

EVALUATION OF THE EFFICIENCY AND TOLERABILITY OF MONO THERAPY WITH ORAL ETOPOSIDE IN ELDERLY PATIENTS (70+ YEARS OF AGE) WITH ADVANCED NON SMALL CELL LUNG CANCER AND POOR PERFORMANCE STATUS

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ABSTRACT

Motivation Until recently it was considered that 65 years is cutoff for defining patients as elderly, but newer reports indicate that this age limit shift to 70 years of age. Elderly patients with advanced non small cell lung cancer, associated comorbidities and poor performance status represent a specific population and a challenge for use of chemotherapy. Primary aim was to evaluate the impact of mono therapy with oral etoposide on overall survival in elderly patients (≥ 70 years of age) with advanced non small cell lung cancer and poor performance status (PS) ≥ 2 (clinical stage IIb and IV), and as well to evaluate tolerability of this therapy. Secondary aim was to evaluate response rate.

Methods Retrospectively, medical records of 79 female and male patients with advanced non small cell lung cancer and poor performance status treated with oral etoposide (2x25 mg 20 days/10 days pause) in period from 2007 till 2010 were checked for relevant data. Data regarding demographics, performance status, overall survival, response rates and drug toxicity were collected. For statistical analysis we used Pearson chi-square test, T-test, Kaplan-Meier product limited method and Cox regression.

Results Median overall survival (OS) was 31 weeks, in patients with PS 2 overall survival was 34 weeks, and in group with PS 3 was only 24 weeks. Partial response was registered in 20.2% of patients, stable disease in 41.85 % and disease progression in 38% of patients. Treatment was well tolerated, febrile neutropenia and toxic deaths were not registered. Toxic effects didn't have statistically significant influence on OS.

Conclusion Oral etoposide used as mono therapy has been shown as moderate effective and very safe in treating elderly patients with advanced non small cell lung cancer and poor performance status so it represents a good therapy option for treating this specific population.

JEL& UDC CODES, KEYWORDS

■ JEL: H25, M89, I01, I10 ■ UDC: ■ Mono Therapy ■ Oral etoposide ■ Elderly patients ■ Lung Cancer

INTRODUCTION

Lung cancer is one of the most common cancers and patients mainly belong to the group of elderly patients [1]. About one third of patients suffering from non small cell lung cancer (NSCLC) are older than years [2]. In addition, cancer is a disease of elder age and old age is a risk factor for its occurrence. It is widely known that the limit used to determine ages has not yet been precisely defined. It is much easier and convenient to use the determination of chronological age in relation to biological, so that the target population can be determined based on the years of age.

In the geriatric oncology the limit of 70 years of age is increasingly being used to define a population as elderly [3]. A population of elderly patients is now being identified as a separate group regarding the challenges of the aging process and the changes in functioning of their organs. The up-to-date investigations indicate that we might expect significant demographic changes in the next several decades, including a longer lifetime of people and an increased incidence and prevalence of cancer, consequently leading this population to the focus of oncological interest [4, 5]. The application of systemic therapies for treatment of cancer, besides other ways of treatment, is an indispensable way of treating patients suffering from cancer. In principle, the indications for chemotherapy are the same in elder and younger patients [6].

There is unequivocal evidence that the use of chemotherapy may prolong life, but that it should be used cautiously and with more careful monitoring in elder persons considering diminished function of organs in elderly patients because of the aging nature itself and that such patients are often suffering from other diseases that also require usage of other drugs thus representing an important prognostic factor [7]. Therefore the application of a combined chemotherapy is often contraindicated in these patients. All of the above applies also to the patients suffering from a non small cell lung cancer. Former research data regarding the treatment of this disease in elderly patients with a poor performance status are very short because the studies are seldom carried out only in the elderly as target population, and the anticipated demographic changes indicate that the number of elder patients would increase, and therefore a need for their treatment and care will also rise.

Etoposide is a semisynthetic anticancer agent that causes a cytotoxic effect by inhibiting the activity of topoisomerase II. Pharmacological studies indicate that oral administration of low doses of etoposide over a longer period of time can be more effective than intermittent use of a high-dose intravenous infusion [8]. In clinical practice it is also shown that a prolonged use of etoposide shows antitumor response in both etoposide sensitive and insensitive malignancies which did not adequately respond to bolus administration of etoposide [9, 10].

Objective of study

The primary objective of this study is to evaluate the influence of application of oral etoposide mono therapy on overall survival of patients aged 70 years or older, with a poor performance status (PS) suffering from a non small cell lung cancer (NSCLC) and also to evaluate tolerability of this therapy, that is the profile of toxicity of this therapy. The secondary objective is to evaluate the rate of response. The therapeutic efficacy has been assessed on the basis of median survival and response rate. The toxicity profile has been evaluated on the basis of overall toxicity (hematological and non-hematological) in relation to the number of patients.

Study methodology

We selected and retrospectively reviewed the medical records of 79 male and female patients who were histologically confirmed to suffer from advanced non small cell lung cancer, and who were treated with mono chemotherapy of oral etoposide. The other criteria used to select the patients were their age of 70 years or more and the Eastern Cooperative oncology group (ECOG) performance status two and higher [11]. The data regarding the toxicity of therapy were collected during the treatment and evaluated on the basis of Common Terminology Criteria for Adverse Events [12]. In all the patients, the survival was calculated from the date of commencement of the first cycle of chemotherapy until the date of death due to any cause, and, if this information was failing, until the date of the last control. The response rate was evaluated on the basis of the Response Evaluation Criteria in Solid Tumors (RECIST).

The composition of the chemotherapy protocol was as follows:

1. Etoposide capsules 25 mg, 2 x 1 capsule a day, 20 days, followed by a 10 days break of administration,
2. Symtomatic therapy as needed.

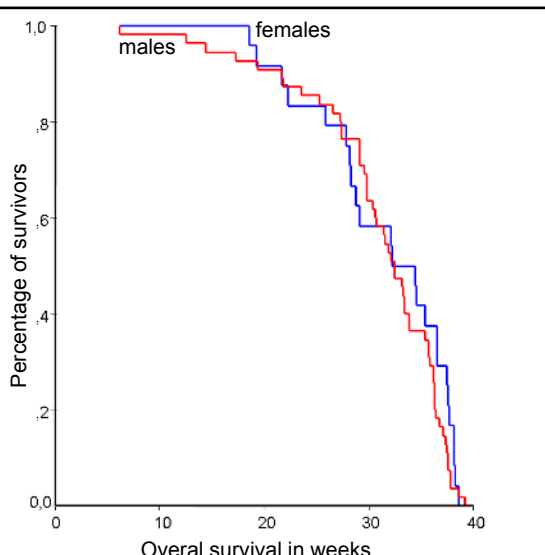
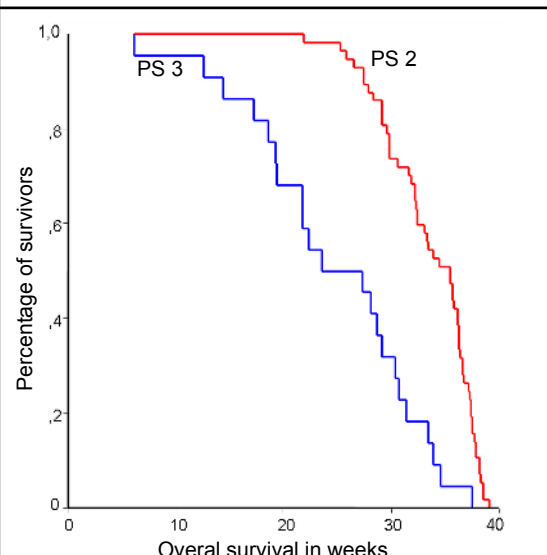
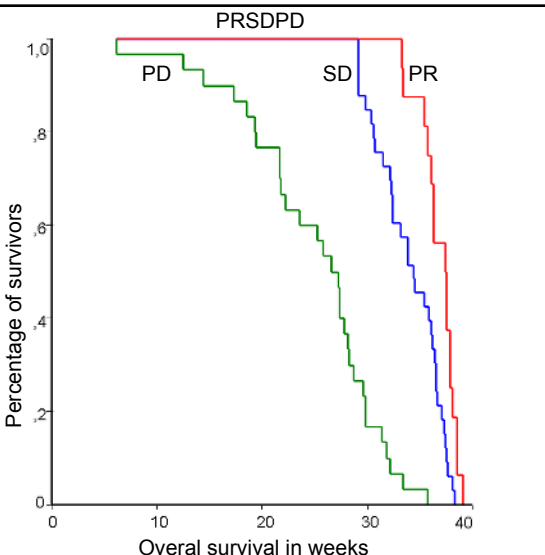
The statistical evaluation included the methods of descriptive statistics - measures of central tendency (mean value, median value) and measures of variability (standard deviation - SD and range - rank); for testing significance of differences we used the Pearson χ^2 -test, T test; for analysis and graphical display of survival of patients we used the Kaplan-Meier method. The Cox regression was also used.

Results

We retrospectively analyzed the data obtained from medical records of totally 79 patients treated in the Medical Center „Bežanijska kosa“ in the period from 2007-2010 according to the protocol with oral etoposide in form of a mono therapy. Out of total number of patients, 55 persons (69.62%) were male, and 24 persons (30.38%) female. Patient age median was 73.76 (range 70 to 77 years of age). The general status of patients was estimated on the basis of the Eastern Cooperative Oncology Group (ECOG) scale. It was recorded that 57 patients had a PS score of 2, and 22 had a PS score of 3. Over 80% of patients had clinical stage IV and 19% had clinical stage IIIb. Pathohistological diagnoses in the selected group of patients were adenocarcinoma and planocellular cancer, out of whom 53.16% (42) of patients had adenocarcinoma and 46.84% patients (37) had planocellular carcinoma. There was no significant statistical difference in survival in relation to pathohistological type of cancer. Totally 374 cycles were applied. The median of applied cycles per patient was 4.73 cycles. In the target group of patients treated with etoposide the survival median was 7.69 months. By comparison of overall survival achieved by this regimen of chemotherapy and the information available on overall survival of patients treated with specific anticancer therapy besides the supportive therapy lasting 21 weeks [13], it was found that the survival median of patients treated with oral etoposide was significantly longer. It was found that there was no difference in overall survival by patient gender (Figure 1), but, as expected, a highly statistically significant difference in survival of patients was recorded in relation to the PS score, far better survival was recorded in patients with PS of 2 compared to those with PS of 3 (Figure 2). Also, a better survival was observed in the patients who achieved a partial response, while the worst was with patients in the progression of disease (Figure 3). There was no significant difference in age of patients in relation to the response that is the age was approximately the same in all the three groups of patients. In 16 patients treated with oral etoposide a partial response was recorded, in 31 a stable disease was registered, and 40% of patients had a progression of disease (Table 1).

Table 1: Therapeutic response		
Therapeutic response	N	[%]
Partial response (PR)	16	20.3
Stabile disease (SD)	33	41.8
Disease in progression	30	38
Source: ECOG - Eastern cooperative oncology group [11]		

Generally, patients well tolerated the therapy. None of them had a febrile neutropenia recorded, also no noted toxic deaths. As for hematologic toxicity, a leukopenia grade I-II was recorded in 62% of patients and grade III leucopenia was recorded in 8, 86% of patients which was the most serious toxic effect registered, together with one recorded case of anemia grade III. In 43 patients (54.43%) anemia grade I-II was recorded. Thrombocytopenia grade I was found only in one patient. Slightly more than a half of patients reported fatigue (53.2%) and vomiting and nausea symptoms were reported by 35 patients (44.3%). Diarrhea and mucositis were reported by one patient each. The toxic effect that was most frequently manifested, but which was of no clinical significance, was alopecia, reported by 50 patients (62.5%). The Table 2 provides an overview of registered toxic effects in comparison with the data from literature [14].

<p>Figure 1: No difference in survival median with respect to gender</p> 	<p>Figure 2: Overall survival of patients with respect to type of performance status</p> 																													
Source: Authors	Source: Authors																													
<p>Figure 3: Overall survival of patients with respect to therapy response</p> 	<p>Table 2: Adverse reactions in our group compared to data from literature</p> <table><tr><th>Adverse reactions</th><th>Our group</th><th>Product monograph data</th></tr><tr><td rowspan="3">Leukopenia</td><td>Gr I-II 62%</td><td rowspan="3">0.611</td></tr><tr><td>Gr III 8.86%</td></tr><tr><td>Σ 70.86%</td></tr><tr><td rowspan="3">Anemia</td><td>Gr I-II 54.43%</td><td rowspan="3">0.393</td></tr><tr><td>Gr III 1.27%</td></tr><tr><td>Σ 55.70%</td></tr><tr><td>Thrombocytopenia</td><td>0.0127</td><td>0.304</td></tr><tr><td>Malaise</td><td>0.532</td><td>0.135</td></tr><tr><td rowspan="2">Nausea and vomiting</td><td rowspan="2">0.443</td><td>Nausea 38.4%</td></tr><tr><td>Vomiting 12.6%</td></tr><tr><td>Alopecia</td><td>0.625</td><td>0.675</td></tr><tr><td>Diarrhea</td><td>0.0127</td><td>0.067</td></tr></table>	Adverse reactions	Our group	Product monograph data	Leukopenia	Gr I-II 62%	0.611	Gr III 8.86%	Σ 70.86%	Anemia	Gr I-II 54.43%	0.393	Gr III 1.27%	Σ 55.70%	Thrombocytopenia	0.0127	0.304	Malaise	0.532	0.135	Nausea and vomiting	0.443	Nausea 38.4%	Vomiting 12.6%	Alopecia	0.625	0.675	Diarrhea	0.0127	0.067
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Discussion

Without the treatment, the overall survival median in patients with advanced NSCLC in stage of advanced disease was 21 weeks [13]. Based on previously performed studies, it is clear that the use of chemotherapy in elderly patients has an effect sufficient to significantly prolong their survival, especially when a combined chemotherapy used. The overall survival median in patients with advanced NSCLC in stage of advanced disease without the treatment was 21 weeks [13]. On the basis of former studies, it is clear that the use of chemotherapy in elderly patients has an effect sufficient to significantly prolong their survival, especially when a combined chemotherapy is applied [15]. Bearing in mind a decreased function of organs in elderly persons because of the nature of aging and that they often suffer other diseases that also require administration of several drugs, and also that they have a significantly lower performance status, therefore a combined use of standard chemotherapy is often challenging in these patients [16]. Etoposide is an antineoplastic agent that has been applied for several decades now, and is known to possess antitumor activity and a favorable effect in the treatment of advanced NSCLC, whether used as mono therapy or combined with other anticancer agents [9, 14, 17, 18, 19]. In medical literature there is no information so far regarding the application of etoposide, its efficiency and expression of toxic effects in elderly patients and if used as mono therapy. There are only few studies where a combined chemotherapy was used because it

is often contraindicated, and besides that, elder patients are less motivated for the treatment. Presently in respect with this specific population there is only data available from several studies where monotherapy was applied together with other anticancer agents against the application of appropriate supportive therapy [13, 20, 21], and data from a somewhat larger number of studies where a combined chemotherapy was used [13, 15, 22]. If we compare the data on overall survival of patients who received only the best possible supportive therapy to our data, it is shown that oral etoposide significantly prolonged the survival median.

The toxicity profile of oral etoposide corresponds to previous data regarding toxicity of etoposide, with one difference that in our group a slightly higher frequency of anemia has been recorded, and consequently a higher frequency of fatigue [14, 18]. This difference is likely just a consequence of age and a reduced ability for recovery. The comparison of toxicity profile of etoposide related to our group is presented in Table 2.

Conclusion

On the basis of the study objectives, methodological assumptions and obtained results, the following conclusions have been drawn. When comparing the available data on overall survival of patients aged 70 years or over, with a poor PS, it can be concluded that oral etoposide therapy significantly prolongs the survival median compared to the survival median of patients who received only the best supportive therapy. For the toxicity profile, it has been shown that it was in accordance with the data from literature, besides a somewhat more pronounced occurrence of anemia which was probably also a consequence of age, the presence of comorbidity and the PS, which is very important for our target population. These data support the usage of oral etoposide in this particular group as secure. Keeping in mind a significant impact on the survival median, a good profile of toxicity, an easy way of taking the medicament and a relatively low cost of it, it can be concluded that oral etoposide represents a valid optional choice for treatment of patients aged 70 years or more, with a poor performance status, suffering from advanced NSCLC, and when a combined chemotherapy is contraindicated or not available. Elderly patients should be encouraged to enter clinical studies specifically designed for their age and sponsors too.

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