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Cancer as a Chronic Disease with which Human can Coexist

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Article Info

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Abstract

The aim of the current study is to establish new physical tumor-markers for the effectiveness of the cancer therapy upon which human can coexist with cancer as a chronic disease. Doubling Time-Energy Conversion (DT-EC) during tumor formation and cancer therapy were investigated in groups of mice i.p. injected with ($1x10^6$) HeyA8 MDR cells and ($2.5x10^5$) HeyA8 cells, and treated by cell cycle specific drug (docetaxel) one week after tumor cell injection. Therapy for HeyA8 tumor model consisted of three groups: (a) Phosphate Buffered Saline (PBS), (b) Maximum Tolerated Dose (MTD) for Docetaxel (15 mg/kg every 2 weeks), (c) metronomic Docetaxel (0.5 mg/kg thrice weekly). Therapy for HeyA8 MDR tumor model consisted of two groups: (a) PBS, (b) MTD Docetaxel (15 mg/kg every 2 weeks) Mice were monitored for adverse effects and tumors were harvested after 3 to 4 weeks of therapy. Tumor of advanced stage (HeyA8 MDR model) was characterized by higher rate (1^{st} derivative) of DT-EC (with respect to the doubling time) and faster deceleration (2^{nd} derivative) of DT-EC (with respect to the doubling time). Energies yield by equivalent doses with same regimen (MTD) in both tumor models were identical regardless to tumor size or resistance. Metronomic regimen was more effective than the standard one in HeyA8 model. Despite the dose of the metronomic regimen (147 μg/mL) was about one fifth of that of the MTD of the standard one (840 μg/mL) the energy yield by the smaller dose was greater than that yield by the higher one with more reduction in the rate of DT-EC and more slowing for the DT-EC deceleration. Thus the effectiveness of the cancer therapy is assessed by how much the 1^{st} derivative of DT-EC has been minimized and by how much the 2^{nd} derivative of DT-EC has been slowed down to treat cancer as a chronic disease with which human can coexist as long as possible.

Keywords: Doubling time-energy conversion; Emad formula; Cell cycle specific chemotherapy drugs; Metronomic regimen.

Introduction

The process of cancer therapy is based mainly on the concept of Doubling Time-Energy Conversion (DT-EC) in which the conversion of doubling time into growth energy takes place [1,2]. The concept of the equivalence of doubling time and energy is obvious in cancer therapy in which the change in doubling time is a relatively large fraction of the initial

doubling time [3]. This type of energy was named cell growth energy due to the increase of the rate of mitosis than the rate of apoptosis which leads to the growth of the population of the tumor cells [4]. The duration of the mitosis stage is defined by the cell doubling time or the division time and denoted by t_D [5]. The fundamental principle for the cell cycle duration in relation to the physical energy condition of a cell has been derived and confirmed. Growth energy (E_D) of the biological cell was expressed in terms of t_D by the DT-EC formula $E_G=\ln\left(\ln\left(\frac{\ln 2}{t_D}\right)\right)^2$ Emad Eqt (1) which is known by Emad formula referring to the unit used in identifying the converted energy [6, 7]. The DT-EC formula represents the total existence energy that the biological cell possesses through its cycle duration [1, 2]. The converting factors of the Emad unit of each of the biological cell and the Iodine-131 were taken equivalent as it is the commonest safely used radionuclide. i.e. 1 Emad = 23234.59 MeV Eqt (2) [8]. This important formula represents the total energy of a biological cell, suggesting that the biological condition for the existing cell growth energy (EG) for all living organisms is t_D > 1n 2 x *e* Sec (1.884169385 Sec), even when a cell is at the natural background radiation (NBR), it still possesses existence energy (E_{NBR}=1.2484MeV) through its cycle duration [5, 6]. This concept for DT-EC in the biological systems was established to asses the limits of energy that are suitable for energy conversion processes. Fundamentally, in tumor formation and in cancer therapy the connection between the cell cycle and its physiological behaviour prior and during therapy is obvious [1, 2]. The increase in t_D of the cancerous cell by an amount $\Delta t_D=t_{D2}-t_{D1}$ induced by the cytostatic effect of the drug therapy results in a corresponding increase in the cell growth energy by an amount $\Delta E_G=\ln\left(\ln\frac{\ln 2}{t_{D2}}\right)^2-\ln\left(\ln\frac{\ln 2}{t_{D1}}\right)^2$.

Thus, $\frac{dE_G}{dt_D}=\lim_{\Delta t_D\to 0}\frac{\Delta E_G}{\Delta t_D}$ is the 1st derivative of the cell E_G as a function of cell t_D expresses the rate of DT-EC, whereas the 2nd derivative $\frac{d^2E_G}{dt_D^2}$ expresses the acceleration or the deceleration of DT-EC. The current approach aims to assess $\frac{dE_G}{dt_D}$ and $\frac{d^2E_G}{dt_D^2}$ as physical tumor-markers by investigating their behavior during tumor formation and during therapy and their relations with cancer staging and effectiveness of the treatment.

Methods and Materials

Identifying the effectiveness of cancer treatment

The 1st derivative of the cell E_G as a function of cell t_D can be derived from Eqt (1) as follows:

$$\frac{dE_G}{dt_D}=\frac{2}{t_D}\times e^{\frac{-1}{2}\times E_G}=\frac{2}{t_D}\times e^{\frac{-1}{2}\times\ln\left(\left(\ln\frac{\ln 2}{t_D}\right)^2\right)}$$ Emad/Sec Eqt (3)

which is always positive along the domain of E_G (t_D>1n2 x e Sec) to indicate that E_G is increasing along its whole domain as shown in figure (1).

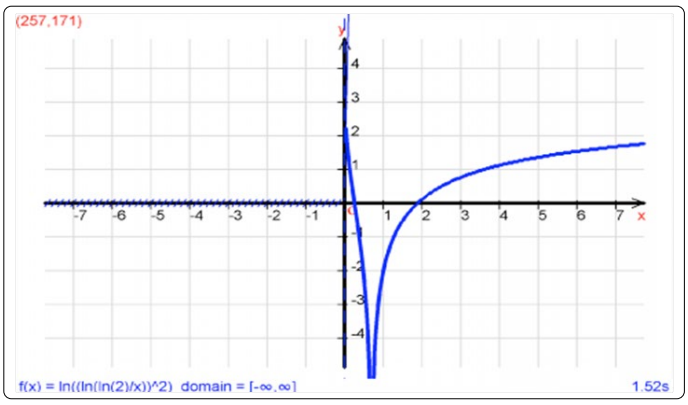

Figure 1. shows EG (y) as a function of cell tD (x) which is always positive for the domain of EG (tD>1n2, X e Sec)

Consequently the 2nd derivative of the cell E_G as a function of cell t_D can be derived from Eqts (1) and (3) as follows:

$$\frac{d^2E_G}{dt_D^2}=\frac{-2}{t_D^2}\times\left[e^{\frac{1}{2}E_G}+e^{-E_G}\right]$$ Emad/Sec^2 Eqt (4)

Which is always negative expressing a deceleration along the domain of E_G (t_D>1.884169385 Sec [4, 5]) to indicate that $\frac{dE_G}{dt_D}$ is decreasing along its whole domain to show that rate of DT-EC decreases by the increase of t_D. Accordingly, it can be deduced that during tumor formation the rate of this conversion decreases gradually.

Similarly, $\frac{d^3E_G}{dt_D^3}$ can be derived from Eqts (1) and (4) as follows:

$$\frac{d^3E_G}{dt_D^3}=\frac{2}{t_D^3}\left[2e^{\frac{1}{2}E_G}+2e^{-E_G}+2e^{\frac{-3}{2}E_G}-1\right]$$ Eqt (5)

Which is always positive along the domain of E_G (t_D>1.884169385 Sec) to indicate that $\frac{d^2E_G}{dt_D^2}$ is increasing along its whole domain to show that the deceleration of DT-EC increases algebraically (slows) by the increase of t_D.

Accordingly, it can be deduced that during tumor formation the deceleration of this conversion increases algebraically (slows) gradually.

Since the behavior of cells during tumor formation or treatment with respect to cell cycle arrest doesn't change acting towards increasing t_D. Thus, the target from therapy which is considered the measure of effectiveness of the treatment from one phase to the next is decreasing the rate of DT-EC and slowing the deceleration of DT-EC than that occurred during tumor formation.

Thus, as much the physical tumor-marker $\frac{dE_G}{dt_D}$ decreases, whereas the other physical tumor-marker $\frac{d^2E_G}{dt_D^2}$ increases algebraically (slows) during therapy than their values during tumor formation as much the treatment would be more efficient.

Influence of pharmacokinetic on the effectiveness of cancer treatment

Half-life time of chemotherapy drugs ($t_{1/2}$) is considered one of the main parameters to distinguish between those drugs in investigating their suitability and approval to treat certain disease [9]. Thus the following proof is to investigate the influence of $t_{1/2}$ on rate of DT-EC and the effectiveness of cancer treatment:

As $\frac{dE_G}{dt_D} = \frac{dE_G}{dt} \div \frac{dt_D}{dt}$ Eqt (6), then rate of DT-EC during therapy depends on two main factors; rate of the growth energy acquired by the cell ($\frac{dE_G}{dt}$) and rate of increase of t_D ($\frac{dt_D}{dt}$). From Eqt (6), as much as $\frac{dE_G}{dt}$ decreases and $\frac{dt_D}{dt}$ increases as much as rate of DT-EC during therapy decreases as well that implies the increase of the effectiveness of the treatment and conversely. Notably, growth energy (E_G) acquired by the cell during an efficient therapy would be equivalent to that yield by the used drug (E_{Dose}) in the therapy duration [2]. Accordingly, the increase of $\frac{dE_{Dose}}{dt}$ contributes in the effectiveness of cancer treatment as follows:

$$E_{Dose} = E_{ï\ Dose} \times (1- e^{\frac{-\ln 2}{t_{1/2}} \times T}) \text{ Eqt (7)}$$

where $E_{ï\ Dose}$ is the energy of the administered dose, $t_{1/2}$ is the half-life time of the used drug and T is the time from initiating the treatment.

Thus, rate of energy yield by the drug during therapy:

$$\frac{dE_{Dose}}{dt} = \frac{\ln 2}{t_{1/2}} \times E_{ï\ Dose} \times e^{\frac{-\ln 2}{t_{1/2}} \times T} \text{ Eqt (8)}$$

which increases by the increase of $E_{ï\ Dose}$ and the decrease of $t_{1/2}$.

From Eqts (3), (6) and (8)

$$\frac{dt_D}{dt} = \frac{\ln 2}{2} \times \frac{t_D}{t_{1/2}} \times E_{ï\ Dose} \times e^{\frac{1}{2}\ln\left(\left(\ln\frac{\ln 2}{t_D}\right)^2\right) - \frac{\ln 2}{t_{1/2}} \times T} \text{ Eqt (9)}$$

which decreases by the decrease of t_D and the increase of $t_{1/2}$. Thus, the opposite impacts of $t_{1/2}$ on the rate of DT-EC during therapy shown by Eqts (8) and (9) demonstrate that $t_{1/2}$ doesn't influence that conversion and consequently the effectiveness of cancer treatment. Hereby it can be concluded that Eqt (3) is valid to express the rate of DT-EC during tumor formation and during therapy as well. On the other hand, it should be noted that during tumor formation or therapy the tumor t_D varies linearly with time as follows;

$$\frac{dt_D}{dt} = \frac{\ln 2}{\ln V_{Final} - \ln V_{Initial}} \text{ Eqt (10) and } t_D = \frac{\ln 2}{\ln V_{Final} - \ln V_{Initial}} \times t \text{ Sec Eqt (11)}$$

Where V is the tumor volume, and as much $\frac{dt_D}{dt}$ increases as more as the treatment would be efficient.

DT-EC kinematics in tumor models treated with cell-cycle specific drug

Next, consider a basic cancer therapy in which drug acts as a cytostatic agent inducing cell cycle arrest to check the above mentioned hypothesis for the effectiveness of cancer treatment. Chemotherapy drugs which are known by cell-cycle specific are the most suitable for the following check because of their non linear effect. Those drugs affect cells only during mitosis such that as long as doubling time of the tumor prolongs as much as tumor cells affected by the drug [11]. The scheduling of such chemotherapy drugs is based on the type of cells, rate at which they divide, and consequently the time at which those drugs are likely to be effective [11]. Docetaxel belongs to this class of chemotherapy drugs [12], which was selected to check the hypothesis of the current approach. As conducted and described by Kamat AA, et al [13] for long-term experiments to assess tumor growth 200 μL of concentrations of $5x10^6$/mL of HeyA8 MDR cells and $1.25x10^6$/mL of HeyA8 cells were i.p. injected in female athymic nude mice. Groups of mice (n = 10 in each group) i.p. injected with ($1x10^6$) HeyA8 MDR cells and ($2.5x10^5$) HeyA8 cells were treated one week after tumor cell injection. Therapy for HeyA8 tumor model consisted of three groups: (a) PB S, (b) Maximum Tolerated Dose (MTD) for docetaxel (15 mg/kg every 2 weeks), (c) metronomic docetaxel (0.5 mg/kg thrice weekly). Therapy for HeyA8 MDR tumor model consisted of two groups: (a) PB S, (b) MTD Docetaxel (15 mg/kg every 2 weeks) Mice were monitored for adverse effects and tumors were harvested after 3 to 4 weeks of therapy. If animals in any group began to seem moribund and required sacrifice, all animals in the experiment were sacrificed together. Mouse weight, tumor weight, and distribution of tumor were recorded. Survival experiments were also done, which were initiated one week after tumor cell injection. Mice of HeyA8 tumor model were treated as described above and individually killed when moribund (unable to move or reach food). The date of death was recorded as the day a mouse was sacrificed.

Results and Analysis

Therapy with different doses was initiated one week after tumor cell injection at which the median weight of the injected tumors was 0.1g. The docetaxel-treated animals exhibited a tumor growth delay along the whole duration of the experiment which terminated after3-4 weeks [13]. Survival data were compared for significance with the log-rank statistic. Treatment with MTD (P = 0.03) and metronomic Docetaxel (P = 0.002) both significantly prolonged survival [13].

Effect of the Maximum Tolerated Dose of Docetaxel in treating HeyA8 tumor model

While the median of control tumors grew to 1.2g at the end of the experiment, the MTD of docetaxel (15 mg/kg/ two weeks) resulted in a reduction in the median tumor weight to 0.42 g after 3-4 weeks of therapy (P < 0.001)[13].

A dose of 15 mg/kg/2 weeks of docetaxel for 3-4 weeks in human (70kg, 2.5L plasma) is equivalent to $\frac{15\times2\times70}{2.5}$ = 840 μ g/mL.

Tumors in the mice received the treatment of docetaxel (840 μ g/mL) had a growth curve with t_D of 11.83352313 days [from 0.1g to 0.42 g in 3.5 weeks (p<0.001)], while t_D was 6.834102168 days only for the group of control tumors [from 0.1g to 1.2g in 3.5 weeks (p<0.001)]. Moawad presented a clinical staging model at the cellular level in which the tumor histologic grade (H_G) can be identified as follows:

$H_G=\ln\left(\ln\frac{\ln 2}{t_D}\right)^2\times C_0\times h\times 23234.59\text{MeV}$ Eqt (12), where C_0xh is number of the hypoxic cells in the tumor or number of the inoculated cells in the transplanted tumor Model (2.5x10^5 HeyA8 cells) [14-22]. Accordingly from Eqt (12), the difference in tumor energy in those groups of tumor Model (2.5×10^5 HeyA8 cells) induced by 840 μ g/mL of Docetaxel was as follows:

$$\left[\ln\left(\ln\frac{\ln 2}{11.83352313\times24\times60\times60}\right)^2-\ln\left(\ln\frac{\ln 2}{6.834102168\times24\times60\times60}\right)^2\right]\times 2.5\text{x}10^5\times$$

23234.59 = 4.57932236x10^8 MeV.

From Eqts (3) and (4), the 1st and the 2nd derivatives of DT-EC ($\frac{dE_G}{dt_D}$ and $\frac{d^2E_G}{dt_D^2}$) for the control tumors of HeyA8 cells were 2.48048912x10^{-7} Emad/Sec and -7.83623712x10^{-11} Emad/Sec^2 respectively, while values of those derivatives for the treated tumors of HeyA8 cells by the MTD of docetaxel (15 mg/kg/2weeks) were 1.37716395x10^{-7} Emad/Sec and -2.71858204x10^{-11} Emad/Sec^2 respectively. From Eqt (10) $\frac{dt_D}{dt}$ for the treated tumors of HeyA8 cells with 840 μ g/mL in standard regimen was 0.4830009441 more than that of the control tumors of HeyA8 cells (0.2789429457) by 73.15%. This confirms the hypothesized role of cancer therapy of increasing of the rate of increase of tumor t_D that leads to decrease the DT-EC. Thus from Eqt (6) and by knowing the value of $\frac{dt_D}{dt}$, the value of $\frac{dE_G}{dt}$ for the treated tumors of HeyA8 cells with 840 μ g/mL in standard regimen was 6.65171488x10^{-8} Emad/Sec less than that of control tumors of HeyA8 cells (6.91914942x10^{-8} Emad/Sec) by 3.9%. This confirms also the second hypothesized role- by current approach-of cancer therapy in decreasing the rate of increase of tumor E_G that leads to decrease also the DT-EC.

Effect of the Maximum Tolerated Dose of docetaxel in treating HeyA8 MDR tumor model

While the median of the control tumors grew to 2.2 g at the end of the experiment, the MTD of docetaxel (15 mg/kg/ two weeks for 3.5 weeks = 840 μ g/mL) resulted in a reduction in the median tumor weight to 2 g after 3-4 weeks of therapy (P < 0.001) [13].

Tumors in the mice received the treatment of Docetaxel (840 μ g/mL) had a growth curve with t_D of 5.66876622 days [from 0.1g to 2 g in 3.5 weeks (p<0.001)], while t_D was 5.493973693 days only for the group of control tumors [from 0.1g to 2.2 g in 3.5 weeks (p<0.001)]. Accordingly from Eqt (12), the difference in tumor energy in those groups of tumor Model (1x10^6 HeyA8 MDR cells) induced by 840 μ g/mL of Docetaxel was as follows:

$$\left[\ln\left(\ln\frac{\ln 2}{5.66876622\times24\times60\times60}\right)^2-\ln\left(\ln\frac{\ln 2}{5.493973693\times24\times60\times60}\right)^2\right]\times 1\text{x}10^6\times$$

23234.59 = 1.08187622x10^8 MeV.

From Eqts (3) and (4), the 1st and the 2nd derivatives of DT-EC ($\frac{dE_G}{dt_D}$ and $\frac{d^2E_G}{dt_D^2}$)for the control tumors of HeyA8 MDR cells were 3.13566995x10^{-7} Emad/Sec and -1.19318468x10^{-10} Emad/Sec^2 respectively, while values of those derivatives for the treated tumors of HeyA8 MDR cells by the MTD of docetaxel (15 mg/kg/ 2weeks) were 3.03191671x10^{-7} Emad/Sec and -1.12334611x10^{-10} Emad/Sec^2 respectively. From Eqt (10) $\frac{dt_D}{dt}$ for the treated tumors of HeyA8 MDR cells with 840 μ g/mL in standard regimen was 0.2313782132 more than that of the control tumors of HeyA8 MDR cells (0.2242438242) by 3.18% only clarifying the low effectiveness to decrease the DT-EC by the standard regimens of cell-cycle specific drug therapy in treating tumors of high mitotic index as HeyA8 MDR tumor model. Thus from Eqt (6) and by knowing the value of $\frac{dt_D}{dt}$, the value of $\frac{dE_G}{dt}$ for the treated tumors of HeyA8 MDR cells

with 840 μg/mL in standard regimen was 7.01519471x10^{-8} Emad/Sec less than that of the control tumors of HeyA8 MDR cells (7.03154621x10^{-8} Emad/Sec) by 0.23% only expressing the low effectiveness to decrease the DT-EC by the standard regimens of cell-cycle specific drug therapy in treating the tumors of high mitotic index as HeyA8 MDR tumor model.

Effect of the optimal metronomic dose of Docetaxel in treating HeyA8 tumor model

While the median of the control tumors grew to 1.2 g at the end of the experiment, all metronomic doses of Docetaxel were highly effective in reducing tumor growth. The metronomic dose of Docetaxel (0.5 mg/kg thrice weekly) resulted in a reduction in the median tumor weight to 0.288 g after 3-4 weeks of the therapy (P < 0.001) [13].

A dose of 0.5 mg/kg thrice weekly of docetaxel for 3-4 weeks in human (70kg, 2.5L plasma) is equivalent to $\frac{0.5\times3\times3.5\times70}{2.5}$ = 147 μ g/mL.

Tumors in the mice received the treatment of docetaxel (147 μg/mL) had a growth curve with t_D of 16.05432194 days [from 0.1g to 0.288g in 3.5 weeks (p<0.001)], while t_D was 6.834102168 days only for the group of control tumors [from 0.1g to 1.2g in 3.5 weeks (p<0.001)]. Accordingly from Eqt (12), the difference in tumor energy in those groups induced by 147μ g/mL of docetaxel was as follows:

$$\left[\ln\left(\ln\frac{\ln 2}{16.05432194\times24\times60\times60}\right)^2-\ln\left(\ln\frac{\ln 2}{6.834102168\times24\times60\times60}\right)^2\right]\times 2.5\text{x}10^5\text{x}$$

23234.59=7.04777881x10^{8}MeV.

From Eqts (3) and (4), the 1st and the 2nd derivatives of DT-EC ($\frac{dE_G}{dt_D}$ and $\frac{d^2E_G}{dt_D^2}$) for the treated tumors of HeyA8 cells by the metronomic docetaxel (0.5 mg/kg thrice weekly) were 9.93756086x10^{-8} Emad/Sec and

-1.50870809x10^{-11} Emad/Sec^2 respectively. From Eqt (10) $\frac{dt_D}{dt}$ for the treated tumors of HeyA8 cells with 147 μg/mL in metronomic regimen was 0.6552784464 more than that of the control tumors of HeyA8 cells (0.2789429457) by 135%. This clarifies the high effectiveness of the metronomic regimens of cell-cycle specific drug therapy compared by the standard regimens. Thus from Eqt (6) and by knowing the value of $\frac{dt_D}{dt}$, the value of $\frac{dE_G}{dt}$ for the treated tumors of HeyA8 cells with 147 μ g/mL in metronomic regimen was 6.51186944x10^{-8} Emad/Sec less than that of control tumors of HeyA8 cells (6.91914942x10^{-8} Emad/Sec) by 5.89%. This confirms also the high effectiveness to decrease the DT-EC of the metronomic regimens of cell-cycle specific drug therapy compared by the standard regimens. These findings confirm the hypothesized role of cancer therapy-by current approach- in decreasing the rate of increase of tumor E_G and increasing the rate of increase of tumor t_D that lead to decrease the DT-EC.

Table 1. shows, docetaxel dose and regimen, energy yield, Cell Growth energy (E_G), Doubling time (t_D), rate of DT-EC, deceleration of DT-EC, rate of increase of t_D, and rate of increase of E_G for control and treated tumors of HeyA8 and HeyA8 MDR Models.

Tumor Model	Control HeyA8	Treated HeyA8 by Metronomic dose	Treated HeyA8 by MTD	Control HeyA8MDR	Treated HeyA8 MDR by MTD
Docetaxel Dose (μg/mL)	0	0.5x3mg/kg/ week (147 μg/mL)	15mg/ kg/2weeks (840μg/mL)	0	15mg/ kg/2weeks (840μg/mL)
Energy Yield (MeV)	0	7.04777881x10^8	4.57932236x10^8	0	1.08187622x10^8
E_G(Emad)	5.22823802	5.34957054	5.30707431	5.19601045	5.20066677
t_D (Days)	6.834102168	16.05432194	11.83352313	5.493973693	5.66876622
$\frac{dE_G}{dt_D}$ (Emad/Sec)	2.480489x10^{-7}	9.9375608x10^{-8}	1.3771639x10^{-7}	3.1356699x10^{-7}	3.0319167x10^{-7}
$\frac{d^2E_G}{dt_D^2}$ (Emad/ Sec^2)	-7.836237x10^{-11}	-1.5087081x10^{-11}	-2.7185820x10^{-11}	-1.1931846x10^{-10}	-1.123346x10^{-10}
$\frac{dt_D}{dt}$ (Sec/Sec)	0.2789429457	0.6552784464	0.4830009441	0.2242438242	0.2313782132
$\frac{dE_G}{dt}$ (Emad/Sec)	6.9191492x10^{-8}	6.51186944x10^{-8}	6.65171488x10^{-8}	7.03154621x10^{-8}	7.01519471x10^{-8}

Thus from table 1 it is obvious that

1. The rate of DT-EC in the control tumor of HeyA8 MDR model was more than that of the control one of the HeyA8 model, while the deceleration of DT-EC in the control tumor of HeyA8 MDR model was faster (less algebraically) than that of the control one of the HeyA8 model.

This provides a clear cut criterion to accept the hypothesis of current approach that tumors of higher rates of DT-EC and faster deceleration of DT-EC which are represented here by HeyA8 MDR model would be more resistant to cell-cycle specific drug treatment.

2. The rate of DT-EC in the treated tumor was lower than that of the control one, while the deceleration of DT-EC in the treated tumor was slower than that of the control one in the three presented therapies.

This confirms the hypothesis of current approach that the targets of therapy are to minimize the rate of DT-EC and slowing the deceleration of DT-EC as minimum as possible. As the deceleration of DT-EC is always negative along the whole domain of E_G as previously shown then slowing its value as minimum as possible means to maximize its algebraic value.

3. Accordingly, the effectiveness of the presented therapies was ranked as follows:

The metronomic dose of 0.5mg/kg of docetaxel thrice a week in HeyA8 tumor model was the most effective one, then followed by the MTD of 15mg/kg/2weeks of docetaxel in HeyA8 tumor model with moderate efficiency and followed by the MTD of 15mg/kg/2weeks of docetaxel in HeyA8 MDR tumor model with lower efficiency.

This rank is consistent with the experimental results presented by Kamat AA, et al in which HeyA8 MDR tumor model was classified as the most resistant model to docetaxel therapy [13].

Discussion

The aims of this study are to investigate the kinematics of DT-EC during tumor formation and their therapeutic responses to establish new physical tumor-markers for cancer staging and effectiveness of cancer treatment. *In-vivo* tumor models in athymic mice were used to identify the treatment efficacy of docetaxel as a one of the cell cycle specific drugs through metronomic and standard regimens. From Eqts (8) and (9), the drug half-life time has equal and opposite impacts on the rate of drug energy yield and the rate of tumor doubling time. Thus, the resultant of those impacts vanished on the DT-EC kinematics to conclude that drug pharmacokinetic has no effect on the effectiveness of cancer treatment. The clinical methodology for staging tumors using Eqt (12) was conducted as described in earlier studies to determine the energy of tumor responses [3,8,14-25]. Estimating the energy yield by docetaxel doses was conducted by monitoring the difference in tumour responses and the accompanied alteration in the tumour H_G before and after therapy as described before in earlier studies [14,17-19,22-25]. The most important issues regarding the use of cell-cycle specific drugs are optimal dosing and scheduling. Thus, selecting docetaxel to test the hypothesis of the current approach was because docetaxel has never demonstrated predictable outcomes yet because of its non aphid accumulative therapeutic effect as it affects cells only when they are dividing [6]. Accordingly it was more suitable to select docetaxel to investigate the kinematical targets of chemotherapy than other non-cell cycle specific drugs which characterized by aphid accumulative and predictable therapeutic effect. Thus, it was not surprisingly for the variation in energies yield by the equivalent doses of docetaxel (840 μg/mL) with the same schedule of standard regimen (15mg/kg/2weeks) in the treated HeyA8 and HeyA8 MDR tumor models that demonstrate the variation in the therapeutic action of cell-cycle specific drugs due to the variation in mitotic indices. HeyA8 MDR tumor model was faster in tumor formation compared by HeyA8 model. Hereby, the rate of mitosis in HeyA8 MDR model was higher than that in HeyA8 model before therapy. Such increase in the rate of mitosis resulted in a shorter doubling time compared to the schedule of MTD regimen that led to expose the drug dose to metabolism in non dividing periods and to substitute the portion of tumor cells that had been triggered to apoptosis by the first dose through mitosis before the second dose. The rate of DT-EC ($\frac{dE_G}{dt_D}$) in the treated tumor of HeyA8 model was lower than that induced in the treated tumor of HeyA8 MDR model. This was because of the greater increase in $\frac{dt_D}{dt}$ and the greater decrease in $\frac{dE_G}{dt}$ of the treated tumor of HeyA8 model (73.15% and 3.9% respectively) than that induced in the treated tumor of HeyA8 MDR model (3.18% and 0.23% respectively) as postulated for minimizing the rate of DT-EC as a therapeutic target in Eqt (6). This explains the greater resistance exhibited by HeyA8 MDR model than that of HeyA8 model to docetaxel therapy. Thus, regimens of cell cycle specific drugs can be designed according to the standards assessed by current approach which should cover the tumor doubling time by more frequent infusion to improve effectiveness of the treatment. Observations at table (1) demonstrated also that despite the dose of the metronomic regimen (147 μg/mL) was about one fifth of that of the MTD of the standard one (840 μg/mL), the energy yield by the lower dose was greater than that yield by the higher one as deduced from the tumor response in each therapy. Accordingly, metronomic regimen was more effective than the standard one as it induced a lower rate of DT-EC and slower deceleration of DT-EC as postulated in our model for the effectiveness of the cancer treatment. In addition, each of the metronomic and the MTD based regimen had a significant effect on the therapeutic survival [14]. This clarifies the evolution towards the metronomic administration of cell cycle specific chemotherapy drugs that attack the cells during various phases of division, or in case of administration of chemotherapeutic drugs when high-dose chemotherapy is not very effective and/or associated with high toxicity [26]. Thereby, these findings suggest that patients with tumors of advanced stages of low mitotic index may particularly more benefit from standard docetaxel regimens than those with tumors of early stages of higher mitotic index. On the contrary, metronomic docetaxel regimens would be more efficient for cases in early stages of higher mitotic index due to their lower histologic grade that needs lower doses of docetaxel. It was possible to correlate between the kinematics of DT-EC during tumor formation and the stage of the tumor model. Advanced stages are characterized by higher rate of DT-EC and faster deceleration of DT-EC (lower algebraic value) as shown for the control tumor of the resistant model (HeyA8 MDR) compared to that of HeyA8 one. Also, reducing the rate of DT-EC and slowing (increasing algebraically) the deceleration of DT-EC during therapy was confirmed in all the presented therapies of different regimens and tumor models. Thus through identifying the effectiveness of the presented treatments, it was possible to deduce the role of therapy which is minimizing the rate of DT-EC and slowing the deceleration of DT-EC as minimum as possible to prolong the survival period as long as possible. From Eqt (3), the rate of DT-EC is an increasing function along its whole domain. Thus, in cancer therapy there are no limits to minimize the rate of DT-EC which can be continued to infinity. Also from Eqt (4), deceleration of DT-EC is a decreasing function along its whole domain. Thus, in cancer therapy there are no limits to slow the deceleration of DT-EC which can be continued also to infinity.

These optimistic findings give the hope to deal with cancer as a chronic disease with which humans can coexist with no survival period limits. DT-EC kinematics for cancer patients can be identified by clinical or pathological tests before therapy for cancer staging and grading [5, 16]. Also during therapy to check the effectiveness of the treatment, modify doses and regimens for optimal dosing and scheduling [7, 13-18,20,21-25]. Ranking the effectiveness of the presented therapies was consistent with the experimental results presented by Kamat AA, et al [13] that classified HeyA8 MDR tumor model as the resistant model to docetaxel therapy. Together with these findings and analysis that irrespectively of the treatment (untreated (control) vs. treated), origin of the cells (HeyA8, HeyA8 MDR), treatment regimen (metronomic, standard), provide a clear cut criterion to accept the hypothesis of the current thesis that during tumor formation the rate of DT-EC decreases, whereas the deceleration of this conversion slows (increases algebraically) gradually. Furthermore, the targets of the cancer therapies are to minimize the rate of DT-EC and slowing the deceleration of DT-EC as minimum and longer as possible. These therapeutic roles are considered physical tumor-markers for the effectiveness of the cancer treatment that helps to treat cancer as a chronic disease with which humans can coexist as long as possible with no survival period limit.

Conflict of interest

The author declares that there is no conflict of interest concerning this paper.

References

1. Moawad EY. Mass-energy conversion in the decaying system and doubling time-energy conversion in the biological system. *Journal of Physics Research and Reviews*. 2015; 1(1): 1-13.
2. Moawad EY. Towards Easier and Straight Foreword Dosimetry Always Inherits Identical Results. *Archives of Radiology*. 2018; 1(1): 1-6.
3. Moawad EY. Isolated System towards a Successful Radiotherapy Treatment. *Nuclear Medicine and Molecular Imaging*. 2010; 44: 123-136. doi: 10.1007/s13139-010-0029-9
4. Moawad EY. Growth Energy of Bacteria and the Associated Electricity Generation in Fuel Cells. *Bioengineering and Bioscience*. 2013; 1: 5-10. doi: 10.13189/bb.2013.010102
5. Moawad EY. Nuclear Transmutation and Cancer in the Biological Cell. *International Journal of Biochemistry and Biophysics*. 2013; 1: 1-8. doi: 10.13189/ijbb.2013.010101
6. Moawad EY. Moawad Cell Growth Energy Represents a Measure for Man Health; Regulates Nuclear Transmutations and Aberrant Activation in Human Cell. *Universal Journal of Medical Science*. 2013; 1: 27-35. doi: 10.13189/ujmsj.2013.010203
7. Moawad EY. Optimizing Bioethanol production through regulating Yeast Growth Energy. *Syst Synth Biol*. 2012; 6: 61-68. doi: 10.1007/s11693-012-9099-6
8. Moawad EY. Radiotherapy and risks of tumor regrowth or inducing second cancer. *Cancer Nanotechnology*. 2011; 2: 81-93. doi: 10.1007/s12645-011-0018-4
9. Moawad EY. Pathologic Cancer Staging By Measuring Cell Growth Energy. *Basic Science and Technology*. 2012; 18: 04. doi: 10.1016/j.jvir.2012.04.029
10. Clarke SJ, Rivory LP. Clinical Pharmacokinetics of Docetaxel. *Clinical Pharmacokinetics*. 1999; 36 (2): 99-114. doi: 10.2165/00003088-199936020-00002
11. Baker SD, Zhao M, Lee CK. Comparative pharmacokinetics of weekly and every-three-weeks docetaxel. *Clin Cancer Res*. 2004; 10(6): 1976-83. doi: 10.1158/1078-0432.CCR-0842-03
12. Lyseng-Williamson KA, Fenton C. Docetaxel: a review of its use in metastatic breast cancer. Drugs 2005; 65(17): 2513-31. doi: 10.2165/00003495-200565170-00007
13. Kamat AA. Metronomic chemotherapy enhances the efficacy of antivascular therapy in ovarian cancer. *Cancer Res*. 2007; 67: 281-288. doi: 10.1158/0008-5472.CAN-06-3282
14. Moawad EY. Administering the optimum dose of L-Arginine in regional tumor therapy. *Ind J Clin Biochem*. 2014; 29(4): 442-51. doi: 10.1007/s12291-013-0379-z
15. Moawad EY. Clinical and pathological staging of the cancer at the nanoscale. *Cancer Nano*. 2012; 3: 37-46. doi: 10.1007/s12645-012-0028-x
16. Moawad EY. Reconciliation between the clinical and pathological staging of cancer. *Comparative Clinical Pathology*. 2012; 23: 255-262. doi: 10.1007/s00580-012-1603-6
17. Moawad EY. Induction of Multiple Sclerosis and Response to Tyrosine Kinase Inhibitors. *Ind J Clin Biochem*. 2013. doi: 10.1007/s12291-013-0387-z
18. Moawad EY. The Mechanism by which Chronic Myeloid Leukemia Responds to Interferon-α Treatment. *Advances in Pharmacology and Pharmacy*. 2013; 1: 88-94. doi: 10.13189/app.2013.010207
19. Moawad EY. Induction of Rheumatoid Arthritis and Response to Tyrosine Kinase Inhibitors. *Universal Journal of Medical Science*. 2013; 50-55. doi: 10.13189/ujmsj.2013.010205
20. Moawad EY. Safe Cancer Screening for Patients after Lumpectomy, Survivors, and Healthy Subjects. *Cancer and Oncology Research*. 2013; 1: 15-23. doi: 10.13189/cor.2013.010201
21. Moawad EY. Safe Doses and Cancer Treatment Evaluation. *Cancer and Oncology Research*. 2013; 1: 6-11. doi: 10.13189/cor.2013.010102
22. Moawad EY. Identifying the optimal dose of ritonavir in the treatment of malignancies. *Metab Brain Dis*. 2013; 1: 6-11. doi: 10.1007/s11011-013-9448-5
23. Emad Moawad Y. "Effect of O6-Methylguanine-DNA Methyltransferase Resistance to Temozolomide in Gliomas or Brain Metastases of Melanoma". Acta Scientific Pharmaceutical Sciences. 2018; 03-12.
24. Moawad EY. Identifying and Predicting the Effectiveness of Fenretinide (4-HPR) Alone or in Combination with Radiotherapy. *International Journal of Pharma and Drug Development*. 2017; 1(2): 49-58.
25. Moawad EY. Cellular Mechanics and Therapeutic Resistance of the Cancer Relapse. *Journal of Radiation and Nuclear Medicine*. 2017; 1(1): 1-12.
26. Nieto Y. The verdict is not yet in. Analysis of the randomized trials of high-dose chemotherapy for breast cancer. *Haematologica*. 2003; 88: 201-11.