Int. J. Radiation Oncology Biol. Phys., Vol. 81, No. 2, pp. 511–520, 2011

0360-3016/$–see front matter

ELSEVIER

doi:10.1016/j.ijrobp.2010.05.047

PREVALENCE OF NEUROPATHIC PAIN IN RADIOTHERAPY ONCOLOGY UNITS

Ana Mañas, M.D.,* Jose Luis Monroy, M.D.,† Avelino Alia Ramos, M.D.,‡ Carmen Cano, M.D.,¶ Vanessa López-Gómez, Pharm.,§ Xavier Masramón, B.S.,** and María Pérez, M.D. § On behalf of TENOR collaborative study group

*Servicio de Oncologia Radioterapica, Hospital Universitario La Paz, Madrid, Spain; †Servicio de Oncologia Radioterapica, Hospital Universitario de la Ribera, Valencia, Spain; ‡Servicio de Oncologia Radioterapica, Hospital Txagorritxu, Vitoria-Alava, Spain; ¶Servicio de Oncologia Radioterapica, Hospital de Torrecárdenas, Almería, Spain; §Medical Unit, Pfizer España, Alcobendas, Spain; and**Department of Biometrics, European Biometrics Institute, Barcelona, Spain

Purpose: Neuropathic pain (NP) in cancer patients severely impacts quality of life. Radiotherapy (RT) may cause NP, and at the same time, cancer patients visit RT units for pain relief. NP prevalence at these sites and current analgesic treatment should be assessed to improve management.

Methods and Materials: This epidemiological, prospective, multicenter study was undertaken to assess NP prevalence, according to Douleur Neuropathique 4 questions questtionaire (DN4) test results, and analgesic management in cancer pain patients visiting RT oncologic units. Secondary analyses assessed NP etiology and pain intensity (using the Brief Pain Inventory—Short Form) and impact (using the Hospital Anxiety and Depression Scale (HADS), Medical Outcomes Study [MOS] for Sleep, and the Health Survey Short Form-12).

Results: A total of 1,098 patients with any kind of pain were registered. NP prevalence was 31.1% (95% confidence interval, 28.4%–33.9%); 291 NP patients (mean age, 62.2 ±12.5 years and 57.7% men) were eligible for study; 49% of patients were overweight. The most frequent tumors were those of breast and lung, and stage IIIB was the most common cancer stage. The tumors caused 75% of NP cases. Anxiety, sleepiness, and depression were common. At 8 weeks, pain intensity and interference with daily activities decreased significantly for 50.8% of responders. Depression and anxiety ($p < 0.0001$) scores on the Physical Component Summary and Mental Component Summary measures ($p < 0.0001$) and all MOS-Sleep subscales, except for snoring, improved significantly. The percentage of satisfied patients increased from 13.8% to 87.4% ($p < 0.0001$) with the current analgesic treatment, which meant a 1.2- and 6-fold increase ($p < 0.0001$) in narcotic analgesics and anticonvulsants, respectively, compared to previous treatment.

Conclusions: NP is highly prevalent at RT oncology units, with sleepiness, anxiety, and depression as frequent comorbidities. There is a need to improve management of NP with increased use of more specific NP-targeting drugs.

Neuropathic pain, Cancer pain prevalence, Radiotherapy oncologic units, Anticonvulsants.

INTRODUCTION

Fifty percent of cancer patients suffer from pain, which reaches 75% to 95% in advanced stages (1–3). Cancer may cause nociceptive or neuropathic pain (NP) (4,5). NP is caused by a lesion or dysfunction of the central or peripheral nervous system (6, 7); the most frequent causes of NP in cancer patients are nervous injury or compression by tumor growth and infiltration and sympathetically maintained pain secondary to therapy (2, 8, 9).

NP is difficult to diagnose and treat (8,10) and is often associated with anxiety, depression, and sleep disorders (11,12), which are frequent cancer comorbidities that also have psychological components (13). Therefore, treatment of cancer NP should include not only pharmacologic therapy, with anticonvulsants and tricyclic antidepressants (TCAs) as the firstline choice (9,14,15), but also psychological coping strategies (2) and sometimes additional analgesic techniques, such as radiotherapy (RT).

Reprint requests to: Vanessa López Gómez, Medical Unit, Pfizer Spain, Avda. Europa, 20 B, 28108 Alcobendas, Madrid, Spain. Tel: 91 490 98 41; Fax: 91 490 97 36; E-mail: Vanessa.LopezGomez@pfizer.com

This study was funded by Pfizer Spain.

Supplementary material for this article can be found at www.redjournal.org.

Conflict of interest: Maria Pérez and Vanessa López-Gómez are full-time employees of Pfizer, the company sponsoring this study. Xavier Masramon is employed by the European Biometric Institute, a clinical research organization contracted by Pfizer to conduct the study.

Acknowledgment—We thank Almudena Pardo Mateos for writing the first manuscript draft.

Received Nov 30, 2009, and in revised form April 7, 2010. Accepted for publication May 18, 2010.

Radiotherapy is used as a curative treatment or coadjuvant and may induce neural damage and cause NP (16,17). RT is also used as a pain palliative in patients with bone metastases and cases of nervous system compression (12,18,19). Therefore, a high prevalence of NP is expected in RT oncology units. RT oncologists must be able to identify NP and ensure the proper pain management is given to their cancer patients. To meet this challenge, they must be aware of the prevalence of NP in their units and the frequency with which cancer pain is inadequately managed. The current study was conducted to find out the prevalence of NP among cancer outpatients with pain visiting RT units and the analgesic treatment currently used for these patients, with the aim of increasing awareness of the disease among RT oncologists.

METHODS AND MATERIALS

Study design and patients

An epidemiological, observational, prospective, multicenter study was conducted to assess the prevalence of clinical NP in patients with pain visiting RT oncology units and the current management of these patients. Secondary analyses were intended to determine NP etiology and pain intensity and duration and to evaluate disease impact on patients by measuring their self-perceived health status (anxiety, depression, sleep disorders, and quality of life worsening). In addition, associated comorbidities were analyzed. The study was noninterventional, since researchers themselves chose the way to manage their patients.

Twenty-seven researchers from 19 RT oncology units throughout Spain participated in the study. Researchers registered up to 75 consecutive cancer outpatients suffering from any kind of pain, visiting their units between October 1, 2007, and October 27, 2008. The registry collected demographic data, tumor diagnosis data,and a Douleur Neuropathique 4 questions questtionaire (DN4) score and recorded whether the diagnosis was NP. Each researcher recruited the first 25 patients who were NP-positive according to the DN4 scale (DN4 $\geq$ 4) and who were 18 years old or older, able to read and fill out health questionnaires in Spanish, and gave written informed consent (themselves or through their legal representative). Patients who were unable to understand the study's objectives or to fill out the questionnaires, or whose health status, in the opinion of the physician, did not allow them to fill them out were excluded.

Measure outcomes

Enrolled patients had a baseline visit and a final visit 8 weeks later. The following data were obtained at baseline: demographic data, tumor characteristics, previous oncologic treatment, NP characteristics, and comorbidities. In addition to baseline data, the following data were also collected at 8 weeks: NP localization, analgesic treatment, patient's evaluation of analgesic treatment efficacy, and results from the scales described below.

The diagnostic DN4 test (20), a 10-item questionnaire with a diagnosis breakpoint of 4, was used to identify patients with NP.

The short form of the Brief Pain Inventory (BPI-SF) (21), whose Spanish version has been validated in cancer patients (22), was completed by the patient and the accompanying person. This form contains 11 items grouped into two dimensions: pain intensity and its interference with life activities.

The Hospital Anxiety and Depression Scale (HADS) (23) consists of 14 items grouped into two subscales: anxiety and depression. On both subscales, a score of 0 to 7 is considered normal; 8 to 10 is mild; 11 to 14 is moderate; and 15 to 21 is intense.

The Medical Outcomes Study of Sleep (MOS-Sleep) scale (24) is a 12-item questionnaire grouped into the following domains: sleep disturbance, sleep quantity, snoring, awakening with shortness of breath or with headache, sleep adequacy, and daytime somnolence. In addition, a 9-item Sleep Problems Index, grouping all items except 2, 10, and 11, can be constructed and is often used as an indicator of sleep quality. The reliability and validity of the Spanish version has been confirmed in NP patients (25).

The 12-item Health Survey short form (SF-12) (26) is an abbreviated form of the Health Survey SF-36 (27), which was validated in Spanish (28). The abbreviated scale has 12 items used to generate a health profile consisting of eight scales and two summary measures: the Physical Component Summary (PCS) and the Mental Component Summary (MCS) measures. The physical and mental component scores were compared to the standardized SF-12 scores of the Spanish population, and results were shown with standardized deviations (Z) adjusted by age and sex.

Statistics

A total of 1,098 patients with pain were registered in the RT oncology units; this sample size had a precision of 2.7% for assessing the prevalence of NP, with a 95% level of confidence. For the second part of the study, 296 patients were enrolled. This number had a sample size sufficient to obtain reliable assessments of the secondary analyses (etiology analysis) in the 95% confidence interval (CI) with a precision of 5.7%. For the analysis of the other secondary quantitative variables, bilateral tests were used with an error level of 5% in the case of unidimensional and independent variables (consisting of total BPI, HADS, MOS, and SF-12 domains), while the error level was adjusted by the number of comparisons in multidimensional variables (individual BPI items), accepted as significant at an α error lower than 1% for these last comparisons.

Due to pairwise contrasts, the effect size was also obtained by calculating the difference between the mean values of a specific measure before and after treatment and then dividing the difference by the standard deviation of that measure at the baseline visit (Kazis *et al*., 1989 [29]). According to the criterion established by Cohen, an effect size of $\geq$0.8 is considered a large change (Kazis *et al*., 1989) and is, therefore, clinically meaningful.

To evaluate the statistical significance of changes due to a particular treatment, the significance level was adjusted by the number of therapeutic group comparisons. Thus, an α error of 1% was accepted as significant for these occasions.

Descriptive statistics were applied to all variables with a bilateral CI of 95% at baseline and at 8 weeks, as well as to all changes from baseline. For the primary analysis, the percentage of NP patients was calculated with a 95% CI among those visiting oncologic RT units with any kind of pain. For pairwise analysis (8 week vs. baseline) Student's t test was used for quantitative variables, the Wilcoxon test was used for nonparametric quantitative variables, and the McNemar test was used for dichotomous qualitative variables. Only patients with available data were included in the analyses; thus, sample sizes varied among variables and were smaller (n = 248) than the eligible population sample. SAS version 8.2 software was used for all statistical analysis, and all statistical tests were bilateral.

The study was developed in agreement with legal stipulations in Spain for observational epidemiologic studies and with the declaration of Helsinki (29), and it was approved by the Research Ethics Committee of Hospital Universitario La Paz (Madrid).