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Mohammad Mozayen MD
Marshall University, mozayen@marshall.edu

Mohamed Alsharedi
Marshall University, alsharedi@marshall.edu

Inderjit Mehmi

Todd W. Gress MD
Marshall University, gress@marshall.edu

Maria Tria Tirona MD
Marshall University, triatirona@marshall.edu

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Delaying Chemotherapy in the Treatment of Stage IV Non-Small Cell Lung Cancer Does Not Adversely Affect Survival Outcome

Mohammad Mozayen, MD
Edwards Comprehensive Cancer Center, Huntington, WV
Joan C. Edwards School of Medicine, Marshall University, Huntington, WV

Mohamed Alsharedi, MD
Edwards Comprehensive Cancer Center, Huntington, WV
Joan C. Edwards School of Medicine, Marshall University, Huntington, WV

Inderjit Mehmi, MD
Edwards Comprehensive Cancer Center, Huntington, WV
Joan C. Edwards School of Medicine, Marshall University, Huntington, WV

Todd Gress MD, MPH
Joan C. Edwards School of Medicine, Marshall University, Huntington, WV

Maria Tria Tirona, MD, FACP
Edwards Comprehensive Cancer Center, Huntington, WV
Joan C. Edwards School of Medicine, Marshall University, Huntington, WV

Corresponding Author: Maria TriaTirona, MD, FACP, Edwards Comprehensive Cancer Center - Medical Oncology Department, 1400 Hal Greer Blvd. Huntington, WV 25701. Email: Maria.Tirona@chhi.org

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Abstract

Background: Whether a delay in the initiation of chemotherapy for advanced non-small cell lung cancer (NSCLC) can affect overall survival is not well studied. We aim to evaluate the effect of the time interval between diagnosis and initiation of chemotherapy on overall survival in patients with stage IV NSCLC.

Methods: A retrospective review of newly diagnosed stage IV NSCLC patients who received chemotherapy between 1995 and 2012 was conducted. Demographics, histology and site(s) of metastases of patients were reviewed. Time interval between the date of diagnosis and the date of starting chemotherapy was calculated in days. Patients were divided in two groups based on median time interval: Group A < 46 days and group B ≥ 46 days. The primary end point was the difference in overall survival between the two groups.

Results: A total of 172 patients were reviewed. Each group had 86 patients. Median age for both groups was 61 years. The most common histology was adenocarcinoma in A and B (43% vs. 45%, respectively). The sites of metastases in A and B were: brain (25% vs. 28%), liver (20% vs. 9%), bone (30% vs. 30%), respectively. Performance status of ECOG (Eastern Cooperative Oncology Group) :(0-1) was 82% vs. 76% in A and B, respectively. The median overall survival for A was 7 months vs.12 months for B (p=0.04).

Conclusion: In this single institution review, delayed chemotherapy for stage IV NSCLC more than 46 days did not have a detrimental effect on overall survival and even suggested a better outcome. Further larger and prospective studies are warranted to validate these findings.

Introduction

Lung cancer is the leading cause of cancer related death for both men and women with 228,190 new cases of lung cancer and 159,480 deaths estimated in 2013 in the United States.[1,2] The majority of newly diagnosed lung cancers have a non–small-cell lung cancer (NSCLC) histological type accounting for 85% of lung malignancies.[3]

The 5- year overall survival of all stages of NSCLCs is 14 %.[4] The intent of treatment in NSCLC is stage dependent. Stages I, II and III are treated with curative intent with either surgical resection, radiotherapy, chemotherapy or combined modalities; whereas stage IV NSCLC is considered as an incurable disease and treated with palliative intent with systemic chemotherapy. The prognosis of stage IV disease remains poor. In a SEER (*Surveillance*, Epidemiology, and End Results) data base review, stage IV NSCLC had median survival of only 4 months.[5]

Although recent advances in targeted therapy have improved survival outcome for select patients with stage IV NSCLC who have EGFR mutations and ALK gene-rearrangement,[6, 7] systemic chemotherapy remains the mainstay of treatment in the majority of patients with stage IV disease with modest improvement in survival for tumors who are not candidates for targeted agents.[8]

The effect of delayed chemotherapy had been studied in colon and breast cancer.[9,10] In a meta-analysis, the delay of adjuvant chemotherapy of more than 8 weeks for colon cancer was associated with an inferior outcome.[9] In breast cancer, delayed adjuvant chemotherapy after 12 weeks negatively affects the progression free and overall survival.[10]

The data evaluating the effect of delaying chemotherapy in stage IV lung cancer is limited. In the adjuvant setting, a retrospective report from Ontario Canada revealed that time between surgery and initiation of chemotherapy in NSCLC of more than 10 weeks did not affect the outcome.[11] A single center retrospective study by Bozcuk et al

Table 1: Characteristics of patients at the early treatment (group A) and delayed treatment (group B).

Variables	Group A	Group B	P value
Age at diagnosis, mean (sd)	60.6 (11.5)	61.3 (13.0)	*0.71*
Race% White(n≠)	96.5 (83)	98.8 (85)	*0.31*
Gender% Male(n)	45.4 (39)	55.8 (48)	*0.17*
ECOG * %(n)			
0	16.3 (14)	16.3 (14)	*0.73*
1	66.3 (57)	59.3 (51)	
2	15.1 (13)	20.9 (18)	
3	2.3 (2)	3.5 (3)	
Histology %(n)			
Adenocarcinoma	43.0 (37)	45.4 (39)	*0.66*
Squamous cell	29.1 (25)	22.1 (19)	
Large cell	19.8 (17)	25.6 (22)	
Carcinoma NOS†	8.1 (7)	7.0 (6)	

*≠ n: number of patients, *ECOG: Eastern Cooperative Oncology Group), †NOS: Non Otherwise Specified.*

reported that the time to treatment for all stages of NSCLC did not affect the survival at any stage.[12] To evaluate the impact of delaying systemic chemotherapy on overall survival mainly in stage IV NSCLC, we conducted a retrospective review of all stage IV NSCLC patients seen in our institution.

Methods

We conducted a retrospective review of the tumor registry records of newly diagnosed Stage IV NSCLC patients who received chemotherapy between 1995 and 2012 at Cabell Huntington Hospital, WV. The study was approved by Marshall University IRB. A total of 357 patients with stage IV pathologically confirmed NSCLC was identified. Patients with lung metastases from other primary malignancies, those with small cell carcinoma of the lung, those who declined therapy or those with no documented date of starting therapy were excluded. Age at diagnosis, race, sex, histology, sites of metastases, date of diagnosis, performance status and date of chemotherapy initiation were collected.

The time interval was defined as the number of days between the date of diagnosis and the date of starting systemic chemotherapy. Patients were divided into 2 groups based on the median time interval: early treatment group with time interval less than 46 days (group A), and delayed treatment group with time interval equal to or more than 46 days (group B). The primary end point was the median overall survival between the two groups.

Results

Out of 357 patients, 172 patients were analyzed with known dates of diagnosis and treatment initiation. As shown in Table 1, patients' characteristics were comparable between groups A and B. Each group included 86 patients. Median age was 61 years for groups A and B with a male to female ratio of 1:1.2 and 1:0.7, respectively. The majority of patients had performance status ECOG of 1 in groups A and B (57% and 51%, respectively). The most common histology was adenocarcinoma in groups A and B (43% and 45%, respectively).

Sites of distant metastases between groups A and B were not statistically different except for higher liver metastases in group A (Table 2).

The specific sites of metastases in groups A and B were: central nervous system (CNS) - 25.6% and 27.9%, liver -19.8% and 9.3%, bone- 30.2%, and 30.2%, respectively (Table 2). Group A had 7patients (8.1%) vs. B with 4 patients (4.6%) with isolated liver metastases. Patients with non-squamous cell lung cancer and had an EGFR mutation were 6 patients (6.9%) in group A vs. 5 patients (5.8%) in group B (P=1.0).

The median time interval was 26 and 67 days in groups A and B, respectively (Table 3). The median overall survival in group A was 7 months versus 12 months in group B (P =0.04). The 12- month overall survival was 36% and 43%, in group A and B, respectively (P=0.01) [Figure 1]. Group B had a favorable overall survival when compared to group A with unadjusted HR 0.73 (95% CI: 0.52 -01.01) (P=0.055). After adjustment for age, performance status and site of metastases, group B had a better outcome with HR 0.72 (95% CI: 0.52 – 0.99) (P=0.05).

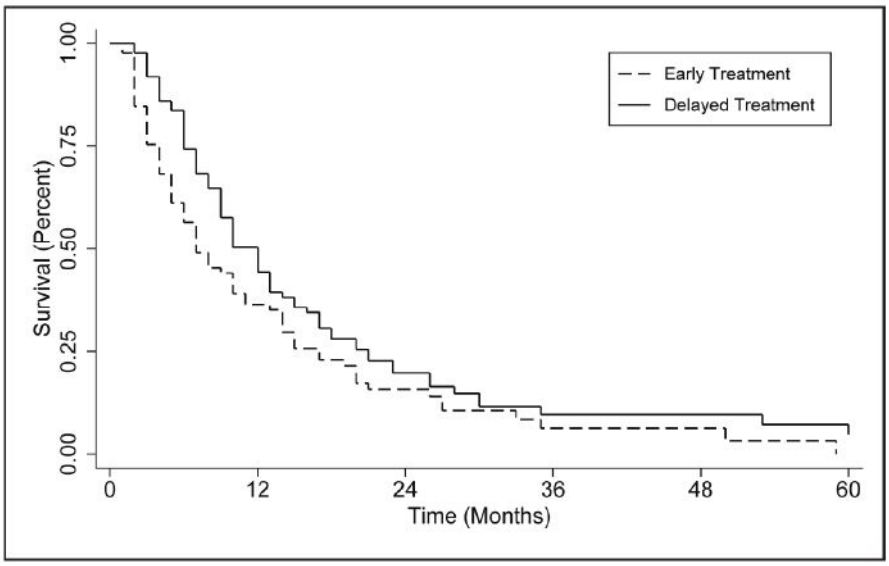
Table 2: Rates of central nervous system (CNS), liver and bone metastases between the early treatment (group A) and delayed treatment (group B).

Sites of Metastases %(n)	Group A	Group B	*P value*
CNS	25.6 (22)	27.9 (24)	*0.73*
Liver	19.8 (17)	9.3 (8)	*0.05*
Bone	30.2 (26)	30.2 (26)	*1.0*

Table 3: Median time interval, median OS, and 12 months OS between the early treatment (group A) and delayed treatment (group B).

	Group A	Group B	*P value*
Median time interval (95% CI)	26 (18-35)	66.5 (56-83)	*<0.001*
Median Survival (IQR)	7 (5-10)	12 (9-13)	*0.04*
12 months overall survival %	36.4	44.3	*<0.01*

Figure 1: ***Kaplan-meier for overall survival between early treatment group A and delayed treatment group B.***



Discussion:

Delaying chemotherapy in the adjuvant setting has been shown to negatively impact the survival outcome in colon and breast cancer.[9,10] Other reports by Biagi et al in meta-analyses showed that a 4 weeks delay of adjuvant systemic therapy decreased the overall survival by 14 % in colon cancer[13] and 6% lower overall survival in breast cancer.[14]

Data on the impact of treatment interval in NSCLC is limited .One retrospective report showed that time between surgery and initiation of adjuvant chemotherapy for more than 10 weeks showed no effect in survival outcome.[11] In another study, which included all stages of NSCLC, it also showed that interval between diagnosis and time to treatment did not have any impact on survival outcome at any stage.[12]

Systemic chemotherapy is well established as a standard of care in stage IV NSCLC and has been shown superior to best supportive care.[15] However, to our knowledge there are no studies which have evaluated the effect of delayed systemic chemotherapy mainly in patients with advanced NSCLC. Our study was conducted to answer an important question for clinicians on whether, for a variety of reasons, delaying systemic chemotherapy in patients with advanced NSCLC affects clinical outcome.

This single institution retrospective study showed that delayed systemic chemotherapy in patients with stage IV NSCLC did not adversely impact the overall survival but rather interestingly, we observed a poorer survival outcome in those patients who were treated earlier. In the delayed treatment group the various reasons which resulted in delaying chemotherapy were as follows: 40% of the patients had to wait to complete their work up (staging imaging studies, mutation analysis of the tumor, re-biopsies), 20% of patients required emergency surgery (eg., resection of isolated brain metastases) whereas only one patient had emergency surgery for brain metastasis resection 1.1% in group A, 25% had a delay in referral or transfer of care, and 30% required radiation therapy for symptomatic metastases.

One explanation for our observation of a poor outcome in the early treatment group would be a higher rate of liver metastases. Involvement of liver metastases is a well known factor that worsens the survival of advanced NSCLC.[12]

There was no significant difference in histology between groups A and B in our study, which likely was not a confounding factor for the difference in overall survival. Furthermore, the prognosis of NSCLC has not been shown to be significantly impacted by the histology subtype.[16]

Limitations of our study include being a single institutional retrospective review, small population size, and a predominantly Caucasian population compared to the national data. The majority of our study population were Caucasians (97%). This is in contrast to the CDC report between 1999-2009, that black men were found to have the greatest risk of developing and dying of lung cancer, whereas white women had the highest risk compared to other races.[17]

Conclusion

Based on our study, it is reassuring to know that delaying chemotherapy, if needed (i.e., to complete work-up or rehabilitation to improve performance status), may not adversely affect overall survival. Further larger studies are required to validate this observation.

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