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Research Article

Maintenance Oral Etoposide Following First Line Cisplatin-Etoposide Chemotherapy in Locally Advanced and Metastatic Non-Small Cell Lung Cancer Patients

Authors
Dr G. Raja[1], Dr K. Kalaichelvi[2*]
[1,2]Madras Medical College
[1]Email: *grajaro78@gmail.com*
*Corresponding author
Dr K. Kalaichelvi
Madras Medical College
Email: *Kalaikannan6000@gmail.com*

Abstract
Background: *Lung cancer is the most common cancer worldwide. Platinum based chemotherapy improved the overall survival up to 8-10 months and 1 year survival rate of 33%. Over the past years attention was focused on the possible effect of prolongation of therapy immediately after first line therapy, the so called Maintenance therapy.*
Objective: *The main objective of this study is to assess the response rate, safety and toxicity profile of oral Etoposide as maintenance therapy in advanced stage Non-Small Cell Lung Cancer (NSCLC).*
Methods and Materials: Stage III/IV NSCLC patients who received 4-6 cycles of platinum based chemotherapy and achieved complete (CR), partial (PR) or stable (SD) response were included in the study. The patients were given oral Etoposide 50mg once daily for 14 days repeated every 21 days and evaluated with Chest X-ray, blood counts, biochemistry.
Results: *Among the 40 patients who received platinum doublet, 32 patients received maintenance therapy. The mean number of cycles received was 7.5 (ranges from 1 to 27 cycles). Twenty one patients (65.6%) received more than or equal to six cycles. Three patients (9.3%) showed complete response, 4 (12.5%) had partial response and 15 (46.8%) were in the stable disease. Overall response rate was 21.8% and the Disease Control Rate was 68.7%. All patients had grade 1 or 2 toxicity only. The median progression free survival was 5 months.*
Conclusion: *Oral Etoposide maintenance therapy following Cisplatin based chemotherapy in advanced NSCLC was well tolerated & shows good disease control with less toxicity.*
Keywords: *Non-Small Cell Lung Cancer, Cisplatin, Etoposide, Maintenance, Progression free survival.*

Introduction

Lung cancer is one of the most common cancers in the world-wide and it has been the leading cause of death due to cancer.(1) In India, Age Adjusted incidence rate of lung cancers, ranges from 7.4 to 13.1 per 100,000 among males and 3.9 to 5.8 among females.(2) The International Agency for Research on Cancer estimated indirectly that

about 635,000 people died due to cancer in 2008, representing about 8% of all estimated global cancer death and about 6% of all cancer deaths in India.[3]

The term, Non-Small Cell Lung Cancer (NSCLC) refers to a large group of pulmonary neoplasm that is often associated with cigarette smoking and they are the commonest group of lung cancers. Over 50% of patients diagnosed with NSCLC present with advanced or metastatic disease (stage III or stage IV) that is not amenable to curative treatment. The remaining half of the patients are treated with curative intent will experience relapse and eventually succumb to disease.

The over-all median survival for stage IV disease is 10-12 months. Currently, platinum-based combination chemotherapy regimens are preferred for the treatment of advanced NSCLC with good performance status. Combination chemotherapy (cispaltin based) gives over-all median survival rate of 6-8 months, with few patients surviving longer than 1 year with good performance status. Etoposide is a phase-specific, schedule-dependent agent that produces a 5% to 15% response rate when used alone in the treatment of metastatic NSCLC.[4] Although its activity as a single agent in NSCLC is moderate, Etoposide is synergistic with Cisplatin, which facilitates the successful use of this combination against a variety of neoplasms, including NSCLC.[5] The cisplatin-etoposide combination was initially developed as an effective regimen for patients with small cell lung cancer and remains the standard of care for this disease[6].

Oral Etoposide is a semisynthetic derivative of podophyllotoxin that has a major role in the management of many human malignancies. Its cytotoxic activity results mainly from the formation of a covalent complex with topoisomerase II-DNA, which results in DNA single-strand breaks.

Numerous efforts have been made to improve the efficacy of first line chemotherapy for advanced NSCLC. One strategy to improve the outcome is to utilize the maintenance chemotherapy. There is emerging data that continuing the non-platinum drug until disease progression may improve overall survival. This approach is called, "continuation maintenance therapy." There is also data that switching to a different, non-cross resistant drug after response or stable disease to 4 cycles of first-line platinum-based combination chemotherapy improves overall survival. This approach is called, "switch maintenance therapy."

Bozoky G, et al, showed an encouraging response rate with long-term daily administration of oral etoposide to treat non-small cell lung cancer.[7]

Meiyu Fang, Shengye Wang evaluated the efficacy and safety of maintenance therapy with oral etoposide following first-line docetaxel-cisplatin chemotherapy in patients with metastatic non-small cell lung cancer. This therapy was well tolerated and moderately active against metastatic metastatic non-small cell lung cancer.[8]

In this present study, we investigated the efficacy, safety and tolerability of Oral Etoposide as a maintenance therapy in advanced and metastatic NSCLC after first line cispaltin based chemotherapy.

Materials and Methods

This is a prospective interventional study aimed to assess the efficacy, response rate and toxicity and Safety of the oral Etoposide as a maintenance therapy in locally advanced and metastatic Non-small cell lung cancer and to assess the Progression Free Survival of the patients.

Patient selection

Patients with Histopathologically confirmed stage III/IV NSCLC were included in this study. Other inclusion criterias were performance status ≤ 2 by ECOG, age 18 – 75 years, creatinine clearance of $\geq$ 50 ml/min and should have normal hepatic function and adequate blood counts. Patients with poor performance status were excluded and patients with brain metastasis, severe renal, hepatic impairment were not included in this study.

All eligible patients were evaluated by physical examination, chest X-ray, computed tomography

(CT) chest, abdominal ultrasonography (USG) and blood parameters. Written informed consent from each patients and ethics committee clearance were obtained before this study.

Treatment

The enrolled patients underwent two courses of treatment: Induction phase and Maintenance phase. In the Induction phase, patients received 4 or 6 cycles of first line Cisplatin- Etoposide chemotherapy intravenously every 21 days. Injection cisplatin 70 mg/m^2 on Day1 and Injection Etoposide 100mg/m^2 Day 1 to Day 3 was given. After chemotherapy the patients were reevaluated with CT chest, ultrasonogram of abdomen. Following induction treatment, patients who achieved disease control (complete response, partial response, or stable disease) were enrolled for the maintenance chemotherapy. Oral Etoposide was administered at 50 mg per day for 14 consecutive days every 21 days along with best supportive care.

Response evaluation and statistical methods

The response rate was evaluated with RECIST version 1.1 criteria and the toxicity to chemotherapy was graded according to CTCAE version 4.0. The Kaplan- Meier method was used for the analysis of Progression free survival (PFS). The COX proportional hazard model was used to estimate hazard rates. Tumor response rate (Partial response + complete response) and disease control rate (Partial response + complete response + stable disease) were analyzed. Statistical analyses were done using the software SPSS version 17.0 for windows. A value of P less than 0.05 will be considered as statistically significant.

Results

This study was done between the periods from July 2013 to February 2014. Totally forty (n=40) patients were enrolled in this study. Eight (n=8) pts (20%) were progressed or the performance status was dropped after first line chemotherapy were removed from the study and the remaining responders (n=32) were taken into the maintenance therapy. The base line characteristics of oral Etoposide received patients (n=32) are shown in the Table.1.

In this group, the median age of the patient is 55 Years (range from 34 to 75 yrs). Among them twenty one patients (n=21) are males and eleven (n=11) are female patients.

All patients received Cisplatin and Etoposide regimen as first line chemotherapy. Twenty four (n=24) patients received 6 cycles of chemotherapy and one patient received 5 cycles of chemotherapy and seven (n=7) patients received 4 cycles of chemotherapy.

Two patients (5%) responded well to the first line chemotherapy and achieved complete response. Twenty three (n=23) patients (57.5%) achieved partial response and seven patients (17.5%) are in stable disease. The results of the first line chemotherapy are given in the Table.2.

These patients were taken into the maintenance therapy group and they were treated with oral Etoposide 50 mg flat dose for 14 days of every 21 days.

Among the maintenance therapy, totally 241 courses of chemotherapy were received by the patients (n=32). The mean number of cycles received is 7.5 cycles (ranges from 1 to 27 cycles). Twenty one patients (65.6%) received more than equal to six cycles oral chemotherapy courses.

Statistical analysis

The response was assessed using RESIST 1.1 Criteria. The toxicity was graded according to the Common Toxicity Criteria for Adverse Events (CTCAE) V.4.02. Kaplan Meier survival curve is used for analysis of progression free survival and Cox Regression co-efficient model is used for assessing hazard ratio and the pathology is used as covariate in this study. Tumor response rate is defined as complete response + partial response and the Disease Control Rate is complete response + partial response + stable disease. Statistical analyses were done using the SPSS v.17.0 for windows. A value of *P* less than 0.05 was considered statistically significant.

When the results of the oral maintenance study were analyzed, three patients (9.3%) showed

complete response, four patients (12.5%) have partial response and 15 patients (46.8%) are in the stable disease with the oral Etoposide maintenance therapy. Ten patients (including the three patients who are considered as progressive disease because of their lost follow up) were progressed in their early period of maintenance itself. Overall response rate is 21.8 %(complete response + partial response) and the Disease Control Rate is 68.7% (22/32)(complete response + partial response + stable disease) (Table.2).

The median progression free survival is 5 months. Kaplan Meier survival analysis says the patients who undergone progression has occurred in a time range from the second month of maintenance therapy to eighth month of the therapy. The patients who are not progressed have achieved a plateau response of survival probability (figure.2). Cox regression co-efficient model analysis revealed that the hazard ratio is increased during the early period of maintenance therapy and the Squamous cell histology has double the time risk for progression with cap Etoposide maintenance (HR value 2.057, CI at 95% and p=0.26 (not significant))(figure.3) and none of the other covariates are found to be significant. All twenty nine patients (90.7%) tolerated the treatment well.

Toxicity assessment (Table.3)

Fatigue is the commonest toxicity (84.5%) seen with oral Etoposide therapy and it is mostly Grade 1. Regarding the hematological toxicities, 18(44.1%) patients had Grade1 and 6 (18.6%) patients had Grade 2 Anemia. Five patients (15.5%) developed Grade 1 neutropenia. No thrombocytopenia was observed.

Four patients (12.4%) developed infections and they are treated with antibiotics and resolved.

Five patients (15.5%) showed elevated renal parameters, dose adjustments done according to the creatinine clearance. Four patients (12.5%) showed elevated Bilirubin (Grade 1).

Ten patients (30.1%) had nausea and severe gastritis and 3 patients (9.3%) had Grade1 weight loss. Almost all of the patients has Grade1 Alopecia noted in this study.

No Grade 3 or Grade 4 hematological and non-hematological toxicities were noted. No treatment related death noted in this study.

Table.1: Base Line Characteristics of n=32 Patients

Base line characteristics	Oral Etoposide n
AGE	
<60 YRS	20
>60 YRS	12
SEX	
MALES	21
FEMALES	11
STAGE	
STAGE IV	20
STAGE III	12
PERFORMANCE STATUS	
ECOG-0-1	19
ECOG-2	13
SMOKING HISTORY	
SMOKERS	18
NON- SMOKERS	14
NO. OF FIRST LINE CHEMO RECEIVED	
6 CYCLES	24
5 CYCLES	1
4 CYCLES	7
PATHOLOGY	
SQUAMOUS CELL CA	9
ADENO CA	23

Table.2: Results of the first line Chemotherapy and Maintenance oral Etoposide Therapy

RESPONSE	n	N
	CISPLATIN & ETOPOSIDE (n=40)	ORAL ETOPOSIDE (n=32)
COMPLETE RESPONSE	2	3
PARTIAL RESPONSE	23	4
STABLE DISEASE	7	15
PROGRESSION OF DISEASE	8	10
OVERALL RESPONSE	25	7
DISEASE CONTROL RATE	32	22

Table.3. Toxicity grades of Oral Etoposide Therapy

PARAMETERS	NUMBER OF PATIENTS IN MAINTENANCE THERAPY	
	Toxicity grade G1+2	Toxicity grade G3+4
ANAEMIA	24	-
NEUTOPENIA	4	-
THROMBOCYTOPENIA	-	-
INFECTION	4	-
RENAL	5	-
HEPATIC	4	-
VOMITING & GASTRITIS	10	-
WEIGHT LOSS	3	-
FATIGUE	27	-
ALOPECIA	29	-

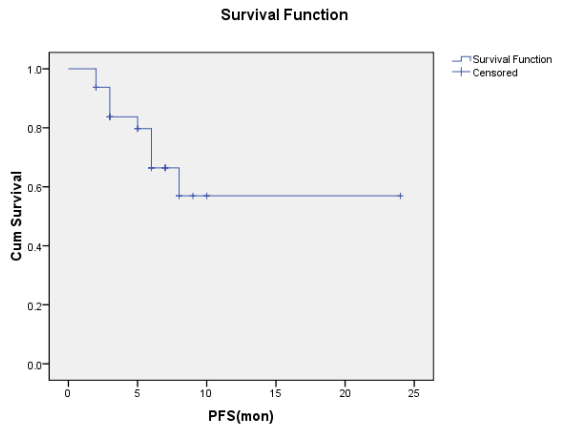

Figure.1 Kaplan Meier survival curve analysis for progression free survival

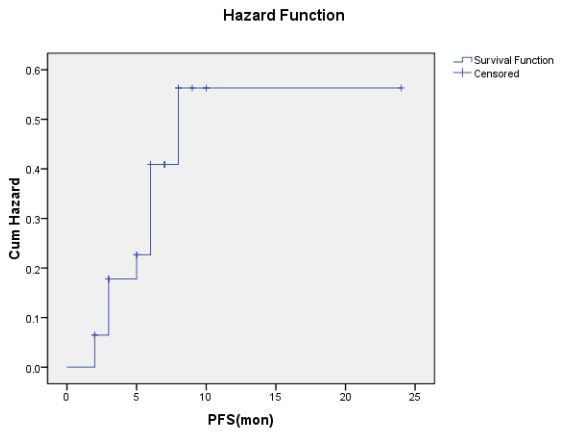

Figure.2 Cox Regression co-efficient model analysis for hazard ratio.

Discussion

More than 50% of patients diagnosed with non-small cell lung cancer are presented with locally advanced and metastatic disease (Stage IIIB and Stage IV), that is not amenable to curative treatment.

Palliative chemotherapy is still the standard of first line management for locally advanced and metastatic NSCLC patients with good performance status. There are many doublet combination is available to give as an induction chemotherapy including Cisplatin and Etoposide, a regimen is being used since long back.

Combination chemotherapy (Cisplatin based) was shown to produce responses in 20% to 30% of advanced NSCLC, the overall median survival of patients receiving chemotherapy was 6 to 8 months only.[9-11]

The efficacy of Cisplatin- Etoposide regimen has been documented well. In a phase 2 study, the response rate was 38% and the median survival was 7.5 months.[6]

Maintenance therapy in non- small cell lung cancer is that continuation of an active treatment until progression of disease in patients who have achieved a stable or partial or complete response in the first line chemotherapy.

The goal of the maintenance therapy is to improve the overall survival, to delay the tumor progression, to maintain the quality of life and to minimize the side effects.

Recently molecular targeted therapy has been used to improve the efficacy of first line chemotherapy in stage IIIB & IV NSCLC. The EGFR TKI's like Erlotinib and Gefitinib were not shown to improve the efficacy when added to the platinum doublet regardless of the EGFR status.[12,13] However, they are effectively used as monotherapy in EGFR mutation positive advanced NSCLC.[14]

The median progression free survival in TKI maintenance therapy of advanced NSCLC is 4.7 months in ATLAS trial, 8.3 months in SWOG OO23 trial and 2.9 months in IFCT 2010 trial and 12.3 weeks in SATURN trial.

The response rate of oral Etoposide varies from 0 to 48% and the toxicity is low and the medial survival time of 5 months was repeatedly confirmed.[4, 15]

In this study, forty patients were enrolled initially and they received 4-6 cycles of i.v cisplatin and Etoposide. Among them 8 pts were progressed after first line chemotherapy. Complete response achieved by 2 patients and 23patients achieved partial response and seven patients were in stable disease status. The overall response rate is 62.5% and the disease control rate is 80%. The patients who have received either 4 or 6 cycles do not show any difference in the response rate.

Thirty two patients were enrolled in maintenance therapy and they are treated with flat 50 mg

Etoposide PO daily for 14 days of every 21 days. The responses achieved in maintenance therapy are, complete response 3 patients, partial response in 4 patients and stable disease in 15 patients. One of the partial responder of first line chemotherapy becomes complete response after maintenance Etoposide. The overall response rate is 21.8% and the disease control rate is 68.7%.

The overall response rate achieved in this study is comparable to the study done by Walls et al, who combined Carboplatin with a 21-day course of oral Etoposide and reported partial responses in eight of 30 patients (27%) with non-small-cell lung cancer. The regimen was well tolerated. Similarly, Thomas M. Waits et al, obtained 23% response rate with 21-day schedule of Etoposide. (16)

The median progression free survival in this study is 5 months. The patients have tolerated the treatment well and it is found to have that it has moderate activity against NSCLC. This is very much comparable with the study done by Waits TM et al(18) who got median response duration of 5 months (range, 2 to 6 months). He concluded that Etoposide given by this dose and schedule has moderate activity as first-line systemic therapy for advanced NSCLC. In previously untreated patients, chronic oral etoposide is well tolerated, and incorporation into combination regimens should be feasible. Etoposide bioavailability may be increased at lower oral doses.

Investigators at Vanderbilt treated 25 patients with advanced NSCLC and no prior chemotherapy with oral Etoposide 50 mg/m 2/d for 21 days every 28 to 35 days. PRs were noted in 23% of these patients with a median duration of 5 months, which compared favorably with standard intravenous schedules of Etoposide.

Miller AA, Tolley EA et al(17) achieved 41% partial response and median progression free survival of 4 months and 2 patient developed neutropenic sepsis in his study.

Jeremic B et al showed 26% response rate and 5 months progression free survival. Correale B, Bottac et al added weekly cicplatin and oral Etoposide with Bevacizumab and obtained 9.53 months progression free survival and 68.8% response rate.

In this study, almost 90% have tolerated the treatment well. The Hematological toxicities assessment showed Grade1 and Grade 2 anemia and Grade 1 Neutropenia. No thrombocytopenia was observed. This toxicity profile favorably compares with other study.

Non- Hematological toxicities like fatigue, alopecia, nausea and gastritis, infection renal and hepatic function alteration have been noted and these are more of Grade 1. There is no treatment related deaths noted. There is no Grade 3 and Grade 4 Hematological and Non-Hematological toxicities noted in this study. This toxicity profile is comparable and even lesser than the other studies.

Conclusion

Oral Etoposide is moderately active against advanced and metastatic non small cell lung cancer. It shows moderate response rate and less toxicity profile in advanced and metastatic Non-small cell lung cancer with good performance. The treatment is very much feasible and almost all the patient tolerated well. The response rate and progression free survival rate achieved in this maintenance therapy study after first line Cisplatin and Etoposide chemotherapy is comparable to the other international studies. This treatment modality is cheaper and cost effective than the other maintenance drugs.

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