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The Role Of EBUS-TBNI Cisplatin Injection Strategies In Lung Tumor Treatment

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Background, Motivation and Objective. Cisplatin is a well-known chemotherapy drug due to its ability to interfere with cell replication. However, the usual administration routes (IP and IV) exposes many off-target tissues to heavy side-effects. Hence, we recently started intratumoral cisplatin administration in lung cancers that are adjacent to airways and reoccurs under a radiation field using endobronchial ulstrasound guided transbronchial needle injection (EBUS-TBNI), allowing higher doses in the tumor and reducing harmful side effects. However not only the number of injections but also their locations remain in an empirical footing. Therefore, we targeted this problem with a mathematical and computational model based not only on a 3D reconstruction of a lung tumor CT scan but also from literature data of cisplatin pharmacodynamics.

Methods. The tumor was modelled as a series of interconnected pairs of extracellular (interstitial fluid and connective tissue) and intracellular (cytoplasm and associate organelles) spaces with small blood vessel perfusing the tumor and acting as sinks to a single well-mixed fluid space (systemic vasculature and some extravascular spaces). Following an intratumoral injection, cisplatin enters the extracellular space and diffuses throughout neighbour extracellular spaces with a diffusion coefficient D, while intracellular sink occurs with a rate-constant k_i and cisplatin clearance to the fluid space with a rate-constant k_f. Lastly, once in the fluid space, cisplatin is filtered by the kidneys with a rate-constant k_r (Fig. 1). We then developed an analytical model for cisplatin concentration in the intracellular space following N injections as a function of time and position:

$$\varphi_i(\vec{r},t) = k_i \sum_{j=1}^{N} \frac{m_j}{2D|\vec{r}-\vec{r}_j|} \begin{bmatrix} e^{-2\alpha\beta}(1-\mathrm{erf}(\alpha-\beta)) \\ -e^{2\alpha\beta}(1-\mathrm{erf}(\alpha+\beta)) \end{bmatrix} \quad (1)$$

where:

$$\alpha = \sqrt{\frac{|\vec{r}-\vec{r}_j|^2}{4D\tau}} \quad \text{and} \quad \beta = \sqrt{(k_i + k_f)\tau}. \quad (2)$$

Lastly, by assuming that cytotoxicity is related to cisplatin concentration of cisplatin in the intracellular space above a certain threshold value we developed an algorithm to optimize injections strategy. All patients referred for potential EBUS-TBNI of cisplatin are reviewed at the Multidisciplinary Lung Tumor Board of the University of Vermont Medical Center to ensure that there are no other more well-established therapeutic options.

Results. While D, k_i and k_r were settled from literature data, k_f was determined from our model fit to cisplatin level in the vasculature of one patient (Fig. 2). Model fit to data is presented in Fig. 2. From injections optimization, minimum cisplatin dose to kill all cells, based on a pre-defined intracellular threshold concentration, significantly diminishes when more injections are apportioned (Fig. 3)

Discussion and Conclusions. There is an enormous apparent benefit of apportioning a given dose of cisplatin between a number of well-placed injections, up to 5, rather than delivering the entire dose into a single central location. However, model is limited to the myriad simplifying assumptions that have been made during construction, e.g. homogeneous and isotropic internal structure of the tumor and cytotoxicity mechanisms.

Figures and Tables.

Figure 1. Model structure. Each labeled rectangle represents a single well-mixed compartment.

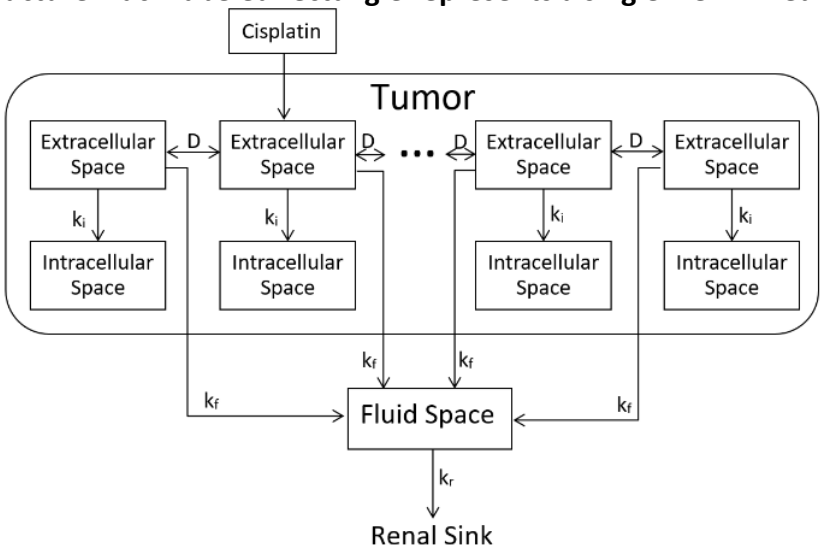


Figure 2. Measured blood concentration of cisplatin (open circles) following five, 8-mg intratumoral injections into this lung tumor. Also shown (solid line) is the model fit to data (r^2 = 0.98) represented by * (P<0.05), ** (P<0.01) and * (P<0.001), respectively. All comparisons were made with Student's T-test.**

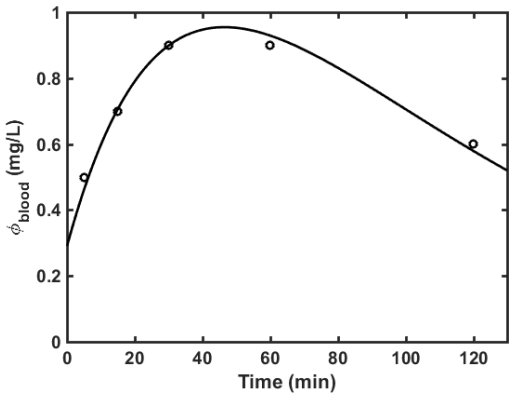
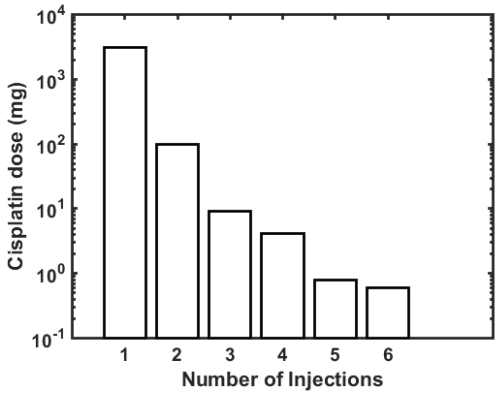


Figure 3. Minimum total cisplatin dose needed for all tumor cells to reach a threshold intracellular concentration of 0.5 × 10^{-7} mg/mL as a function of the number of injections. Equal doses are given with each injection, and the injection sites are located optimally



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