

Research Paper

Monitoring changes in quality of life in patients with lung cancer under treatment with chemotherapy and co administration of zoledronic acid by using specialized questionnaires

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Abstract

Background: Due to the severity of the primary disease in patients with lung cancer, quality of life (QoL) is often overlooked. Factors that form QoL should be taken in consideration when planning the appropriate treatment and determining therapy targets, because of the increasing frequency of bone metastasis leading to high levels of pain. Purpose of this study is to assess quality of life in patients with lung cancer, before and after treatment combined with zoledronic acid.

Methods and materials: QoL was assessed in 80 patients (49 males-31 females), of which 45 developed bone metastasis. Prior and post treatment (with co administration of zoledronic acid) seven reliable scales: Pittsburgh Sleep Quality index (PSQI), Epworth Sleeping Scale (ess), Dyspnea Scale (ds), Fatigue Severity Scale (FSS), Brief Pain Inventory (BPI), Fact-G scale for sleep quality and EQ-5D for general health condition.

Results: Statistically positive correlations were verified between PSQI-DS, PSQI-FSS, BPI-ESS, DS-FSS, DS-BPI and BPI-FSS ($p < 0,005$) prior and post treatment. Patients sleep quality was improved, pain levels decreased and betterment in quality of life was marked ($p < 0,001$). Although significant decrease in fatigue levels was observed ($p < 0,001$) there has been an increase in dyspnea symptoms ($p < 0,001$).

Conclusions: Significant improvement was apparent when zoledronic acid was co administered in any treatment in patients with lung cancer. Sleep quality, fatigue and pain parameters also improved, with no positive impact on the symptoms of dyspnea.

Key words: sleep quality, lung cancer, bone metastasis, zoledronic acid

Introduction

Quality of life is a factor that consists of many parameters and unfortunately, its importance is overlooked in severe diseases like lung cancer, due to the primary disease and the adjacent symptoms.[1] In cases where conservative (symptomatic) treatment does not prolong life expectancy, like lung cancer, our main concern is to improve the QoL and relief patients from their symptoms as many of them are elderly with complex medical history and high rates of morbidity.[2] Symptoms in patients with cancer regardless type, classification and treatment are persistent and cause fatigue to any individual.[3] In particular, pain and fatigue represent two of the most important issues of a cancer patient with the latter affecting both the way of life and psychological condition, interfering with daily functionality.[4] Limitations to daily activities combined with severity of the disease can often lead to depression, which is often overlooked. Data from clinical studies show that there is a strong correlation between lung cancer and bad psychological state, anxiety and depression [5, 6] even after three months from the initial diagnosis.[7] Although pain is the main issue for the vast majority of the patients, it is also inadequately treated in up to 55% of the cases under palliative treatment.[8]

Bone metastasis are common in advanced stages of the disease, reaching 70-80% in breast and prostate cancer and 40% in lung cancer.[9] Pathological fractures, bone surgery and spinal cord compression events (Skeletal Related Events-SREs) are the most common causes of pain in cancer patients influencing mobility, functionality, social life and quality of life.[10] Approximately 2/3 of the patients with bone metastasis develop pain, which in 50% of the cases ranges from moderate to severe.[11] In a relevant meta-analysis it was found that SREs increase the need of strong opioids for pain management.[12] In addition, patients that have developed even one SRE during their course of life are at a higher risk of developing new with a great impact on their life expectancy.[13] Pain in cancer patients affects not only the quality of life[14], but also the ability to work, mobilize and interact with others, resulting in bad psychological condition with frequent sleep disorders leading to a vicious circle.[15, 16]

Combination of opioids and radiotherapy could prove effective in pain relief in patients with metastatic bone disease [17], but frequent visits to the hospital and tolerance in drugs should be taken in consideration to evaluate QoL.[18] Bone targeted therapies like bisphosphonate and denosumab show high speciality in treating skeletal events and pain due to metastasis.[19] They are administered to patients

with mild pain in order to treat, or prevent, bone metastasis, reducing the need of strong opioids.[20] In a clinical study that compared the efficiency of clodronic to zoledronic acid in patients with metastatic prostate cancer, the latter showed better results in relieving the pain.[21] It has been proven that administrating zoledronic acid with radiotherapy shows better results in preventing bone metastasis, reducing pain levels and improving QoL than radiotherapy as a sole treatment. The specific treatment for each patient and early administration is crucial for pain management and reduction of the exhausting effects of metastatic bone pain.[22]

The purpose of this study is to assess the quality of life in patients with primary lung cancer, with and without bone metastasis, with the use of seven reliable scales.

Method

Patients

This prospective study included 80 patients, with and without bone metastasis, with primary lung cancer. Each was questioned before and after treatment with co administration of zoledronic acid. Age varies from 43 to 69 years with average 54 years. 49 of the participant were male and 31 female of which 43.8% (26m and 9f) showed no bone metastasis and 56.2% (23m and 22f) had metastatic bone disease. All patients suffered from non-small cell lung cancer (NSCLC). Histological distribution was 46.1% adenocarcinoma, 38.4% squamous and 15.3% large cell carcinoma.

Patients were referred for treatment at the Pulmonary Department-Oncology Unit at G. Papanikolaou University Hospital of Thessaloniki over a period of 24 months and interviewed in the order of their arrival. Moreover it was conducted according to the World Medical Association Declaration of Helsinki. In order to show variations in sleep quality, severity of symptoms of fatigue and pain, quality of life and general condition of patients health we used t test for paired samples. Furthermore, we used correlation techniques and more specific the Pearson correlation. Table 1.

Table 1. Scales

Seven reliable scales were used:

- (1) PSQI (Pittsburgh Sleep Quality Index)
 - (2) ESS (Epworth Sleeping Scale)
 - (3) DS (Dyspnea Scale)
 - (4) FSS (Fatigue Severity Scale)
 - (5) BPI (Brief Pain Inventory)
 - (6) FACT-G (Functional Assessment of Cancer Therapy - General Scale)
 - (7) EQ-5D (European Quality of Life-5 Dimensions Scale)
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Pittsburgh Sleep Quality Index (PSQI) is an effective tool to assess quality and patterns of sleep in adults, by differentiating good from bad sleep. This is achieved by measuring seven parameters (sleep latency, subjective sleep quality, duration, sleep efficiency, sleep disturbances, use of sleep medication, and daytime dysfunction over the past month). Scoring is on a 0 to 3 scale with 3 reflecting bad sleep quality.[23] PSQI has a high diagnostic sensitivity and specificity distinguishing bad from good sleep.[24] The scale has been applied to patients with malignancy [25] and lung cancer [26], although it is not yet clear if QoL in these patients is affected because of the pain or psychological disorders.

Epworth Sleeping Scale (ESS) is a simple and valid, which is used to estimate the patients average sleep propensity in daily life. It is a self-administered questionnaire. Patients are requested to rate on a scale from 0 to 3 their usual chances of dozing off or falling asleep while engaged in eight different activities(sitting and reading, watching TV, sitting inactive in a public place, as a passenger in a car for at least one hour, lying down in the afternoon to rest, sitting and talking to someone, sitting quietly after a lunch without any alcohol, in a car while stopped for a few minutes in traffic).[27] ESS has shown good results combined either with other scales, or on patients with primary and metastatic brain cancer [28] and lung cancer.[29]

Dyspnea Scale (DS) is a five-question scale that describes the entire range of respiratory disability and it is completed by either the patient or the physician in the form of an interview.[29] Its main purpose is to quantify the disability associated with breathlessness by identifying that it occurs when it should not. It correlates well with other lung function measurements to provide a better view of the patients' health.[30]

The Fatigue Severity Scale (FSS) is a nine-item scale, which measures the severity of fatigue and its effect on a person's activities and social life. It was initially designed for patients with multiple sclerosis and lupus but gradually [31] found application in a variety of disorders that cause fatigue proving its reliability. Fatigue in these patients is related to psychological disorders, pain and dyspnea.[32]

The Brief Pain Inventory (BPI) evaluates the intensity, quality, relief and interference of pain in cancer patients. It is a self-administered questionnaire that handles intensity of the pain and the degree to which it interferes with the patients daily activities. It is reliable and highly sensitive in estimating the alternation in intensity and the effect of pain.[33] With BPI we can examine a wide range of pain as the patient is required to provide information on the

intensity of pain during the past week and on time of examination, on a scale from 0 to 10 while also a contour of a human body is provided to pin point the exact origin of pain. BPI reflects quantitatively and qualitatively the effects of pain making it a useful tool applied on clinical and epidemiological studies in global scale.[34]

The Functional Assessment of Cancer Therapy - General Scale (FACT-G) is a most useful tool that helps to evaluate QoL in patients that undergo treatment for cancer, by evaluating the effect of the certain treatment in four fields-physical, social/family, emotional, functional. It consists of 27 questions, each rates from 0 to 4, with the higher score representing better quality of life. Studies proved that FACT-G is the best tool in assessing QoL in cancer patients[35], but also combined with other variables (histological type, gender, weight loss) offers prognostic value for the patients' course.

Finally, the European Quality of Life-5 Dimensions Scale (EQ-5D) is a general health condition measurement scale applied in a variety of cases and is composed of two parts with the first covering five fields (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression). Each field has 5 levels. The second (EQ VAS) records the patients' health on a vertical scales cored from 0 to 100, where 100 represents the best imaginable health state and 0 the worst at the time it is completed.[36] The scale has been applied to cancer patients with high specificity.[37]

Results

The significant statistical correlation between the results of the scales used in patients before treatment was assessed. There was a statistically significant correlation between PSQI and DS($r=0,279$, $p=0,012$) and FSSN ($r=0,263$, $p=0,018$) signifying that low sleep quality is related to high levels of fatigue and dyspnea. In addition, the higher the level of experienced pain, the higher the levels of sleepiness and vice versa ($r=0,259$, $p=0,020$)[1]. High statistical correlation was indicated between the severity of dyspnea and fatigue ($r=0,845$, $p<0,001$), and severe dyspnea was associated with high levels of pain ($r=0,310$, $p=0,005$). Further comparison showed that high levels of pain show high levels of fatigue ($r=0,416$, $p<0,001$), with a negative result in fatigue levels regarding patients' general condition ($r= -0,246$, $p=0,028$). Lastly contradictory is the fact that the correlation between levels of pain and QoL during treatment was positive ($r=0,275$, $p=0,014$), despite the fact that high levels of pain show good general condition ($r=-0,373$, $p=0,001$). **Table 2.**

Regarding the results of paired sample

correlations of the scales after the appropriate treatment, they seem to be in partial correlation with the results prior to treatment. The correlation between PSQI -DS and PSQI-FSS is statistically significant ($r=0,259$, $p=0,021$ and $r=0,291$, $p=0,009$ respectively). High levels of sleepiness are associated with high levels of pain ($r=0.280$, $p=0,012$), high levels of dyspnea are correlated with increased fatigue ($r=0,796$, $p=<0,001$) and pain ($r=0,281$, $p=0,013$) and high levels of fatigue are followed by high levels of pain ($r=0,380$, $p=<0,001$) **Table 3.**

Table 2. Pearson correlations of the examined scales before the treatment

	PSQI	ESS	DS	FSS	BPI	Fact-G	EQ-5D
PSQI	r 1						
	P						
ESS	r -0,208	1					
	p 0,064						
DS	r 0,279	0,174	1				
	p 0,012	0,122					
FSS	r 0,263	0,157	0,845	1			
	p 0,018	0,163	0,000				
BPI	r 0,050	0,259	0,310	0,416	1		
	p 0,662	0,020	0,005	0,000			
Fact-G	r -0,156	0,087	-0,020	0,066	0,275	1	
	p 0,167	0,444	0,857	0,558	0,014		
EQ-5D	r -0,062	-0,025	-0,194	-0,246	-0,373	0,001	1
	p 0,585	0,829	0,085	0,028	0,001	0,990	

(Author's own, 2017)

Table 3. Pearson correlations of the examined scales after the treatment

	PSQI	ESS	DS	FSS	BPI	Fact-G	EQ-5D
PSQI	r 1						
	P						
ESS	r -0,184	1					
	p 0,103						
DS	r 0,259	0,149	1				
	p 0,021	0,190					
FSS	r 0,291	0,183	0,796	1			
	p 0,009	0,104	0,000				
BPI	r 0,057	0,280	0,281	0,380	1		
	p 0,619	0,012	0,013	0,001			
Fact-G	r -0,212	0,065	-0,140	-0,050	0,188	1	
	p 0,059	0,565	0,220	0,656	0,098		
EQ-5D	r -0,067	0,056	-0,198	-0,169	-0,189	0,032	1
	p 0,555	0,622	0,081	0,134	0,096	0,781	

(Author's own, 2017)

Observing the results that arise from the comparison of the mean scoring of the scales prior and after treatment, initially is obvious that sleep quality of patients with lung cancer is improved after treatment ($p<0,001$). In addition, based on the mean score of ESS scale, the degree of sleepiness is decreasing ($p=0,001$). In contrast, symptoms of dyspnea are more frequent ($p<0,001$) after treatment as the mean score of DS scale is higher after compared

to prior treatment. Despite the increase on dyspnea an improvement in fatigue is observed by the end of treatment ($p=0,008$). In addition, levels of pain are lower after treatment in patients with cancer ($p<0,001$), with the estimated quality of life based on the mean score of FACT-G to be significantly improved ($p<0,001$). Lastly, no statistically important differentiations in patients general health status is observed before and after treatment ($p=0,573$)

Table 4.

Table 4. Paired samples t-tests of the examined scales before & after the treatment

	Before treatment		After treatment		t	p
	Mean Scores	S.D.	Mean Scores	S.D.		
PSQI	6,00	2,48	5,36	1,80	5,872	0,000
ESS	7,40	3,15	7,21	2,99	3,495	0,001
DS	2,73	1,54	2,95	1,38	-4,056	0,000
FSS	45,55	16,40	45,18	16,49	2,736	0,008
BPI	2,11	2,30	1,79	1,81	3,939	0,000
Fact-G	52,72	8,85	54,93	7,99	-4,192	0,000
EQ-5D	71,75	19,64	70,95	13,18	0,567	0,573

(Author's own, 2017)

Discussion

Quality of life in patients with cancer and all skeletal and non-skeletal related effects is crucial in order to plan the appropriate treatment. Variables under test associated with psychological state and functionality involve pain, fatigue and sleep quality.[4-6] In this study, the results showed that patients with lung cancer fatigue before initiation of treatment had bad sleep quality, which is combined with significant dyspnea and fatigue. It has been corroborated that sleep quality in such patients is poor and associated with everyday fatigue.[27] Moreover statistically significant correlations exist between pain and sleepiness, dyspnea and fatigue, dyspnea and pain, pain and fatigue whereas appears to be negative correlation between general state of health and fatigue. Our results showed that poor quality of life in patients with lung cancer is due to pain and fatigue. This also reflects as poor sleep quality and dyspnea, established also by other studies with cancer patients.[8, 14-16] However there is a contradiction in our findings regarding the effect of pain in quality of life which was positive. This can be attributed to methodological limitations and to the fact that quality of life is a multifaceted notion affected by a variety of parameters.

In addition, our study showed existence of statistically significant correlation amongst the above variables, after treatment initiation, pointing out the connection between poor sleep quality and dyspnea symptoms, poor sleep quality and fatigue, dyspnea and fatigue, dyspnea and pain, fatigue and pain, but

also a positive correlation between sleepiness and pain. These results show the specificity and eligibility of the used scales in evaluating QoL in cancer patients. Regarding post treatment QoL, results from the FACT-G and rest of the scales showed that it was significantly improved, in accordance with previous studies on patients that were treated with chemotherapy, radiotherapy and surgery.[38-40] Also, there was improvement in sleep quality, sleepiness, fatigue and pain. Although dyspnea occurrence increased, fatigue was not affected. Previous study showed that quality of sleep is not improved with chemotherapy [26], which is in contradiction with our results.

The most important observation in this study is the significant improvement in QoL in patients with lung cancer, when zoledronic acid is co administered with the appropriate chemotherapy. Zoledronic acid is a bone targeting agent, with high specialization in metastatic bone pain, reducing the need of opioids.[19, 20] In this study the co administration of zoledronic acid to radiotherapy, reduced levels of pain when compared to radiotherapy and clodronic acid.[21] This showed the importance of zoledronic acid in improving QoL. Denosumab shows high affinity and specificity against RANKL, which is important in osteoclast formation, differentiation, and survival. It is also a key activator of osteoclasts, essential for mediating bone resorption through tumor-releasing growth factors and cytokines. Increasing evidence has suggested that denosumab inhibits osteoclast-mediated bone resorption and prevents bone metastases. Zoledronic acid reduces proliferation and viability of cancer cells, adherence and filtration and reduces the secretion of metalloproteinases all of which are properties of metastatic cancer disease. Moreover bisphosphonates have anti-angiogenic effect by obstructing substances that promote angiogenesis like fibroblast growth factor.[41] In our study we chose zoledronic acid over denosumab because of the significantly higher cost of the later. A limitation of our study is the different methods of staging between the patients, with and without bone metastases, which doesn't affect our results as we tried to examine changes in quality of life in patients with lung cancer under treatment with co administration of zoledronic acid, without taking in consideration the presence of metastatic disease. Another limitation of this study has to do with the fact that most of the questionnaires are self-administered, and partiality is inevitable. With our relatively small sample, further research with larger sample is required in order to confirm the above results.

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Competing Interests

The authors have declared that no competing interest exists.

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