RESEARCH ARTICLE

Oral Cyclophosphamide and Etoposide in Treatment of Malignant Pleural Mesothelioma

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Abstract

Background: Malignant mesothelioma (MM) is almost always fatal and few treatment options are available. The aim of this study was to evaluate the efficacy of oral cyclophosphamide and etoposide for patients who underwent standard treatment for advanced MM. Materials and Methods: This study included 22 malignant pleural mesothelioma patients who were treated with oral cyclophosphamide and etoposide (EE). Results: The average follow-up period of the patients was 39.1 months. Under the treatment of oral EE, median progression-free survival was 7.7 months [95%CI HR (4.3-11.1)] and median overall survival was 28.1 months [95%CI HR (5.8-50.3)]. The treatment response rates were as follows: 4 patients (27.3%) had a partial response (PR), 12 (54.5%) had stable disease (SD), and progressive disease (PD) was observed in 6 (35.9%). Conclusions: Oral EE can be administered effectively to patients with inoperable malignant mesothelioma who had previously received standard treatments.

Keywords: Malignant mesothelioma - cyclophosphamide - etoposide

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Introduction

Malignant mesothelioma is a rare neoplasm that arises most commonly from the mesothelial surfaces of the pleural cavity and less commonly from the peritoneal surface. It was reported that asbestos exposure, radiation therapy, carbon nanoparticles, viral oncogens, fibrous silicates, growth factors and genetic predisposition may play a role in the development of mesothelioma. Eastern Asia the incidence of mesothelioma is very low. In some countries, the incidence of malignant pleural mesothelioma (MPM) was higher compared to other regions. Turkey is one of those such countries and the incidence of MPM was higher in Cappadocia, a region in central Anatolia. In this region, MPM are linked to exposure to erionite, which is a mineral fiber (Bott et al., 2011; Bianchi and Bianchi, 2012; Berk et al., 2012; Kim et al., 2013; Van Gosen et al., 2013).

The vast majority of MPM patients are diagnosed with advanced disease. It has an extremely poor prognosis; the median survival is 4 to 13 months for untreated patients and 6 to 18 months for treated patients, regardless of the therapeutic approach (Aisner et al., 1995; Ong and Vogelzang, 1996; Ibrahim et al., 2013; Utkan et al., 2013).

Cisplatin in combination with pemetrexed is the standard first-line treatment for MPM patients in advanced disease but there is no standard second-line treatment for MPM (Vogelzang et al., 2003; Mutlu et al., 2013; Porpodis et al., 2013).

The tumor's vasculature is an important target in cancer therapy. Tumor growth is strongly dependent on angiogenesis (Folkman, 1971). Mesothelioma cells often express VEGF and fibroblast growth factor (bFGF) (Kumar-Singh et al., 1999). Some trials showed patients with malignant pleural mesothelioma expressing serum VEGF concentrations that are higher than with other solid tumors or healthy individuals. High serum concentrations of VEGF and bFGF and microvessel density have been identified as negative prognostic factors for malignant pleural mesothelioma (Kumar-Singh et al., 1997; Ohta et al., 1999).

There are a lot of studies which have evaluated the efficacy of cylophosphamide and etoposide, which are an anti-angiogenic agents, on solid tumors (Kieran et al., 2005; Collova et al., 2011; Kucukoner et al., 2012).

The aim of this study was to evaluate the efficacy of oral EE for patients who used standard treatment for advanced MPM.

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Materials and Methods

Patients

We retrospectively screened the files of 53 patients who were diagnosed with malignant pleural mesothelioma in the Department of Medical Oncology at Akdeniz University Hospital between February 2008 and May 2012. This study included 22 malignant pleural mesothelioma patients who were treated with oral cyclophosphamide and etoposide (EE).

Protocols of treatment

Metronomic: Oral cyclophosphamide 50mg 1*1 /Daily and etoposide 50 mg 2*1, two days a week.

Semi-metronomic: oral cyclophosphamide 50mg 1*1/ Daily and etoposide 50mg 2*1, five days in 3 weeks.

Tumor Response: Tumor response was evaluated by CT or PET CT and Response Evaluation Criteria In Solid Tumors (RECIST) criteria 3 months after the treatment.

Statistical analysis

Overall survival was defined as the time between the initiation of treatment and death. The progression-free survival (PFS) was defined as the period of time between the first treatment application and the detection of the first progression based on radiological criteria or until death. Survival was analyzed by the Kaplan-Meier survival analysis and the univariate Cox regression analysis. Variables with $p<0.1$ in univariate analysis were also evaluated by multivariate analysis. All values of $p<0.05$ were considered to be statistically significant.

Results

The median age of the patients was 55 years (range 24-66 years). Among the 22 patients included in our study, nine (40.9%) were female and thirteen (59.1%) were male. 68.2% of the patients with malign mesothelioma were advanced local inoperable patients. The average follow-up period of the patients was 39.1 months. The baseline characteristics of the patients are listed in Table 1.

The ratio of the patients who received first-line-chemotherapy before oral EE was 59.1%. Fifteen of the patients (68.2%) received the metronomic treatment protocol. When the response to treatment under oral EE intake was evaluated, the clinical response rate (stable disease and partial response) was 72.7% (Table 2).

Under the treatment of oral EE, median progression-free survival was 7.7 months [95%CI HR (4.3-11.1)] and median overall survival was 28.1 months [95%CI HR (5.8-50.3)] (Figure 1 and 2). When the factors that affect PFS were analyzed, they were independent from the usage of oral EE [p=0.9 (95%CI HR (4.3-11.1)], age [p=0.77 (95%CI HR (0.96-1.05))], or how many lines of chemotherapy were received before the oral EE [p=0.19 (95%CI HR (0.18-1.41))] and gender [p=0.61 (95%CI HR (1.34-1.04)] (female *vs* male, 7.8 months *vs* 5.3 months).

The mean standardized uptake value (SUV) max value by Positron emission tomography-computed tomography (PET-CT) of the tumor was 9.5 (range 2.6-17) and PET

Table 1. Baseline Characteristics of Patients

Characteristic		Patient No (22)	%
Sex	Male	13	59.1
	Female	9	40.9
Age	Median	55	
	Range	24-66	
Metastases area			
	No metastases	15	68.20
	Lung	5	22.70
	Intraabdominal	1	4.50
	Bone	1	4.50
Prior lines of treatment			
	1	13	59.1
	2	9	40.9
First-line treatment			
	Cisplatin + Pemetrexed	19	86.40
	Carboplatin + Pemetrexed	3	13.60
Type of chemotherapy (EE)			
	Metronomic	15	68.20
	Semi-metronomic	7	31.80

Table 2. Best Overall Response

Response	No	%
Complete Response (CR)	0	0
Partial Response (PR)	4	18.2
Stable Disease (SD)	12	54.5
Progressive Disease (PD)	6	27.3

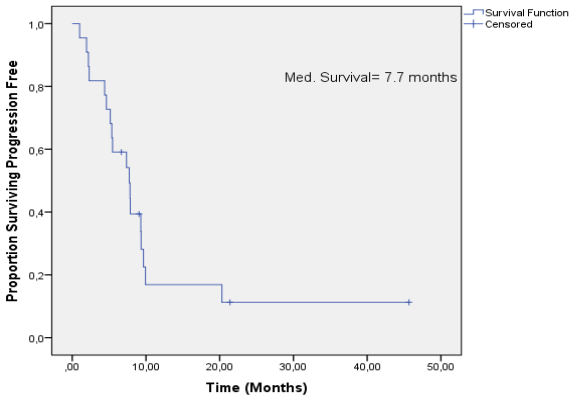

Figure 1. Progression Free Surrvival with Oral Cyclophosphamide and Etoposide

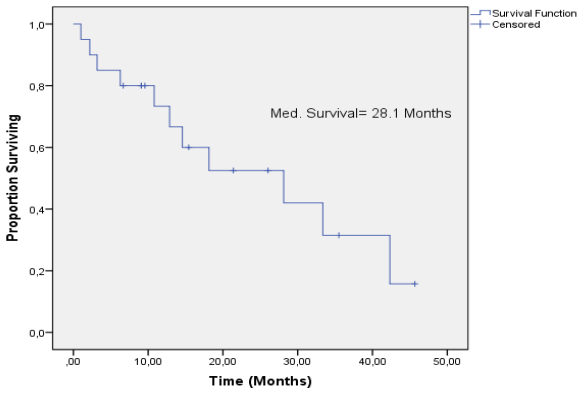

Figure 2. Over Survival with Oral Cyclophosphamide and Etoposide

fluorodeoxyglucose (FDG) uptake activity were found to be not related to the progression-free survival [p=0.44 (95%CI HR (0.92-1.18))].

Discussion

This study is the first study to show the effectiveness of oral cyclophosphamide etoposide (EE) treatment on malignant pleural mesothelioma (MPM).

With a randomized phase III study, it was proven that administering cisplatin (75 mg/m2) and pemetrexed (500mg/m2) in combination to the patients who did not receive chemotherapy was superior to administering cisplatin alone in terms of survival rate. The response rate under this combination regime was 41.3%, the median time to progression was 5.7 months and median overall survival was 12.1 months (Vogelzang et al., 2003). This regime constitutes the standard first-line treatment regime. As a single agent, the response rate to gemcitabine varied between 0 and 31% (Janne, 2003). In patients who did not receive chemotherapy, the combination of gemcitabine with cisplatin resulted in a response rate which varied between 12% and 48%, and the median survival varied between 9.4 months and 13 months (Tsao et al., 2009). In salvage treatment, with the combination of gemcitabine and vinorelbine, the disease stabilization was 37%, the response rate was 7.4%, and the median progression-free survival was 2.8 months (Zucali et al., 2006). In a phase II study in which 63 patients were administered single agent vinorelbinin, the response rate was 16% and the overall survival was 9.6 months (Stebbing et al., 2009). Nowadays, although there is no standardized treatment regime which has been proven to be useful for survival in secondary care, in clinical practice, the patients with epiteloid MPM who are young and have good performance status are increasingly being treated by secondary care treatments (Ceresoli et al., 2011). Among our patients, the rate of patients who received first-line-chemotherapy before Oral EE was 59.1%, whereas 40.9% received second-line-chemotherapy. With the treatment of Oral EE, in 18.2% of the patients, we achieved partial response and in 54.5% stable disease was achieved. Under the treatment of Oral Cyclophosphamide etoposide, the median progression-free survival (PFS) was 7.7 months [95%CI HR (4.3-11.1)] and the median overall survival (OS) was 28.1 months [95%CI HR (5.8-50.3)].

It is proven in the study that the number of chemotherapy lines before Oral EE intake has no effect on progression-free survival. In patients with malignant pleural mesothelioma, male gender, extensive disease, poor performance status, and the existence of sarcomatoid differentiation in histological findings are related to poor prognosis (Herndon et al., 1998; O'Byrne et al., 2004; Yip et al., 2011). In our study, no relevance was detected between the age, gender of patients and progression-free survival.

Positron emission tomography/computed tomography (PET/CT) can be used to discriminate between benign and malignant pleural bulk. In malignant pleural mesothelioma, these techniques are useful to demonstrate extrathoracic disease, and in particular to identify the existence of nodal metastasis, which enables the tumor to be staged. In patients with late diagnosis and early stage MPM, the occult metastasis rate defined by PET-CT is 15%. Moreover, in PET-CT, high standardized uptake value ratios (SUVmax) are related to poor prognosis (Flores et al., 2003; Plathow et al., 2008). In our study, no relevance was detected between the SUVmax value shown by PET-CT before chemotherapy and progression-free survival.

Consequently, according to our survival results and the high clinical response rate of the treatment, Oral EE can be administered effectively to the patients with inoperable malignant mesothelioma who previously received standard treatment.

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