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Research article

An elementary mathematical modeling of drug resistance in cancer

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Supplementary

The biological descriptions underlying the parameters along with their symbols, units, estimated values and reference sources are listed as follows.

Table S.1. Values of parameters used in simulations.

Symbol	Value	Unit	Description	Reference
l	0.2	day^{-1}	Birth rate constant of cancer cells	Estimated from [3]
d	0.1	day^{-1}	Death rate constant of cancer cells	Estimated from [3]
μ	$1.0 * 10^{-4}$	–	Mutation rate of sensitive cells to resistant cells	[8]
M	1.0	10^9	Critical size of total cancer cells can be detected	[2]
N_0	1.0	10^2	Initial size of drug-sensitive cells	[3]
h	0.366	day^{-1}	Maximal death of drug on drug-sensitive cells	Assumed
D_1	none	–	Concentration of drug-1	none
D_2	none	–	Concentration of drug-2	none
K_1	0.5	–	Michaelis constant of drug-1	Assumed
K_2	0.1	–	Michaelis constant of drug-2	Assumed

Remark: " – " in the above Table S.1 denotes dimensionless unit.

S.1. The case of three drugs

Consider the case of treatment with three drugs are being simultaneously used. The system that describes the dynamics of pre-treatment phase ($t \le t^*$) is given by

$$\begin{cases} N'(t) = (l-d)N(t), \\ R_1'(t) = (l-d)R_1(t) + \mu N(t), \\ R_2'(t) = (l-d)R_2(t) + \mu N(t), \\ R_3'(t) = (l-d)R_3(t) + \mu N(t), \\ R_{1,2}'(t) = (l-d)R_{1,2}(t) + \mu R_1(t) + \mu R_2(t), \\ R_{1,3}'(t) = (l-d)R_{1,3}(t) + \mu R_1(t) + \mu R_3(t), \\ R_{2,3}'(t) = (l-d)R_{2,3}(t) + \mu R_2(t) + \mu R_3(t), \\ R'(t) = (l-d)R(t) + \mu R_{1,2}(t) + \mu R_{1,3}(t) + \mu R_{2,3}(t). \end{cases} \qquad t \le t^*.$$

The system that describes the dynamics after the treatment starts ($t > t^*$) is given by

$$\begin{cases} N'(t) = (l - d - \sum_{i=1}^{3} \frac{h \cdot D_i}{K_i + D_i})N(t), \\ R_1'(t) = (l - d - h(\frac{D_2}{K_2 + D_2} + \frac{D_3}{K_3 + D_3}))R_1(t) + \mu N(t), \\ R_2'(t) = (l - d - h(\frac{D_1}{K_1 + D_1} + \frac{D_3}{K_3 + D_3}))R_2(t) + \mu N(t), \\ R_3'(t) = (l - d - h(\frac{D_1}{K_1 + D_1} + \frac{D_2}{K_2 + D_2}))R_3(t) + \mu N(t), \\ R_{1,2}'(t) = (l - d - \frac{h \cdot D_3}{K_3 + D_3})R_{1,2}(t) + \mu R_1(t) + \mu R_2(t), \\ R_{1,3}'(t) = (l - d - \frac{h \cdot D_2}{K_2 + D_2})R_{1,3}(t) + \mu R_1(t) + \mu R_3(t), \\ R_{2,3}'(t) = (l - d - \frac{h \cdot D_1}{K_1 + D_1})R_{2,3}(t) + \mu R_2(t) + \mu R_3(t), \\ R'(t) = (l-d)R(t) + \mu R_{1,2}(t) + \mu R_{1,3}(t) + \mu R_{2,3}(t). \end{cases} \qquad t > t^*.$$

The notations D_i, K_i ($i = 1...3$) represent concentration and Michaelis constant of ith drug, respectively.

S.2. Parameter calibration

The biological meaning and values underlying the parameters are listed in Table S.1. Most of parameters used in simulations are collected or estimated from literatures, while others are assumed for numerical illustration. The detailed descriptions of the parameter values are given as follows.

(1) Parameters involved in cancer cells load

Previous studies [1] have reported that the total tumor load M should be less than 10^{13} cells, which comes from white blood cell count measurements that range from 10^5 to 10^6 cells/ml of blood in advanced cancers. Meanwhile, it should be more than 10^9 cells or a 1-cm mass, which is approximately the lower limit of clinical detection [2]. Moreover, the initial number of cancer cells N_0 should not be too large, so the resistance before N_0 is reached can be ignored. Thus, the initial number of cancer cells N_0 is set to 10^2 as in ref. [3].

(2) Parameter involved in mutation of cancer cells

The experimental and clinical data in Refs. [4–6] have indicated that the resistance is mainly caused by point mutation and gene amplification. The point mutation leads to the failure of the drug to bind to the target protein, which has been estimated to occur at a rate of 10^{-9} per base per cell division [7]. However, due to genetic instability, the rate of gene duplication is much higher than that of point mutation, which has been measured to be 10^{-4} per cell division [8]. Therefore, we set the mutation rate μ within a range of 10^{-9} to 10^{-4}.

(3) Parameters involved in birth and death of cancer cells

Although the experimental data in Ref. [3] suggested that the relative death rate of cancer cells d along with the turnover rate d/l are estimated to range from 0.1 to 0.5, there is no study on direct measurement of turnover rate d/l. In order to include all possibilities, we use the similar way as in ref. [3] to set the turnover rate d/l from 0 to 1. The scenario where $d/l \ll 1$ represents very low-turnover, low death cancer, while the scenario where $d/l \approx 1$ corresponds to extremely high-turnover, high death cancer.

S.3. The secondary mutation occurs before or after treatment

Consider the generation of resistance in the case where the secondary mutation occurs before or after treatment. First, we set the secondary mutation rate to zero after time of the beginning of the treatment, then $R_2^{\uparrow}(t)$ is the solution of $R(t)$ in system (2.4) with the initial condition

$$R(t^*) = M\Big[\frac{\mu \ln \frac{M}{N_0}}{l-d}\Big]^2,$$

we have

$$R_2^{\uparrow}(t) = M\Big[\frac{\mu \ln \frac{M}{N_0}}{l-d}\Big]^2 e^{(l-d)(t-t^*)}.$$

Next, we only set the secondary mutation rate to zero in the pre-treatment phase, and turn it back after the treatment starts. In this case, $R_2^{\downarrow}(t)$ is the solution of system (2.4) with the initial conditions

$$\begin{cases} N(t^*) = M, \\ R_1(t^*) = \dfrac{M\mu \ln \frac{M}{N_0}}{l-d}, \\ R_2(t^*) = \dfrac{M\mu \ln \frac{M}{N_0}}{l-d}, \\ R(t^*) = 0, \end{cases}$$

and therefore

$$\begin{aligned} R_2^{\downarrow}(t) =& \frac{M\mu^2(K_1+D_1)(K_2+D_2)}{h^2\cdot D_1D_2}\Big[e^{(l-d)(t-t^*)} - e^{(l-d-\frac{h\cdot D_1}{K_1+D_1})(t-t^*)} - e^{(l-d-\frac{h\cdot D_2}{K_2+D_2})(t-t^*)}\Big] \\ &+ \frac{M\mu^2(K_1+D_1)\ln\frac{M}{N_0}}{h\cdot D_1(l-d)}\Big[e^{(l-d)(t-t^*)} - e^{(l-d-\frac{h\cdot D_1}{K_1+D_1})(t-t^*)}\Big] \\ &+ \frac{M\mu^2(K_2+D_2)\ln\frac{M}{N_0}}{h\cdot D_2(l-d)}\Big[e^{(l-d)(t-t^*)} - e^{(l-d-\frac{h\cdot D_2}{K_2+D_2})(t-t^*)}\Big] \\ &+ \frac{M\mu^2(K_1+D_1)(K_2+D_2)}{h^2\cdot D_1D_2}e^{(l-d-\frac{h\cdot D_1}{K_1+D_1}-\frac{h\cdot D_2}{K_2+D_2})(t-t^*)}. \end{aligned}$$

For any $t > t^*$, $R_2^{\uparrow}(t) > R_2^{\downarrow}(t)$ is satisfied under the condition

$$M\Big[\frac{\mu\ln\frac{M}{N_0}}{l-d}\Big]^2 \geq \frac{2M\mu^2(K_1+D_1)(K_2+D_2)}{h^2\cdot D_1D_2} + \frac{M\mu^2(K_1+D_1)\ln\frac{M}{N_0}}{h\cdot D_1(l-d)} + \frac{M\mu^2(K_2+D_2)\ln\frac{M}{N_0}}{h\cdot D_2(l-d)},$$

which implies that

$$\Big[\frac{h\cdot D_1\ln\frac{M}{N_0}}{K_1+D_1} - (l-d)\Big]\Big[\frac{h\cdot D_2\ln\frac{M}{N_0}}{K_2+D_2} - (l-d)\Big] \geq 3(l-d)^2.$$

Thus, it is clear that for the treatment intensity

$$D_1 \geq \frac{K_1(l-d)}{h+d-l} \quad \text{and} \quad D_2 \geq \frac{K_2(l-d)}{h+d-l},$$

we have $R_2^{\uparrow}(t) > R_2^{\downarrow}(t)$. This result holds under the assumption that $\frac{M}{N_0} \geq e^{1+\sqrt{3}}$. Now, we can see that the pre-treatment phase always plays a more important role.

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