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Numerical Study of Therapeutic Effectiveness of Bolus Injection and Continuous Infusion on Drug Delivery to Vascularized Solid Tumor

M. Soltani*, M. Kiani Shahvandi

Department of Mechanical Engineering, Khajeh Nasir Toosi University of Technology, Tehran, Iran

ABSTRACT: Effective delivery of drugs to tumor cells is essential for the success of most anticancer therapies. In this study, two-dimensional modeling for spatiotemporal distribution of doxorubicin concentration under bolus injection and the continuous infusion is presented. Mathematical simulations have been performed considering the main physical and biochemical processes in drug delivery to tumor cells. Anticancer effectiveness is evaluated through changes in tumor cell density based on predicted intracellular concentrations. Unlike most computational models, which assume a uniform distribution of blood vessels in the tumor, the vascular network is produced using a sprouting angiogenesis method. The results demonstrate that the drugs accumulate more in areas with high vascular density, resulting in improved drug cytotoxicity. Compared to bolus injection, continuous infusion leads to longer high level maintenance of intracellular drug concentrations in the tumor, which is more effective in improving the cytotoxic effect. Although bolus injection leads to a 90% higher extracellular concentration peak, there is the risk of severe side effects. Also, continuous infusion by keeping doxorubicin at a higher level in the tumor leads to improved anticancer effectiveness by about 26% relative to the effectiveness of bolus injection at the end of the treatment.

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1- Introduction

Cancer is one of the leading causes of death around the world. Anticancer treatments depend on the effective delivery of therapeutic agents to the tumor cells [1-3]. Chemotherapy is a systemic treatment in which anticancer agents circulate in the bloodstream and can reach cancerous cells around the body. The therapeutic effectiveness strongly depends on the amount of drugs that accumulate in the tumor and the duration of drug exposure. The route and method of anticancer drug administration affect the biodistribution kinetics and chemotherapy effectiveness [4, 5]. Therefore, studies on mode of injection with the aim of maximizing intracellular drug concentration are very important.

In this study, we generated a semi-realistic microvascular network by a hybrid angiogenesis model for simulating the spatiotemporal delivery of doxorubicin to solid tumors. The computational model incorporates the major physical and biological processes involved in the transport of drugs from microvascular to interstitium. We also calculate the interstitial fluid flow that influences the distribution and transport of drugs. Anticancer efficacy is evaluated based on the percentage of survival tumor cells obtained by directly solving the pharmacodynamics equation.

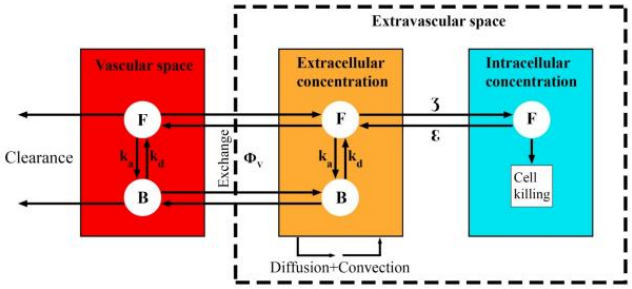

Fig. 1. Schematic diagram of the multi-compartment model (F: Free drug, B: Bound drug).

2- Methodology

The block diagram of the multi-compartment model of the current study is shown in Fig. 1. The details of the rules of the mathematical model of angiogenesis and blood flow simulation have been determined in our previous study [6].

The fluid flow in the porous medium is based on Darcy's law (Eq. (1)) that can modify by adding source (ϕ_b) and sink (ϕ_L) terms for biological tissues:

$$v_i = -K\nabla P_i \quad (1)$$

*Corresponding author's email: msoltani@kntu.ac.ir

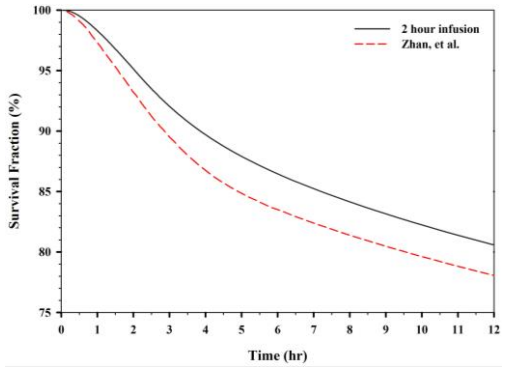

Fig. 2. Comparison of tumor cell survival percentage over time in the present study with results of Zhan and Xu [7].

$$\nabla . v_i = \phi_b - \phi_L \tag{2}$$

Where v_i is the interstitial fluid velocity, K is the hydraulic conductivity of the interstitium, and ϕ_b and ϕ_L are the rates of fluid flow per unit volume from blood vessels into the interstitium and from the interstitium into lymph vessels, respectively.

Drug transport is governed by convection-diffusion-reaction equations for free drug (C_{fe}) and bound drug (C_{be}) in the interstitial fluid:

$$\frac{\partial C}{\partial t} = D_{eff}\nabla^2 C - v_i \cdot \nabla C + P_v + P_b + P_u \tag{3}$$

Where D_{eff} is the effective diffusion coefficient, and P_v, P_b, and P_u represent the net rate of doxorubicin gained from the blood/lymphatic vessels, association/ dissociation with protein, and influx/efflux from tumor cells, respectively. Intracellular concentration is also defined by Eq. (4), where ζ and ε are cellular uptakes and efflux functions.

$$\frac{\partial C_i}{\partial t} = \zeta - \varepsilon \tag{4}$$

The change in tumor cell density with time is shown by a pharmacodynamics model:

$$\frac{dD_C}{dt} = -\frac{f_{\max} C_i}{EC_{50} + C_i} D_C + k_c D_C + k_g D_C^2 \tag{5}$$

Where f_{max} is the cell-kill rate constant and EC_{50} is the drug concentration producing 50% of f_{max}. k_c and k_g are cell proliferation rate constant and physiological degradation rate, respectively.

3- Validation

Fig. 2 shows the numerical validation of this study by comparing the percentage of tumor cell survival resulting from a 2-hour continuous infusion with the results of Zhan and Xu [7]. There is a good agreement as the trend of both curves is quite identical. However, this discrepancy is due to that Zhan and Xu [7] used the maximum vascular density throughout the tumor.

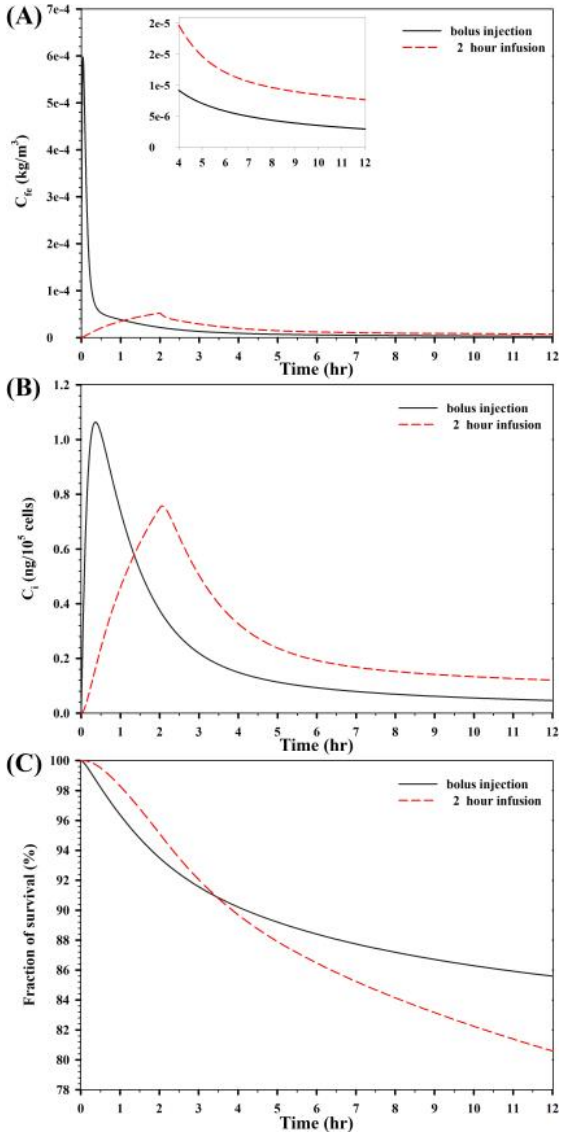

Fig. 2. Comparison of tumor cell survival percentage over time in the present study with results of Zhan and Xu [7].

4- Results and Discussion

In Fig. 3, regardless of the mode of injection, the extracellular concentration in the tumor increases rapidly during the initial period after drug administration and reaches its peak value at the end of the infusion. The extracellular concentration peak of bolus injection is about 90% higher than the continuous infusion peak. Although continuous infusion decreases the peak value, it maintains a higher drug concentration in the tumor. As shown in Fig. 3B, intracellular concentration follows the trend of extracellular concentration. Intracellular

concentration initially shows a sharp increase until reaches the peak value and then decreases. The peak value of bolus injection is 29% higher than the peak of continuous infusion, but at the end of the treatment, continuous infusion retains the drug at 67% higher in the tumor. Therefore, under continuous infusion, more cancer cells are affected by the drug. As shown in Fig. 3C During the initial period after drug administration (about 3.5 hours), the anticancer efficacy of bolus injection is greater than continuous infusion, but it weakens over time. According to the results, although the 2-hour infusion leads to a lower intracellular concentration peak, the drug concentration remains at a higher level after administration, so at the end of the treatment, the continuous infusion has 26% more anticancer effectiveness than bolus injection. Therefore, the treatment effectiveness, beyond the peak value, depends on the intracellular concentration during the total exposure time of the drug.

5- Conclusion

In this study, the spatiotemporal distribution of doxorubicin concentration under different injections is investigated. The results showed that to improve the therapeutic efficacy, the drug must remain in the tumor for a long time. According to the results, although the 2-hour infusion leads to a slower increase and a lower peak of intracellular concentration, the drug concentration remains at a higher level after the peak time and the cytotoxic effect is better. Therefore, the cytotoxic effectiveness depends more on the intracellular concentration over the entire time of exposure than on the peak value. Therefore, for the same total dose injected, a continuous infusion can be more effective than a bolus injection.

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