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Mathematical Understanding of the Autologous Stem Cell Transplantation

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Abstract. A simple mathematical model is provided for understanding the cell dynamics after autologous stem cell transplantation, concluding about the effectiveness of this therapeutic procedure for acute myeloid leukemia and suggesting some biological and clinical directions of further possible investigation.

Key Words: mathematical model, medical application, dynamic system, numerical simulation, stem cell transplantation, acute myeloid leukemia
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1 Introduction

1.1 Medical background

Acute myeloid leukemia (AML) is a cancer of the hematopoietic bone marrow stem cells, due to the expansion of an abnormal mutated stem cell

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clone which leads to the inhibition of surrounding normal cells. Current therapy for AML includes chemotherapy, radiation therapy and stem cell transplantation. The first two treatments are intended to destroy the cancer cells in patient's bone marrow, while the third one aims to replace the leukemic stem cells by healthy stem cells able to repopulate the marrow and reconstruct the hematopoietic process. The infusion by healthy stem cells is made after the conditioning treatment consisting in high doses of chemotherapy and radiotherapy which are given in order to destroy as much as possible patient's cells. The infused cells can be collected from a matched donor (allogeneic transplant), or from patient's own marrow (autologous transplant) [6]. In the last case, the cells are harvested from the patient before the conditioning treatment and purified of cancer cells. Obviously, the success of the autologous transplant depends upon the efficacy of the conditioning regimen in freeing the body of remaining traces of cancer and the complete purification of the infused collection of cells. Since none of the two conditions for the theoretical successful of the autologous transplantation can be guaranteed, there are doubts and controversy about the effectiveness of this procedure for the treatment of AML [8], [12].

1.2 Aim and basic hypotheses

The aim of this paper is to provide a simple mathematical model enough for understanding the cell dynamics after autologous stem cell transplantation (ASCT), concluding about the effectiveness of this therapeutic procedure for AML and suggesting some biological and clinical directions of further possible investigation.

Mathematical approach to complex real processes always focuses on one or a number of defining aspects for the investigated processes and omit other aspects which can be taken into account by further refined models. Hence mathematical models, their analysis and conclusions are founded on a number of assumptions. Thus, the hypotheses on which our model for the autologous stem cell transplantation in AML is based are as follow:

(H1) the conditioning regimen destroys patient's cells as much as possible, but does not succeed total elimination of cancer cells;

(H2) the infused cell collection does not contain tumor cells;

(H3) the conditioning treatment induces cell damage for both residual normal and cancer cells given vitality advantage to the infused cells;

(H4) there is distinction between cell damage (weakness) due to chemo and radiotherapy and severely damage of the bone marrow microenvironment caused by too much administration of high-dose treatments [1].

1.3 Mathematical modeling framework

It is commonly accepted that the mathematical law governing the growth of a population on a finite, not too long time interval is the Malthus equation

$$p' = rp,$$

where $r = a - c$ and a, c are the "natality" and respectively, "death" rate per capita. Thus for this basic model the absolute rate of population growth, $\frac{p'}{p}$ is constant and correspondingly, the trajectories are unlimited exponential functions of time. More realistic models of long-time evolution in population dynamics take into account the growth limitation after a time duration due to such factors as crowding or limited resources. Such kind of self-limiting models are the Verhulst logistic equation, the Gompertz equation and Mackey and Glass equation (without delay) of blood cell production process:

$$p' = \frac{a\theta^n}{\theta^n + p^n}p - cp, \tag{1.1}$$

where a, c, θ are positive constants and $n \geq 1$ (see [5] and [7]).Here the growth rate a is stressed by the feedback factor $\frac{\theta^n}{\theta^n+p^n}$ simulating the crowding effect in the bone marrow microenvironment, which is close to one for small size of cell population and goes to zero for large p. A simple look to the sign of the right-hand side of the equation shows that p is increasing as long as p is less than the homeostatic threshold $\theta\sqrt{\frac{a}{c} - 1}$ and decreasing for p over this value. Notice that the change of variable $q = \theta^{-1}p$ transforms

(1.1) to the equation

$$q' = \frac{a}{1+q^n}q - cq.$$

A quite similar equation has been suggested in [4], namely

$$p' = \frac{a}{1+bp}p - cp.$$

Here the feedback factor changing the growth rate is $\frac{1}{1+bp}$ and a new parameter b is introduced as an expression of cell sensibility to microenvironment. This factor again is close to one if the size of cell population is small, and approaches zero for large p. Also p increases as long as p is less than the homeostatic threshold $\frac{1}{b}\left(\frac{a}{c}-1\right)$ and decreases for p over it. The model was adapted in [4] to describe the evolution of two hematologic cell lines, normal and leukemic and yielded the planar system

$$\text{(1.2)} \qquad \begin{cases} x' = \frac{a}{1+b(x+y)}x - cx \\ y' = \frac{A}{1+B(x+y)}y - Cy. \end{cases}$$

Here $x(t), y(t)$ are the normal and leukemic cell populations at time t, and a, b, c and A, B, C are the growth, microenvironment sensitivity and death rates of the two populations, respectively, where it is assumed that $a > c$ and $A > C$. We note that in [4], x, y stand for primitive stem cells with practically undetermined size, and two additional consequential equations have been considered for the progenitor differentiated cells whose size can established by lab tests. The stability analysis performed in [3] showed that system (1.2) has two non-zero equilibria (steady-states), namely, the good equilibrium $[d, 0]$ and the bad one $[0, D]$, where

$$d = \frac{1}{b}\left(\frac{a}{c}-1\right), \quad D = \frac{1}{B}\left(\frac{A}{C}-1\right),$$

and that normal and leukemic states of the hematopoietic system, which mathematically are expressed by the asymptotic stability of the correspond-

ing equilibrium, are characterized by the inequalities:

$$d > D \ \text{ (normal state)}; \ \ d < D \ \text{ (leukemic state)}.$$

The relationships between normal parameters a, b, c and A, B, C which guarantee the malignant situation $d < D$ were put in [3] in connection with basic pathways leading to leukemia. According to this approach, any therapy against cancer should try to inverse over a time interval as long as possible, the bad inequality $d < D$. Chemotherapy, radiotherapy, autologous and allogeneic transplants, as well as drug treatments are mathematically aimed to this purpose.

In [9], for a model of non-myeloablative allogeneic stem cell transplantation, system (1.1) with x, y standing for the host cells was modified and completed by a third equation corresponding to the new population z of donor cells, as follows:

$$\begin{cases} x' = \frac{a}{1+b(x+y+z)} \frac{x+y}{x+y+gz} x - cx \\ y' = \frac{A}{1+B(x+y+z)} \frac{x+y}{x+y+Gz} y - Cy \\ z' = \frac{a}{1+b(x+y+z)} \frac{z}{z+h(x+y)} z - cz. \end{cases}$$

Here the growth inhibitory factors

$$\frac{1}{1+g\frac{z}{x+y}}, \quad \frac{1}{1+G\frac{z}{x+y}}, \quad \frac{1}{1+h\frac{x+y}{z}}$$

take into account the cell-cell interactions, quantitatively by ratios $\frac{z}{x+y}$ and $\frac{x+y}{z}$, and qualitatively by parameters h, g, G standing for the intensity of anti-graft, anti-host and anti-leukemia effects, respectively. Parameters g, G, h totalize a large number of cell biophysical properties, as well as exterior stimulants and inhibition during the immunotherapy. Values of these parameters $\simeq 0$ correspond to weak interactions, while values $\gg 0$ quantify strong effects. Their estimations would be crucial for transplant strategy (conditioning treatment and dose of infused cells) and post-transplant immunosuppressive treatment and correction therapies (see [11]).

According to the main result in [10] the system has, as the numerical simulations suggested in [9], only two asymptotically stable equilibria, namely the "bad" equilibrium $[0, D, 0]$ and the "good" one $[0, 0, d]$. Also the octant of the positive states $[x, y, z]$ divides into two basins of attraction of the two equilibria, the "bad" basin corresponding to $[0, D, 0]$, and the "good" one for $[0, 0, d]$. If at a given time $t_0 \geq 0$ the state $[x(t_0), y(t_0), z(t_0)]$ belongs to the basin of attraction of any of the two equilibria, then the entire trajectory $[x(t), y(t), z(t)]$ for $t \geq t_0$ remains in the same basin and, as a result, in time, approaches the corresponding equilibrium. Thus a transplant appears as successful if the initial cell concentration $[x_0, y_0, z_0]$ is located in the good basin, which happens if z_0 is sufficiently large compared with x_0 and y_0. Also, an unsuccessful transplant could be turned into a successful one if by any methods/therapies one can move the state $[x, y, z]$ from the bad basin into the good one, or if we can enlarge the good basin to catch the state inside. In fact, for any transplant one could preventively apply the same strategy in order to move the state $[x, y, z]$ (even if located in the good basin) away from the separating surface between the two basins, to be sure that further perturbations can not change the good evolution towards equilibrium $[0, 0, d]$. In [11] we imaged such kind of therapies and we explained that their success depends on their intensity, their length of time interval they are applied and the post-transplant moment they come.

In the present paper, system (1.1) serves once again as the starting point for a three-dimensional system modelling, this time, the autologous stem cell transplantation.

2 Mathematical Models

Assume that the assumptions (H1)-(H4) hold. Mathematically, the weakness of the residual patient's cells after the conditioning treatment can be expressed by modifications of the kinetic parameters a, b, c and A, B, C. In a first approximation, we shall consider that the cell damage is permanent (or at least on a sufficiently large time interval) - first model. Then, as a more realistic case, we shall assume that the damage regresses from one cell generation to the others tending to restore the initial cell vitality - second model. Finally, we shall discuss the effect of permanent damage of patient's

bone marrow caused by too much previous conventional chemotherapy and radiotherapy.

2.1 First model: permanent cell damage

Let a_1, b_1, c_1 and A_1, B_1, C_1 be the new values, after conditioning treatment, at the transplant moment, of the growth, sensibility and death parameters for normal and cancer cells, respectively. The weakness effect means a possible decrease of the growth rates and possible increase of the sensibility and death rates, i.e.,

$$a_1 \le a, \quad b_1 \ge b, \quad c_1 \ge c, \quad A_1 \le A, \quad B_1 \ge B \quad \text{and} \quad C_1 \ge C.$$

Correspondingly, the homeostatic levels of residual weakened cells after high intensity conditioning regimen, at the transplant moment, are

$$d_1 = \frac{1}{b_1}\left(\frac{a_1}{c_1} - 1\right), \quad D_1 = \frac{1}{B_1}\left(\frac{A_1}{C_1} - 1\right),$$

while the homeostatic level of the infused cells is $d = \frac{1}{b}\left(\frac{a}{c} - 1\right)$. Recall that we have assume the leukemic state characterized by the inequality $d < D$. Clearly

$$d_1 \le d \quad \text{and} \quad D_1 \le D.$$

Thus there is a chance that inequality $d > D_1$ holds, that is,

the initial leukemic state $d < D$ turns into the normal state $d > D_1$.

Our model for this situation is given by the following three-dimensional *autonomous* system

$$\left\{\begin{array}{l} x' = \frac{a_1 x}{1+b_1(x+y+z)} - c_1 x \\ \\ y' = \frac{A_1 y}{1+B_1(x+y+z)} - C_1 y \\ \\ z' = \frac{az}{1+b(x+y+z)} - cz. \end{array}\right. \tag{2.1}$$

Assume d_1, D_1, d are distinct and that the conditioning regimen do not change the leukemic state, i.e., $d_1 < D_1$. The steady-states of the system, i.e., the constant solutions are $[0,0,0]$, $[d_1,0,0]$, $[0,D_1,0]$ and $[0,0,d]$. The stability analysis based on the Jacobi matrix shows that the first two equilibria are unstable, the equilibrium $[0,D_1,0]$ is asymptotically stable if and only if $d < D_1$(when transplant fails), while $[0,0,d]$ is asymptotically stable if and only if $d > D_1$ (transplant successful).

2.2 Second model: time-depending cell damage

Assume now that the conditioning regimens cause to patient's residual cells, normal and cancer as well, only temporal damages. This means that the weakness affects the first generations of cells and reduces from one generation to the other tending to disappear. Hence for our model, parameters a_1, b_1, c_1 and A_1, B_1, C_1 referring to the patient's cells before the transplant infusion, will be time-dependent and the dynamic system (2.1) becomes *nonautonomous* with a much complex behavior of the orbits:

$$\begin{cases} x' = \frac{a_1(t)x}{1+b_1(t)(x+y+z)} - c_1(t)\,x \\ y' = \frac{A_1(t)y}{1+B_1(t)(x+y+z)} - C_1(t)\,y \\ z' = \frac{az}{1+b(x+y+z)} - cz. \end{cases}$$

To simulate the return of parameters from their values $a_1, b_1, c_1, A_1, B_1, C_1$ at transplantation, to the initial values a, b, c, A, B, C, we take the functions

$$\begin{aligned} a_1(t) &= a_1 + (a-a_1)\frac{t^2}{t^2+3t_1^2}, \quad b_1(t) = b_1 + (b-b_1)\frac{t^2}{t^2+3t_2^2}, \\ c_1(t) &= c_1 + (c-c_1)\frac{t^2}{t^2+3t_3^2} \end{aligned}$$

and the similar ones

$$\begin{aligned} A_1(t) &= A_1 + (A - A_1)\frac{t^2}{t^2 + 3t_1^2}, \quad B_1(t) = B_1 + (B - B_1)\frac{t^2}{t^2 + 3t_2^2}, \\ C_1(t) &= C_1 + (C - C_1)\frac{t^2}{t^2 + 3t_3^2}. \end{aligned}$$

Here t_1, t_2, t_3 stand for the time moments where the corresponding functions change abruptly their monotonicity, from a slow increasing/decreasing to a fast one. Looking at the function $a_1(t)$ we remark that it increases from a_1 at $t = 0$ (transplant time) to limit a for t going to infinity. In addition it is convex for $0 < t < t_1$ and concave for $t > t_1$. The behavior of $A_1(t)$ is similar. As regards $b_1(t)$, it decreases from b_1 at $t = 0$, to limit b for t tending to infinity. Also it is first concave for $0 < t < t_2$ and then convex for $t > t_2$. The behavior of $c_1(t), B_1(t)$ and $C_1(t)$ is similar.

The homeostatic levels of residual weakened cells after high intensity conditioning regimen, at the transplant moment, are now time depending,

$$d_1(t) = \frac{1}{b_1(t)}\left(\frac{a_1(t)}{c_1(t)} - 1\right), \quad D_1(t) = \frac{1}{B_1(t)}\left(\frac{A_1(t)}{C_1(t)} - 1\right),$$

while the homeostatic level of the infused cells is the constant value $d = \frac{1}{b}\left(\frac{a}{c} - 1\right)$. We have

$$d_1(t) \leq d \quad \text{and} \quad D_1(t) \leq D$$

and the normal hematopoietic state is restored as long $d > D_1(t)$. Unfortunately this happens until a time moment t_r, where $d = D_1(t_r)$, and the leukemic state sets up for $t > t_r$. The time of relapse t_r can be calculated as root of the equation $d = D_1(t_r)$ and is more or less long depending on parameters A, B, C, A_1, B_1, C_1 and t_1, t_2, t_3.

2.3 The case of damaged bone marrow

Here we discuss the case of a patient which was subjected to previous and repeated cures of standard chemotherapy and radiotherapy which

led to a permanent damage of his or her bone marrow. Mathematically this can be expressed by a diminution of the relative growth rates and an increase of the sensibility rates. This allows us to adjust the sensitivity parameters $b, b_1(t), B_1(t)$ and the relative growth rates a/c, $a_1(t)/c_1(t)$ and $A_1(t)/C_1(t)$ as follows

$$\eta b,\ \eta b_1(t),\ \eta B_1(t),\ \varepsilon\frac{a}{c},\ \varepsilon\frac{a_1(t)}{c_1(t)},\ \varepsilon\frac{A_1(t)}{C_1(t)},$$

where $\eta > 1$ and $\varepsilon < 1$. As a consequence, the homeostatic levels d_{1m}, D_{1m}, d_m of residual normal and leukemic cells and infused cells are decreased, namely

$$\begin{aligned} d_{1m}(t) &= \frac{1}{\eta b_1(t)}\left(\varepsilon\frac{a_1(t)}{c_1(t)}-1\right), \quad D_{1m}=\frac{1}{\eta B_1(t)}\left(\varepsilon\frac{A_1(t)}{C_1(t)}-1\right), \\ d_m &= \frac{1}{\eta b}\left(\varepsilon\frac{a}{c}-1\right). \end{aligned}$$

Thus, by transplant, patient's hemathopoietic state is switched from the leukemic to the normal one as long inequality $d_m > D_{1m}(t)$ holds. Calculation shows that

$$d_m - D_{1m}(t) = \frac{\varepsilon}{\eta}\left(d - D_1(t)\right) + \frac{1-\varepsilon}{\eta}\left(\frac{1}{B_1(t)}-\frac{1}{b}\right),$$

hence the desired relation $d_m > D_{1m}(t)$ is guaranteed provided that the following condition stronger than $d - D_1(t) > 0$,

$$d - D_1(t) > \frac{1-\varepsilon}{\varepsilon}\left(\frac{1}{b}-\frac{1}{B_1(t)}\right) \tag{2.2}$$

is satisfied. Let t_{rm} be the time moment (time of relapse) at which equality occurs in (2.2). Therefore, $t_{rm} < t_r$ proving the shorter remission period for this case.

3 Conclusions

1. Compared to standard cures of chemotherapy striking in the same measure normal and tumor cells, long-term outcomes are obtain by ASCT due to the difference of "vitality" between patient's cells after conditioning treatment and the re-infused cells. This also explains why outcomes are better by using of grafts obtained entirely in the first complete remission [2].

2. Our theory proves that permanent damage of the bone marrow caused by successive cures of chemotherapy and radiation is in patient's detriment at ASCT shorting the remission periods. It also gives mathematical proof for the statistical observation that outcomes are better for patients in first complete remission.

3. The main conclusion of our investigation is that autologous stem cell transplantation in AML does not succeed total elimination of the disease unless the ideal case when conditioning therapy killed all patient's leukemic cells. However, as can be shown by numerical simulations, long-term outcomes would be possible over time intervals as long as desired provided that patient's cells could be "marked" during conditioning treatment and a sequential drug post-transplant target therapy is administrated in order to perpetuate weakness of the descendants of "marked" cells without affecting vitality of the progenitors of "unmarked" infused cells. Although our approach is a pure mathematical one, the derived theoretical and numerical results are in concordance with statistical clinical data and medical conclusions. It can be seen as a pleading for a multidisciplinary mathematical-biological and clinical research directed to the improvement and optimization of therapeutic procedures for AML.

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