Restless Legs Syndrome as a Cause of Sleep Disturbances in Cancer Patients Receiving Chemotherapy

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Abstract

Context

Sleep disturbances are frequent in cancer patients during chemotherapy; the contributory role of restless legs syndrome (RLS) in this setting has never been assessed.

Objectives

This study investigated the role of RLS in causing sleep disturbances and altering the quality of life in cancer patients during chemotherapy.

Methods

Evaluation tools included the Pittsburgh Sleep Quality Index (PSQI), the RLS questionnaires, the Functional Assessment of Cancer Therapy-General, and the Hospital Anxiety and Depression Scale for quality of life and anxiety/depression assessment. The study population was 173 cancer patients. The questionnaires were administered during the third chemotherapy cycle. Patients positive for RLS were reassessed six months after the end of chemotherapy.

Results

In all, 58.8% of patients reported experiencing sleep disturbances (PSQI ≥ 5) and 20% screened positive for RLS. Neither sleep disturbances nor RLS was associated with anemia, neurotoxic cytotoxic drugs, or benzamide treatment. A direct relationship was found between the PSQI and RLS (P = 0.007); both PSQI and RLS scores were significantly associated with poor quality of life (P = 0.008 and 0.01, respectively) and anxiety (P = 0.0001 and 0.01, respectively). PSQI score also was associated with depression (P = 0.0001). RLS persisted in four of the 25 RLS-positive patients reassessed at six months after chemotherapy. RLS recovery was associated with a significant reduction in sleep disturbances and improvement in quality of life.

Conclusion

RLS can be a contributory factor in sleep disturbances in cancer patients undergoing chemotherapy. Screening for RLS could aid in tailoring a potentially more efficacious treatment of such disturbances.

Key Words

Cancer; chemotherapy; sleep disturbances; restless legs syndrome; quality of life; anxiety; depression

Introduction

Sleep disruption is common among cancer patients receiving chemotherapy.1, 2 and 3 Probably multifactorial, its underlying pathophysiology is not fully understood.4 Insomnia and other symptoms, such as pain, fatigue, and mood disturbance, often occur in clusters and can negatively impact patients' quality of life and possibly the outcome of their diseases.5 and 6 It recently has been suggested that fatigue, sleep disturbance, and depression stem from distinct biologic processes in which inflammatory signaling may be a contributory factor.7

Restless legs syndrome (RLS), a neurologic condition that causes sleep and movement disorders, is defined as an irresistible desire to move the limbs. Usually associated with paresthesias/dysesthesias and motor restlessness, the symptoms start or worsen at rest and improve with activity. Worsening of symptoms in the evening and/or at night often results in disturbance of sleep and daytime tiredness.8

RLS is generally considered to be idiopathic (primary) or symptomatic (secondary). The primary form (60%–80% of all RLS) might be better defined as cryptogenic, indicating that in most cases the etiology and pathogenesis are uncertain, while leaving the possibility open of finding its exact origin and mechanisms. Secondary or RLS-associated conditions include end-stage renal disease, iron deficiency (with or without anemia), neuropathies and radiculopathies, rheumatoid arthritis, myelopathies, syringomyelia, Parkinson's disease, and pregnancy.9

The prevalence of clinically significant RLS is estimated to be 2%–4% in the U.S. and Western Europe.10

Most patients with RLS respond robustly to dopaminergic agents.11 Levodopa improves RLS but, because of its short half-life, the drug is associated with a high incidence of symptom rebound and augmentation. Augmentation, mainly characterized by the occurrence of RLS symptoms earlier in the day, is less frequently observed with dopamine agonists. Since ergot-derived compounds can cause pleural, pericardial, and retroperitoneal fibrosis, treatment with non-ergot dopamine agonists is preferred instead. Extensive data are available for pramipexole, ropinirole, and transdermal rotigotine in the treatment of RLS.12

The prevalence of RLS among cancer patients rarely has been investigated.13 A recent study by our group demonstrated that RLS is frequent in cancer patients during chemotherapy, with a prevalence of 18%, which is at least double that expected in the general population. RLS is correlated with poor quality of life,

anxiety, and depressive symptoms. Because the questionnaires were administered in a blinded format in our previous study, we were unable to search for clinical features associated with RLS.14

The present study was undertaken to assess the contributory role of RLS in sleep disorders occurring in cancer patients during chemotherapy. The secondary aim was to explore the relationship of sleep disorders and RLS with demography and patient characteristics, laboratory data, treatments, and patient anxiety, depression, and quality of life.

Methods

Patients

From November 2008 to April 2009, all consecutive patients undergoing chemotherapy at the Day Hospital of the Medical Oncology Department, Azienda Ospedaliero-Universitaria San Luigi Gonzaga, Orbassano, Italy, who gave informed consent were included in the study if they met the following eligibility criteria: histologically confirmed diagnosis of cancer, chemotherapy treatment between the third and fourth cycle, adequate compliance with treatment, age >18 years, written informed consent, and Eastern Cooperative Oncology Group performance status <2.15 Exclusion criteria were major dopaminergic alterations (i.e., Parkinson's disease), other relevant neurologic disorders, treatment with neuroleptics, diagnosed psychiatric disorders and subsequent treatment with psychotropic agents including antidepressants (i.e., selective serotonin reuptake inhibitors), known history of RLS (before the start of chemotherapy), molecular target therapies administered alone, renal impairment and hepatic impairment defined as serum creatinine ≥1.5 × normal value, and total bilirubin, alanine aminotransferase, and aspartate aminotransferase defined as ≥1.5 × normal value.

The following clinical data were retrieved from hospital records: primary site of malignancy, metastatic sites (if present), ongoing cancer treatment, concomitant drugs, concomitant medical conditions, and baseline hemoglobin level.

Explorative information about the duration of RLS was obtained by reassessing RLS-positive patients at six months after the end of chemotherapy for RLS according to essential diagnostic criteria, the Functional Assessment of Cancer Therapy-General (FACT-G), the Hospital Anxiety and Depression Scale (HADS), and the Pittsburgh Sleep Quality Index (PSQI). No specific treatment for RLS was prescribed during this time.

The study protocol was approved by the local ethics committee, and written informed consent was obtained from all patients before entry into the study.

Questionnaires

The PSQI16 assesses sleep quality; it measures subjective sleep quality in the preceding one-month period and comprises 19 self-rated questions and five questions rated by a bed partner or roommate. The 19 items are grouped into seven component scores: sleep quality, sleep latency, sleep duration, sleep efficiency, sleep disturbances, use of sleep medication, and daytime dysfunction. The global PSQI score (range, 0–21) is calculated by summing the component scores, whereby a higher score indicates worse sleep condition. A global PSQI score of five has been suggested to distinguish poor (PSQI ≥ 5) from good sleepers (PSQI < 5), with diagnostic sensitivity of 89.6% and specificity of 86.5%. Internal consistency as measured by Cronbach's alpha was 0.78.

The RLS essential diagnostic criteria9 were used for the diagnosis of RLS. All patients first completed this screening questionnaire. Those who identified the presence of RLS symptoms on the questionnaire subsequently underwent a structured interview conducted by two of the authors (L. F. S. and V. C.), both board-certified sleep medicine specialists, to confirm the diagnosis. Patients with clinical conditions that could mimic RLS symptoms (eg, neuropathic pain syndromes, leg akathisia, nocturnal leg cramps, and propriospinal myoclonus) were excluded.17 If the diagnosis of RLS was confirmed, the International Restless Legs Syndrome Study Group rating scale (IRLS)18 and 19 was administered to assess the severity of the condition.

The FACT-G20 addresses health-related quality of life and was developed and validated for use in clinical trials. The FACT-G is a 29-item self-report questionnaire comprising five subscales: Physical Well-Being (PWB), Functional Well-Being (FWB), Social/Family Well-Being, Emotional Well-Being (EWB), and Relationship with Doctor (RWD). Each item is rated from 0 (not at all) to 4 (very much); the range of scores is 0–108, with higher scores indicating better quality of life. Patients were asked to rate how they felt that day and over the previous seven days. The internal consistency on all five subscales was good (Cronbach's alpha of at least 0.82).

The HADS21 assesses levels of anxiety and depression. A simple but reliable tool to assess mood disorder in hospitalized populations and hospital outpatients, it consists of two subscales: one to determine anxiety status and one to determine depression status. Each subscale contains seven items that patients respond to on a 4-point (0–3) scale, where scores range from 0 to 21 for both anxiety and depression. For each subscale, a score of 0–7 indicates normal condition, 8–10 is suggestive of anxiety/depression, although not at the level of mood disorder, and 11 or higher indicates the probable presence of mood disorder. Patients were asked to indicate for each item how he/she felt in the past week. The internal consistency on the two subscales was good (Cronbach's alpha 0.81 and 0.74, respectively).

The questionnaires were administered to all patients during their stay in the Day Hospital by two well-trained nurses (B. R. and P. L. G.), who also were available to answer questions about completing the questionnaires.

Statistical Analysis

The sample size of this study was calculated assuming a frequency of RLS in the general population as 10% (Ho) and an expected frequency of 18% in cancer patients (H1) on the basis of a previous publication by our group.14 For an alpha error of 0.05 and a power of 90%, 172 patients had to be enrolled to demonstrate such a difference.

Normal distribution of continuous variables was assessed using the Kolmogorov-Smirnov test. The t-test or Mann-Whitney U test, when indicated, was applied for comparisons of continuous variables. Chi-square or Chi-square for trend, when indicated, was employed for comparisons of categorical variables. The nonparametric Wilcoxon rank-sum test and Kruskal-Wallis test were used, when applicable, to compare paired continuous variables. All statistical tests were two-sided and, taking into account the multiple comparisons performed, a $P \leq 0.01$ was considered statistically significant. All statistical analyses were performed using the SPSS for Windows, v. 17.0, software package (SPSS Inc., Chicago, IL).

Results

Patient Characteristics

A total of 173 patients (94 [54.3%] males and 79 [45.7%] females) were included in the study (Table 1). Chemotherapy was administered in an adjuvant setting to 60 (34.7%) patients and to 113 (65.4%) patients for advanced or metastatic disease.

Table 1.

Patient Characteristics and Treatments Administered

Variable	n	%
Sex (n=173)		
Male	94	54.3
Female	79	47.7
Age (years), mean±SD (range)	58.8±12.3 (20–80)	
Site of primary tumor (n=173)		
Colon-rectum	56	32.4
Breast	30	17.3
Prostate	13	7.5

Ovary	11	6.4
Bladder	10	5.8
Gastroenteropancreatic neuroendocrine	10	5.8
Pancreas	6	3.5
Testis	6	3.5
Stomach	6	3.5
Lung	5	2.9
Adrenal cortical	5	2.9
Uterus	4	2.3
Kidney	4	2.3
Head and neck	3	1.7
Thymus	2	1.2
Esophagus	1	0.6
Thyroid	1	0.6
Sites of metastases (n=112)		
Liver	52	46.4
Lung	31	27.7
Nodes	28	25.0
Bone	27	24.1
Peritoneum	16	14.3
Local relapse	9	8.2
Other	12	10.7
Anemic patients	34	19.7
Patients treated with opioids	20	11.6
Patients treated with benzamides (metoclopramide, levosulpiride)	100	57.8
Treatment administered		
Non-neurotoxic drugs	61	35.2
Potentially neurotoxic drugs	112	64.8

Cisplatin/carbopatin/oxaliplatin-containing regimens	69	39.9
Taxanes/vinca alkaloids/camptothecine derivative-containing regimens	43	24.9

Table options

The most frequent primary malignancies were colorectal (32.4%), breast (17.3%), and prostate (7.5%) cancer. The most frequent metastatic sites were liver (46.4%), lung 31 (27.7%), lymph nodes 28 (25%), and bone 27 (24.1%).

Potentially neurotoxic chemotherapeutic agents were administered to 90 (52.3%) patients; the remaining 83 patients received non-neurotoxic therapies consisting of anthracyclines, cyclophosphamide and other nitrogen mustards, fluoropyrimidines (both oral and intravenous), antimetabolites, and epipodophyllotoxins (Table 1).

Frequency of Sleep Disturbances and RLS

In all, 153 (88.4%) patients completed the PSQI questionnaire. The majority (mean ± SD, 6.14 ± 3.95) reported experiencing sleep disruption during chemotherapy: 90 (58.8%) patients had a PSQI score ≥5 (overall poor sleep quality), 28 (18.3%) rated their sleep quality as fairly/very bad, 100 (65.4%) reported increased sleep latency, and 63 (41.2%) reported sleeping less than seven hours per night. In addition, 49 (42.0%) patients reported using a sleep medication at least once during the prior month and 95 (62.1%) had experienced daytime dysfunction as the result of poor sleep.

All patients completed the RLS questionnaires; 38 met all the essential screening criteria for RLS, but two were excluded from the analysis because of a neuropathic pain syndrome. Thus, 36 patients (20.8%) met all the essential diagnostic criteria for RLS and the diagnosis was confirmed by means of a structured interview and evaluation conducted by a sleep medicine specialist (L. F. S.). On the basis of the IRLS severity score,19 eight (22.2%) patients showed mild RLS, 14 (38.9%) moderate RLS, 12 (33.3%) severe RLS, and two (5.6%) very severe RLS.

Relationship of Sleep Disturbance and RLS With Patient Characteristics and Cancer Treatment

The frequency of episodes of sleep disturbances and RLS was assessed by stratifying the patients according to their characteristics and type of treatment. As depicted in Table 2, sleep disturbances (PSQI ≥ 5) were more frequent among females than males but failed to correlate with age, anemia, and treatment with opioids, benzamides, and neurotoxic chemotherapeutic regimens. Also, the mean corpuscular volume values were similar in the RLS patients (median 86.4 fL [95% CI 85.5–91.4]) as opposed to their counterparts (median 88.3 fL [95% CI 86.6–93.8]) (P = 0.288). Furthermore, there was no difference in the distribution of RLS frequency between metastatic and non-metastatic status and the most frequent primary sites of malignancy.

Table 2.

Distribution of Sleep Disturbances and RLS According to Demographic Characteristics, Laboratory Parameter, Supportive Drug Intake, and Chemotherapy Neurotoxic Regimens

Variable	RLS (n = 36), n (%)	P	Sleep Disturbances, n (%)	P
Gender				
M	17/94 (18.0)	0.34	45/82 (54.9)	0.048
F	19/79 (24.0)		50/71 (70.4)	
Age 20–55 years (1° tertile)	13/59 (22.0)	0.23a	37/55 (67.3)	0.60a
Age 56–65 years (2° tertile)	16/59 (27.1)		31/54 (57.4)	
Age 66–80 years (3° tertile)	7/55 (12.7)		27/43 (62.7)	
Anemia	7/39 (17.9)	0.92	20/31 (64.5)	0.85
No anemia	28/134 (20.9)		75/114 (65.7)	
Opioid treatment	6/20 (30)	0.28	9/16 (56.2)	0.61
No opioid treatment	27/153 (19.6)		86/137 (62.8)	
Benzamide treatment	21/100 (21)	0.94	48/83 (57.8)	0.24
No benzamide treatment	13/73 (20.5)		47/70 (67.1)	
Non-neurotoxic regimens	15/61 (24.6)	0.31a	35/55 (63.6)	0.55a
Taxanes/vinca alkaloid/camptothecin derivative-containing regimens	8/43 (20.9)		25/38 (65.7)	
Cisplatin/carbopatin/oxaliplatin-containing regimens	12/69 (17.4)		35/60 (58.3)	
Non-metastatic	14/61 (23)	0.67	33/61 (54.1)	0.93
Metastatic	22/112 (19.6)		62/112 (55.4)	
Breast primary site	7/30 (23.3)	0.81	18/30 (60.0)	0.61
Colon/rectum primary site	9/56 (16.1)		29/56 (51.7)	
Prostate primary site	3/13 (23.1)		6/13 (46.2)	

RLS = restless legs syndrome; M = male; F = female.

a

Chi-square for trend.

Table options

Relationship Between RLS and Sleep Disorders

Among the 90 patients classified as “poor sleepers,” 26 (28.8%) were affected by RLS, whereas 10 of 63 “good sleepers” (15.8%) had RLS. The relationship between RLS and sleep disorders is depicted in Table 3. There was a significant progressive increase in the total PSQI score as RLS severity increased (P = 0.007). Considered as categorical variables, the scores for the single items on the PSQI showed a trend for a step-wise deterioration in the quality of sleep (P = 0.011) and an increase in the use of sleep-inducing drugs, such as benzodiazepines (P = 0.023), together with an increase in RLS severity. Noteworthy was that both severe anxiety and severe depression correlated in a step-wise manner with RLS severity (P = 0.0008 and P = 0.0007, respectively) (Table 3).

Table 3.

Relationship of RLS With Sleep Disorders

Psychometric Evaluation	No RLS n (%)	Mild-to-Moderate RLSn (%)	Severe-to-Very Severe RLSn (%)	P
PSQI				
Quality of sleep (fairly/very bad)	18/121 (14.9)	4/18 (22.2)	6/14 (42.8)	0.011
Sleep latency	76/121 (62.8)	12/18 (67.1)	12/14 (85.7)	0.11
Sleep duration <7 hours	47/121 (38.8)	8/18 (44.4)	8/14 (57.1)	0.19
Sleep efficacy (<85%)	54/121 (44.6)	6/18 (33.3)	11/14 (78.5)	0.09
Sleep disturbances during last month (at least one per week)	102/121 (84.3)	18/18 (100)	13/14 (92.8)	0.20
Intake of sleep-inducing drugs	34/121 (28.1)	7/18 (38.9)	8/14 (57.1)	0.023
Daytime dysfunction	73/121 (60.3)	10/18 (55.5)	12/14 (85.7)	0.15

Total PSQI score, mean±SD	5.64±3.52	6.78±4.62	10±4.8	0.007
HADS				
No anxiety	81/121 (66.9)	11/18 (61.1)	0/14 (0)	0.01
Moderate anxiety	21/121 (17.4)	4/18 (22.2)	3/14 (21.4)	0.66
Severe anxiety	19/121 (15.7)	3/18 (16.6)	11/14 (78.6)	0.0008
No depression	90/121 (74.4)	13/18 (72.2)	4/14 (28.5)	0.15
Moderate depression	22/121 (18.8)	3/18 (16.6)	3/14 (21.4)	0.87
Severe depression	9/121 (7.4)	2/18 (11.1)	7/14 (50)	0.0007
Total HADS score, mean±SD	12.01±6.51	13.13±8.92	22.29±5.92	0.008
FACT-G, mean±SD				
PWB	22.21±5.05	21.11±4.35	12.35±9.11	0.0001
Social Well-Being	18.16±4.34	17.27±5.59	18.71±3.11	0.35
RWD	6.27±1.76	6.27±1.49	6.21±1.93	0.94
EWB	6.42±4.47	7.27±5.14	6.22±3.01	0.03
FWB	15.76±5.45	15.82±4.95	11.76±4.41	0.04
Total FACT-G score	69.13±9.06	68.35±9.86	60.58±7.94	0.05

RLS = restless legs syndrome; PSQI = Pittsburgh Sleep Quality Index; HADS = Hospital Anxiety and Depression Scale; FACT-G = Functional Assessment of Cancer Therapy-General scale; PWB = Physical Well-Being; RWD = Relationship with Doctor; EWB = Emotional Well-Being; FWB = Functional Well-Being.

Table options

Evaluation of quality of life showed a trend of a progressive decrease in the total FACT-G score with increased RLS severity (P = 0.05): PWB subscale scores significantly decreased as RLS severity increased (P = 0.0001) (Table 3).

Relationships of Sleep Disturbances and RLS With Quality of Life, Anxiety, and Depression

Sleep disturbances were significantly associated with lower quality of life scores (P = 0.01): sleep disturbances were associated with lower FWB (P = 0.0001) and higher EWB scores (P = 0.002). No

significant correlation emerged for Social/Family Well-Being, RWD, and FWB. Also, anxiety (P = 0.0001), depression (P = 0.0001), and total HADS scores (P = 0.0001) were significantly associated with sleep disturbances (Table 4).

Table 4.

Relationship Between Sleep Disturbances and RLS With Quality of Life, Anxiety, and Depression

Psychometric Evaluation	No (Mean ± SD)	Yes (Mean ± SD)	P
FACT-G			
Restless leg syndrome			
PWB	22.21±5.05	6.61±5.65	0.0001
Social Well-Being	18.16±4.34	18.28±4.73	0.796
RWD	6.27±1.76	6.17±1.71	0.896
EWB	9.39±5.80	6.41±4.47	0.002
FWB	15.76±5.45	13.74±5.21	0.05
Total Fact-G score	69.13±9.06	65.38±10.16	0.01
Sleep disturbances			
PWB	22.88±4.49	20.20±6.81	0.027
Social Well-Being	18.56±3.27	17.93±5.01	0.99
RWD	6.57±1.59	6.05±1.82	0.084
EWB	4.67±3.32	8.39±5.13	0.0001
FWB	18.48±4.83	13.47±4.91	0.0001
Total Fact-G score	71.24±8.64	66.51±9.39	0.008
HADS			
Restless legs syndrome			
Anxiety	6.57±3.81	9.94±5.41	0.01
Depression	5.43±3.58	7.22±4.66	0.03
Total HADS score	12.01±6.51	17.16±9.42	0.005
Sleep disturbances			

Anxiety	5.44±3.26	8.56±4.49	0.0001
Depression	3.98±2.79	7.14±4.05	0.0001
Total HADS score	9.42±4.79	15.70±7.75	0.0001

RLS = restless legs syndrome; PWB = Physical Well-Being; RWD = Relationship with Doctor; EWB = Emotional Well-Being; FWB = Functional Well-Being; FACT-G = Functional Assessment of Cancer Therapy-General scale; HADS = Hospital Anxiety and Depression Scale.

Table options

RLS was significantly associated with the poorest quality of life (P = 0.01): lower levels of PWB (P = 0.0001) and EWB (P = 0.002) were observed in patients with RLS. RLS-positive patients were noted to have higher levels of anxiety (P = 0.01) and higher total HADS scores (P = 0.005) (Table 4).

Reassessment of Patients Screening Positive for RLS

Of the 36 patients initially screening positive for RLS, 25 could be reassessed at six months after the end of chemotherapy. The remaining 11 were not evaluable because of worsening of clinical condition (n = 4), death (n = 6), and refusal (n = 1).

On reassessment, four patients still met all the essential diagnostic criteria for RLS and 21 did not. Specifically, a comparison between quality of life, anxiety and depression levels, and quality of sleep at the first assessment during chemotherapy (T0) vs. that at reassessment (T1) was performed. Among the 21 patients who recovered from RLS, a significant improvement in quality of life was noted, particularly for PWB (P = 0.0001), RWD (P = 0.01), EWB (P = 0.0001), and total FACT-G score (P = 0.001), as well as quality of sleep (P = 0.01), although the levels of anxiety and depression did not differ significantly between T0 and T1 (Table 5). Conversely, no improvement in quality of life, sleep quality, or levels of anxiety and depression was found for the four patients who did not recover from RLS: the values of the total scores and the single items on the FACT-G, HADS, and PSQI were substantially unchanged between T0 and T1 (data not shown).

Table 5.

Changes in Quality of Life, Anxiety, Depression, and PSQI Score in 25 Patients With RLS Resolution After the End of Chemotherapy

Psychometric Evaluation	T0 (Mean ± SD)	T1 (Mean ± SD)	P

PWB	6.05±5.63	19.22±7.01	0.0001
Social Well-Being	15.31±5.23	15.56±3.95	0.796
RWD	5.86±1.64	6.64±1.48	0.01
EWB	6.69±3.80	15.53±4.94	0.0001
FWB	15.33±5.67	14.17±5.39	0.265
Total Fact-G score	49.14±9.68	72.97±13.38	0.001
Anxiety	9.65±5.29	9.46±4.77	0.806
Depression	7.11±4.43	7.01±4.05	0.866
Total HADS score	16.76±8.76	16.46±7.73	0.795
Total PSQI score	7.64±4.44	6.08±3.56	0.01

PSQI = Pittsburgh Sleep Quality Index; RLS = restless legs syndrome; PWB = Physical Well-Being; RWD = Relationship with Doctor; EWB = Emotional Well-Being; FWB = Functional Well-Being; FACT-G = Functional Assessment of Cancer Therapy-General scale; HADS = Hospital Anxiety and Depression Scale.

Table options

Discussion

Sleep disturbances are frequent in cancer patients receiving chemotherapy.22 and 23 The pathophysiology underlying these disturbances is notoriously complex and multifactorial.24 Such disturbances are often secondary to disease-associated pain, fatigue, patient anxiety, and/or depression linked to uncertainties about treatment outcome, drug interactions, or psychosocial factors. Moreover, primary sleep disorders including obstructive sleep apnea, periodic limb movements (PLMs), and RLS, although common in the general population,25 and 26 have received little attention from the oncology community.

The present study confirms the high prevalence of sleep disorders in cancer patients during chemotherapy. We observed that RLS also is frequent. The proportion of 20% of RLS-positive patients is similar to that observed in our precedent series and is consistently higher than the expected frequency in the general population. Noteworthy is that RLS was severe in 8% of the patients in this study.

As expected, both RLS and sleep disorders were associated with worse quality of life and greater anxiety and depression. Future studies will need to address whether these conditions can be improved with early treatment of RLS.

The mechanisms underlying the occurrence of RLS in cancer patients are unknown and both cancer-related and treatment-related causes can be considered. To limit potential biases, patients with renal impairment or currently treated with selective serotonin reuptake inhibitors were excluded from this study. In our series, none of the predictive factors of RLS in the general population (e.g., sex, anemia) were significantly associated with the development of this disturbance. The presence of iron deficiency was not directly assessed in this study, but mean corpuscular volume values, as a marker of iron status, did not differ between the RLS-positive and RLS-negative patients.

Among the 25 RLS-positive patients who could be reassessed six months after the end of chemotherapy, the disorder persisted in only four of them. This observation suggests a causative role of cytotoxic treatment in RLS onset. Many chemotherapeutic drugs are, in fact, neurotoxic. Added to these are frequently used antiemetic drugs, such as benzamides, which interfere with the dopamine system and so may lead to RLS. In this study, however, no correlation was found between RLS and either neurotoxic chemotherapy or benzamides. Other mechanisms, therefore, need to be taken into account. Moreover, because RLS not infrequently shows an intermittent pattern, a longer follow-up is needed to assess this phenomenon.27 Noteworthy is that no improvement in quality of life, anxiety and depression, or sleep disturbances was observed in the four patients with persistent RLS, suggesting a link between RLS and psychophysical impairment.

As reported in a recent Cochrane review,28 levodopa in the short-term treatment of RLS is efficacious by reducing symptom severity and PLMs during sleep. Dopamine agonists were associated with greater improvement on IRLS scores compared with placebo.29 Also, the occurrence of PLMs was found to be significantly reduced by dopamine agonists compared with placebo, and sleep efficiency also was slightly improved. Although the patients rated their quality of sleep and quality of life as markedly improved, they were more likely to discontinue dopamine agonist treatment compared with placebo.

Among the 28 RLS-positive patients who were assessed for sleep disturbances, 15 (53.6%) reported using a benzodiazepine as a sleep inducer. Data supporting the use of benzodiazepines for RLS are scarce. Although several studies showed that benzodiazepines may improve sleep quality in RLS patients, their therapeutic effects on RLS symptoms have been reported to be either modest or nonsignificant.30 In a recently published prospective study, switching from clonazepam to pramipexole in patients with RLS was associated with a significant reduction in RLS-related symptoms.31

The strengths of this study are the relatively large number of patients consecutively enrolled at a single institution and the number of psychometric tools administered. Although patients with known RLS before

beginning chemotherapy were excluded, the absence of RLS assessment at baseline is a limitation. Another limitation is that the diagnosis of RLS was not confirmed by polysomnographic evaluation. It should be noted, however, that the number of PLMs and the number of arousals (an expression of sleep fragmentation) vary from night to night in RLS patients.32 Polysomnographic evaluation for several nights would necessarily have involved additional visits to the study center, which might not have been willingly accepted by a population of cancer patients during chemotherapy.

In conclusion, this study confirms that sleep disturbances are highly prevalent in cancer patients undergoing chemotherapy and are associated with a significant burden on the individual in terms of functional impairment, reduced quality of life, and increased anxiety and depression. RLS is a frequent cause of sleep disturbances during chemotherapy. Further study is needed to determine whether this adverse event is transient or not. The diagnosis of RLS is clinical9 but it is usually misdiagnosed unless validated questionnaires are administered. We believe that screening for RLS in patients during chemotherapy is important because it can aid in tailoring a possibly more efficacious treatment of sleep disturbances. The best therapeutic approach to RLS during chemotherapy warrants a prospective randomized clinical trial.

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