Evaluation of Irinotecan as a Third- or Fourth-line Treatment for Advanced Non-small Cell Lung Cancer

By James Keener

Abstract

Lung cancer is the leading cause of cancer-related deaths in the United States. There are two major types of lung cancer: non-small cell lung cancer (NSCLC), which comprises approximately 85% of all lung cancers, and small cell lung cancer. Currently, the most prevalent third- and fourth- line treatment for non-small cell lung cancer is cisplatin-based therapy. This form of therapy has been long established as the chief treatment for advanced NSCLC; however, cisplatin-based therapy also impairs the replication of beneficial cells. Furthermore, insufficient research has been conducted regarding alternative third- and fourth-line treatments. We plan to test the efficacy of irinotecan, a drug that inhibits nuclear enzymes associated with DNA replication and transcription, as a third- or fourth-line treatment for advanced NSCLC in a phase III study. Irinotecan could provide NSCLC patients with an alternative treatment with lower risk of excessive toxicity. Furthermore, this study would supply the foundation for future research concerning later-line treatments for advanced NSCLC.

Introduction

Lung cancer is the deadliest type of cancer for both men and women in the U.S. Non-small cell lung cancer (NSCLC) is the most frequent form of lung cancer. Today, cisplatin-based therapy is the most accepted third- and fourth- line treatment of NSCLC. This form of chemotherapy slows the spread of cancer by prompting apoptosis in cancerous cells; however, cisplatin-based therapy has a major drawback: it also prompts apoptosis in beneficial cells and increases toxicity levels in patients. **Our objective is to test the success of irinotecan as a third- or fourth-line treatment for advanced NSCLC in a phase III study by analyzing toxicity levels and alterations in cancer size**. Irinotecan is a semi-synthetic derivative of camptothecin that inhibits topoisomerase I. Topoisomerase I is a nuclear enzyme that relaxes DNA strands before reassembling them. By inhibiting this enzyme, irinotecan prevents cancerous cells from replicating. In his phase II study, Matsubara evaluated the efficacy and safety of irinotecan as a third- or fourth-line treatment for advanced NSCLC patients (Matsubara, et. al. 2013). Since the results from his research suggest that irinotecan offers a suitable later-line treatment for advanced NSCLC patients, we believe that our study will reflect his encouraging results with more certainty. Nevertheless, we will take into account the fact that irinotecan may cause relatively high toxicity levels.

Specific Aim 1: Intravenously apply irinotecan to subjects and analyze toxicity levels.

The current cisplatin-based therapy for advanced NSCLC has a high risk of toxicity. Assessments will include a medical history and physical examination, complete blood count with differential and platelet counts, hepatic and renal function tests, and urinalysis. Toxicity will be evaluated at least once a week during the first cycle of treatment. Before each cycle, we will repeat the medical history assessment, physical examination, laboratory assessments, and

toxicity evaluations. Toxicity will be evaluated using the National Cancer Institute Common Toxicity Criteria Ver. 3.0 (Matsubara et. al. 2013). If any patients experience high toxicity levels, we will discontinue irinotecan treatment and provide the standard cisplatin-based therapy. This aim is vital because it could provide patients with an alternative, low-toxic treatment.

Specific Aim 2: Intravenously apply irinotecan to subjects and analyze alterations in cancer size.

Assessments for cancer size will include a 12-lead electrocardiogram, chest radiography, chest and abdominal computed tomography (CT), and brain CT or magnetic resonance imaging (MRI). Patient outcomes will be classified as complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD) according to the Response Evaluation Criteria In Solid Tumors criteria version 1.0. Imaging analyses will be repeated every 4 weeks until significant alterations in tumor size are verified. An external review committee will evaluate all responses (Matsubara et. al. 2013). This research is significant because insufficient studies have investigated the efficacy of alternative third- and fourth-line treatments and many NSCLC patients progress into this stage of treatment.

Background

Since this proposal regards third- and fourth-line treatments, it is appropriate to provide current guidelines for first- and second-line treatments for advanced NSCLC. In 2007, Andrea Ardizzoni and her colleagues published an article on their findings concerning carboplatin and cisplatin. Randomized trials compared carboplatin to cisplatin in the first-line treatment of advanced NSCLC. The treatments did not yield statistically significant different palliative results; however, carboplatin was linked to a higher mortality rate. Both treatments were associated with drawbacks when used in high concentrations: cisplatin was connected to renal

toxicity and carboplatin was related to thrombocytopenia, the state of having a low blood-platelet level (Ardizzoni, et. al. 2007). According to this data, cisplatin-based third-generation treatments are the most effective standard first-line treatments for patients with advanced NSCLC. Although cisplatin is the primary drug for chemotherapy treatments, proper agents within the medication depend on whether a patient has squamous or non-squamous advanced NSCLC. A research paper regarding appropriate treatments for both squamous and non-squamous tumors was published in 2008 by Giorgio Scagliotti. More specifically, his research compared cisplatin plus pemetrexed versus cisplatin plus gemcitabine. This phase III randomized study compared the overall survival between treatment arms in patients with stage IIIB or IV NSCLC and an Eastern Cooperative Oncology Group performance status of 0 to 1. The pemetrexed-based combination treatment produced less toxicity than the cisplatin plus gemcitabine combination treatment. There was also a greater efficacy and more convenient administration for cisplatin plus pemetrexed over cisplatin plus gemcitabine in patients (Scagliotti, et. al. 2008). According to this data, cisplatin plus pemetrexed is the superior treatment for patients with squamous advanced NSCLC. As for patients with non-squamous tumors, Martin Reck published a research paper in 2009. Patients were randomly assigned to receive cisplatin and gemcitabine plus low-dose bevacizumab, high-dose bevacizumab, or placebo every 3 weeks. Response rates were 20.1%, 34.1%, and 30.4% for placebo, low-dose bevacizumab, and high-dose bevacizumab, respectively (Reck, et.al. 2009). In non-squamous advanced NSCLC, cisplatin plus gemcitabine and bevacizumab is the suggested option. The previous recommendations are not always true for elderly patients over the age of 70. Patients within this age group are more susceptible to toxicity because of impaired organ function and co-morbidities. In his research paper, Cesare Gridelli discussed the appropriate treatments for patients with NSCLC. A phase III study on 707 randomized patients compared single agent chemotherapy with vinorelbine or gemcitabine to

polychemotherapy with gemcitabine+vinorelbine. According to this study, the combination treatment did not improve results when compared to single agent treatments. Other combination treatments were effective, but increased toxicity. The choice of the drug should be based on the toxicity profile of each drug and type of co-morbid conditions. (Gridelli, 2002). In clinical practice, single-agent chemotherapy is the standard treatment for patients over 70 with NSCLC; however, various combination treatments are appropriate for elderly patients with high performance statuses. Assuming none of the previous first-line recommended treatments are successful, patients must receive different chemotherapy regimens. Published in 2004, Nasser Hanna's research investigated the efficacy of the new drugs pemetrexed and docetaxel in second-line treatments for NSCLC. A randomized phase III trial was created to compare single-agent pemetrexed versus docetaxel (taken every three weeks), with the aim of demonstrating the efficacy of pemetrexed. Pemetrexed was shown to be a viable drug and was associated with better toxicity levels (Hanna, et. al. 2004). Docetaxel and pemetrexed are the recommended drugs concerning the second-line treatment of advanced NSCLC. Although early-line treatments have been extensively studied, later-line treatments have not. Our study will provide indispensable information concerning an alternative treatment with potentially lower risk for toxicity.

Research Design/Methods

Hypothesis

We hypothesize that the application of irinotecan will provide NSCLC patients with an alternative treatment that produces less toxicity and similar tumor reduction to the current cisplatin-based treatment.

I. Eligibility Conditions

We will conduct a phase III study to evaluate toxicity levels and alterations in cancer size as a result of irinotecan as a third- or fourth-line treatment for advanced NSCLC patients. Our procedure will be conducted similar to that of Matsubara's study. Patients with histologically confirmed NSCLC who have received several chemotherapy regimens, including at least one platinum treatment, and have experienced disease progression following their last chemotherapy regimen will be allowed to register for this study. Other eligibility conditions include an Eastern Cooperative Oncology Group PS of 0–2, expected survival of more than 3 months, leukocyte count of ≥3000/m3, platelet count of≥100,000/m3, hemoglobin concentration of ≥10.0 g/dL, serum aspartate aminotransferase and alanine aminotransferase levels of less or equal to twice the normal upper limit, serum bilirubin level of≤1.5 mg/dL, serum creatinine level within the normal range according to the criteria of each hospital or a creatinine clearance calculated according to the Cockcroft–Gault formula of≥50 mL/min, and peripheral arterial partial pressure of oxygen (PaO2) of ≥60 Torr (Matsubara et. al. 2013). As a safety precaution, patients with brain metastasis or severe comorbidities will not be accepted for this study. We will need 300 individuals for this study. This trial will be conducted once written informed consent is obtained from enrolled patients, and approval from the institutional review board of each participating hospital is ascertained.

II. Procedure

This study will be conducted at the Kaiser Foundation Hospital and Saint Agnes Medical Center in Fresno. Irinotecan at a dose of 80 mg/m2 diluted in 500 mL of saline or 5% glucose will be administered by intravenous infusion the first day of every week for 24 weeks. We will regularly administer dexamethasone to counteract side effects. If leukopenia of ≥ grade 2,

neutropenia of ≥ grade 2, platelet count of <100,000/mm3, fever of ≥ grade 1, and/or diarrhea of ≥ grade 1 are noted within 24 hours prior to the start of the next cycle, treatment will be discontinued until the patient recovers. If a patient does not recover within four weeks, the treatment will be discontinued. The treatment will continue for 24 weeks unless patients experience hazardous results or disease progression. Furthermore, we will provide the standard cisplatin-based therapy to patients who desire to stop participation in the study.

III. Assessments

Baseline assessments will include a medical history and physical examination, complete blood count with differential and platelet counts, hepatic and renal function tests, urinalysis, 12-lead electrocardiogram, chest radiography, chest and abdominal CT, and brain CT or MRI. Toxicity levels in the blood will be evaluated at least once a week during the first cycle of treatment. Before each cycle, we will repeat the medical history assessment, physical examination, laboratory assessments, and toxicity evaluations. Patient outcomes will be classified as complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD) according to the Response Evaluation Criteria In Solid Tumors criteria version 1.0. Imaging analyses will be repeated every 4 weeks until significant alterations in tumor size are recorded. An external review committee will evaluate all responses. Toxicity will be evaluated using the National Cancer Institute Common Toxicity Criteria Ver. 3.0 (Matsubara et. al. 2013). We expect results to indicate that irinotecan is a viable treatment plan – providing patients with low-toxic results while simultaneously effectually reducing tumor size.

IV. Rationale

We will use the National Cancer Institute Common Toxicity Criteria Ver. 3.0 and the Response Evaluation Criteria In Solid Tumors criteria version 1.0 to test whether the application

of irinotecan provides NSCLC patients with similar tumor reduction and less toxicity than the current cisplatin-based treatment. We intend to conduct this study on irinotecan because insufficient studies have investigated the efficacy of alternative third- and fourth-line treatments and many NSCLC patients cannot cope with the current cisplatin-based treatment. Another motivation for conducting this study on irinotecan is because it has yielded the most promising results for later-line treatments; Matsubara's study displayed that Irinotecan yields less toxicity and similar cancer reduction to cisplatin-based treatments (Matsubara, et. al. 2013). This study is vital in providing NSCLC patients with a suitable alternative for later-line treatments. Furthermore, this study would provide critical information for future research on later-line treatments for NSCLC.

Data Management

This application requests support to collect data from a participatory study of 300 individuals with advanced NSCLC for 24 weeks. Data outcomes from this study will be made available without cost to researchers and analysts; however, non-vital information concerning the participants will be kept confidential. User registration is required in order to access or download files. Users must agree to the conditions of use regarding public access including the following: instructions against attempting to identify participants in the study, restrictions on redistribution of the data to third parties, and acknowledgement of the data source.

Budget

The estimated budget for this 24 week study is approximately $2,572,238.81. Most of our equipment will be leased from the Kaiser Foundation Hospital and Saint Agnes Medical Center.

Required Items/Services	Required Funds
Dexamethasone ($41.99 per patient)	$25,194.00
Irinotecan ($138.07 per patient)	$41,421.00
Oncology Staff (3 oncologists)	$109,136.21
Nursing Staff (20 nurses)	$123,425.60
Research Leader	$40,000.00
Hospital Leasing (includes beds, sheets, MRI and CT machines, IV infusion set, utilities, gloves)	$2,233,062.00

NIH Public Audience Abstract

Lung cancer is leading cause of cancer-related deaths in the United States. In fact, more people die of lung cancer than of breast, colon, and prostate cancers combined. There are two main types of lung cancer: non-small cell lung cancer (NSCLC), which includes the majority of lung cancers, and small cell lung cancer. Currently, the most effect treatment for non-small cell lung cancer is cisplatin-based chemotherapy. This form of therapy inhibits pathways involved in cell growth and replication in order to alleviate cancers. Cisplatin-based therapy has been long established as the foremost third- and fourth-line treatment for advanced NSCLC; however, insufficient research has been conducted regarding alternative third- and fourth-line treatments. Later-line treatments are reserved for patients who experience disease progression after multiple therapies. We plan to test the efficacy of irinotecan, a drug that inhibits nuclear enzymes associated with DNA replication and transcription, as a third- or fourth-line treatment for advanced NSCLC in a study to determine its prospect for actual use. This treatment could provide NSCLC patients with an alternative treatment with lower risk of excessive toxicity.

Public Health Impact Statement

Although there has been recent progress in the treatment of advanced NSCLC, the significant number of patients with progressed advanced NSCLC requires investigation. This experiment will determine if irinotecan is a practical third- or fourth-line treatment for advanced NSCLC in clinical practice. If our study confirms the success of irinotecan, NSCLC patients will have an alternative treatment available that provides a lower risk of toxicity. Finally, research regarding irinotecan as a third- or fourth- line treatment for advanced NSCLC would produce invaluable knowledge for future research in the field.

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Winner of the Writing 116 Proposal Contest, James E. Keener is a junior majoring in chemistry at the University of California, Merced. He is from a small town, Easton, which is located in Fresno, California. After college, James plans to pursue a career in materials science. His interests include video games, sports, and music