulating lymphocytes level
t=time
fig.2


x 10^11
Tomour level
C=Lymph
fig.3


x 10^16
CD8+T eefectiveness level
t=time
fig.4



6.0 Conclusion:

We have been able to establish a more realistic and practical model for the population dynamic of cancer cells. We have been able to show the effect of the immune systems on the malignant tumour cells (called Cancer cells). We can see that with chemotherapy alone, we can reduce the cancer level or even eradicate it. We were equally able to show how each of the immune system varies in the presence of the cancer cells and even themselves. Comparing our results here with what obtains in [16], we can see that our results appear more realistic. For further analysis, we can see this in [11]

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