RESEARCH ARTICLE

Outcome of Daily Cisplatin with Thoracic Chemoradiotherapy in Advanced Non-small Cell Lung Cancer Patients with Comorbid Disorders: a Pilot Study

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Abstract

Background: Lung cancer is the most common cancer in males worldwide. The principal mode of treatment in the early stage of non-small cell lung cancer (NSCLC) is surgery. However, five-year survival is only about 15% for all stages. The aim is to investigate the effect of daily low dose cisplatin concurrently with radiation therapy in advanced NSCLC patients with poor performance status. Materials and Methods: Ten patients diagnosed as inoperable Stage IIIB NSCLC with comorbid disease were assessed retrospectively in Bezmialem Vakif University, Faculty of Medicine, Department of Radiation Oncology, between 2011 to 2013. ECOG performance status was between 3 and 4. Cisplatin was administered at 6mg/m^2 daily, for 5 days a week concurrently with radiotherapy using 160-200 cGy daily fractions, 54 Gy being the lowest and 63 Gy being the highest dose. Results: Complete response at the primary tumour site was obtained in 20% patients. Grade I esophagitis was seen 70 percent of patients, and the grade II haematological toxicity rate was 20 %. Median survival time was 7 months. Conclusions: Median survival time was reasonable, despite the patients ECOG performance status of 3-4, which is similar to groups even without comorbid disorders in comparison to other published papers in the literature. Acceptable toxicity, high response rates and quality of life of patients are the other favourable features.

Keywords: Daily cisplatin - comorbid disease - thoracic radiochemotherapy - ECOG performance status - NSCLC

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Introduction

Lung cancer is the most common cancer in male gender worldwide. The primary treatment in patient with early stage of non-small cell lung cancer (NSCLC) is surgery. Five-year survival is about 15% for all stages. Seventy percent of patients are in the advanced stages at the time of diagnosis. Therefore, curative treatment can be offered to only 30% of the patients (Goldstraw et al., 2007). While chemotherapy administered in the advanced stage provides a 1-3 months benefit in terms of median survival, no change is observed in the patients' quality of life (Spiro et al., 2004). A decline of 31% in 5-year survival rates was reported for patients with serious comorbidity, even in T1 disease.

Most patients in NSCLC are locally advanced stage III or IV disease. Current newer generation agents such as vinorelbine, gemcitabine, paclitaxel and docetaxel may use for advanced NSCLC treatment. (Non-Small Cell Lung Cancer Collaborative Group, 1995; Schiller et al., 2002; Natukula et al., 2013). Paclitaxel or docetaxel plus cisplatin containing regimes are usually considered standard treatments for advanced NSCLC (Chen et al., 2005; Li et al., 2014).

Advanced stage lung cancer patients with comorbidities are generally administered palliative radiotherapy or supportive treatment (Luchtenborg et al., 2012; Simon et al., 2012). Therefore, survival rates are low, declining even further in the later stages (Cheng and Wood, 2011). The 5-year survival rate with 60-64 Gy radiotherapy in non-small cell lung cancer is 27%, even in the early stage. In Stage IIIB, accepted as advanced disease, the 5-year survival rate with radiotherapy alone is 0-5% (Gauden et al., 1995). For this reason, combination treatments which administered concurrently with radiotherapy have now become as standard treatment modalities in Stage IIIB (Non-small cell lung cancer collaborative group, 1995). Addition of chemotherapy provides a survival benefit of 4-6% in 5-year survival rates. An additional benefit of 2 months in median survival can be obtained by the contribution of target specific drugs. In patients with an ECOG performance status of 3, median survival is 4.1 months and grade 3-4 haematological toxicity is above 50% with standard chemotherapy regimens. The response

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rate to treatment is 14% (Ramalingam et al., 2008). In NSCLC lung cancer with comorbid disorders, patients with ECOG performance status of 1-2 can be given standard treatment regimens, while those with an ECOG performance status of 3-4 are generally left untreated.

Materials and Methods

Study population: Ten patients diagnosed as inoperative Stage IIIB non-small cell lung cancer with comorbid diseases were assessed retrospectively. ECOG performance status of the patients was between 3 to 4 (Table 1). These patients received also radiotherapy at the primary tumour site accompanied by daily cisplatin chemotherapy (Table 2).

Treatments: Cisplatin was administered 6mg/m^2 daily, 5 days a week, concurrently with radiotherapy. Radiotherapy was applied with Linac based three dimensional conformal multileaf collimator (MLC) teletherapy machine. The radiotherapy planning was performed with 0.5-1 cm margins to the primary tumour location in the lung, including the lymph nodes sites at the mediastinum close to the primary tumour, and radiotherapy was administered with 180-200 cGy daily fractions, 54 Gy being the lowest and 63 Gy being the highest dose. Adaptive radiotherapy was applied, with weekly renewed plans for those with tumours larger than 8 cm. Radiation volume was reduced according to the shrinking tumor volume. For the patients with tumour size smaller than 8cm, tumour volume was also checked every 15 days, and the application volume was decreased for those whose tumours got smaller. Weekly port films were taken to check the tumour location. Cisplatin 6mg/m^2 could be given for minimal 11 days and maximal 17 days (Table 2). Median follow up time was 24 months (6-24 months).

Results

All patients show some various degree responses and therefore overall response rate was 100% (Table 3, Figure 1). Two patients had complete reponse and 8 patients had partial response. Median survival time was 7 months (1-24 months) (Figure 2). The 24 months living patient being still healthy at present. Another patient survived 21 months, who initially had an 11 cm tumour. Both long living patients had complete response after treatment. While two patients died of accompanying comorbid disorders and another three died due to distant metastasis after 2-21 months. The others are still being followed up. Thus, even better results can be expected after a longer follow-up period.

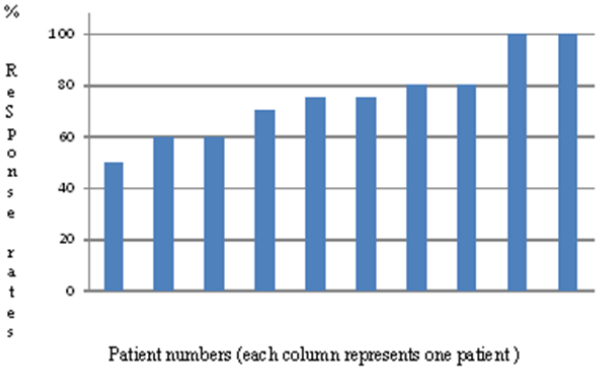

Figure 1. Response Rates

Table 1. Patient Characteristics

Characteristics		Number of Patients	%
PS	ECOG 3	7	70
	ECOG 4	3	30
Gender	Male	9	90
	Female	1	10
Age (years)	50-65	7	70
	65-75	3	30
Comorbid diseases	DM+IHD+COPD	2	20
	DM+IHD	3	30
	COPD+HT+CVD	1	10
	CAH	1	10
	IHD+HT	3	30

*PS: Performance status; NSCLC: Non-small cell lung cancer; DM: Diabetes mellitus, IHD: Ischemic heart disease; COPD: Chronic obstructive pulmonary disease, HT: Hypertension CAH: Chronic active hepatitis; CVD: Cerebrovascular disease

Table 2. Treatment Characteristics

Characteristics		Number of Patients	%
Cisplatin (6mg/m^2)		10	100
	Time (days)		
	11-15	7	70
	15-17	3	30
Radiotherapy total dose	54-60 Gy	3	30
	60-63 Gy	7	70
Radiotherapy fraction	160cGy/day	1	10
	180cGy/ day	3	30
	200cGy/ day	6	60

Table 3. Response and Survival Rates After Treatments

Treatment outcomes	PR (%)	CR (%)	Median OS (m)	Median PFS (m)	1-year survival (%)
Values	80	20	7	5	26

*CR: Complete response; PR: Partial response; PFS: Progression free survival; OS: Overall survival; m: Months

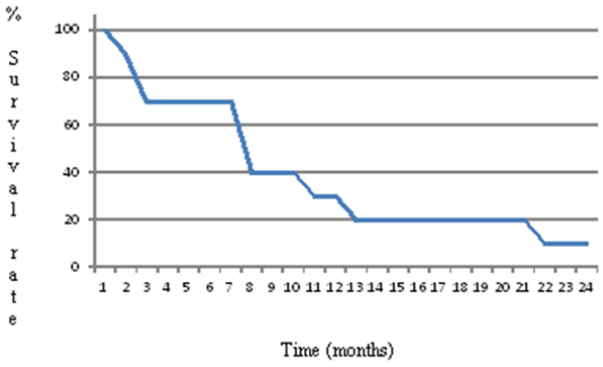

Figure 2. Survival Rates

Grade I eosophagitis was 70%, and grade II haematological toxicity was 20%.

Discussion

Significant costs are consumed shortly before death, because of continued oncological treatment during the

terminal stage of disease. Hospital death occurred in 70% of patients who received active oncologic treatment during this period. Multivariate analysis showed that the presence of superior vena cava compression was one of the important predictors of active therapy during the last month of life in patients with non-small cell lung cancer. (Nieder et al., 2014; Pujol et al., 2014).

Most patients of advanced non-small cell lung cancer (NSCLC) cases receive supportive treatments to manage disease-related symptoms as alone or vith other oncologic treatments. It is usually called Best Supportive Care (BSC). The BSC drugs contain narcotic and non-narcotic analgesics, corticosteroids and gastrointestinal medication. (Lester et al., 2013) But some low toxic chemoradiotherapy treatment protocols as alone or with BSC may be succesful more than BSC alone in NSCLC patients.

In non-small cell lung cancer patients who receive concurrent chemotherapy with radiotherapy, chemotherapy regimens with cisplatin are known to result in more beneficial outcomes (Non-small cell lung cancer collaborative group, 1995; Ramalingam et al., 2008). The increase in response rates were reported to originate from the radio sensitizing effect of cisplatin. Historically, chemotherapy regimens employing daily cisplatin were utilized in relatively small number of studies and despite the continued use at present time published studies are still scarce (Biedermann et al., 2000; European Organization for Research and Treatment of Cancer, 2000; Schaake-Koning et al., 1992). There are some papers reporting that low dose treatments mostly administered as oral chemotherapies or weekly chemotherapies and termed as metronomic chemotherapy can be more efficacious than classical chemotherapies (Noronha et al., 2013). With these types of treatments, the goal is both to reduce the adverse effects of chemotherapy and sensitize the tumour to treatment increasing the effect by reducing tumour vasculature.

The other metronomic chemotherapy schedule that weekly chemotherapy and this regime has been evaluated with some studies (Akerley et al., 2003). Weekly paclitaxel/docetaxel is a other safe protocol for advanced NSCLC. This schedule of paclitaxel advantages are enhanced cytotoxicity, increase dose intensity and reduce toxicity in NSCLC compared with 3-week dosage regimens (Chang et al., 2001; Jatoi et al., 2003; Camps et al., 2006). Weekly administration of docetaxel shown that a higher dose intensity and less myelosuppression (Hainsworth et al., 1998; Greco, 1999). The overall response rate for weekly docetaxel has been 31.6%-45% (Tsunoda et al., 2004; Kaira et al., 2005) and grade 3 and grade 4 leukopenia occurred in about 20% (Zhou et al., 2009).

In our patient group, median survival is 7 months, which is similar to groups even without comorbid disorders in comparison to other published papers in the literature (Non-small cell lung cancer collaborative group, 1995; Ramalingam et al., 2008). Better results are naturally expected in NSCLC patients without accompanying comorbidity. The studies in the literature are mostly conducted in patient groups without comorbid disorders and with a performance score of maximum 3. While chemotherapy with daily cisplatin accompanying radiotherapy was administered as long as mean 20 days in the published studies, it could be administered for only between 11-17 days in our study (Schaake-Koning et al., 1992). It might be due to the comorbid disorders our patients had. Despite this fact, the results obtained are quite successful; survival time, low toxicity, high response rates and quality of life of patients are the favourable features. However, small numbers of patients, short duration of follow-up and retrospective methodology are the major shortcomings of our study.

In conclusion, this study may shed light that daily and low dose treatments might be effective in untreatable lung cancer subjects with comorbid disorders. New studies are warranted both with radiotherapy methods accompanied with metronomic chemotherapy employing cisplatin, and in wider patient populations with lung cancer having comorbid disorders.

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