Assessment of quality of life in patients with advanced non-small cell lung carcinoma treated with a combination of carboplatin and paclitaxel*

Avaliação da qualidade de vida de pacientes com carcinoma pulmonar de células não pequenas em estágio avançado, tratados com carboplatina associada a paclitaxel

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Abstract

Objective: Non-small cell lung carcinoma (NSCLC) is the most common type of lung cancer. Most patients are diagnosed at an advanced stage, palliative chemotherapy therefore being the only treatment option. This study was aimed at evaluating the health-related quality of life (HRQoL) of advanced-stage NSCLC patients receiving palliative chemotherapy with carboplatin and paclitaxel. Methods: This was a multiple case study of advanced-stage NSCLC outpatients receiving chemotherapy at a public hospital in Rio de Janeiro, Brazil. The European Organization for Research and Treatment of Cancer Core Quality of Life Questionnaire was used in conjunction with its supplemental lung cancer-specific module in order to assess HRQoL. Results: Physical and cognitive functioning scale scores differed significantly among chemotherapy cycles, indicating improved and worsened HRQoL, respectively. The differences regarding the scores for pain, loss of appetite, chest pain, and arm/shoulder pain indicated improved HRQoL. Conclusions: Chemotherapy was found to improve certain aspects of HRQoL in patients with advanced-stage NSCLC. Keywords: Carcinoma, non-small-cell lung; Quality of life; Palliative care; Carboplatin; Paclitaxel.

Resumo

Objetivo: O carcinoma pulmonar de células não pequenas (CPCNP) é tipo mais comum de câncer de pulmão. Como a maioria dos pacientes é diagnostizada em estágio avançado, a quimioterapia paliativa é a única opção de tratamento. Este estudo avaliou a qualidade de vida relacionada à saúde (QVRS) de pacientes com CPCNP avançado no decorrer da quimioterapia paliativa com carboplatina e paclitaxel. Métodos: Trata-se de um estudo de casos múltiplos de pacientes ambulatoriais com CPCNP em estágio avançado recebendo quimioterapia em um hospital público no Rio de Janeiro (RJ). Para a avaliação da QVRS, foram usados o European Organization for Research and Treatment of Cancer Core Quality of Life Questionnaire e seu módulo específico para câncer de pulmão. Resultados: Houve diferenças significativas na pontuação nas escalas de capacidade física e cognitiva durante a quimioterapia, indicando melhora e piora da QVRS, respectivamente. As diferenças na pontuação nos itens dor, perda de apetite, dor no tórax e dor no braço ou ombro indicaram melhora da QVRS. Conclusões: Observou-se que a quimioterapia melhora alguns aspectos da QVRS de pacientes com CPCNP avançado. Descritores: Carcinoma pulmonar de células não pequenas; Qualidade de vida; Cuidados paliativos; Carboplatin; Paclitaxel.

Introduction

For 2015, the estimated incidence of tracheal, lung, and bronchial cancer in the Brazilian population is 27,330 cases. Lung neoplasms are the most common cancers in the world, accounting for nearly 15% of all cancers; the death rate is high, and the 5-year survival rate is less than 15%. Non-small cell lung carcinoma (NSCLC) has the highest incidence of all lung neoplasms, accounting for 80-85% of all cases of lung...
cancer.\(^2\) The biology of NSCLC and delayed diagnosis are the main reasons why NSCLC is the leading cause of cancer death worldwide.\(^3\)

It is believed that 70% of patients present with advanced disease at diagnosis,\(^4\) and palliative chemotherapy is often indicated.\(^5\) Its goal is to control the signs and symptoms of advanced disease, which can affect the performance status, quality of life, and survival of patients.\(^6,8,9\)

Currently, the palliative treatment of advanced-stage (stage IIIB and stage IV) NSCLC frequently involves the use of platinum coordination compounds such as carboplatin in combination with other antineoplastics, such as paclitaxel.\(^2\) Nevertheless, the scientific literature is inconclusive regarding the impact of these drugs on the quality of life of patients with advanced-stage NSCLC,\(^6,8\) which is an underexplored topic in clinical practice.

Health-related quality of life (HRQoL) can be described as the perception of patients of their own physical well-being, daily activities, psychological well-being, social relations, and disease symptoms.\(^9,10\) Assessment of patients with lung cancer is of great importance because of the increased morbidity and mortality associated with NSCLC.\(^11-13\)

Studies have indicated that quality of life assessment is the main predictor of survival, describing it as a relevant outcome in the context of palliative chemotherapy.\(^4,13\) The use of questionnaires and periodic review of HRQoL facilitate communication between the health care team and the patients, optimizing the treatment.\(^13\)

The objectives of the present study were to evaluate the HRQoL of advanced-stage NSCLC patients receiving palliative chemotherapy with carboplatin-paclitaxel and to promote a scientific discussion of this issue, which is currently underexplored, particularly in Brazil.

**Methods**

This was a multiple case study with a prospective descriptive analytical design. The study was conducted between May and July of 2013 at the adult chemotherapy outpatient clinic of a public cancer hospital located in the city of Rio de Janeiro, Brazil. The study included advanced-stage lung cancer patients receiving chemotherapy with carboplatin (area under the curve = 4-6) and paclitaxel (175 mg/m\(^2\)), with a 21-day interval between cycles. Patients with IIIB or IV stage NSCLC were sequentially enrolled in the study. Patients under 18 years of age were excluded, as were those who had undergone chemotherapy less than 5 years prior to the study, those who were diagnosed with a second primary malignancy, those who were unable to answer the questions clearly, and those who were already participating in another research protocol.

For the evaluation of quality of life, the instruments used were the European Organization for Research and Treatment of Cancer Core Quality of Life Questionnaire (EORTC QLQ-C30) and its supplemental lung cancer-specific module (QLQ-LC13),\(^14\) both of which had previously been translated into Portuguese and validated for use in Brazil.\(^12\) The EORTC QLQ-C30 consists of five functional scales evaluating physical, role, emotional, cognitive, and social functioning; global health status/QoL; three scales measuring symptoms (nausea/vomiting, fatigue, and pain); and 6 items assessing the occurrence and severity of symptoms related to cancer and its treatment.\(^4,11,12\) The QLQ-LC13 consists of 13 questions regarding the symptoms associated with lung cancer and the most common reactions to the medical treatment of lung cancer.

All HRQoL scores were calculated in accordance with the rules established by the EORTC.\(^9\) Higher scores on the functional and quality of life scales translated to better HRQoL, whereas higher scores on the symptom scales translated to worse HRQoL. For a better understanding of the results, the symptom scales and items were inverted so that higher scores translated to fewer reports of symptoms and better quality of life.\(^15\)

In each chemotherapy cycle, all HRQoL evaluations were used as a unit of analysis. The questionnaires were completed by the patients themselves before the 1st, 2nd, and 4th cycles of chemotherapy in order to compare pre-chemotherapy HRQoL, HRQoL during chemotherapy, and post-chemotherapy HRQoL. When asked to, the interviewer read the questions out to patients.

We collected data on the following sociodemographic and clinical variables: age; gender; self-reported race; marital status; number of years of schooling (0-7 years or ≥ 8 years); occupation; histological type; clinical stage; performance status; comorbidities; number of
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Adenocarcinoma was the most prevalent type of NSCLC in the study population, being found in 56.3% of the participants. In addition, 62.5% had stage IV NSCLC.

Most (75%) of the participants were found to have a performance status of 1 before the 1st cycle of chemotherapy. In addition, nearly 56% had previously diagnosed chronic diseases and were on polypharmacy (≥ 5 different types of drugs).

Of the 16 participants, 13 (81.3%) declared themselves to be smokers or former smokers and 7 (53.9%) reported smoking at least 20 cigarettes

| Patient characteristic | n | %  |
|------------------------|---|----|
| Age, years             |   |    |
| < 65                   | 6 | 37.5|
| ≥ 65                   | 10| 62.5|
| Gender                 |   |    |
| Male                   | 9 | 56.3|
| Female                 | 7 | 43.8|
| Race                   |   |    |
| White                  | 9 | 56.3|
| Black                  | 3 | 18.8|
| Others                 | 4 | 25.0|
| Histological type of NSCLC | |    |
| Adenocarcinoma         | 9 | 56.3|
| Others                 | 7 | 43.8|
| Stage at diagnosis     |   |    |
| IIIB                   | 6 | 37.5|
| IV                     | 10| 62.5|
| Performance status     |   |    |
| 1                      | 12| 75.0|
| 2                      | 4 | 25.0|
| Comorbidities          |   |    |
| Yes                    | 9 | 56.3|
| No                     | 7 | 43.8|
| Number of drugs used   |   |    |
| < 4                    | 1 | 6.3 |
| 5-7                    | 9 | 56.3|
| 8-10                   | 6 | 37.5|
| Family history of cancer | |    |
| Yes                    | 8 | 50.0|
| No                     | 8 | 50.0|
| History of smoking     |   |    |
| Yes                    | 13| 81.3|
| No                     | 3 | 18.8|
| History of alcoholism  |   |    |
| Yes                    | 8 | 50.0|
| No                     | 8 | 50.0|

NSCLC: non-small cell lung carcinoma.

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Taking into consideration the criteria proposed by Osoba et al.\cite{15} for interpreting the significance of changes in HRQoL scores and the different numbers of patients at each assessment time point, we found a moderate change (of 11.7 points) in the role functioning score between the 1st and 4th cycles of chemotherapy (Figure 1C), a finding that shows a trend toward an improvement in HRQoL.

There were no changes in the global quality of life/QoL scores between the 2nd and 4th cycles of chemotherapy. However, there was a small change (of 6.3 points) in the global quality of life/QoL scores between the 1st and 2nd cycles of chemotherapy (Figure 1A), showing improved HRQoL in the 1st cycle of chemotherapy.

The symptom scale scores and the scores on the items assessing the occurrence and severity per day. In addition, 50% reported consuming or having consumed alcoholic beverages.

The mean scores on the EORTC QLQ-C30 functional and quality of life scales were ≥ 59.8. This indicates that the study participants had lower HRQoL scores in the 1st cycle of chemotherapy (Table 2).

Figure 1 shows a comparison of the mean EORTC QLQ-C30 functional scale scores in each treatment cycle. There were no significant differences among the scores, the exception being the physical functioning scale scores in the 1st and 2nd cycles (p = 0.002; Figure 1A), showing improved HRQoL in the 2nd cycle of chemotherapy, and in the 1st and 4th cycles (p = 0.028; Figure 1C), showing improved HRQoL in the 4th cycle of chemotherapy.
Table 2 - Mean European Organization for Research and Treatment of Cancer Core Quality of Life Questionnaire and European Organization for Research and Treatment of Cancer Core Quality of Life Questionnaire supplemental lung cancer-specific module scores during chemotherapy.

| Questionnaire Module/Item | 1st cycle (n = 16) | 2nd cycle (n = 16) | 4th cycle (n = 13) |
|--------------------------|--------------------|--------------------|--------------------|
| EORTC QLQ-C30 Functional scale | | | |
| Global health status/QoL | 67.2 ± 28.0 | 62.5 | 73.4 ± 21.6 | 79.2 | 77.6 ± 21.9 | 83.3 |
| Physical functioning | 59.8 ± 27.7 | 60.0 | 80.4 ± 18.6 | 83.3 | 81.5 ± 20.9 | 93.3 |
| Role functioning | 70.7 ± 39.7 | 91.5 | 79.2 ± 34.2 | 100.0 | 91.0 ± 22.2 | 100.0 |
| Cognitive functioning | 79.0 ± 35.9 | 100.0 | 85.4 ± 24.2 | 100.0 | 73.1 ± 30.1 | 83.3 |
| Emotional functioning | 63.9 ± 28.6 | 75.0 | 73.4 ± 25.5 | 75.0 | 66.0 ± 32.2 | 83.3 |
| Social functioning | 91.6 ± 16.3 | 100.0 | 96.9 ± 12.5 | 100.0 | 91.0 ± 18.8 | 100.0 |
| Symptom scale | | | |
| Fatigue | 55.6 ± 36.7 | 66.7 | 69.5 ± 27.4 | 66.7 | 77.8 ± 20.8 | 88.9 |
| Pain | 60.4 ± 35.4 | 58.4 | 80.2 ± 28.0 | 81.7 | 78.2 ± 23.9 | 83.3 |
| Dyspnea | 62.5 ± 40.1 | 66.7 | 75.0 ± 35.5 | 100.0 | 74.4 ± 38.9 | 100.0 |
| Insomnia | 77.1 ± 35.9 | 100.0 | 72.9 ± 38.9 | 100.0 | 71.8 ± 38.1 | 100.0 |
| Appetite loss | 41.7 ± 46.4 | 16.5 | 79.2 ± 40.1 | 100.0 | 79.5 ± 39.8 | 100.0 |
| Nausea/vomiting | 91.7 ± 16.1 | 100.0 | 89.6 ± 21.0 | 100.0 | 92.3 ± 18.8 | 100.0 |
| Constipation | 47.9 ± 50.1 | 33.4 | 64.6 ± 44.7 | 100.0 | 76.9 ± 43.9 | 100.0 |
| Diarrhea | 100.0 ± 0.0 | 100.0 | 91.7 ± 25.8 | 100.0 | 92.3 ± 27.7 | 100.0 |
| Financial difficulties | 70.8 ± 41.9 | 100.0 | 83.3 ± 32.2 | 100.0 | 87.2 ± 25.6 | 100.0 |
| QLQ-LC13 Dyspnea | 68.8 ± 37.0 | 83.4 | 75.7 ± 32.5 | 88.9 | 86.3 ± 25.3 | 100.0 |
| Cough | 47.9 ± 40.3 | 50.0 | 58.3 ± 35.5 | 66.7 | 48.7 ± 44.3 | 66.7 |
| Hemoptysis | 93.8 ± 13.4 | 100.0 | 87.5 ± 24.0 | 100.0 | 94.9 ± 18.5 | 100.0 |
| Sore mouth | 89.6 ± 29.1 | 100.0 | 97.9 ± 8.3 | 100.0 | 94.9 ± 12.5 | 100.0 |
| Dysphagia | 87.5 ± 24.0 | 100.0 | 93.8 ± 18.1 | 100.0 | 82.3 ± 27.7 | 100.0 |
| Peripheral neuropathy | 83.3 ± 29.8 | 100.0 | 77.1 ± 39.8 | 100.0 | 76.9 ± 39.4 | 100.0 |
| Alopecia | 97.9 ± 8.3 | 100.0 | 22.9 ± 33.8 | 0.0 | 53.8 ± 51.9 | 100.0 |
| Chest pain | 58.3 ± 46.4 | 83.4 | 85.4 ± 27.1 | 100.0 | 82.1 ± 37.6 | 100.0 |
| Arm/shoulder pain | 60.4 ± 45.9 | 83.4 | 81.3 ± 29.7 | 100.0 | 84.6 ± 29.2 | 100.0 |
| Pain in other body parts | 58.3 ± 49.4 | 100.0 | 77.1 ± 35.9 | 100.0 | 71.8 ± 42.7 | 100.0 |

of cancer-related symptoms were higher at the first assessment of quality of life, the exception being the scores for diarrhea. This indicates that the HRQoL of the study participants was worse at that time (Table 2).

Figure 2 shows a comparison of the mean EORTC QLQ-C30 symptom scores in each cycle of chemotherapy. There was little or no change in the scores during chemotherapy. There were significant differences in pain scores between the 1st and 2nd cycles of chemotherapy (p = 0.027; Figure 2A), as well as in the scores for loss of appetite between the 1st and 2nd cycles (p = 0.037; Figure 2A) and between the 1st and 4th cycles (p = 0.026; Figure 2C). There was a large change in the scores for constipation between the 1st and 4th cycles of chemotherapy (Figure 2C). There were moderate changes in the scores for fatigue, insomnia, and financial difficulties between the 1st and 4th cycles of chemotherapy. These changes suggest an improvement in all of the aforementioned HRQoL aspects except insomnia, which was reported more frequently in the 4th cycle of chemotherapy.

The QLQ-LC13 scores for dyspnea, cough, sore mouth, chest pain, arm/shoulder pain, and body pain were lower at the first assessment of HRQoL (i.e., in the 1st cycle of chemotherapy). Hemoptysis and alopecia were found to be more common and more severe at the second assessment of HRQoL, whereas dysphagia and peripheral neuropathy were found to be worse in the 4th cycle of chemotherapy.

Figure 3 shows a comparison of the mean QLQ-LC13 scores in each chemotherapy cycle. There was a significant improvement in chest
The use of structured methods for collecting data and the interpretation of the data brought internal validity to our conclusions, as did the use of multiple sources of evidence and the consistency between such evidence and the results of the study. The possibility of reproducing the present study and the use of statistical analysis brought greater reliability to the study, allowing us to make inferences. Therefore, the present study presents relevant data for the evaluation of clinical oncology patients and raises new hypotheses regarding the possible connections of clinical and sociodemographic variables with the quality of life of patients with advanced-stage NSCLC.

Discussion

In the study population, there was a predominance of White, married, male smokers or former smokers, with stage IV adenocarcinoma. The median age was 63.7 years. Although the logistics and operational aspects of data collection represented a limitation to the selection of study participants, the clinical and sociodemographic characteristics of the participants were consistent with those reported in the literature, ensuring the external validity of the study.

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Braun et al. (23) demonstrated that improvement in physical function was a predictor of survival in patients with lung cancer, confirming that every 10-point increase in physical function is associated with a 10% increase in survival time. However, the changes in the aforementioned aspects might have been influenced by factors such as the use of antineoplastic drugs and drugs for the management of symptoms, as well as by variables such as age.

With regard to the EORTC QLQ-C30 functional scale scores, we noted a trend toward stability at all assessment time points. Wintner et al. (22) stated that chemotherapy alone, regardless of the number of cycles, had no impact on the quality of life of patients with lung cancer. The authors found that the HRQoL scores remained unchanged throughout the treatment period, a finding that is consistent with ours.

Despite the demonstrated trend toward stability, a significant difference was observed regarding physical function improvement and cognitive function worsening. Braun et al. (23) demonstrated that improvement in physical function was a predictor of survival in patients with lung cancer, confirming that every 10-point increase in physical function is associated with a 10% increase in survival time. However, the changes in the aforementioned aspects might have been influenced by factors such as the use of antineoplastic drugs and drugs for the management of symptoms, as well as by variables such as age.

Figure 3 - Changes in mean European Organization for Research and Treatment of Cancer Core Quality of Life Questionnaire supplemental lung cancer-specific module (EORTC QLQ-LC13) scores. In A, differences in mean EORTC QLQ-LC13 scores between the 1st and 2nd cycles of chemotherapy (n = 16); in B, differences in mean EORTC QLQ-LC13 scores between the 2nd and 4th cycles of chemotherapy (n = 13); and in C, differences in mean EORTC QLQ-LC13 scores between the 1st and 4th cycles of chemotherapy (n = 13).
gender, performance status, histological type, stage of the disease, and preexisting comorbidities.

Gronberg et al.\(^{[24]}\) reported that, among NSCLC patients receiving platinum-based chemotherapy, clinical complications appear to be more common in those with severe comorbidities than in those without. Larsson et al.\(^{[25]}\) demonstrated significant associations of HRQoL with performance status, age, gender, and disease stage, as well as with EORTC QLQ-C30 and QLQ-LC13 symptom scales and items. Quinten et al.\(^{[26]}\) found a correlation between patient-reported physical function and performance status, raising questions regarding the association between self-reported quality of life and the prediction of survival. However, further studies are needed in order to confirm these hypotheses.

In the present study we found moderate changes in the mean global health status/QoL scores between chemotherapy cycles, with a trend toward improved quality of life, when we used the criteria of Osoba et al.\(^{[16]}\) These findings differ from those of Braun et al.\(^{[23]}\) who demonstrated that HRQoL is worse in previously treated patients than in newly diagnosed patients, suggesting that chemotherapy has a negative impact on HRQoL.

With regard to the most common signs and symptoms experienced by the NSCLC patients investigated in the present study, the results showed an improvement in fatigue, pain, and appetite during chemotherapy, indicating low HRQoL at the first evaluation. Park et al.\(^{[19]}\) evaluated the HRQoL of NSCLC patients treated with chemotherapy after a surgical intervention and found no significant changes in fatigue or pain. However, appetite improved during treatment, a result that is similar to ours. Increased loss of appetite has been reported to be associated with shorter survival.\(^{[23]}\) Maric et al.\(^{[17]}\) reported that although chemotherapy had beneficial effects on fatigue, dyspnea, insomnia, and appetite loss, NSCLC patients undergoing chemotherapy had higher pain scores than did newly diagnosed NSCLC patients. Lin et al.\(^{[27]}\) demonstrated that concomitant occurrence and increased severity of the aforementioned symptoms have a negative impact on HRQoL.

We found no significant changes in the scores for nausea/vomiting and diarrhea when we compared the scores obtained at the first HRQoL assessment with those obtained subsequently. This might be due to the pharmacological characteristics of the drugs in the chemotherapy protocol. Literature data show a low incidence of the aforementioned symptoms when platinum coordination compounds are used in combination with paclitaxel, a factor that should be considered in the choice of drug therapy because it affects the quality of life of patients.\(^{[28]}\)

Alopecia is a very common side effect of antineoplastic drugs. The study participants reported increased occurrence of alopecia after the 1st chemotherapy cycle, a result that indicates low HRQoL. According to Bonassa and Molina,\(^{[29]}\) hair loss is the most devastating effect and can directly affect social and emotional aspects of the quality of life of patients undergoing chemotherapy.

Our finding of a moderate improvement in cough during chemotherapy is consistent with those of Rolke et al.\(^{[30]}\) and Park et al.,\(^{[19]}\) who reported that cough tends to improve during chemotherapy. Given that cough negatively influences HRQoL, there is a need for therapeutic interventions for the management of this symptom.\(^{[31]}\)

Rapid detection of the emergence or worsening of a sign or symptom through periodic assessment of HRQoL allows therapeutic interventions to be performed in a more immediate way, optimizing the treatment of cancer patients and, consequently, impacting their survival.\(^{[10,13]}\) However, the assessment of quality of life in daily clinical practice is little discussed in the literature, despite its recognized importance for monitoring the disease and improving communication between the health care team and the patient.\(^{[10,23,32]}\)

The present study explored self-reported quality of life in advanced NSCLC patients receiving chemotherapy, with the objective of gaining a better understanding of how chemotherapy with carboplatin and paclitaxel influences HRQoL. The importance of patient perception of their own health is highlighted within the context of the complexity of cancer, which is a disease that affects every dimension of life and the way in which individuals perceive the environment, the diagnosis, and the therapy.\(^{[10]}\) Therefore, the combination of periodic quality of life assessments and clinical practice should be more extensively discussed in the scientific literature in order to improve the understanding of aspects that define patient health and the benefits arising from it. Although the changes in HRQoL scores between chemotherapy cycles were small, chemotherapy
was found to improve the HRQoL of the study participants, having a greater impact on physical and cognitive functioning and on cancer-related symptoms such as pain and loss of appetite.

With regard to the state of the art, the present study can be considered innovative because it provides elements that are essential to the assessment of quality of life in clinical practice. Further studies should be conducted in order to evaluate the association of sociodemographic and clinical variables such as polypharmacy and comorbidities with aspects of the quality of life of patients undergoing chemotherapy. Because of their extensive knowledge of drugs and their toxicity profile, pharmacists should be involved in studies of quality of life assessment, analyzing the connection between drug therapy and the severity of signs and self-reported symptoms, given their impact on certain aspects of HRQoL.

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