Evolution of performance status, body mass index, and six-minute walk distance in advanced lung cancer patients undergoing chemotherapy*

Evolução do status de performance, índice de massa corpórea e distância percorrida no teste de caminhada de seis minutos em pacientes com câncer de pulmão avançado submetidos à quimioterapia

Luciana Machado, Ivete Alonso Bredda Saad, Helen Naemi Honma, André Moreno Morcillo, Lair Zambon

Abstract

Objective: To evaluate the effect of chemotherapy on the physical condition of patients with advanced lung cancer. Methods: We evaluated 50 patients with non-small cell lung cancer (in stages IIIB and IV) and Eastern Cooperative Oncology Group (ECOG) performance status scale scores between zero and two. All patients underwent chemotherapy using paclitaxel and platinum derivatives and were evaluated at three time points (prechemotherapy, postchemotherapy and six months after starting the treatment), at which the ECOG scale, the body mass index (BMI) and the six-minute walk distance (6MWD) were assessed. Results: Of the 50 patients included in the study, 14 died, 5 were excluded due to the worsening of their performance status, and 31 completed the six-month follow-up. There was no statistically significant difference between the time points of assessment for BMI (prechemotherapy vs. postchemotherapy, p = 1.00; and prechemotherapy vs. six months later, p = 0.218) or for 6MWD. Performance status improved, and this was especially due to the increase in the number of asymptomatic patients after the six-month follow-up (p = 0.031). Conclusions: Chemotherapy had a beneficial effect on the performance status of the patients. No significant changes in BMI or 6MWD were found during the study period, which might suggest the maintenance of the physical condition of the patients.

Keywords: Drug therapy; Lung neoplasms; Exercise tolerance.

Resumo

Objetivo: Avaliar o efeito da quimioterapia sobre a condição física de pacientes com câncer de pulmão avançado. Métodos: Foram avaliados 50 pacientes com câncer de pulmão não pequenas células nos estágios IIIB e IV e com status de performance segundo a escala do Eastern Cooperative Oncology Group (ECOG) entre zero e dois. Todos receberam quimioterapia com as drogas paclitaxel e derivados da platina e foram avaliados em três momentos (pré-quimioterapia, pós-quimioterapia e seis meses após o início do tratamento), nos quais a escala ECOG, o índice de massa corpórea (IMC) e a Distância percorrida no Teste de Caminhada de Seis minutos (DTC6) foram avaliados. Resultados: Dos 50 pacientes incluídos, 14 foram ao óbito, 5 foram excluídos do estudo por apresentar piora do status de performance, e 31 concluíram o seguimento de seis meses. Não houve diferença estatisticamente significativa para o IMC (p = 1,00, pré-quimioterapia vs. pós-quimioterapia; e p = 0,218, pré-quimioterapia vs. seis meses após) ou para a DTC6 entre os momentos de avaliação. O status de performance melhorou, principalmente com o aumento do número de pacientes assintomáticos após seis meses de acompanhamento (p = 0,031). Conclusões: O uso de quimioterapia teve um efeito benéfico no status de performance dos pacientes. Não houve alterações no IMC ou na DTC6 durante o período do estudo, o que pode sugerir a manutenção da condição física dos pacientes.

Descritores: Quimioterapia; Neoplasias pulmonares; Tolerância ao exercício.

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Introduction

Lung cancer is a serious public health problem. It is currently the leading cause of cancer-related mortality, accounting for more than one million deaths worldwide. [1] It was estimated that, in 2008, there were 215,000 new cases of lung cancer, as well as 161,500 deaths from the disease, in the United States. [10] Estimates for Brazil indicate that 27,000 individuals (18,000 males and 9,000 females) had lung cancer in 2008 and 2009. [3] The comparison between the smoking populations in the two countries indicates that the incidence of lung cancer in Brazil is underestimated.

Although there have been advances in clinical research into the treatment of cancer, the mortality rate from lung cancer has not decreased significantly in the last three decades, principally because there are no methods for establishing an early diagnosis of this type of neoplasia. Because the vast majority of cases are diagnosed at advanced stages, [4] principally in Brazil. Although chemotherapy and radiotherapy are widely used, the role of these types of treatment in increasing survival and principally in improving quality of life is still subjective. [5,6]

In patients with advanced lung cancer, chemotherapy has been shown to have advantages over palliative treatment. [5] However, these patients experience symptoms and side effects, such as nausea, vomiting, infection, loss of appetite, and fatigue, which have been associated with reduced exercise capacity, inactivity, and impaired quality of life. [8-11]

The objective of the present study was to analyze the effect of chemotherapy on the physical condition of patients with advanced non-small cell lung cancer (NSCLC) by monitoring the evolution of the performance status (PS), as well as by evaluating body mass index (BMI) and assessing functional capacity with the six-minute walk test (6MWT).

Methods

This was a nonrandomized longitudinal clinical trial that evaluated the impact of chemotherapy on patients with lung cancer. Between May of 2006 and July of 2008, we evaluated 50 adult patients with NSCLC (stage IIIB or IV) and Eastern Cooperative Oncology Group (ECOG) PS scale scores between 0 and 2. All of the patients received clinical treatment with paclitaxel and platinum derivatives. The drugs were administered in a single dose, every three weeks, for four cycles. In each cycle of chemotherapy, patients < 70 years of age received paclitaxel (175 mg/m²) and cisplatin (80 mg/m²), whereas those ≥ 70 years of age received paclitaxel (200 mg/m²) and carboplatin (area under the curve/5 = 300-600 mg/m²).

The initial exclusion criteria were as follows: having previously undergone lung surgery; and presenting with brain metastasis. During the study period, patients who presented with an ECOG PS score > 2 were excluded, in accordance with the treatment protocol of our facility, where chemotherapy is not given to such patients. [7] Therefore, the only exclusion criterion adopted during the follow-up visits was presenting with an elevated ECOG PS scale score (>2).

All of the patients gave written informed consent. The study was approved by the local research ethics committee (ruling no. 209/2006).

The patients were selected during medical visits to the Lung Cancer Outpatient Clinic of the State University at Campinas Hospital das Clínicas, located in the city of Campinas, Brazil. After the inclusion criteria had been applied, the patients were evaluated and data were collected.

The evaluations and data collection were carried out at three time points: prechemotherapy; postchemotherapy (two weeks after the last cycle of chemotherapy); and six months after the start of treatment. The evaluation consisted of collecting personal data, determining PS, evaluating BMI, and administering the 6MWT.

In order to determine the PS, we used the ECOG scale, which measures the overall functional performance of patients, the score on which is also an important therapeutic parameter. Patients are classified by score, which ranges from 0 to 4: 0 = asymptomatic; 1 = presenting with disease symptoms but able to perform activities normally; 2 = symptomatic and often requiring outpatient treatment; 3 = bedridden for more than 50% of the time; and 4 = completely bedridden. [12]

The BMI was calculated as the weight in kilograms divided by the square of the height in meters (kg/m²). [13] The patients were divided into three groups: underweight (BMI <
As can be seen in Table 2, the baseline (prechemotherapy) ECOG scale results for the 50 patients evaluated were as follows: a score of 0 (asymptomatic) in 4 (8%); a score of 1 (symptomatic) in 33 (66%); and a score of 2 (symptomatic and requiring treatment) in 13 (26%).

The postchemotherapy ECOG scale scores revealed an increase in the number of asymptomatic patients. Of the 38 patients evaluated, 15 (39.5%) had a score of 0, 22 (57.9%) had a score of 1, and only 1 (2.6%) had a score of 2. At six months after the start of treatment, the distribution of the ECOG scale scores was similar to that observed for the postchemotherapy time point (Table 2).

Table 3 shows the comparison between the initial PS and the final PS. Of the 31 patients who completed the six months of follow-up, 4 (12.9%) presented worsening of the PS, the ECOG scale score increasing from 1 to 2 in 3 patients and from 0 to 1 in 1. In addition, 13 (41.9%) of the 31 patients maintained their prechemotherapy PS (ECOG scale score: 0 in 2 patients; and 1 in 11 patients), whereas the PS improved in 18 (58.1%), the ECOG scale score decreasing from 1 to 0 in 14 (45.2%) and from 2 to 1 in 4 (12.9%).

Table 1 - Characteristics of the study sample at the initial evaluation (n = 50).

<table>
<thead>
<tr>
<th>Variable</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>18 (36)</td>
</tr>
<tr>
<td>Male</td>
<td>32 (64)</td>
</tr>
<tr>
<td>Age bracket, years</td>
<td></td>
</tr>
<tr>
<td>40-49</td>
<td>6 (12)</td>
</tr>
<tr>
<td>50-59</td>
<td>12 (24)</td>
</tr>
<tr>
<td>60-69</td>
<td>21 (42)</td>
</tr>
<tr>
<td>≥70</td>
<td>11 (22)</td>
</tr>
<tr>
<td>Stage</td>
<td></td>
</tr>
<tr>
<td>IIIB</td>
<td>35 (70)</td>
</tr>
<tr>
<td>IV</td>
<td>15 (30)</td>
</tr>
<tr>
<td>Performance status</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>4 (8)</td>
</tr>
<tr>
<td>1</td>
<td>33 (66)</td>
</tr>
<tr>
<td>2</td>
<td>13 (26)</td>
</tr>
<tr>
<td>Smoker</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>42 (84)</td>
</tr>
<tr>
<td>No</td>
<td>8 (16)</td>
</tr>
</tbody>
</table>

* Determined by the Eastern Cooperative Oncology Group Performance Status scale.
Evolution of performance status, body mass index, and six-minute walk distance in advanced lung cancer patients undergoing chemotherapy


Table 2 - Evaluation of the Eastern Cooperative Oncology Group Performance Status scale scores of patients at the three evaluation time points.

<table>
<thead>
<tr>
<th>ECOG scale score</th>
<th>Prechemotherapy</th>
<th>Postchemotherapy</th>
<th>Six months after the start of treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td>0</td>
<td>4 (8.0)</td>
<td>15 (39.5)</td>
<td>12 (38.7)</td>
</tr>
<tr>
<td>1</td>
<td>33 (66.0)</td>
<td>22 (57.9)</td>
<td>16 (51.6)</td>
</tr>
<tr>
<td>2</td>
<td>13 (26.0)</td>
<td>1 (2.6)</td>
<td>3 (9.7)</td>
</tr>
<tr>
<td>Total</td>
<td>50 (100)</td>
<td>38 (100)</td>
<td>31 (100)</td>
</tr>
</tbody>
</table>

ECOG: Eastern Cooperative Oncology Group.

Table 4 shows that the mean BMI was 23.4 ± 5.0 (range, 14.8-39.4 kg/m²) at the prechemotherapy time point, 23.2 ± 4.8 kg/m² (range, 15.5-38.0 kg/m²) at the postchemotherapy time point, and 23.9 ± 5.7 kg/m² (14.4-41.2 kg/m²) at six months after the start of treatment. Of the 38 patients who completed the first two phases of the study, 10 (26.3%) had been classified as underweight at baseline, whereas 14 (36.8%) had been classified as normal-weight and 14 (36.8%) had been classified as overweight. At the postchemotherapy time point, these proportions were, respectively, 10 (26.3%), 18 (47.4%), and 10 (26.3%), respectively. For the evaluation of the impairment of the nutritional status, we compared the proportion of patients in the underweight group with the proportion of patients in the remaining groups. The proportion of patients in the underweight group was the same at the prechemotherapy and postchemotherapy time points (p = 1.000; two-tailed binomial distribution).

At six months after the start of treatment, 9 patients (29%) were in the underweight group, 13 (42%) were in the normal-weight group, and 9 (29%) were in the overweight group. It should be pointed out that, at six months after the start of treatment, 1 patient who was initially in the underweight group migrated to the normal-weight group and 4 patients who were initially in the normal-weight group migrated to the underweight group (p = 0.218; two-tailed binomial distribution).

The mean six-minute walk distance (6MWD) at the three time points (prechemotherapy, postchemotherapy, and six months after the start of treatment) was 431.5 ± 75.9 m (range, 280-585 m), 437 ± 79.6 m (range, 180-550 m), and 431.5 ± 74.1 m (range, 280-585 m), respectively. One of the patients declined to perform the 6MWT at the final evaluation. The differences in mean 6MWD between the time points were not statistically significant (p = 0.781; Table 5).

Discussion

The combination of palliative treatment and chemotherapy, when compared with palliative treatment in isolation, has been shown to be effective in increasing the survival of patients with advanced lung cancer.(17) For patients with stage IIIB or IV NSCLC, chemotherapy regimens based on platinum derivatives have been shown to be beneficial in terms of survival and quality of life.(18,19) However, the treatment can have side effects and can impede the performance of activities of daily living.(11,20,21)

The present study monitored a group of patients with advanced NSCLC, with the objective of observing the evolution of aspects related to physical performance during chemotherapy and the effects of chemotherapy at six months after the start of treatment. We used simple instruments of measurement that can be easily employed in routine outpatient practice, instruments that can aid professionals in collecting information and identifying the consequences of the treatment.

The results of the present study showed that a large number of patients died, which reduced the sample size over the follow-up period. In fact, this was expected, since only patients with advanced lung cancer were included in the present study. Unfortunately, 75% of the patients who present to our pulmonology-oncology facility have stage IIIB or IV lung cancer. In the study sample, 30% of the patients...
this was especially due to the increase in the number of asymptomatic patients from baseline to six months after the start of treatment (4 vs. 12), a finding that is in agreement with those of other studies.\(^{(7,19)}\)

Weight loss is a common symptom in patients with lung cancer; however, the etiology of such weight loss has yet to be fully understood.\(^{(26)}\) In the present study, for the evaluation of nutritional impairment, we considered the proportion of patients in each weight group at the three evaluation time points. The proportion of patients included in the underweight group was equal at the three evaluation time points. There were no significant differences among the three nutritional status groups at any of the three evaluations, which was evidence that there was no nutritional impairment after chemotherapy or at six months after the start of treatment (Table 4).

The 6MWT is used to evaluate submaximal exercise capacity and reproduce the effort put forth during routine activities. The 6MWT evaluates the overall and integrated responses of all systems involved in the exercise. However, it does not provide specific information regarding the mechanism of exercise limitation. The 6MWT is a simple, easily applicable, validated test that has been widely used in patients with respiratory and heart diseases.\(^{(14)}\)

Although lung cancer is among the most common malignancies, the impact of chemotherapy on the exercise capacity of patients presented with distant metastasis. New strategies should be developed in order to allow earlier diagnosis, thus increasing the chances of patient survival.\(^{(22-24)}\)

Determination of the PS is of great importance to the prognosis of cancer patients, and presenting with a PS within a given range has often been used as an inclusion criterion in clinical trials.\(^{(25)}\) The patients included in the present study presented with preserved functional capacity, as evidenced by their ECOG scale scores, which ranged from 0 to 2. This criterion was chosen because adverse effects are more common in patients with an ECOG scale score > 2,\(^{(18)}\) and the inclusion of such patients might have interfered with the monitoring of the clinical evolution and with the subsequent analysis of the effects of the treatment.

Of the 50 patients with advanced lung cancer who received chemotherapy, 14 (28\%) showed improvement in the PS, 13 (26\%) remained stable, and 23 (46\%) showed worsening of the PS or died before or after the six-month follow-up period. It is of note that 54\% of the patients investigated in the present study showed improvement in the PS or remained stable at the end of the six-month follow-up, which suggests that chemotherapy is beneficial for patients with advanced lung cancer.

As can be seen in Table 3, the analysis of the 31 patients who completed the six-month follow-up showed that the use of chemotherapy was clearly beneficial for the PS (\(p = 0.031\)), and

\[
\begin{array}{|c|c|c|}
\hline
\text{Group} & \text{Prechemotherapy} & \text{Postchemotherapy} \\
\hline
\text{Underweight, n (%)} & 10 (26.3) & 10 (26.3) & 9 (29.0) \\
\text{Normal-weight, n (%)} & 14 (36.8) & 18 (47.4) & 13 (42.0) \\
\text{Overweight, n (%)} & 14 (36.8) & 10 (26.3) & 9 (29.0) \\
\hline
\text{Total, n [%]} & 38 (100.0) & 38 (100.0) & 31 (100.0) \\
\hline
\end{array}
\]

\(^{*}p = 1.00\) (prechemotherapy vs. postchemotherapy); \(^{*}p = 0.218\) (prechemotherapy vs. six months after the start of treatment); two-tailed binomial distribution. \(^{*}\)Patients who did not complete at least two of the three phases of the study were excluded from this analysis.

\[
\begin{array}{|c|c|c|c|c|}
\hline
\text{Time point} & \text{Patients, n} & \text{Mean ± SD} & \text{Median} & \text{Range} & \text{Interquartile range} \\
\hline
\text{Prechemotherapy} & 30 & 431.3 ± 75.9 & 435.0 & 280.0-585.0 & 365.0-490.0 \\
\text{Postchemotherapy} & 30 & 433.2 ± 86.7 & 437.5 & 180.0-550.0 & 380.0-505.0 \\
\text{Six months after the start of treatment} & 30 & 424.4 ± 72.5 & 420.0 & 270.0-572.0 & 380.0-465.0 \\
\hline
\end{array}
\]

\(p = 0.781\); the Friedman test.
with NSCLC has yet to be fully understood. In the present study, the 6MWT results allowed us to evaluate whether patients were able to perform their activities of daily living, such as walking, as well as aiding us in identifying the factors involved in the changes in the functional capacity of patients with advanced NSCLC who received chemotherapy.

The prognostic value of the 6MWT in patients with NSCLC has been investigated, and the results have shown that the 6MWD decreases after the second cycle of chemotherapy and that a 6MWD ≥ 400 m can be a positive prognostic factor for these patients.[27] A recent study investigating patients with NSCLC who were evaluated before and one month after chemotherapy reported that there was no significant reduction in the 6MWD after the treatment,[26] a finding that was similar to those of the present study, in which there was no reduction in the 6MWD after chemotherapy or at six months after the start of treatment.

We conclude that chemotherapy did not reduce the body mass or submaximal exercise capacity of patients with advanced NSCLC. Chemotherapy was beneficial for the PS, and this was principally due to the increase in the number of asymptomatic patients after the six-month follow-up. New studies, involving larger samples, are needed in order to confirm these findings.

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