Project on

A review on Metronomic Chemotherapy for Non-Small Cell Lung Cancer

[In the partial fulfillment of the requirements for the degree of Bachelor of Pharmacy]

Submitted To

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DECLARATION

I hereby declare that this project report, **"A review on Metronomic Chemotherapy for Non-Small Cell Lung Cancer"**. I am declaring that this Project is my original work. I also declare that neither this project nor any part thereof has been submitted elsewhere for the award of Bachelor or any degree.

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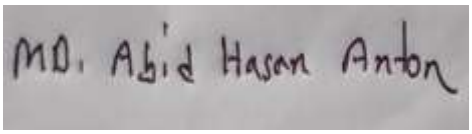

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Abstract

Metronomic chemotherapy (MCT) is the rhythmic administration of low-dose cytotoxic drugs over an extended length of time with little to no drug-free intervals. MCT has an impact on the tumor milieu and tumor cells. The low-dose timetable, in specific, hinders endothelial cells' ability to repair themselves, which has an anti-angiogenesis impact. MCT causes immunological stimulation, which prompts the immune system to attack tumor cells. Anti-angiogenic medications also improve the effectiveness of MCT when used in conjunction with targeted treatment. The current analysis provides a summary of phase I, phase II, and phase III clinical trials examining the effectiveness, side effects, and method of action of MCT in patients with non-small cell lung cancer. (NSCLC). The potential of MCT in treating NSCLC has also been considered. According to the current study, MCT is an effective treatment for specific NSCLC patients with manageable systemic side effects and financial viability for public health.

Contents

Chapter 1
Introduction

1. Introduction

With an estimated 1.6 million cases emerging per year (12.7% of the overall), cancer of the lungs has been and continues to be by far the most prevalent malignancy in the globe for a number of years. With an expected 1.38 million deaths annually, it also ranks first in cancer-related mortality. Between 10% and 15% of lung cancer cases are small-cell lung cancer (SCLC), which is strongly correlated with the quantity and frequency of cigarette use. [1] As a result, normal SCLC patients tend to be older people, heavy smokers who currently or previously have numerous cardiovascular and pulmonary comorbidities that may prevent them from receiving the best care. [2] The invasive nature of SCLC is characterized by its quick development, paraneoplastic endocrinopathy, as well as early metastasis. The number of cases of SCLC in industrialized nations increased in the 1980s, coinciding with the peak rates of cigarette smoking 20 years earlier, but is now gradually declining as a result of shifting smoking habits. Untreated SCLC has a two- to four-month fatality rate. If SCLC was determined to be incurable, the initial treatment options included surgery or radiotherapy alone. Both treatment options ended up to be less than ideal due to extremely poor long-term survival percentages and early relapses, which were typically accompanied by distant metastases. [3] When compared to best supportive treatment alone, cyclophosphamide chemotherapy doubled survival in 1969. Combination chemotherapy was subsequently tested and found to be better to single medicines. In the 1980s, dramatic response rates, including complete responses (CR), advanced the alluring prospect of a remedy. Although SCLC originally responds well to chemotherapy and radiotherapy, relapse is almost always present, and the effectiveness of further treatment as the disease becomes more refractory to therapy declines. [4] The survival rate has increased for many other solid-tumor malignancies as a consequence of improvements in detection and therapy. Still, the 5-year survival rates for SCLC have plateaued over the past 40 years and have not substantially increased. In Australia, the 5-year survival rate increased only slightly among 1982–1987 and 2000–2007, with men experiencing an increase of 3%–5% and females experiencing a rise of 5%–8%. [5] Only a two-month increase in median survival time has been seen over the past 30 years in phase III trials of chemotherapy for SCLC. Prophylactic cranial irradiation (PCI), a form of radiotherapy, has incrementally helped those who received beginning chemotherapy and experienced a full or nearly full

recuperation (5.4% increase in 3-year overall survival from 15.3% to 20.7%). [6] The survival rate has increased for many other solid-tumor malignancies as a consequence of improvements in detection and therapy. Still, the 5-year survival rates for SCLC have plateaued over the past 40 years and have not substantially increased. In Australia, the 5-year survival rate increased only slightly among 1982–1987 and 2000–2007, with men experiencing an increase of 3%–5% and females experiencing a rise of 5%–8%. [5] Only a two-month increase in median survival time has been seen over the past 30 years in phase III trials of chemotherapy for SCLC. Prophylactic cranial irradiation (PCI), a form of radiotherapy, has incrementally helped those who received beginning chemotherapy and experienced a full or nearly full recuperation (5.4% increase in 3-year overall survival from 15.3% to 20.7%). [6]

1.1 Lung cancer susceptibility gene

In the last 60 years, there have been numerous reports of familial clustering or accumulation of lung cancer, which may indicate a hereditary basis for the illness. Carriers of TP53 germline variations in sequence were found to have an increased chance of lung cancer, and they were found to be more likely to smoke cigarettes than non-carriers. This research also covered cancers of the larynx and throat. Three separate genetic investigations have recently discovered a marker on chromosome 15 that is linked to lung cancer. [8] In all 3 studies, individuals with 1 copy of the marker and those with 2 copies were at an increased chance of about 30% and 70% to 80%, respectively. [9] essentially the three studies concur that people who carry an altered copy of the gene have a higher chance of getting lung cancer, one of the researchers believes that the genes may actually help people acquire cancer by increasing their susceptibility to nicotine addiction.

1.2 Staging of lung cancer

Correct TNM staging of lung cancer after the original diagnosis of NSCLC is essential for choosing the best course of treatment. Patients with advanced forms of the cancer may be prospects for nonsurgical therapy, while most patients with phases I to II NSCLC are helped by surgical resection. CT of the thorax and higher belly is most frequently used for traditional clinical staging. [10-12] These innovations could provide less intrusive alternatives to cervical mediastinoscopy, especially when combined with PET scanning to

help with localization and boost biopsy output. Cervical mediastinoscopy, however, continues to be the gold standard in preoperative nodal staging today and for the foreseeable future since it offers nearly perfect specificity and exceptionally high sensitivity. [13] Transcervical extended mediastinal lymphadenectomy (TEMLA), a novel variant of cervical mediastinoscopy, has been explored in a few centers in Europe. However, the most recent randomly assigned trial contrasting TEMLA to conventional cervical mediastinoscopy was stopped early since it was believed that the sensitivity issue had been resolved, disposing of the trial data insufficient to make any meaningful conclusions about the two procedures' relative safety, which is also a crucial issue. [11]

1.3 Lung cancer screening

15% is the pitiful 5-year survival percentage for lung cancer. A timely diagnosis in those who are susceptible could stop, halt, or postpone the development of lung cancer. The precise identification of those who are at risk is the first challenge to be surmounted in order to achieve the objective of timely diagnosis. [12] After preliminary studies that were not definitive in the 1970s, a seminal paper by Henschke et al in 1999 sparked a debate about lung cancer screening using radiographic methods. Henschke recently stated that for the 302 individuals with clinical stage I cancer who experienced surgical resection within 1 month of being diagnosed, the survival rate was 92%. Henschke was writing for the International Early Lung Cancer Implementation Initiative. [13] However, there are currently no recommendations for widespread lung cancer monitoring. Additionally, according to the US Prevention Programs Task Force, the evidence currently available is insufficient to either suggest or caution against using tools to identify lung cancer in asymptomatic patients. The American Cancer Society also opposes monitoring for those who are at risk. The National Lung Detection Trial, which contrasts spiral CT and conventional chest radiography as two methods of identifying lung cancer, will most likely put an end to this debate. Nearly 50,000 present or former smokers had signed up for this trial by February 2004; the final findings of this trial are avidly anticipated. [14]

1.4 Epidemiology of Non-small cell lung cancer

The incidence and mortality rates for lung cancer are greatest in developed nations. On the other hand, it's believed that lung cancer rates are lower in underdeveloped regions like the

majority of Africa and Central South America. The fact that many lung cancer cases go unnoticed is a result of the fact that a number of developing countries lack standardized reporting systems, which hides the true prevalence of the illness. According to the World Health Organization, tobacco use will increase globally, especially in Asia, and this will lead to an increase in lung cancer death rates. Incidence and mortality rates from lung cancer have been declining in the United States for males, while these figures started rising for women until about 2000 as well as since leveled off. [15] Lung cancer death rates in women dropped over a decade after they did in men due to modifications to the prevalence of lung cancer in women. Although it is decreasing for both white and black males, the rate of lung cancer is about 20% higher for black men. [16] On the other hand, Asian American, Pacific Islander, and Hispanic women exhibit the lowest incidence and mortality rates. Socioeconomic position, occupational exposures, and lifestyle contacts combine in intricate ways to produce race-related variations. Lung cancer still has a low incidence among individuals under the age of 40. It then gradually starts to increase, reaching its peak among 65 and 84 years of age. [17]

Chapter 2

Purpose of the study

2.1 Purpose of the study

Aim of this review for the following **mentioned output**.

- To know better understand and diagnosis procedure of Non-Small Cell Lung Cancer.
- To find out clinically developed **chemotherapy** for Non-Small Cell Lung Cancer.
- To gain a better understanding of the risk factors that affect the progression of Non-Small Cell Lung Cancer.
- To obtain a systematic awareness of the illness, including its source, signs and symptoms, effects, and available medical and nursing treatment routes.
- To know preventive parameter for this ailment.
- To find the causative agent for the developed Non-Small Cell Lung Cancer.

Chapter 3
Methodology

3.1 Data collection procedure

A agenda of research methodologies, as well as methods for gathering and analyzing data, is provided by a methodological review. This chapter discusses the techniques used in the investigation. Key phrases including " Non-Small Cell Lung Cancer " " Non-Small Cell Lung Cancer etiology" " Non-Small Cell Lung Cancer treatment," and " Non-Small Cell Lung Cancer diagnostic." were searched for utilizing web-based search engines, academic bibliographic databases, PubMed, Research Gate, Google scholar and Medline. It gives an account of the learning environment. There are many variables to take into account, including the study sample, the study population, the research tools, the methodology, and the data analysis. This is a summary of earlier research on the manifestation of Non-Small Cell Lung Cancer. All research on the causes, diagnoses, and therapies of the Non-Small Cell Lung Cancer ailment. A piece of the information was collected by directly reading previous research articles, while the other part came from scouring the internet for pertinent data. The activities of many treatments were recorded. All of the information gathered from prior study publications was numerically coded and imported. I was learned more by reading every composed review paper. The information acquired has been finally summarized.

3.2 Data analysis strategy

Data analysis strategies cover the mutually exclusive operations of data assembly, purification, and organizing. To get ready the data for business use, it has to pass via various processes, which often require the use of data research tools. Data analytics, a different term for data analysis, is well-defined as the science of looking at raw data to draw reasonable conclusions from it.

Chapter 4
Literature Review

4.1 Non-Small Cell Lung Cancer: Epidemiology, Screening, Diagnosis, and Treatment

The top cause of cancer-related deaths in the US continues to be lung cancer. Significant progress has been achieved in the study of non-small cell lung cancer over the past ten years. (NSCLC). The purpose of evaluation is to facilitate early identification. According to the National Lung Monitoring Trial, using low-dose chest computed tomography in high-risk people resulted in a 20% reduction in lung cancer mortality and a 6.7% drop in all-cause mortality. With the development of several lines of tyrosine kinase inhibitors for individuals with EGFR, ALK, ROS1, and NTRK mutations, the way that lung cancer is treated has also changed. Immune checkpoint inhibitors (ICIs) have had a similar significant impact on NSCLC therapy. ICIs are now a component of the first-line NSCLC therapy arsenal as monotherapy, in combination with chemotherapy, or following definitive chemoradiotherapy in patients with stage III unresectable NSCLC. Additionally, the outcomes of new trials keep helping us in understanding the role of these novel agents and which patients are more likely to benefit. Malignant cell production of programmed cell death protein-ligand 1 has been investigated as a possible biomarker for ICI response. Yet significant flaws restrict its ability to discriminate. To choose the best prospects for ICI therapy, reliable predictive biomarkers beyond programmed cell death protein-ligand 1 expression must still be found. Although the field is developing quickly, many issues regarding the ideal order and combinations of these new agents continue unresolved. [18]

4.2 Chemotherapy of Lung Cancer

Even the most steadfast optimists must be shaken by population-based data on lung cancer in the United States. Lung cancer was the second most prevalent cancer and the main reason for cancer-related deaths in 2017.1 Only a slight improvement in five-year survival among 1974 and 1987 can be attributed to the stagnant therapeutic outcomes in this disease. Despite the fact that smoking cessation started to result in an age-adjusted decline in the incidence illnesses in males around 1988, the prevalence of illness in women is going in a different direction, more than doubling between the 1973 and 1988. Furthermore, it would take 20 years for the reduction in lung cancer mortality to become completely apparent even if all smokers stopped today. These data points make it clear that lung cancer will continue to pose a serious threat to the public's health for many years. This review outlines

the conventional approach to treating lung cancer, examines available and novel chemotherapeutic options, and highlights recent advancements that could portend a more hopeful future. [19]

4.3 Chemotherapy in non-small cell lung cancer

Chemotherapy is no longer thought to be effective against non-small cell lung cancer due to significant advancements in both the development of new medicines and the use of older agents. Additionally, a recent meta-analysis has supported the idea that chemotherapy may provide only marginal mortality advantages. fortunately, the criteria for efficacy in the treatment of stage IV disease have primarily focused on tumour effectiveness, it has lately become clear that these patients can also benefit from better symptom control. There have been significant advances showing the value of chemotherapy and thoracic irradiation as merged modality treatments for patients with locally advanced stage III disease. [20]

Chapter 5

Results & Discussion

5.1 Single agent of Metronomic chemotherapy in first-line treatment

Regardless of proof that vinorelbine or gemcitabine monotherapy did not substantially prolong overall survival (median OS, 10.3 months vs. 6.2 months), greater toxicity prevented their use (neutropenia, 48% vs. 12%). For patients who are less appropriate for mixture chemotherapy, especially older patients, single-agent chemotherapy is an option, and an oral agent may be a better choice of administration. A noteworthy medicinal advantage of metronomic oral vinorelbine, which is used to treat established NSCLC, is the long-term maintenance of the illness. [21-22] Oral vinorelbine 30 mg or 40 mg three times per week—action was given one day on and one day off—was given to patients who were older than 60, had stage IIIB or IV cancer, were ECOG 1 and had 1 major comorbidity. The overall control rate was 63%, the median OS was 12 months, and the median PFS was 9 months. A meta-analysis of 418 folks treated with verbal vinorelbine revealed an OS of 8.7 months (95% confidence interval, 7.6-9.5). (20). An uninterrupted regimen of 20–30 mg each other day showed excellent tolerance and therapeutic benefits. [23]

5.2 Vinorelbine and cisplatin (DDP)

One of these patients perished from sepsis, and three of these patients had febrile neutropenia. even though myelotoxicity was a side effect of the combined schedule, the therapy was still a successful first-line choice for patients with advanced NSCLC. [24] In elderly or previously treated patients, oral metronomic vinorelbine caused non-negligible survival and displayed stable long-term blood concentrations. Vinorelbine (30 mg/day) was taken orally every day for 21 days, with a 1-week break in the course of therapy, and it was well tolerated with no dose-limiting toxicity. Another investigation found that a continuous schedule of 20–30 mg every other day resulted in excellent tolerability and clinical efficacy. Moreover, pretreated NSCLC patients received oral vinorelbine at a dosage of 50 mg three times per week; their median OS was 9.4 months, and their 1-year survival rate was 30.1%. [25]

5.3 Temozolomide (TMZ)

A novel oral alkylating drug called TMZ has shown anticancer action toward brain metastases in a variety of solid tumors, involving NSCLC. (30). The overall OS was 3.3

months, and the 1-year rate of survival was 22.5% when TMZ was given at a dose of 75 mg/m2 daily for 21 days every 28 days. fortunately, a different phase II trial found that patients with advanced NSCLC who had never received chemotherapy had no clinical reaction to TMZ. Patients with NSCLC who receive inefficient care and have an especially grim outcome may stop their treatments. [27]

5.4 Tegafur and gefitinib

Tegafur/uracil (UFT) is appropriate for MCT and has a fundamental anti-angiogenesis impact. When UFT was given repeatedly at low doses, this inhibiting impact was more pronounced. The inclusion of UFT substantially increased PFS for patients with EGFR mutations. (14.4 vs. 7.6 months). Longer PFS was seen for individuals receiving gefitinib in addition to UFT when they had low microvessel density. (median PFS, 11.8 vs. 2.8 months). In the gefitinib alone group, the median OS was 18.3 months, whereas in the gefitinib with UFT group, it was 23.6 months. [28]

5.5 Oral vinorelbine and erlotinib

In order to assess the security, tolerability, and pharmacokinetics of treatments, Sutiman et al. created a phase I trial of oral vinorelbine combined with erlotinib employing traditional (CSV) and metronomic (MSV) dosing regimens in NSCLC. On days 1 and 8, oral vinorelbine dosages of 40 mg/m2 for the CSV group (n=16) and 100 mg/week for the MSV group (n=14) were given. 38 and 29%, respectively, of the CSV and MSV categories received an intended answer. In the end, both groups were able to tolerate the oral vinorelbine and erlotinib combo. In sophisticated NSCLC, neither pharmacogenetic nor pharmacokinetic tracking seemed to be helpful when forecasting overall survival (OS). [29] Metronomic vinorelbine substantially decreased the production of cyclin-D1, ATP-binding cassette superfamily G member 2, and protein kinase B, prevented the phosphorylation of ERK1/ERK2, and protein kinase B, and made resistant cells more susceptible to tyrosine kinase inhibitors of the EGFR. [30]

5.6 Vinorelbine and sorafenib

Patients got an established metronomic dose of oral vinorelbine at 60, 90, or 120 mg/week in addition to a starting dose of sorafenib at 200 mg twice daily for 4 weeks. Sorafenib dosages were raised in patients without dose-limiting toxicities to 400 mg twice daily for

4 weeks, 600 mg twice daily for 4 weeks, and then 800 mg twice daily. 48 individuals in total were examined. Four patients (8.3%) showed a partial reaction (PR), and seven (14.6%) showed a cavitary response, according to the findings. [31] Treatment of metastatic NSCLC with sorafenib and metronomic oral vinorelbine was successful. The number of circulating endothelial cells was also cited as a promising indicator of increased longevity. [32]

5.7 DDP, VP16 and bevacizumab

We previously investigated whether MCT improved the effectiveness of anti-angiogenesis therapy in the management of progressing NSCLC using DDP and oral VP16 MCT in combination with bevacizumab. An ORR of 77.5% was achieved in a total of 40 patients who got combination therapy. The median TTP was 7.6 months, and hematological toxicity was the most prevalent grade 1-2 toxicity. The stable disease incidence was 15%. The optimal biological dose of bevacizumab determined by the research was 5 mg/kg, and the highest tolerated dose was 7.5 mg/kg. MCT and bevacizumab were thought to be a safe and workable combination that had substantial antitumor effects and anti-angiogenic movement. [33] For 45 patients with advanced NSCLC, Correale et al. administered metronomic daily oral VP16 in 2011 along with the addition of bevacizumab to DDP. Every three weeks, the patients got oral VP16 (50 mg, days 1–15), DPP (30 mg/m2, days 1-3), and bevacizumab (5 mg/kg, day 3). Thirty-one patients (68.9%) had a PR, eight (17.8%) had stable NSCLC, and six (13.3%) had cancer progression. PFS was 9.53 months as well. The bio-chemotherapy regimen showed efficiency in established NSCLC; despite this, patients enrolled in subsequent studies should be carefully chosen due to hematological toxicity and gastroenteric toxicity. [34]

5.8 DIAGNOSIS

NSCLC frequently goes undiagnosed until it has reached an advanced state.2,28 Hemoptysis, chest pain, and dyspnea are the next most typical symptoms, occurring in 50% to 75% of cases.28 Laboratory anomalies or paraneoplastic syndromes are other, less frequent signs. Biopsy is necessary for histologic proof of the diagnosis. Determining the size of the tumor is also necessary for diagnosis in order to establish the TNM stage, which will eventually influence cancer treatment options. [35] A Danish controlled study

examined mediastinoscopy and mediastinal lymph node biopsy with echoendoscopy with staging using positron emission tomography (PET) combined with CT vs. the conventional invasive staging alone. Their results indicated that PETCT provided a better classification of N stage diagnosis. As verified by the analysis of a secondary objective from another controlled trial, any positive region on PET-CT must be examined. Patients who are receiving treatment with the goal of curing them or who exhibit signs or symptoms that indicate brain metastasis should have a head CT scan or MRI. [36] Getting enough tissue material is essential, based to the new multidisciplinary categorization of lung cancer developed by the International Association for the Study of Lung Cancer, American Thoracic Society, and European Respiratory Society. At the initial assessment of all suspected lung cancers, the potential for mutation detection and customized management has consequences. [37]

Chapter 6
Conclusion

6.1 Conclusion

The way people with NSCLC are treated has been significantly altered by the use of specific therapy and ICI. In the instance of immunotherapy, it has evolved into the typical first-line therapy when used alone or in conjunction with chemotherapy. Despite the fact that there are still many unanswered questions about the order and arrangement of these new agents, the field is fortunately developing at a very rapid rate as a consequence of the rapid dissemination of NSCLC clinical trial and other research findings. The present review gave information about the underlying mechanisms and summarized preclinical and clinical trials aimed at assessing MCT either alone or in combination with other treatments in the treatment of NSCLC. MCT has not yet been completely proven to be as effective as traditional chemotherapy in front-line settings or to be a viable substitute for subsequent lines of chemotherapy in NSCLC, especially in the areas of targeted therapy and immune therapy. Although MCT showed potential in the treatment of NSCLC, there is currently insufficient evidence to conclusively prove that it is superior to conventional chemotherapy. However, MCT is less toxic, more tolerable, and has more acceptable efficacy when compared to supportive treatment.