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Optimal standard regimen and predicting response to docetaxel therapy

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ABSTRACT

The purpose of this research is optimizing and predicting the potent activity of docetaxel through an efficient regimen to settle down a new protocol for the treatment of cancer. Effectiveness of docetaxel was examined in vivo in several mouse models engrafted either subcutaneously or intravenously with several types of cell lines. The effects of 147–5040 mg/L of docetaxel in treatments of different regimens in those xenograft growths were monitored and quantified to identify energy of those doses as described before in earlier studies. Mock processes were performed on untreated groups of mice for controls. Docetaxel had significant influence on all sizes of treated tumors compared to the control animals. The longer the induced tumor doubling time intraday to more than half the time period from the start of therapy to the time of delivery of the dose, the higher the energy of docetaxel doses and hence the effectiveness of the treatment and vice versa. The energy yield by drug doses in optimal standard regimens was perfectly power correlated ($r = 1$) with the drug dose. An efficient dose-energy model with a perfect fit ($R^2 = 1$) estimating the energy yield by docetaxel doses in optimal standard regimens has been established to administer the personalized dose. Administration of docetaxel doses should be patient-specific and sufficient for the suggested regimen. Time periods from the start of therapy to the time of dose delivery of the efficient regimen are shorter than twice the tumor doubling time intraday on time of dose delivery. Patients with tumors of lower mitotic index may particularly benefit more from optimal standard regimens, whereas metronomic regimens would be more efficient in patients with tumors of higher mitotic index that need lower doses of docetaxel.

1. Introduction

Microtubules are part of a structural network (the cytoskeleton) within the cell's cytoplasm play a huge role in movement within a cell [1]. They are essential in a number of cellular processes and play a crucial role in multiple steps of mitosis including the formation of mitotic spindles [2]. They form the spindle fibers that manipulate and separate chromosomes during mitosis [3]. Docetaxel (as generic or under the trade name Taxotere) is an antimicrotubule agent belongs to a class of chemotherapy drugs called cell-cycle specific affect cells only when they are dividing [4]. Docetaxel is a clinically well-established anti-mitotic chemotherapy medication (that is, it interferes with cell division) [5]. Docetaxel binds to microtubules reversibly with high affinity and has a maximum stoichiometry of 1 mole docetaxel per mole tubulin in microtubules [6]. This binding stabilizes microtubules and prevents depolymerisation from calcium ions, decreased temperature and dilution, preferentially at the plus end of the microtubule [6]. The main mode of therapeutic action of docetaxel is the suppression of microtubule dynamic assembly and disassembly, rather than microtubule bundling leading to apoptosis, or the blocking of bcl-2 which also encourages apoptosis [4,6]. As microtubules do not disassemble in the presence of docetaxel, they accumulate inside the cell and cause initiation of apoptosis [6]. Furthermore, it has also been found that docetaxel leads to the phosphorylation of oncoprotein bcl-2, which is apoptosis-blocking in its oncoprotein form [4]. Both in vitro and in vivo analysis show the anti-neoplastic activity of docetaxel to be effective against a wide range of known cancer cells, cooperate with other anti-neoplastic agents activity, and have greater cytotoxicity than paclitaxel, possibly due to its more rapid intracellular uptake [4]. Many studies have been shown that docetaxel has been found to accumulate to higher concentration in ovarian adenocarcinoma cells than kidney carcinoma cells, which may contribute to the more effective treatment of ovarian cancer

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by docetaxel [4,6]. But effectiveness of docetaxel treatment was related to the mitotic index of the treated tumors as all cell cycle specific drugs so that in some cases docetaxel treatment had not shown a significant effect on the tumor stage. However the effectiveness of docetaxel versus paclitaxel and other taxanes is still controversial. Several more recent articles have found "no evidence those regimens containing docetaxel yield greater benefits than those including paclitaxel [7]. Additionally, the optimal scheduling of docetaxel and other taxanes remains unconfirmed. Recently, Moawad developed a model of clinical based staging of the cancer at the cellular level in which the effect on the cancer stage due to therapy can be estimated and consequently effectiveness of the treatment can be determined [8–13]. Further exploration into the mechanism(s) of action is required for optimizing docetaxel administration through an efficient regimen for this anticancer molecule whose full therapeutic potential is yet to be realized. Current approach investigates several regimens of docetaxel treatments applied on models of murine tumors xenografts of different types and cell lines. Assessment of the efficient regimen for optimizing cell-cycle specific therapy would be based on achieving an accumulated doubling time-energy conversion [8–24] in the tumor cells by the regimen doses.

2. Materials and methods

2.1. Monitoring the mechanical behavior of the tumor response to therapy

Comparing the mechanical behavior of tumor response of the treated groups to that of the control groups is assessed by determining the growth/or shrinkage constants of those tumors of different volumes along the corresponding periods [25,26]. The growth/or shrinkage constant of the tumor at a certain time expresses the rate of the difference between Mitosis and Apoptosis with respect to the total number of the tumor cells (M–A) that characterize the tumor response at that time [8–19]. If rate of mitosis is greater than that of apoptosis, tumor grows by growth constant of $\ln 2/t_D$, where t_D is the tumor doubling time and vice versa if rate of mitosis is less than that of apoptosis, tumor shrinks by shrinkage constant of $\ln 2/t_{1/2}$, where $t_{1/2}$ is the tumor half-life time [8–19,25,26], i.e.

$$(M-A) = \frac{\ln 2}{t_D} S^{-1} \text{ in case of tumor growth,}$$
$$\text{and} \quad (1)$$
$$(A-M) = \frac{\ln 2}{t_{1/2}} S^{-1} \text{ in case of tumor shrinkage}$$

where t_D and $t_{1/2}$ in seconds, Eq. (1)

The clinical staging model presented by Moawad showed that the tumor histologic grade (H_G) that expresses tumor response can be identified by using Emad formula [8–24] as follows:

In case of tumor growth:

$$H_G = \ln\left(\ln \frac{\ln\ 2}{t_D}\right)^2 \times C_0 \times h \times 23234.59\,\text{MeV} \quad (2)$$

where $C_0 \times h$ is number of the hypoxic cells in the tumor or number of the inoculated cells in the transplanted tumor in xenografted models.

In case of tumor shrinkage:

The chemotherapeutic drugs affect the tumor cells such that the more the drug dose the less of mitotic cells or the more of apoptotic cells. Since the portion of tumor cells underwent apoptosis due to anti-microtubule agents therapy had been prevented first from mitosis. Thus to apply Eq. (2) in the shrinking case, the apoptotic tumor portion of half-life time ($t_{1/2}$) would be replaced by virtual growing portion of doubling time (t_D) which had been prevented first from mitosis. The greater the shrinkage portion of the tumor, the more the efficiency of the treatment and hence replaced by a smaller virtual growing portion and vice versa. Thus, rate of the virtual growth would be inversely proportional to the rate of the tumor shrinkage as follows:

$$\left(\frac{V_{\text{Initial}} - V_{\text{Final}}}{V_{\text{Initial}}}\right)_{\text{Shrinkage}} = \left(\frac{V_{\text{Initial}}}{V_{\text{Final}} - V_{\text{Initial}}}\right)_{\text{Virtual growth}} \quad (3)$$

where V is the tumor volume.

Accordingly from Eqs. (1) and (2), the alteration in the treated tumor H_G to that of the control tumor induced by the drug dose would be equivalent to the energy yield by the drug dose according to the following model:

$$E_{\text{Dose}} = [\ln(\ln(M-A)_{\text{Treated}})^2 - \ln(\ln(M-A)_{\text{Control}})^2] \times C_0 \times h \times 23234.59\,\text{MeV} \quad (4)$$

3. Effectiveness of docetaxel treatment assay

It should be noted that, clinical evidence indicates tumor growth is not constant over the life cycle of a tumor, but varies over time with increased doubling time and decreased growth. This model allows the tumor to approach, but not exceed, a maximum volume as it ages, consistent with the biological behavior of tumors in which tumor growth rate decreases as the metabolic demands of the enlarging tumor exceed the host's capacities to provide nutrients. Thus, tumor t_D intraday increases linearly with time for specific initial and final volumes according to the exponential growth model as follows:

$$\text{Tumor}t_D \text{ intraday} = \frac{\ln\ 2}{\ln\ V_{\text{Final}} - \ln\ V_{\text{Initial}}} \times t \text{ sec} \quad (5)$$

as the time period (t) from initiating therapy increases the tumor doubling time (t_D) intraday increases and hence the effectiveness of the treatment. Accordingly, the criterion of the efficient regimen of docetaxel treatment can be determined by comparing the tumor t_D intraday to the time period from initiating therapy on time of dose delivery in the studied regimen.

As described and conducted by several authors, Table 1 shows growth inhibition in tumors of different cell lines in murine experiments by docetaxel in different regimens [27–34].

4. Results and analysis

From data shown in Table 1 and Eqs. (1)–(5), tumor t_D and energy yield by docetaxel doses were derived as follows:

4.1. For treatment 1 of metronomic regimen

4.1.1. HeyA8 xenograft

From Table 1 and Eq. (5), the average tumor size of control group grew from 100 mm^3 (0.1 g) at the beginning of the treatment to 1200 mm^3 in 24.5 days (3.5 weeks) with doubling time (t_D) of 6.834102168 days. While, the average tumor size of the treated group grew from 100 mm^3 to 288 mm^3 in 24.5 days with t_D of 16.05432194 days. Metronomic regimen of 0.5 mg/kg docetaxel thrice a week for 3.5 weeks in human (70 kg, 2.5 L plasma) is equivalent to $(0.5 \times 3 \times 3.5 \times 70\,\text{mg}/2.5\,\text{L})$ 147 μg/mL. Thus from Eqs. (1) and (4), the energy yield by 147 μg/mL of docetaxel ($E_{\text{Docetaxel(147 μg/mL)}}$) in tumor xenograft of transplanted 2.5×10^5HeyA8 cells was equivalent to: