INTRODUCTION

The existence of long-term survivors of advanced non-small cell lung cancer (NSCLC) resulted in necessity of studying these cases in an attempt to identify some characteristic features of these patients, features that could become prognostic factors for survival of these patients or predictors of response to chemotherapy and target therapy.

MATERIALS AND METHODS

The medical records of 76 patients with advanced bronchopulmonary cancer ( stages IIIB and IV) hospitalized within the period 2008-2013 in the Oncologic Institute of Bucharest have been examined. The selection criteria were: patients who have had more than three treatment lines, patients who have had Erlotinib in one of the treatment lines, the performance status ECOG 0-1, the absence of associated significant pathologies that would not allow the performance of standard chemotherapy, and patients who have had a survival of less than 2 years.

The data were processed by using the Student t-test, the Chi-square test and for the computation of the survival was used the Kaplan-Meier Curve. The computation of the sample size was not used, as it was estimated that the study can have a significant statistical power and the number of patients could not be increased in order to have a sample size necessary to a high statistical power. Practically all patients were included who were treated with Tarceva within the given time interval.

The main data monitored for the characteristics of the long-term survival
patients included in the study were: histological and/or immunohistochemical confirmation of the diagnosis, age, sex, performance status, associated pathology, reaction and tolerance to chemotherapy, reaction and tolerance to therapy with Erlotinib.

RESULTS

The data of 76 patients [Tables 1-3] with advanced NSCLC have been examined: 35 with stage IIIB and 41 with stage IV. Twenty patients had ECOG performance status 0, 49 patients had ECOG 1 and 7 had ECOG 2.

Patients have had between 1 and 5 lines of chemotherapy. Erlotinib was administered in treatment line II, III and IV. The average monitoring time of patients was of 4 years. The overall survival time was of 4.2 years [Figure 1].

The global survival increased according to the number of chemotherapy lines, so that patients, who received one single chemotherapy line, the average survival was of 2.8 years and those who received between 3 and 5 chemotherapy lines have had an average survival of 6 years, \( P = 0.0146 \) (log-rank test) [Figure 2].

Survival was higher, but without the possibility of computing a reliable interval at patients to whom chemotherapy was administered also after Erlotinib (when the progression of the disease under treatment with Erlotinib was recorded) [Figure 3].

DISCUSSION

The general prognostic of patients with advanced NSCLC is generally poor, despite of the new therapeutical agents that brought only a benefit of a couple of months in survival. Nevertheless, evolution is heterogeneous, as there is a subpopulation of patients exceeding 2 years of

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**Table 1: Characteristics of patients: Age and sex**

<table>
<thead>
<tr>
<th>Sex</th>
<th>( N )</th>
<th>Mean</th>
<th>Standard deviation</th>
<th>Minimum</th>
<th>Average</th>
<th>Maximum</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women</td>
<td>24</td>
<td>58.75</td>
<td>9.76</td>
<td>39</td>
<td>58.5</td>
<td>78</td>
</tr>
<tr>
<td>Men</td>
<td>52</td>
<td>60.23</td>
<td>8.83</td>
<td>35</td>
<td>59</td>
<td>80</td>
</tr>
<tr>
<td>Total</td>
<td>76</td>
<td>59.76</td>
<td>9.09</td>
<td>35</td>
<td>59</td>
<td>80</td>
</tr>
</tbody>
</table>

Test t-Student: 0.5130

**Table 2: Type of concurrent associated diseases**

<table>
<thead>
<tr>
<th>Concurrent diseases</th>
<th>( N )</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory diseases</td>
<td>6</td>
<td>7.89</td>
</tr>
<tr>
<td>Cardiovascular diseases</td>
<td>25</td>
<td>32.89</td>
</tr>
<tr>
<td>Metabolic diseases</td>
<td>6</td>
<td>7.89</td>
</tr>
<tr>
<td>Diseases of the digestive tract</td>
<td>7</td>
<td>9.21</td>
</tr>
<tr>
<td>Other diseases</td>
<td>10</td>
<td>13.16</td>
</tr>
</tbody>
</table>

**Table 3: Number of concurrent diseases per patient**

<table>
<thead>
<tr>
<th>Number of concurrent diseases per patient</th>
<th>( N )</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>W/o concurrent diseases</td>
<td>39</td>
<td>51.32</td>
</tr>
<tr>
<td>Cu 1 concurrent disease</td>
<td>25</td>
<td>32.89</td>
</tr>
<tr>
<td>Cu 2 concurrent diseases</td>
<td>8</td>
<td>10.53</td>
</tr>
<tr>
<td>Cu 3 concurrent diseases</td>
<td>3</td>
<td>3.95</td>
</tr>
<tr>
<td>Cu 4 concurrent diseases</td>
<td>1</td>
<td>1.32</td>
</tr>
<tr>
<td>Total</td>
<td>76</td>
<td>100</td>
</tr>
</tbody>
</table>
survival. This subpopulation of patients is called “long survivors” (LS). Prognostic factors should be found that should help us assess the survival of patients with advanced NSCLC since diagnosis is also nowadays difficult despite of many studies, especially retrospective ones upon LS with NSCLC. Generally, it was not possible to standardize the prognostic factors although there are joint some particularities of this LS group.

From the results of our study, the characteristic of the LS population are: Average age 59 years, approximately one third of the patients were above 65 years on enrollment, the majority being men. Certain factors, such as age above 65 years, the reaction to chemotherapy, the high number of chemotherapy lines permitted by the performance status and the previous reaction, the presence of Erlotinib in one of the treatment lines resulted in an increasing survival tendency. Our patients received sequential chemo-radiotherapy for stage III B and generally palliative radiotherapy for bone metastasis. An older study approached the issue of LS after chemoradiotherapy at patients with inoperable NSCLC. At this group of patients, who received an irradiation dose of 60 Gy concurrently with chemotherapy with Cisplatin and Etoposid or Carboplatin plus 5 Fluorouracil, the global average survival was of 2.1 years. We can explain the difference from our study by the launch of the new cytostatics of third-generation that increased the global survival, as well as by the appearance of targeted therapy. At the other hand, we have to consider that cited study is a prospective study.

A study from 1984 using as a chemotherapy: Metrotrexate + Adriamycine + Cyclophosphamide + Lomustin obtained for a minority of the study population a global survival of 18 months. The comparison is difficult to perform as patients are divided into patients that performed only chemotherapy or only radiotherapy or combined therapy and the used cytostatic drug scheme has been long ago abandoned due to the poor results obtained and the significant toxicity.

Japanese researchers published a study in which they revealed the fact that the majority of patients with advanced NSCLC that survived more than 5 years have had Tyrosine-kinase inhibitors in the treatment line II or III.

As LS are still a challenge to understand the factors incriminated in their evolution, even case presentations have been of significance to elucidate certain issues related to the evolution of such patients. However, sometimes these case presentations raise new questions. Such is the case of a patient from China, who had no genetic modification indicating a targeted therapy or a predictive factor for chemotherapy, but nevertheless reacted very well to chemotherapy associated with Bevacizumab, having a progression free survival PFS of 39 months. A similar case was presented by an Indian researcher.

The scope of certain studies was the quality of life of long survivor patients. Thus, an American study described some of the characteristics of these patients, related to quality of life that enable an assessment of delayed secondary effects of the applied treatments, of the therapy results and may represent even prognostic factors.

The impact of certain therapeutic agents was also studied. So chemotherapy with Vinorelbine in first line for patients with advanced NSCLC could have an impact in survival. In the study of Vinorelbine the main factors correlated to LS were the performance status (0-1), the loss of weight below 5 kg and the reaction to chemotherapy. The inclusion of the data in a multivariate logistic regression model resulted in the determination of the response to chemotherapy as the only independent prognostic factor. Authors discuss the observation that a small dose of Vinorelbine per week has a positive impact upon survival, even if no significant response rate is obtained.

In the study on the impact of Vinorelbine for LS of advanced NSCLC, the TNM stages had no prognostic role for survival. The explanation given by the authors is related to the multiple complicated medical conditions that resulted in the early demise of certain patients with less advanced stages.

This issue occurred also in our study for which we have an explanation besides the fact that it is a retrospective study where patients are over-selected and non-randomized and significant biases may occur.

Analysis of the database of France is regarding LS with cancer. This analysis showed that in comparison to small cell lung cancer (SCLC), NSCLC may have a long-term survival also without treatment.

Hiroaki Satoh and collaborators concluded in their study that a lot of 12.8% and another lot of 6.4% patients treated within a period of 9 years survived more than 2 and above 3 years, respectively. All these patients have had a performance status of 0 or 1 and had a chemotherapy line I with a base of platinum salts. Patients subsequently received also Gefitinib. By a mono-varied analysis it was proven that a good performance status and therapy with Gefitinib are good prognostic factors for survival. The impact of treatment with Gefitinib for survival in NSCLC patients is also assessed in another Japanese study.
An unexpected result is our study was the better survival in stage IV versus stage III TNM. This is probably an error resulting from the over-selection of patients, but that may also have an explanation related to the interference of old and new TNM staging used for these patients. Cristina P. Rodriguez shows that there could be an error of 10-15% in staging by trying to restaging the patients classified by the old TNM system.[12]

For patients who have had cerebral metastases, the prognostic was poorer in our study, but as we had few cases, we cannot draw a conclusion close to reality. In studies the scope of which was the analysis of long-term survival of patients with NSCLC and cerebral metastases it was revealed that a survival of 3 years and more is a rarity.[13,14]

Another retrospective study for LS in NSCLC differs from our study by the fact that it is destined also to incipient stages of NSCLC that certainly have another evolution and prognostic. Authors highlighted the large heterogeneity of LS patients that cannot result in the identification of joint factors that should have the prognostic value. This observation makes us think about a genetic factor that could play a role in the determination of a particular evolution.[13]

Other prognostic factors for survival of more than 2 years were: the presence of few metastatic sites, the absence of bone metastases, the performance status ECOG 0-1, cancer tumors controlled by the first and second line of chemotherapy, maintenance therapy, the time until the first progression of the tumor longer than 3 months, nominal values of LDH, values above 11 g/dl of hemoglobin on the first progression of the tumor.[16,17]

CONCLUSIONS

The survival average of 4.2 years is consistent with the current therapeutic effect regarding advanced NSCLC, namely to make a chronic evolution of this disease.

The heterogeneity of cases studied in clinical view, with a similar prognostic, can lead us to the conclusion that there might be a joint genetic structure of these patients.

The better survival of cases in stage IV versus stage IIIB could be caused by the differences in the TNM classification, as certain patients are classified according to the old TNM stages, which could have determined a sub-stadalization.

Survival according to age revealed the fact that patients aged above 65 had a better survival and this is a result confirmed also in other studies.

Another conclusion that may be drawn further to analyzing the data of this study is the fact that the increased number of chemotherapy lines has had a positive impact upon survival.

The administration of Erlotinib resulted in an increase of survival in this lot of patients regardless of treatment line. Administration of chemotherapy after Erlotinib was efficient and beneficial in favor of increasing survival.

REFERENCES