Mathematical Model in Side Effects of Chemotherapy Treatment for Lung Cancer

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Abstract

Cancer is one of the most flourishing diseases of all over the world. Cancer incidences and death rates are rapidly increasing worldwide. The cancer occurrence could be associated with various environmental, social, cultural, life-style, hormonal and genetic factors [4]. In addition smoking, reduced physical activity and consumption of highly processed and calorie-rich food are the major causes of cancer. There are many types of cancer treatments available now, but all of them have some associated side effects. Chemotherapy is the most effective and widely used treatment in most types of malignancies [1]. It was thought that chemotherapy drugs specifically kill the cancer cells only but now it is well known that it also damages to the normal cells resulting the chemotherapy dose dependent side effects such as fatigue, nausea, hair loss vomiting, etc. and even death may also occur in severe cases [4]. The main strategy of chemotherapy drugs based on the phenomenon that these drugs selectively target the tumor cells, largely by the means of genotoxicity partially caused by the production of reactive oxygen species, which does not specifically damages the cancer cells but also the normal cells. In this study, the method and side effects of chemotherapy treatment for cancer is discussed. In particular the side effects of chemotherapy treatment for lung cancer.

Keywords: Chemotherapy, Immunotherapy, CVD, Apoptosis

I. INTRODUCTION

The treatment of cancer is the early detection of the disease. Often, cancer is detected in its later stages, when it has compromised the function of one or more vital organ systems and is widespread throughout the body. Methods for the early detection of cancer are of utmost importance and are an active area of current research. After the initial detection of a cancerous growth, accurate diagnosis and staging of the disease are essential for the design of a treatment plan [4]. This process is dependent on clinical testing and the observations of physicians. It is important for cancer patients and their families to understand the results given to them so that they can take an active role in the planning of the treatment protocol to be used. Anticancer agents induce apoptosis in normal tissues as well as in tumors. In fact, many of the pathologists who identified apoptosis in tumors realized that apoptotic cell death was induced in a subset of normal tissues (e.g. bone marrow and intestine), and it was suggested that the process might contribute to the ‘toxicity’ associated with chemotherapy [[3]]. Moderate doses of radiation and chemotherapy induce apoptosis in the murine thymus, spleen, bone marrow and intestine, the same tissues that account for the deleterious side-effects of chemotherapy. Total 132 cancer chemotherapy drugs are approved by the US Food and Drug Administration, of which 56 drugs have been reported to cause oxidative stress.

A. Side Effects of Chemotherapy Treatment

Earlier these chemotherapeutic drugs were considered to be quite targeted and selective for tumor cells, but now it is a well-known that normal cells are also damaged by chemotherapeutic drugs, which leads to various side effects and in some cases even death. These side effects include headache, fatigue, weakness, hair loss, nausea, vomiting, diarrhea, abdominal cramps, mouth sores, dry mouth, memory impairment and Numbness. Chemotherapy given to treat cancer patients is powerful medication – used to kill cancer cells and it’s impossible to avoid causing some damage to other cells and tissues in the body[3]. So when we give the medication to kill the cancer cells patients get sick - sometimes very sick and some may die. Getting the balance right on which patients to treat aggressively and which not to treat, can sometimes be hard. The most frequently reported side effects were weakness (95%), fatigue (90%), nausea (77%), hair loss (76%) and vomiting (75%). Each of these side effects was experienced by more than 70% of the patients. Prominent side effects include mouth sores, dry mouth and numbness whereas diarrhea, abdominal cramps and memory impairment were less commonly occurring side effects. Some other side-effects which were also reported by some patients i.e. temperature, constipation, mood swings and weight loss [4]. We see that most of the people who died within one month were in the palliative treatment group – 7.5% (569/7,602) of women with breast cancer and 10% (720/7,673) of people with non-small cell lung cancer. These are patients who could not be cured of their disease and between 8-9% of this group died within a month of starting therapy. There were also deaths in those patients given treatment with the intention to try and achieve cure [3]. These were much fewer; 0.3% (41/15,626) of breast cancer patients and 2.7% (53/1,961) of non-small cell lung cancer patients [7].

These side effects were subjected to statistical test to determine their relation with different variables, but these results are less reliable due to the absence of common factor in the patients. As this survey included a great variety in cancer types, disease time,
and age of patient, chemotherapy cycle and the drug being used, so there was a great variation in results. If the patients of a same group are considered then the actual relation of side effects could be derived with other variable like gender, age, other diseases etc. [1]. Somehow it is a reality that chemotherapy side-effects are highly disastrous. Improvements in treatment and earlier diagnosis have both contributed to increased survival for many cancer patients. Unfortunately, many treatments carry a risk of late effects including cardiovascular diseases (CVDs), possibly leading to significant morbidity and mortality. The variety of cardiovascular side-effects from systemic cancer therapies is diverse and includes the induction of cardiac dysfunction [5].

Myocardial ischemia, arrhythmias, thromboembolism, arterial and pulmonary hypertension, peripheral arterial occlusive disease and pleural effusion [6]. Cardiotoxicity following systemic treatment is typically associated with loss of myocardial mass, leading to progressive cardiac remodelling and dysfunction [6]. Patients experiencing cardiotoxicity develop heart failure (HF) months to years after the initial cancer therapy and have a severely impaired cardiovascular prognosis. Radiation-related heart disease includes a variety of cardiac pathologies, such as coronary artery disease, myocardial dysfunction, pericarditis and valvar heart disease. Other radiation-related heart diseases typically present 10–15 years later [3]. Radiation related ischemic heart disease (IHD) is generally observed at a younger age than IHD in the general population. These side effects limit the effect of chemotherapy. Classical risk factors for coronary artery disease also influence the risk of radiation-related CVDs [3]. Higher risks of developing CVDs following exposure of the heart to radiation have been observed in patients with classical risk factors for CVDs. So, there is a need of novel cancer treatment approach, which specifically reduces the tumor with minimum or no side effects.

B. Chemotherapy Treatment for Lung Cancer

1) Evolution of Lung Cancer

Historically, in India, tobacco was introduced in Karnataka by the Portuguese during A.D 1600. A couple of centuries later, the British introduced commercially produced cigarettes and established tobacco production in the country. Beedi (0.2-0.3gm of tobacco wrapped in a temburni leaf and tied with a small string) smoking was reported as early as 1711 in India. One of the reasons for increased beedi consumption was the call for boycott of imported cigarettes as part of swadeshi movement (movement to boycott foreign goods) that enhanced a shift from cigarettes to beedies. Tobacco use is responsible for five million deaths (one in ten adults) in the world every year, with 2.41 million being attributed to developing countries and 2.43 million in developed countries [4].

Lung cancer is classified as small cell (13% of cases) or non-small cell (83%) for the purposes of treatment (3% of cases in the SEER database lack information on histologic type). Most patients with small cell lung cancer receive chemotherapy. In addition, some patients are also treated with thoracic radiation therapy [5]. For stage I and II non-small cell lung cancers (NSCLC), the majority of patients (69%) undergo surgery, and about 25% of surgical cases also receiving chemotherapy and/or radiation therapy. Most patients with stage III and IV NSCLC receive chemotherapy with or without radiation (53%).

The 1-year relative survival for lung cancer increased from 34% during 1975 through 1977 to 45% during 2008 through 2011, largely because of improvements in surgical techniques and chemo radiation. The majority of lung cancers (57%) are diagnosed at a distant stage, because early disease is typically asymptomatic; only 16% of cases are diagnosed at a local stage. The 5-year survival rate is 55% for cases detected when the disease is still localized, 27% for regional disease, and 4% for distant stage disease [2]. The 5-year survival for small cell lung cancer (7%) is lower than that for NSCLC (21%).

Many lung cancer survivors have impaired pulmonary function, although some may have had preexisting respiratory problems. In some cases respiratory therapy and medications can improve fitness and allow survivors to resume normal daily activities. Treatment with EGFR inhibitors can lead to a severe aceniform rash. Immunotherapy drugs used in lung cancer treatment can lead to several immune mediated toxicities, including pneumonitis, colitis, nephritis, and endocrinopathy. Lung cancer survivors who are current or former smokers are at increased risk for subsequent smoking-related cancers, especially lung, head and neck, and esophageal, as well as other smoking-related health problems [4]. Survivors may feel stigmatized because of the social perception that lung cancer is a self-inflicted disease, which can be particularly difficult for those who never smoked. Data suggest that there is a benefit to smoking cessation even after a lung cancer diagnosis. It is estimated that there are 526,510 men and women living in the United States with a history of lung cancer, and an additional 224,390 cases will be diagnosed in 2016[1]. The median age at diagnosis for lung cancer is 70 years.

When chemotherapy drugs travel through the bloodstream to reach cells throughout the body, it is called systemic chemotherapy. When chemotherapy drugs are directed to a specific area of the body, it is called regional chemotherapy. Chemotherapy-associated side effects vary greatly and it does not depend upon cancer type. But these side effects depend on multiple factors such as the type and dose of chemotherapeutic drug, patient’s health status and stage of cancer.

2) Lung Cancer Chemotherapy Treatments are used in Three Primary Ways [7]

- Neoadjuvant or primary systemic lung cancer chemotherapy: It may be used before surgery to destroy cancer cells. It also allows your oncologist to determine the effectiveness of a particular lung cancer treatment regimen on the tumor.
- Adjuvant chemotherapy: It is used after surgery or radiation to target cancer cells that were not removed during lung cancer surgery, and helps prevent the cancer from spreading to other parts of your body.
- Systemic chemotherapy: It means the circulation of chemotherapy drugs through the bloodstream to cancer cells through the body, plays an important role in the treatment of locally advanced or metastatic lung cancer.
C. Side effects of Chemotherapy in Lung Cancer

Chemotherapy is often used to treat people with lung cancer. The drugs have side effects which vary from one drug to another and according to the number of treatments given. Chemotherapy drugs are usually given into a vein[1]. After many treatments these veins may collapse or may become hard and uncomfortable. Occasionally, if chemotherapy has to be given repeatedly it is delivered via a Hickman line, tube going into a bigger vein in the chest which is left in place[2]. The body’s reaction to chemotherapy, radiation, or targeted treatments depends on a number of factors such as length of treatment, dosage prescribed, and a person’s health history. Most side effects are short term, but some can last throughout your treatment and even for some time afterward. The red blood cells that contain hemoglobin and carry oxygen may also be affected[7]. Abnormally low levels may lead to breathlessness. The white cell count (those that fight infection) can drop to dangerous levels too. White blood count and immune system would be badly affected by the treatment.

Cancer treatments may also affect your bones. Cancer that starts in or spreads to the bones can lead to bone pain and an increase in risk for complications, including weakening of the bone, fractures, and high calcium levels in the blood[5]. People with cancer are at risk for developing blood clots for various reasons, but steps can be taken to prevent and treat blood clots. Problems with memory and concentration, along with a general feeling of not functioning as well mentally as usual, are informally referred to by patients as chemobrain[5]. Side effects from cancer treatment may include tooth decay and other mouth issues, including dry mouth and mouth sores. Diarrhea may be caused by some types of chemotherapy and radiation to certain areas of the body. Fatigue is the most commonly reported side effect of cancer and its treatment. Hair loss from chemotherapy treatment occurs because hair follicles are weakened by chemotherapy, which causes your hair to fall out much more quickly than it would normally.

People with cancer who have undergone lymph node removal and/or radiation as part of their treatment are at risk for developing lymphedema, a painful swelling that happens when your body’s lymphatic fluid is unable to circulate properly and builds up in your soft tissues instead. “Oral mucositis” refers to mouth sores caused by irritation of the mucosa—the soft tissues that cover the tongue and inside of the mouth, and can be a serious side effect of chemotherapy treatment[4]. While many people who are treated for cancer experience nausea and vomiting, medicines exist that can help control these side effects. Although side effects can be uncomfortable or painful, doctors now have many ways to reduce and even prevent side effects from treatment.

II. Result

In India, the presentations of lung cancer patients with various symptoms are shown in the following fig. [5].

<table>
<thead>
<tr>
<th>S.No.</th>
<th>Symptoms</th>
<th>Minimum(%)</th>
<th>Maximum(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Cough with expectoration</td>
<td>40.0</td>
<td>94.3</td>
</tr>
<tr>
<td>2.</td>
<td>Chest pain</td>
<td>16.0</td>
<td>66.7</td>
</tr>
<tr>
<td>3.</td>
<td>Loss of weight</td>
<td>11.4</td>
<td>90.0</td>
</tr>
<tr>
<td>4.</td>
<td>Breathlessness</td>
<td>24.0</td>
<td>59.0</td>
</tr>
<tr>
<td>5.</td>
<td>Weakness</td>
<td>4.0</td>
<td>90.0</td>
</tr>
<tr>
<td>6.</td>
<td>Hemoptysis</td>
<td>8.0</td>
<td>69.2</td>
</tr>
<tr>
<td>7.</td>
<td>Fever</td>
<td>19.6</td>
<td>68.6</td>
</tr>
<tr>
<td>8.</td>
<td>Anorexia</td>
<td>20.5</td>
<td>90.0</td>
</tr>
<tr>
<td>9.</td>
<td>Hoarseness of voice</td>
<td>9.0</td>
<td>33.0</td>
</tr>
<tr>
<td>10.</td>
<td>Nausea and vomiting</td>
<td>6.0</td>
<td>25.0</td>
</tr>
<tr>
<td>11.</td>
<td>Puffiness of face</td>
<td>2.9</td>
<td>19.8</td>
</tr>
<tr>
<td>12.</td>
<td>Dysphagia</td>
<td>2.9s</td>
<td>20.8</td>
</tr>
</tbody>
</table>

![Fig. 1: Presentations of lung cancer patients with various symptoms](image)

Various side effects of chemotherapy treatment of lung cancer patients are given below [4].
S. No. | Side effects | %
--- | --- | ----
1. | General weakness | 95
2. | Fatigue | 90
3. | Nausea | 77
4. | Hairloss | 76
5. | Vomiting | 75
6. | Headache | 43
7. | Diarrhea | 31
8. | Abdominal cramps | 40
9. | Mouth sores | 47
10. | Drymouth | 74
11. | Memory impairment | 14
12. | Numbness | 49

The maximum values of various symptoms of lung cancer and various side effects of chemotherapy treatment of lung cancer are analyzed, the correlation coefficient \( r = 1.1246 \).

So there is no relation between symptoms and side effects of chemotherapy treatment for lung cancer patients [8].

### III. CONCLUSION

While chemotherapy targets cancer cells, it can also damage healthy cells and cause unpleasant side effects, such as nausea, vomiting, hair loss, fatigue and mouth sores. The symptoms of lung cancer are discussed. A secondary cancer may be a new primary cancer. Or, it may be a cancer that has spread to other parts of the body from where it started. Lung cancer accounts for
more deaths than any other type of cancer. It may develop as a late effect of previous cancer treatments, such as chemotherapy and radiation therapy. Chemotherapy and radiation therapy can also damage bone marrow stem cells. This increases the risk of either acute leukemia or blood cancer. A quarter of the cigarette or Beedi smokers in India would be killed by tobacco at the age of 25-69 years losing 20 years of life expectancy. In avoiding tobacco products and alcohol drink, eating foods rich in calcium and vitamin D, doing more physical activities are the various methods for prevention of lung cancer. Chemotherapy treatment causes various side effects for cancer patients and the survival period of cancer patients is a very short period of their lifetime. We conclude that the cancer patients need better and no side effect treatment for getting longer survival period.

REFERENCES