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Mathematical Modeling with T Cell in Nasofaringeal Carcinoma

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Abstract

Nasopharyngeal carcinoma triggered by Ebstein Barr virus is a cancer of the first malignancy in the head and neck, which is located in nasopharynx, behind the nose. Cupping and habbatussauda consumption is a process of detoxification of toxins in the body so as immunity increases. Prophet Muhammad delivered quite a lot about cupping and habbatussauda consumption. In this paper, we employ the mathematical model approach to understand nasopharyngeal carcinoma cell level. The formulated mathematical models focus on two cases. First, it is focused on modelling low immunity without cupping and habbatussauda consumption, and second, it is focused on modelling low immunity with the cupping and habbatussauda consumption. In this research, we focus on the second one as the first one has been conducted previously. The model consists of eight sub-populations which are normal cells, lesion cells, low dysplastic cells, the infected cells, high dysplastic cells, invansive carcinoma cells, viruses, and T cells. In this second case, increasing T cell hamper invansive carcinoma because characteristic T cell kill abnormal cells.

Keywords: nasopharyngeal carcinoma; cupping; habbatussauda; mathematical modeling; Ebstein-Barr Virus; T cell.

Introduction

Nasopharyngeal Carcinoma (NPC) is a malignancy that originates from the epithelium or mucosa and crypts that line the nasopharyngeal surface (Sugiyanto et al., 2014). In Yogyakarta, the NPC has the highest incidence rate in men, which is 5.7 per 100,000 population and is in the 3rd position of sharing a flashlight in Indonesia. At Sardjito Hospital there are an average of 100 - 120 new NPC cases per year. NPC is mostly caused by the habit of smoking and eating immature salted fish. Because of the non-specific symptoms, generally NPC patients arrive at Sardjito hospital at an advanced stage (Stage III and IV) after a lump develops in the side, so that the treatment results are not optimal (Aryati et al., 2016).

The word "Al Hijamah" comes from an Arabic term which means "release of dirty blood" and not "Al Fashd" (bloodletter) or in English called "Cupping". and in Malay it is known as "Cupping". In Indonesia we are familiar with the terms Kop or Cantuk. Recording can relieve pain in the shoulders and throat if done on the cervix. It can also relieve pain in the head such as face, teeth, ears and nose if the disease is caused by a blockage in the blood or damage to blood tissue. From Anas RA that the Prophet said: "Indeed if there is something that can heal then it is cupping and qustul bahri" HR. Muslim (Pederson & Anderson, 1980).

Habbatussauda or Nigella Sativa is a black seed that has been known for thousands of years which is widely used by the people of India and the Middle East to treat various diseases. Habbatussuda was found in Tutankhamen's tomb in Ancient Greece where at that time the kings were buried together with Nigella to help at the end of his life. Black Seed contains 40% constant oil and Black Seed contains 40% constan oil and 1.4% aviari oil, also contains 15 amino acids, protein, calcium, iron, sodium and pottasium. While the most important compositions are: Thymoquinone (TQ), Dithymouinone (DTQ), Thymohydroquinone (THQ) and Thymol (THY) (Randhawa et al., 2011).

Development and Analysis of the Model

This research is an extension of model developed in Aryati et al. (2016) mainly due to the addition of habbatussauda so that the immunity of a person susceptible to NPC can be increased, so that NPC does not occur due to EBV genome damage. In this study there are additional subpopulations of T Cells. T cells contribute greatly to the immune defense and work in two methods. First, it mostly regulates complex operations of the immune response; second, it is partly

cytotoxic and directly related to infected cells and destroying them. Regulatory T Cell is Helper T Cell which activates many immune cells including T Cells. Cytotoxic T Cells (sometimes called Killer T Cells) help get rid of body cells that have been infected by viruses including cells that are transformed by cancer (Michaela & Natalie, 2015).

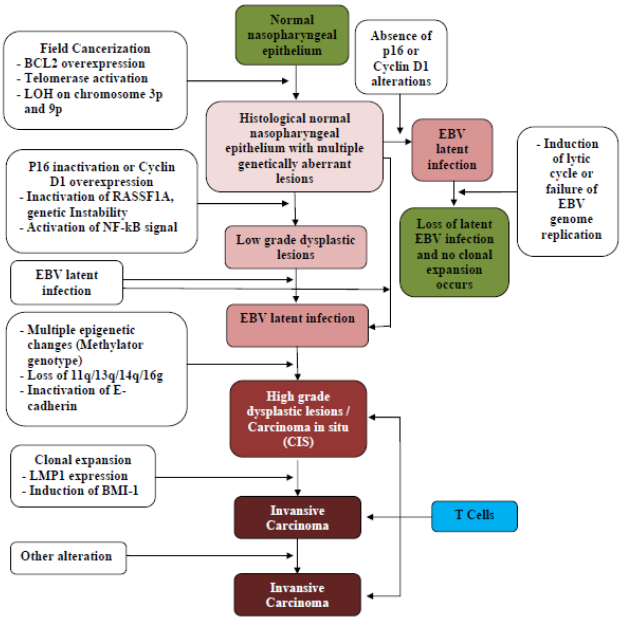

Figure 1. The process of the occurrence of NPCs with the addition of T cells subpopulations.

In Figure 1, subpopulations and rate of change are made in Figure 2.

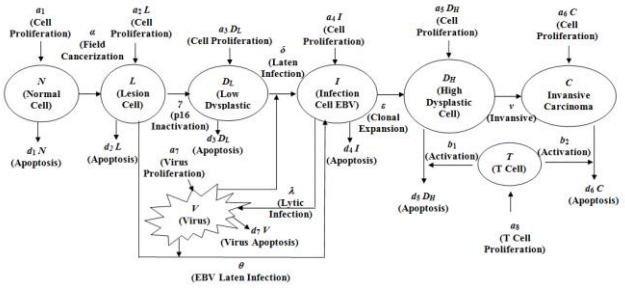

Figure 2. The system model formed on NPC and T Cell activation.

All nasopharyngeal epithelium cells are considered to have the same receptor so that EBV latent can become EBV active and infect any nasopharyngeal cell, without preference. In other words, it is assumed that random contact between nasopharyngeal epithelial cells and EBV virus. Nasopharyngeal cell population is divided into six sub-populations, normal cells, lesion cells, low dysplastic cells, EBV infected cells, high dysplastic cells, invasive carcinoma cells. Normal cells (N) get injured (L), can be due to preservative or tobacco foods. The nasopharyngeal cells that wound can continue to low diplomatic cells (D_L) due to weak immune system. Therefore, there is no improvement in genes or apoptosis. Epstein-Barr Virus (V) infects low wounds or diplomatic cells, and hence cells become infected. Nasopharyngeal cells that are infected (I) that do not occur apoptosis can continue to become high diplomatic cells (D_H). High diplomatic cells can continue to become carcinoma invasion cells (C). Cell invasion carcinoma cannot be cured, until it ends with the death of the patient. The presence of cupping and hudausuda increase T Cell (T). The mathematical equation system is as follows.

The equation system is formed as follows.

$$\frac{dN}{dt} = a_1 - \alpha N - d_1 N \tag{1a}$$

$$\frac{dL}{dt} = a_2 L + \alpha N - \theta LV - \gamma L - d_2 L \tag{1b}$$

$$\frac{dD_L}{dt} = a_3 D_L + \gamma L - \delta D_L V - d_3 D_L \tag{1c}$$

$$\frac{dI}{dt} = a_4 I + \delta D_L V + \theta LV - \varepsilon I - d_4 I \tag{1d}$$

$$\frac{dD_H}{dt} = a_5 D_H + \varepsilon I - \nu D_H - (d_5 + b_1 T) D_H \tag{1e}$$

$$\frac{dC}{dt} = a_6 C + \nu D_H - (d_6 + b_2 T) C \tag{1f}$$

$$\frac{dV}{dt} = a_7 + \lambda a_4 I - d_7 V \tag{1g}$$

$$\frac{dT}{dt} = a_8 - b_1 T - b_2 T \tag{1h}$$

where

$N(t)$	:	Subpopulation of normal cells
$L(t)$	:	Subpopulation of lesion cells
$D_L(t)$	:	Subpopulation of low dysplastic cells
$I(t)$	:	Subpopulation of EBV infected cells
$D_H(t)$	:	Subpopulation of high dysplastic cells or Carcinoma In Situ (CIS)
$C(t)$	:	Subpopulation of invasive carcinoma cells
$V(t)$	:	Population of viruses
$T(t)$	:	Population of *T cell*
α	:	The rate of interaction between normal cells that become low dysplastic cells (field cancerization)
γ	:	The rate of interaction between lesion cells that become low dysplastic cells (p16 in activation).
θ	:	The rate of interaction between lesion cells that become EBV-infected cells (EBV latent infection).
δ	:	The rate of interaction between low dysplastic cells that become EBV-infected cells (EBV latent infection).

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ε : The rate of interaction between EBV-infected cells that become high dysplastic cells (clonal expansion). Clonal expansion is medical form for a model of how the immune system responds to infection.

υ : The rate of interaction between high dysplastic cells that become invasive carcinoma cells (invasive).

λ : The rate of EBV increase due to the proliferation of EBV-infected cells (lytic infection).

a_1 : The rate of proliferation of normal cells

a_2 : The rate of proliferation of lesion cells.

a_3 : The rate of proliferation of low dysplastic cells.

a_4 : The rate of proliferation of EBV infected cells.

a_5 : The rate of proliferation of high dysplastic cells.

a_6 : The rate of proliferation of invasive carcinoma cells.

a_7 : The rate of proliferation of lytic EBV.

d_1 : The rate of apoptosis of normal cells.

d_2 : The rate of apoptosis of lesion cells.

d_3 : The rate of apoptosis of low dysplastic cells.

d_4 : The rate of apoptosis of EBV infected cells.

d_5 : The rate of apoptosis of high dysplastic cells.

d_6 : The rate of apoptosis of invasive carcinoma cells.

d_7 : The rate of apoptosis of lytic EBV.

b_1 : The rate of T cell activation for high dysplastic cells.

b_2 : The rate of T cell activation for invasive carcinoma cells.

The equilibrium point is $(N^*, L^*, D_L{}^*, I^*, D_H{}^*, C^*, V^*, T^*)$ where

$$N^* = \frac{a_1}{\alpha + d_1},\ L^* = \frac{\alpha N^*}{\left(\theta V^* + \gamma + d_2 - a_2\right)},$$

$$D_L{}^* = \frac{\gamma L^*}{\delta V^* + d_3 - a_3},\ D_H{}^* = \frac{\varepsilon I^*}{\nu + d_5 + b_1 T^* - a_5},$$

$$C^* = \frac{\nu D_H{}^*}{(d_6 + b_2 T^*) - a_6},\ V^* = \frac{a_7 + \lambda a_4 I^*}{d_7},$$

$$T^* = \frac{a_8}{b_1 + b_2}.$$

The next I^* is a solution of the polynomial equation with a degree of three in I, i.e.

$$e_1 I^3 + e_2 I^2 + e_3 I + e_4 = 0$$

where

$$e_1 = \delta\theta(\lambda)^2 (a_4)^2 d_1 \left(d_4 + \varepsilon - a_4\right)$$

$$e_2 = \left(d_3 d_7 + \delta a_7 - a_3 d_7\right)\theta\lambda a_4 d_1 \left(d_4 + \varepsilon - a_4\right) + \left[(\alpha + d_1)(d_2 + \gamma - a_2)d_7 + \theta a_7(\alpha + d_1)\right] \delta\lambda a_4 \left(d_4 + \varepsilon - a_4\right) - \delta(\lambda)^2 (a_4)^2 \theta\alpha a_1$$

$$e_3 = \left(d_3 d_7 + \delta a_7 - a_3 d_7\right) \left[(\alpha + d_1)(d_2 + \gamma - a_2)d_7 + \theta a_7(\alpha + d_1)\right] \left(d_4 + \varepsilon - a_4\right) - \delta\alpha\gamma a_1 d_7 \lambda a_4 - (d_3 d_7 + \delta a_7 - a_3 d_7)\theta\alpha a_1 \lambda a_4 - \delta\lambda a_4 \theta\alpha a_1 a_7$$

$$e_4 = \delta\alpha\gamma a_1 d_7 a_7 + \left(a_3 d_7 - d_3 d_7 - \delta a_7\right)\theta\alpha a_1 a_7$$

It is assumed that someone infected with EBV is in the position of Poorly Immunogenic. In infected sub-populations, the birth rate is greater than the cell death rate. In this case the proliferation rate of infected cells minus the rate of death of infected cells is greater than the rate of clonal expansion. This is due to the fact that the nature of infected cells into very high dysplastic cells is only one or two, but has the nature of "magic" or immortality and considering the fact that the carcinogenesis process in humans can last quite a long time i.e. 10-30 years according to (Straathof et al., 2005). From these facts can be written with,

$$a_4 - d_4 > \varepsilon \text{ or } d_4 + \varepsilon - a_4 < 0$$

meaning

$$e_1 = \delta\theta(\lambda)^2 (a_4)^2 d_1 \left(d_4 + \varepsilon - a_4\right) < 0.$$

Similar to the infected cell subpopulation, in the low dysplastic subpopulation, the birth rate is greater than the death rate. The difference in birth rate and mortality rate multiplied by the rate of death of the virus is greater than the rate of latent infection from low dysplastic cells to infected cells multiplied by the rate of birth of the virus. This is due to the fact that when someone with low immunity, someone to become a cancer cell is bigger.

From these facts can be written with,

$$a_3 d_7 - d_3 d_7 > \delta a_7 \text{. Or } a_3 d_7 - d_3 d_7 - \delta a_7 > 0$$

Meaning

$$e_4 = \delta\alpha\gamma a_1 d_7 a_7 + \left(a_3 d_7 - d_3 d_7 - \delta a_7\right)\theta\alpha a_1 a_7 > 0.$$

Theorem 1:

If the equation $e_1 I^3 + e_2 I^2 + e_3 I + e_4 = 0$, $e_4 > 0$, and $e_1 < 0$, then fulfill one of the following:

i. has one positive real root and two conjugate complex roots.
ii. has three positive real roots.
iii. one positive root and two negative roots

Proof:

Let I_1, I_2, and I_3 roots $e_1 I^3 + e_2 I^2 + e_3 I + e_4 = 0$. It can be shown that

$$I_1 + I_2 + I_3 = -\frac{e_2}{e_1} \tag{2}$$

$$I_1 I_2 + I_1 I_3 + I_2 I_3 = \frac{e_3}{e_1} \tag{3}$$

$$I_1 I_2 I_3 = -\frac{e_4}{e_1}. \tag{4}$$

Because $e_4 > 0$, and $e_1 < 0$ then equation (4) becomes $I_1 I_2 I_3 = -\frac{e_4}{e_1} > 0$. From here there are three possibilities, namely:

i. has one positive real root and two conjugate complex roots.
ii. has three positive real roots
iii. one positive root and two negative roots.

The equilibrium point has at least one positive real root of the cubic equation $e_1 I^3 + e_2 I^2 + e_3 I + e_4 = 0$, the roots are

$$I_1 = -\frac{e_2}{3e_1} - \frac{1}{3e_1}\sqrt[3]{\frac{1}{2}\left[f_1 + \sqrt{f_1^2 - 4f_2^3}\right]} - \frac{1}{3e_1}\sqrt[3]{\frac{1}{2}\left[f_1 - \sqrt{f_1^2 - 4f_2^3}\right]}$$

$$I_2 = -\frac{e_2}{3e_1} + \frac{1-i\sqrt{3}}{6e_1}\sqrt[3]{\frac{1}{2}\left[f_1 + \sqrt{f_1^2 - 4f_2^3}\right]} + \frac{1+i\sqrt{3}}{6e_1}\sqrt[3]{\frac{1}{2}\left[f_1 - \sqrt{f_1^2 - 4f_2^3}\right]}$$

$$I_3 = -\frac{e_2}{3e_1} + \frac{1+i\sqrt{3}}{6e_1}\sqrt[3]{\frac{1}{2}\left[f_1 + \sqrt{f_1^2 - 4f_2^3}\right]} + \frac{1-i\sqrt{3}}{6e_1}\sqrt[3]{\frac{1}{2}\left[f_1 - \sqrt{f_1^2 - 4f_2^3}\right]}$$

where $f_1 = 2e_2^3 - 9e_1e_2e_3 + 27e_1^2e_4$ and $f_2 = e_2^2 - 3e_1e_3$.

Simulation Model

The selecting parameters are given in Table 1. The first case is a low immunity system without cupping and habbatussauda. The first case was explained in the previous study: case with a low immune system (Sugiyanto et al., 2014), (Aryati et al., 2016). The second case of parameter values is presented in Table 1.

Figure 3 is a process of cell development in the nasopharyngeal epithelium with a case of low immunity with cupping and habbatussauda. In this second case, normal cells decrease very rapidly in the early years along with very rapid increase of lession cells. Because of the low immunity so that the increase in lesion cells increases sharply, this is accompanied by other abnormal cells. However, because of the presence of cupping and contact, the T cell also increases. Therefore, in the second year, there is a decrease in abnormal cells. This increase in T cell results in the development of carcinoma infective cells can be controlled. This means that cupping and habbatussauda are preventive against nasopharyngeal carcinoma.

Conclusion

In the second case (because the second case has been studied beforehand) immunity is low, but because of the cupping and habbatussauda, it increases T cell. The nature of T cells is to kill abnormal cells, so that infectious cell carcinoma does not develop. The lack of development of this infectious carcinoma cell does not result in nasopharyngeal carcinoma. This is a guideline that cupping and habbatussauda can be effective in preventing nasopharyngeal carcinoma.

Table 1. Estimation parameters of nasopharyngeal carcinoma model parameters for cases of low immune system with cupping and habbatussauda.

No.	Parameter	Value	Unit
1.	a_1	100	cell.mm^{-2}.day^{-1}
2.	a_2	2	day^{-1}
3.	a_3	1	day^{-1}
4.	a_4	1	day^{-1}
5.	a_5	2	day^{-1}
6.	a_6	2.5	day^{-1}
7.	a_7	2	day^{-1}
8.	d_1	1	day^{-1}
9.	d_2	2	day^{-1}
10.	d_3	2	day^{-1}
11.	d_4	2	day^{-1}
12	d_5	3	day^{-1}
13.	d_6	3	day^{-1}
14.	d_7	2	day^{-1}
15.	α	5	day^{-1}
16.	γ	6	day^{-1}
17.	θ	1	day^{-1}
18.	δ	0.5	day^{-1}
19.	ε	1	day^{-1}
20.	ν	2	day^{-1}
21.	λ	1	day^{-1}
22.	b_1	1	day^{-1}
23.	b_1	1	day^{-1}

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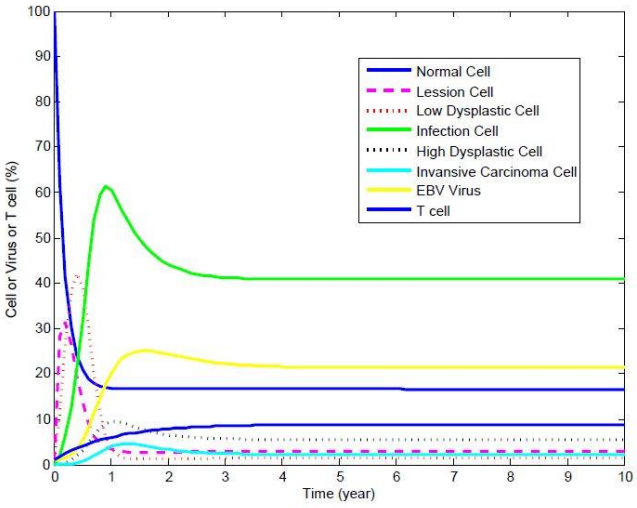

Figure 3. The process of developing nasopharyngeal cells in the low immune system case with cupping and hudausudauda.

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