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Testing Doses and Treatment Timelines of Anti-Angiogenic Drug Bevacizumab Numerically as a Single-Agent for the Treatment of Ovarian Cancer

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Abstract: An anti-angiogenic drug in cancer treatment prevents the growth of new blood vessels in tumors by binding to VEGF molecules, which otherwise induce endothelial cells inside blood vessels to sprout the blood supply toward the tumor. This would prevent the growth of new blood cells which will deprive the tumor of nutrients, thus decreasing its carrying capacity, and ultimately shrinking its volume. With new vascularization absent, the tumor will be isolated, making it easier to treat. Although there is an availability of various anti-angiogenic drugs, their effectiveness is low compared to other cancer treatments. We are specifically pinpointing the various combination of doses and the treatment timelines as reasonable factors to increase the effectiveness of the anti-angiogenic drug Bevacizumab, which can possibly prolong the patient's survival rate and offer lower toxicity compared to other treatment modalities such as radiotherapy and chemotherapy. We have numerically analyzed different doses of Bevacizumab, including 15 mg/kg, an FDA-approved dose if offered in conjunction with chemotherapy drugs, carboplatin and paclitaxel, as a single-agent treatment option. Based on the results, the tumor volume was observed to be stabilizing for the duration of the treatment, which was chosen to be 400 days. The toxicity levels of these doses with Bevacizumab as a single-agent treatment option have not been tested in a clinical setting. However, these mathematically promising results can provide a gateway for the successful treatment of ovarian cancer in the future.

Keywords: ovarian cancer; numerical analysis; anti-angiogenic drug; Bevacizumab; single-agent treatment option; toxicity

MSC: 97N40; 62P10

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1. Introduction

Ovarian cancer is the most lethal gynecologic cancer and is described as "an uncontrolled growth of cells that forms in the ovaries". This cancer tends to "invade and destroy healthy body tissue" and can go undetected for a long time because its symptoms—such as weight loss, fatigue, back pain, abdominal bloating/swelling, frequent urination, changes in bowel habits, and quickly feeling full when eating—are attributed to other conditions that are more common [1]. As of 2022, it is estimated that about 19,880 women will receive a new diagnosis of ovarian cancer in the United States [2], and about 12,810 women will die from ovarian cancer. Ovarian cancer lethality ranks fifth in cancer deaths among women and accounts for more deaths than any other cancer of the female reproductive system [2].

The survival rates for ovarian cancer vary and depend on if the cancer is localized, regional, or distant. Epithelial ovarian cancer (EOC), the most common type of ovarian cancer, has a 93% survival rate if localized, a 75% survival rate if regional, a 31% survival rate if distant, and a 48% survival rate if all the stages are combined [3]. EOC is characterized by poor prognosis, resulting in a 5-year survival rate of only 30% due to vague initial

symptoms that lead to delayed diagnosis (approximately 70% of cases are diagnosed at an advanced stage). In addition, disease recurrence is frequent, occurring in 70–80% of EOC cases [4].

The current standard of care for ovarian cancer includes the removal of the bulk part by surgery, followed by a standard chemotherapy regimen, carboplatin–paclitaxel. The higher level of toxicity, both short-term and long-term, is associated with the chemotherapy drugs including carboplatin–paclitaxel [5,6]. Other treatment options that may offer less toxicity are also being studied and used. One notable option is anti-angiogenic drugs, which aim to block the formation of new blood vessels specifically in a tumor's vascular stage. Bevacizumab's (brand name: Avastin) ability to "slow the growth of cancer or sometimes shrink it" [7] deems it as a focal point of this research. This anti-angiogenic drug is FDA-approved for the treatment of ovarian cancer if used along with chemotherapy drugs carboplatin and paclitaxel.

The high metabolic activity and lack of enough nutrients cause some parts of cancer cells to usually become hypoxic. The vascular endothelial growth factor (VEGF), which is secreted by the tumor under hypoxic condition, bind and activate VEGF receptors that are found on the surface of endothelial cells. They play an important role in the development of angiogenesis by the recruitment and proliferation of endothelial cells [8].

Bevacizumab acts by selectively binding circulating VEGF, thereby inhibiting the binding of VEGF to its cell surface receptors, VEGFRs. This inhibition leads to a reduction in microvascular growth of tumor blood vessels, thus limiting the blood supply to tumor tissues. According to Kazazi-Hyseni et al. [8], these effects also lower tissue interstitial pressure, increase vascular permeability, may increase delivery of chemotherapeutic agents, and favor apoptosis of tumor endothelial cells.

When treating ovarian cancer, Bevacizumab and surgery are typically used together in conjunction with chemotherapy to achieve the best results. The treatment plan consists of the patient's surgery, followed by 15 mg/kg of Bevacizumab, in combination with chemotherapy drugs carboplatin and paclitaxel. These drugs are given once every three weeks for up to six cycles. These six cycles will be followed by 15 mg/kg of Bevacizumab alone as maintenance therapy, given once every three weeks for up to 22 cycles total [9], which is equal to 84 weeks (=588 days).

There have been numerous clinical trials to check for the efficacy of Bevacizumab used in conjunction with carboplatin and paclitaxel; however, none of them has indicated a noticeable increase in overall survival [10–12]. Bevacizumab has not been tested clinically as a single-agent except for relapsing ovarian cancer [13]. Thus, a mathematically successful result can provide an initial gateway for exploring treatment viability in the clinical setting.

In this research, various doses of Bevacizumab as a single-agent treatment option after surgery will be tested in the mathematical model proposed by Poleszczuk et al. [14]. The various combinations of treatment days, such as Monday and Thursday or Monday, Wednesday, and Friday, will be tested using different doses of Bevacizumab. In addition, a dosing plan that starts with a small dose (5 mg/kg or 10 mg/kg) that then increases by a small but equal amount on each subsequent treatment is tested here. If the tumor volume is stabilized for the duration of treatment, then it will be considered a reasonably positive outcome for these trials. The clinical viability of such trial doses, if successful mathematically, will also be discussed based on the available literature.

2. Methodology

The current FDA-approved dosing plan for Bevacizumab in combination with chemotherapy drugs, carboplatin and paclitaxel, followed by Bevacizumab alone, is 15 mg/kg [15] once every three weeks (q3w) for a total of 28 cycles (≈590 days). We will be testing three different doses, 5, 10, and 15 mg/kg, in our mathematical model for the use of Bevacizumab as a single-agent treatment modality.

The classical mathematical model that governs the growth of tumor volume (V) and the carrying capacity (K), maximal tumor volume that current vasculature can hold, in absence of clinical intervention, are given by Hahnfeldt et al. [16]:

$$\frac{dV}{dt} = -\epsilon V \log\left(\frac{V}{K}\right) \tag{1}$$

$$\frac{dK}{dt} = -\mu K + bV - dKV^{\frac{2}{3}} \tag{2}$$

where the time evolution of V is described by a Gompertzian growth. The second term bV, which represents the stimulatory contribution due to factors such as VEGF, is focused here from the treatment aspect of Bevacizumab. As suggested by Poleszczuk et al. [14], the contribution of the second term (2) should be lower (compared to the original term bV) if an anti-angiogenic drug, particularly Bevacizumab, is used, as it mainly suppresses the formation of the new blood vessel by binding with VEGF. Since this paper aims to use Bevacizumab as a single-agent treatment option (chemo drugs excluded), we believe that the following modification in the second term of Equation (3) for carrying capacity K, as proposed in [14], is justifiable.

$$\frac{dK}{dt} = -\mu K + \frac{b}{1+eg(t)}V - dKV^{\frac{2}{3}} \tag{3}$$

where $g(t)$ represents the time-dependent concentration of the administered Bevacizumab. The above Equation (3) together with (1) will be adopted in this paper for the numerical analysis. Under the pharmacokinetic assumptions [17], $g(t)$ is expressed as

$$g(t) = \int_0^t c(s)\exp^{-clr(t-s)}\, ds, \tag{4}$$

where $c(s)$ is the administration rate of the drug and clr is the clearance rate of the drug (how fast the drug moves out of the body).

We are pinpointing tumor volume vs. time graphs by bringing the following variations. The treatment regimen will span over a period of 400 days.

- Three different doses of Bevacizumab 5, 10, and 15 mg/kg are administered every Monday and Thursday, with the day count starting one day after the surgery. They are compared against the control (without anti-angiogenic intervention). These doses are also tested for the three day treatment option, i.e., Monday, Wednesday, and Friday. The administration rate $c(s)$ is given as

$$c(s) = D(\delta(s-t_1) + \delta(s-t_2) + \ldots), \tag{5}$$

  where D is the administered dose (for example, 15 mg/kg) and t_i are the injection days ($t_1 = 1$, $t_2 = 4$, etc.).
- Start with a moderate dose of 5 mg/kg or 10 mg/kg and increase the dose slightly by an equal amount after every treatment for the period of 400 days.

$$c(s) = D_1((\delta(s-t_1)) + D_2(\delta(s-t_2)) + \ldots, \tag{6}$$

  where D_1 is the initial dose (for example, 5 mg/kg) given on day 1 ($t_1 = 1$) and D_2 (5.5 mg/kg for dose increment of 0.5 mg/kg) is the second dose given on Day 4 ($t_2 = 4$), and so on.

Numerical integration of Equations (1) and (3) is carried out in MATLAB by Euler's forward difference scheme with a time step $dt = 0.01$ for 400 days. The duration of the treatment used here is 175 days less than the suggested timeline for the current standard of care, which involves surgery followed by adjuvant chemotherapy and the anti-angiogenic drug Bevacizumab. The shorter treatment timeline of 400 days selected for the numerical

analysis here is to see if the complication associated with the toxicities (if any) of the drug can be spared to some level. The constant parameters and the initial values in Table 1 are adopted from Poleszczuk et al. [14].

Table 1. Estimated tumor growth parameters [14].

Symbol	Description	Units	Control (No Angiogenic Drug)	Model Value
e	drug impact	$\text{day}^{-1}\ \text{conc}^{-1}$		0.4755
clr	clearance rate	day^{-1}		0.0799
ϵ	growth rate	day^{-1}	0.0741	0.0741
μ	loss of vessels	day^{-1}	0.0021	0.0021
b	stimulation	day^{-1}	1.3383	1.3383
d	inhibition	day^{-1}	0.002	0.002
V_0	initial V	mm^3	71.2553	71.2553
K_0	initial K	mm^3	71.6675	71.6675

3. Results

The time evolution of tumor volume was observed with and without administering the anti-angiogenic drug, Bevacizumab. The three trial doses of 5, 10, and 15 mg/kg were compared against the control (no angiogenic intervention) in Figure 1, with the treatment offered every Monday and Thursday or Monday, Wednesday, and Friday, for each week. Among them, 15 mg/kg is an FDA-approved dose of Bevacizumab if used in combination with chemotherapy drugs, carboplatin and paclitaxel. However, the same dose has been tested here with Bevacizumab as a single-agent treatment option. In the case of 15 mg/kg, the tumor volume is stabilized quickly and stays close to its initial value for the duration of treatment. This trend is less significant for 10 and 5 mg/kg. Still, the tumor volume does not noticeably increase compared to the control. An almost identical trend (from the perspective of V_{max}) was visible in the V vs. t graph with 10 mg/kg offered every Monday, Wednesday, and Friday vs. 15 mg/kg given every Monday and Thursday (Figure 1), allowing these treatment plans to serve as logistical alternatives in the treatment.

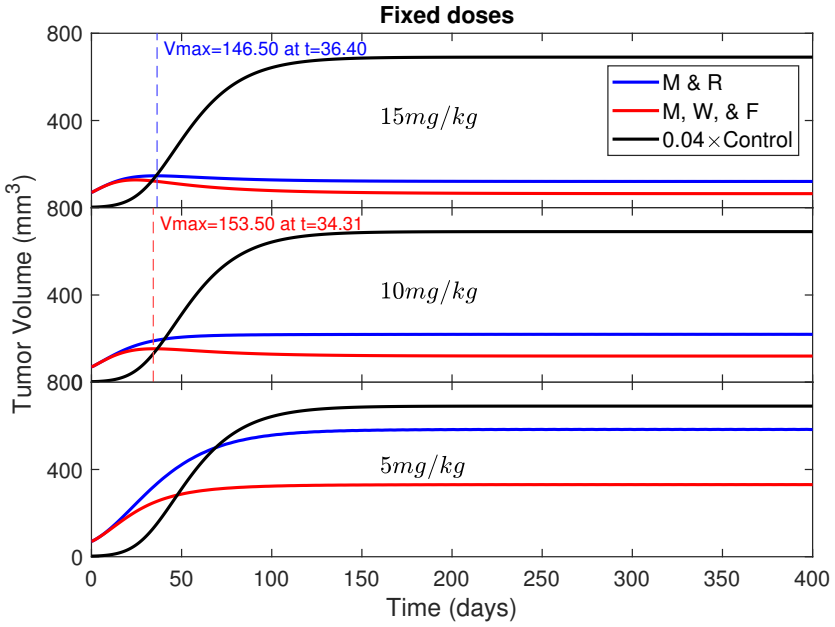

Figure 1. Comparison of three different doses versus control. These doses are given every Monday and Thursday or Monday, Wednesday, and Friday, with the first dose, starting from the day (counted as Day 1) after surgery. The maximum tumor volume $V(t)$ associated with a 10 mg/kg dose offered every Monday, Wednesday, and Friday was found to be almost identical to the value associated with a 15 mg/kg dose given every Monday and Thursday.

The dosing plan for the tumor volume versus time graph in Figure 2 is different from the above approach. It starts with a moderate initial dose of either 5 or 10 mg/kg, then the dose is increased by a fixed but small amount in every successive treatment. Figure 2 compares the following two increasing dose cases

- Initial dose $D_{ini} = 10$ mg/kg with an increment of 0.05 mg/kg
- Initial dose $D_{ini} = 5$ mg/kg with an increment of 0.1 mg/kg

Certainly, the 5 mg/kg dose option had superiority in the sense of controlling tumor volume in the long run.

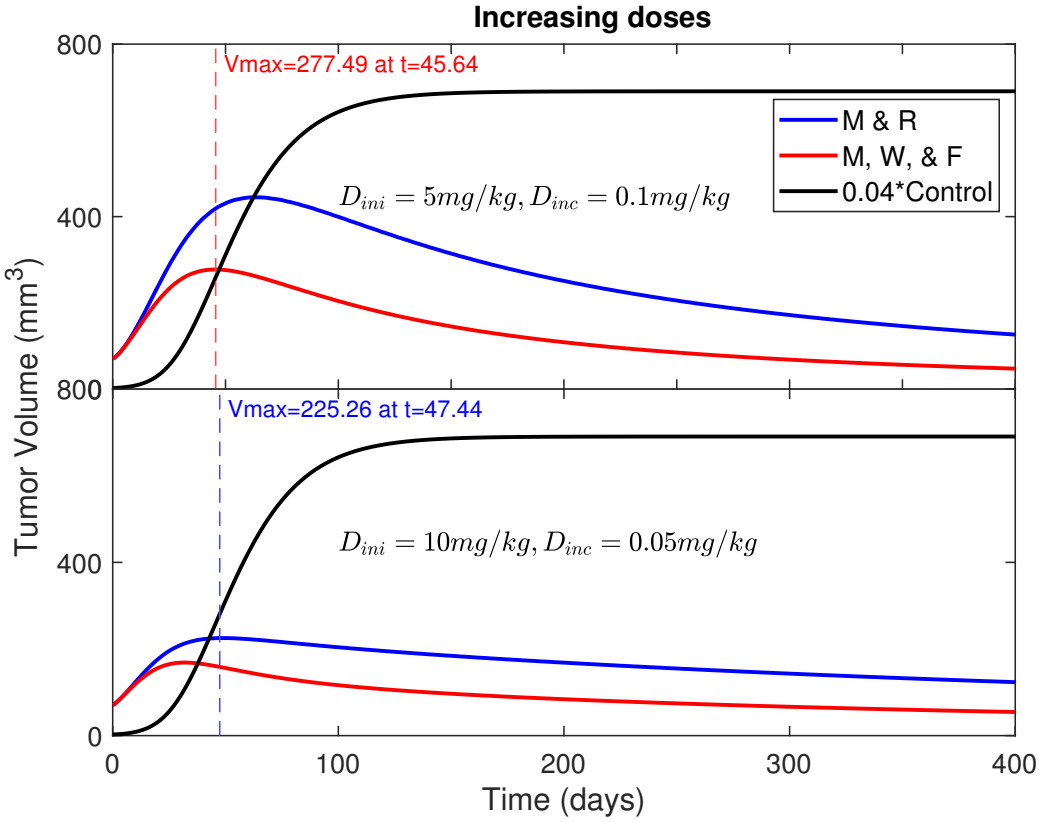

Figure 2. A comparison of increasing dose pattern for two different starting doses $D_{ini} = 5$ and 10 mg/kg and respective dose increments $D_{inc} = 0.1$ and 0.05 mg/kg. Both of these dose combinations were tested for the treatments offered every Monday and Thursday or Monday, Wednesday, and Friday. Ultimately, the final tumor volumes were seen to be settled in proximity to their initial volumes despite the different initial patterns.

4. Conclusions and Discussion

In both the constant and increasing dose trials, the tumor volume was observed to be stabilizing quickly (Figures 1 and 2). Importantly, the volume does not expand for the duration of the treatment, which is 400 days (≈57 weeks). Based on these graphs, a better outcome was evident with the higher dose (15 mg/kg vs. 10 mg/kg); however, there can be a bigger concern of toxicity with such an aggressive treatment plan compared to the 15 mg/kg dose, FDA-approved dose of Bevacizumab if offered with chemotherapy once in every three weeks. Bevacizumab has not been tested as a single-agent treatment option in a clinical setting, specifically for the treatment of ovarian cancer. This toxicity associated with Bevacizumab offered two or three times a week is a vastly unearthed area for now. Thus, it is a challenging task to compare the success of Bevacizumab solely based on the mathematical result. Nevertheless, results from the numerical analysis are very promising and will possibly yield a prolonged survival if the toxicity offered by Bevacizumab as a single-agent treatment is within the tolerance level. Even with the currently approved

dose of Bevacizumab that is offered in conjunction with the chemo drugs, there are major concerns about the level of toxicity. However, these toxicities may not be counted as exclusive to Bevacizumab since chemotherapy drugs also offer a high level of toxicity on their own.

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