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ORIGINAL REPORT

Effects of Melatonin on Appetite and Other Symptoms in Patients With Advanced Cancer and Cachexia: A Double-Blind Placebo-Controlled Trial

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See accompanying editorial on page 1257

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ABSTRACT

Purpose
Prior studies have suggested that melatonin, a frequently used integrative medicine, can attenuate weight loss, anorexia, and fatigue in patients with cancer. These studies were limited by a lack of blinding and absence of placebo controls. The primary purpose of this study was to compare melatonin with placebo for appetite improvement in patients with cancer cachexia.

Patients and Methods
We performed a randomized, double-blind, 28-day trial of melatonin 20 mg versus placebo in patients with advanced lung or GI cancer, appetite scores ≥ 4 on a 0 to 10 scale (10 = worst appetite), and history of weight loss ≥ 5%. Assessments included weight, symptoms by the Edmonton Symptom Assessment Scale, and quality of life by the Functional Assessment of Anorexia/Cachexia Therapy (FAACT) questionnaire. Differences between groups from baseline to day 28 were analyzed using one-sided, two-sample *t* tests or Wilcoxon two-sample tests. Interim analysis halfway through the trial had a Lan-DeMets monitoring boundary with an O'Brien-Fleming stopping rule. Decision boundaries were to accept the null hypothesis of futility if the test statistic $z < 0.39$ ($P \geq .348$) and reject the null hypothesis if $z > 2.54$ ($P \leq .0056$).

Results
After interim analysis of 48 patients, the study was closed for futility. There were no significant differences between groups for appetite ($P = .78$) or other symptoms, weight ($P = .17$), FAACT score ($P = .95$), toxicity, or survival from baseline to day 28.

Conclusion
In cachectic patients with advanced cancer, oral melatonin 20 mg at night did not improve appetite, weight, or quality of life compared with placebo.

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INTRODUCTION

Melatonin is a pleiotropic hormone that may modulate multiple mechanisms promoting cancer cachexia, including inflammation, autonomic failure, and malabsorption. Initially believed to be synthesized exclusively in the pineal gland and primarily involved as a circadian messenger of light and dark, melatonin is now recognized to have multiple actions[1] and is synthesized in diverse tissues.[2] Circulating melatonin is primarily derived from the pineal gland but is synthesized in even greater quantities locally by the GI system,[3] possibly in response to feeding.

Melatonin supplementation stimulates appetite in animals,[4] and its presence in the digestive tract is associated with intestinal transit and nutrient absorption.[5] Melatonin may also have antitumor activity through an antimitotic[6] effect and suppression of tumor linoleic acid uptake,[7] and in a preliminary trial, it improved the efficacy of arterial chemoembolization for hepatocellular carcinoma.[8]

Several studies have evaluated the effect of melatonin on symptoms such as poor appetite, fatigue, and depression in patients with cancer. Patients with metastatic solid tumors randomly assigned to supportive care plus melatonin for 3 months had better weight stabilization and lower levels of tumor necrosis factor α than patients receiving supportive care alone.[9]

A similar subsequent trial of melatonin for patients with untreatable solid tumors showed that cachexia, weakness, anorexia, and depression occurred more frequently in the group receiving supportive care alone.[10] In more recent trials, the same group of investigators reported decreased symptoms,

improved survival,[11] and fewer adverse effects in patients with solid tumors who were also given melatonin at night. No adverse effects were reported in any of these trials despite the use of a relatively high dose of 20 mg at night. Although patients were randomly assigned, it is important to note that none of the trials were double blind or placebo controlled. On the basis of these studies, it seemed that an inexpensive medication such as melatonin could improve symptoms and quality of life in patients with cancer, without causing adverse effects.

The primary objective of this study was to determine whether melatonin would improve appetite in patients with advanced cancer with cachexia, as defined by an improvement of 1.5 in appetite score from baseline on the Edmonton Symptom Assessment Scale (ESAS). Our secondary objective was to determine whether melatonin would increase weight and lean body mass and improve symptoms and quality of life as measured by the ESAS, Functional Assessment for Chronic Illness Therapy–Fatigue (FACIT-F), and Functional Assessment of Anorexia/Cachexia Therapy (FAACT) scores, respectively.

PATIENTS AND METHODS

Design

This study was a single-center, double-blind, parallel-group trial of adult patients with advanced lung or GI cancer equally randomly assigned (1:1) to 28 days of melatonin 20 mg at night versus placebo. All patients were given the option of receiving melatonin after 28 days.

Patients were enrolled from the supportive care clinic and solid tumor clinics at The University of Texas MD Anderson Cancer Center (MDACC). During the trial, the study was expanded to a second site, the Joan Karnell Cancer Center at University of Pennsylvania. This second site was terminated after enrolling two patients because continued support for a research coordinator was not possible.

Intervention

Melatonin (Medisca, Plattsburgh, NY) and matching placebo were compounded into capsules by the investigational pharmacy at MDACC. Investigational pharmacists dispensed either melatonin or placebo capsules according to a computer-generated random assignment list. The RANLST program, software prepared in the Department of Biostatistics at MDACC and supported by a National Cancer Institute grant, was used. Treatment allocation was concealed from patients, investigators, and study coordinators enrolling the participants. All patients were counseled and given dietary advice by a dietician at baseline.

Patients

Advanced cancer was defined as metastatic or locally recurrent disease, and patients were stratified according to those actively receiving treatment for their cancer versus those who were not. Inclusion criteria were age $\geq$ 18 years, appetite score $\geq$ 4 on a 0 to 10 scale (10 = worst appetite), and a history of weight loss $\geq$ 5% within 6 months. Premenopausal women with childbearing potential who had a positive pregnancy test were excluded. Patients unable to maintain oral intake or with dementia, delirium, or a Karnofsky performance score less than 40 were excluded. Patients who had uncontrolled symptoms that could impact appetite or caloric intake such as nausea, pain, or depression were excluded until their symptoms had stabilized for at least 2 weeks. Patients with untreated vitamin B_{12} deficiency or endocrine abnormalities that could affect appetite, such as thyroid dysfunction (thyroid-stimulating hormone $\leq$ 0.50 or $\geq$ 10 mIU/L) and hypoadrenalism, were excluded. Patients on melatonin supplements or medications with potential appetite-stimulating activity, such as megestrol acetate, corticosteroids, or thalidomide, were excluded unless they had been on a stable dose for more than 2 weeks and continued to experience poor appetite.

Assessments

Demographic data included performance status, tumor type, sex, age, and percentage weight loss.

ESAS. The ESAS[12] assesses the following 10 symptoms experienced by patients with cancer during the previous 24 hours: pain, fatigue, nausea, depression, anxiety, drowsiness, dyspnea, anorexia, sleep disturbance, and feelings of well-being. The severity of each symptom is rated on a numerical scale of 0 to 10 (0 = no symptom, 10 = worst possible severity). The ESAS is both valid and reliable in the assessment of the intensity of symptoms in patients with cancer.

FACIT-F. The FACIT-F[13] is a well-validated quality-of-life instrument widely used for the assessment of cancer-related fatigue in clinical trials. It consists of 27 general quality-of-life questions divided into four domains (physical, social, emotional, and functional), plus a 13-item fatigue subscore. The patient rates the intensity of fatigue and its related symptoms on a scale of 0 to 4. The total score ranges between 0 and 52, with higher scores denoting less fatigue.

FAACT subscale. The 12-item FAACT subscale questionnaire[14] has been validated in patients with advanced cancer.

Body composition and weight. Body composition and weight were measured using bioimpedance analysis (BIA). BIA is a noninvasive method of estimating body composition based on the ability of lean tissue to conduct an electrical current better than fat. The Tanita TBF-310 (Tanita, Tokyo, Japan) body composition analyzer/scale was used to measure total weight, total body fat, and total body lean mass.

Toxicity. A toxicity questionnaire was done at baseline and then at 14-day intervals until day 56.

Statistical Analysis

The trial was approved by the MDACC Institutional Review Board. Informed consent was obtained from each participant before study enrollment.

Patients were randomly assigned to receive melatonin or placebo in a 1:1 ratio, with the change in appetite between baseline and 4 weeks being the primary end point. The two groups were stratified at the time of random assignment by whether or not the patient was receiving systemic chemotherapy. Appetite was measured with a 0- to 10-point scale using the ESAS. Previous studies by the senior author using appetite stimulators[15,16] have shown significant increases in the range of one half a standard deviation, or approximately a 1.5-point change on a 0 to 10 scale. We also believe that this difference is of clinical importance.

To declare the above difference to be statistically significant, assuming a one-sided significance level of .05 and 80% power, we needed 50 evaluable patients per group. We believed that this medium effect size corresponded to the minimal clinically relevant difference. We used a one-sided test for the primary end point because of previous knowledge of differences expected to be found. All other tests were two-sided. No corrections were made for multiple tests. A *t* test was used to evaluate the difference between groups.

Intent-to-treat analysis was conducted using repeated measures analysis of variance including the time point of 4 weeks, with baseline included as a covariate. These analyses included the main effects of group and time and a group-time interaction. Other variables analyzed and compared by group included weight gain and changes in percent lean muscle mass, the FAACT, the FACIT-F, and other variables from the ESAS.

The interim analysis of efficacy and toxicity was scheduled when half of the patients had been evaluated (25 patients per group). To provide for an overall one-sided significance level of approximately $P = .05$ for the study, the interim analysis had a Lan-DeMets monitoring boundary with an O'Brien-Fleming stopping rule (EaSt, version 5; Cytel Software Corporation, Cambridge, MA). The decision boundaries for the interim test were to accept the null hypothesis of no treatment difference (futility) if the test statistic z was less than 0.39 ($P \geq .348$) and to reject the null hypothesis if z was greater than 2.54 ($P \leq .0056$). Analyses were conducted using SAS version 9.3 (SAS Institute, Cary, NC).

RESULTS

For each group, the numbers of patients who were randomly assigned, received intended treatment, and were analyzed for the primary outcome are shown in Figure 1. The diagram includes information on the

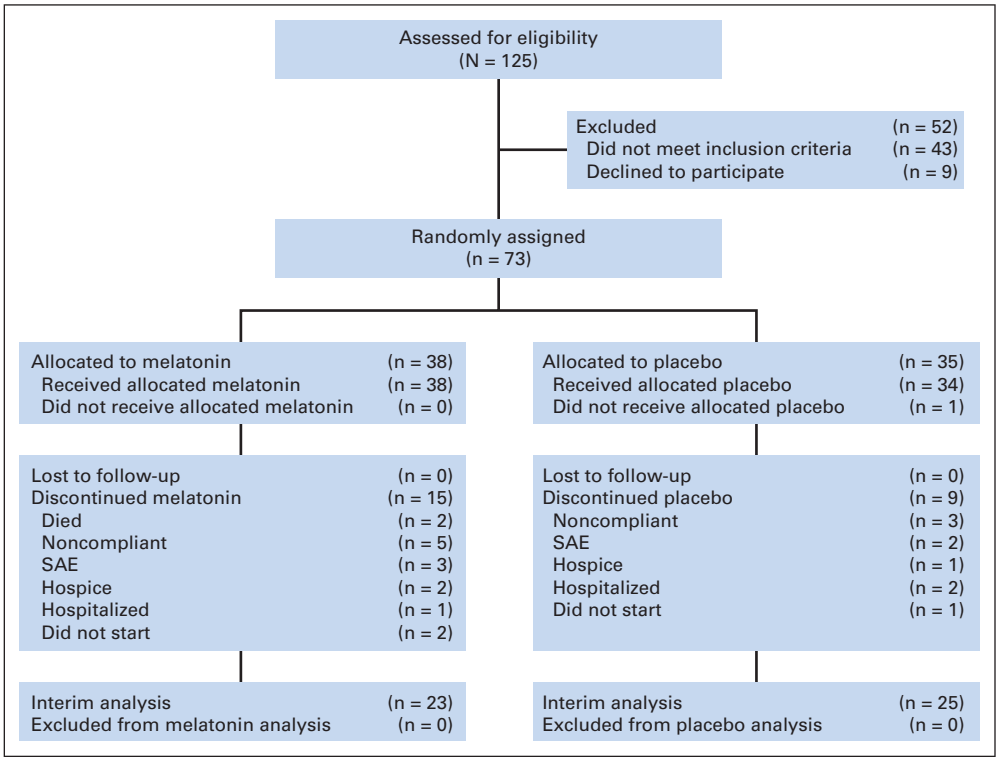

Fig 1. CONSORT diagram. SAE, severe adverse event.

excluded patients. Age-eligible patients were recruited from July 2006 to October 2010. Of the 73 randomly assigned patients with baseline scores, 48 patients had both baseline and week 4 measurements. Baseline characteristics of the two groups are listed in Table 1. No significant differences between groups were found in changes from baseline to week 4 in the appetite score using a one-sided two-sample *t* test ($P = .80$). There were also no differences between melatonin and placebo groups after 4 weeks regarding weight, body composition including fat-free mass, symptom scores, and quality-of-life outcomes as measured by FACIT-F and FAACT (Table 2). There was no difference in survival between the two groups (Fig 2), although all patients were given the option of continuing on melatonin after 4 weeks of enrollment. There were no treatment-related deaths, and the number of patients experiencing adverse events by maximum grade was similar in the melatonin (n = 37) and placebo groups (n = 34). We found no significant differences between patients receiving systemic chemotherapy and those on no systemic chemotherapy. The statistical collaborator presented the results to the MDACC Data Monitoring Committee at the yearly Data and Safety Monitoring Board (DSMB) review, while the primary investigator and other collaborators remained blinded. At the fourth yearly DSMB review, when 48 of 50 patients were evaluated for the primary end point, the DSMB requested a modification to the interim test to be made because the number of patients was close to the formal interim stopping rule. The stated early stopping rule was slightly modified to have its first review when 48 patients had been evaluated. The boundary for early stopping was crossed, and the DSMB recommended early stopping because of a low probability of finding significant results for the primary end point if the study were to continue.

This planned interim analysis, when half of the patients were enrolled, had stopping rules in place a priori that allowed for the early termination of the study in light of evidence that patients in the two groups had similar improvement (early stopping as a result of futility). Although there were no significant findings for group differences in appetite, when melatonin and placebo patients were analyzed as a group, significant correlations were found between percent weight change (from baseline to day 28) and appetite ($P = .024$) and depression ($P = .03$). The change in C-reactive protein (CRP) levels from baseline to day 28 showed no difference ($P = .98$) between the melatonin and placebo arms. Subgroup analysis was performed on 15 patients receiving melatonin who had CRP levels obtained at baseline and at day 28. Wilcoxon two-sample tests did not find significant differences in appetite ($P = .75$), fatigue ($P = .18$), or other ESAS scores when comparing patients with a decline in CRP versus those with the same or an increase in CRP.

DISCUSSION

Melatonin was not effective for improving appetite or other symptoms and did not improve quality of life in patients with advanced GI or lung cancer. Our study was stopped for futility after interim analysis of the data, which suggested that the results were not likely to change even with a larger sample size. Our dose of 20 mg of melatonin is unlikely to be the cause of the negative result. This dose is much higher than the 0.5- to 5-mg dose typically used for other conditions such as jet lag,[17] and there was no difference in the frequency of adverse effects between melatonin and placebo. Other

Table 1. Baseline Demographic and Clinical Characteristics

Characteristic	Placebo Arm (n = 35) No. of Patients	%	Melatonin Arm (n = 38) No. of Patients	%
Age, years				
Mean	59		62	
Range	36-76		32-86	
Female	15	43	12	32
Race				
White	26	74	21	56
Black	6	17	13	34
Hispanic	2	6	3	8
Asian	1	3	0	
Cancer				
Digestive	22	63	19	50
Respiratory	13	37	19	50
Performance score				
70-90	27	77	27	71
50-60	8	23	11	29
Weight, kg				
Median	66		67	
Interquartile range	55-76		56-79	
Extent of weight loss, %				
Median	10		11	
Interquartile range	7-15		8-16	
Fat-free mass, kg				
Median	51		51	
Interquartile range	43-62		44-60	
ESAS scores				
Pain				
Median	2		3	
Interquartile range	0-4		2-5	
Fatigue				
Median	5		5	
Interquartile range	2-7		3-7	
Nausea				
Median	0		1	
Interquartile range	0-3		0-3	
Depression				
Median	0		2	
Interquartile range	0-5		0-5	
Anxiety				
Median	0		2	
Interquartile range	0-3		0-5	
Drowsiness				
Median	3		3	
Interquartile range	0-5		0-5	
Shortness of breath				
Median	0		2	
Interquartile range	0-5		0-6	
Appetite				
Median	6		7	
Interquartile range	4-9		6-8	
Sleep				
Median	3		5	
Interquartile range	1-7		3-7	
Well-being				
Median	5		5	
Interquartile range	2-7		3-7	

Abbreviation: ESAS, Edmonton Symptom Assessment Scale.

Table 2. Quality-of-Life Questionnaires and Symptom Scale Outcomes

Outcome	Change in Score (day 28 − baseline) Melatonin (n = 23)	Placebo (n = 26)	*P*
FAACT cachexia subscale			.95
Median	0	−0.5	
Interquartile range	−3 to −2	−2 to −1	
FACIT-F			.65
Median	−1	3.2	
Interquartile range	−13 to −12	−7 to −12	
Weight*			.17
Median	−0.8	−1.0	
Interquartile range	−2.3 to 0.15	−2.6 to 2	
Appetite*			.80
Mean	−0.83	−1.19	
SD	2.6	2.3	
95% CI	−1.9 to 0.2	−2.1 to −0.3	
Depression*			.28
Median	0	0	
Interquartile range	−1 to 0	−1 to 0	
Pain*			.30
Mean	0.09	0.38	
SD	2.0	2.0	
95% CI	−0.73 to 0.91	−0.39 to 1.15	
Well-being*			.72
Median	−0.39	−0.96	
Interquartile range	−1.9 to 1.1	−2.2 to 0.3	
Insomnia*			.62
Median	−1	−0.5	
Interquartile range	−3 to −1	−2 to −1	

Abbreviations: FAACT, Functional Assessment of Anorexia/Cachexia Therapy; FACIT-F, Functional Assessment for Chronic Illness Therapy–Fatigue; SD, standard deviation.
*According to a 0 to 10 score by the Edmonton Symptom Assessment Scale where 10 equals worst score.

trials showing improved clinical outcomes also used doses of 20 mg, but unfortunately, interpretation of their results is severely limited by methodologic issues such as a lack of blinding and absence of placebo controls.[9,10] The 4-week duration of treatment is also of sufficient length to obtain benefit from an effective intervention for appetite. Past studies of thalidomide and megestrol acetate have shown a rapid improvement of symptoms within 10 days and 2 weeks, respectively. There was no difference in survival between the two groups, and although patients receiving placebo were allowed to receive melatonin after the primary end point had been measured, the median survival of patients was only 134 days on placebo and 140 days on melatonin. Despite the option to change treatment and the possibility of a wash out of any positive effects on survival, analysis of survival was reasonable because patients were on study for more than 20% of the time until death.

There may be other reasons why no difference was found between melatonin and placebo regarding appetite and other clinical outcomes. Both melatonin and placebo groups in our study received symptom control and palliative care in an outpatient clinic throughout the duration of the study, and there was a significant association between weight gain (or less weight loss) and improved appetite and depression. There was no difference, however, in the change from baseline to day 28 between the two arms.

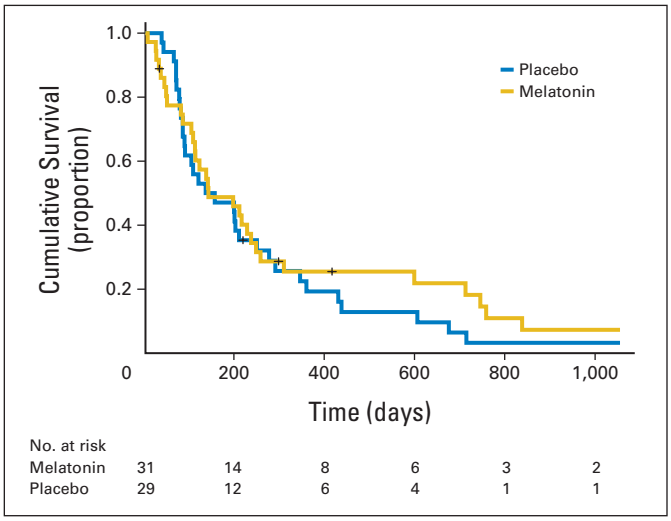

Fig 2. Survival between melatonin (gold; median survival, 140 days; 95% CI, 37 to 243 days) and placebo (blue; median survival, 134 days; 95% CI, 4 to 264 days; $P = .43$) arms.

It is possible that the measured benefit from a specific therapeutic intervention such as melatonin may be not be as marked when accompanied by optimal symptom management in the placebo arm. Although melatonin is reported to modulate tumor necrosis factor α levels and other cytokines[19,20] in patients with solid tumors, melatonin had no effect on CRP levels in our study. Elevated CRP levels have been associated with poor prognosis in patients with cancer, and CRP is regarded as a surrogate marker for the proinflammatory cytokine interleukin-6.

This apparent lack of an anti-inflammatory effect is compatible with the findings of another study in patients with advanced GI cancer, in whom melatonin had no effect on tumor necrosis factorα and other proinflammatory cytokines.[21] The overall inconsistent effect of melatonin on the proinflammatory response associated with cachexia is difficult to explain but may be a result of heterogeneity of tumor type and stage between studies. Although some patients in both groups responded with improvement in symptoms, it is possible that others may have been refractory[22] to the intervention because of their advanced disease. However, all patients enrolled onto our study were ambulatory and had similar characteristics as those admitted to previous studies of melatonin reporting positive outcomes. These unblinded studies found melatonin to be an effective intervention for cachexia, fatigue, and depression in patients with advanced cancer with untreatable metastatic solid tumors.[9,10]

Other intervention studies using ghrelin[23] and megestrol acetate[15,16] have also shown improved appetite and symptom burden in patient populations with advanced cancer where specific tumor therapy was no longer effective or indicated. A consensus classification of cancer cachexia has attempted to define patients who may be at the early precachexia phase and those who may be at the other end of the cachexia trajectory who are refractory to any interventions targeting weight or lean body mass. The concept of refractory cachexia, as defined by this expert panel, has no empirical confirmation, although a recent trial of fish oil for patients with GI cancer showing objective improvements in lean body mass provides some preliminary support for this model of cachexia staging. Patients were referred at initial diagnosis,[24] suggesting the benefit was likely a result of the early inception point, because two large randomized controlled trials and several prior systematic reviews had concluded that fish oil was of no benefit in patients with advanced cancer.

Melatonin might also be a more effective therapy if used much earlier in the disease trajectory, and this should be a consideration in the design of any future intervention trials for appetite or cachexia. However, it should be noted that based on current criteria, which includes a WHO performance status of 3 to 4 and survival less than 3 months, our trial participants would not be considered as having refractory cachexia. Our patients had better performance status, with a Karnofsky score between 70 and 90 in more than 70% of trial participants, and a longer median survival.

The strengths of our study include the double-blind, placebo-controlled design. Although 32% of our patients did not complete the study, this is consistent with other symptom intervention trial[25,26] in the palliative care population with advanced disease. Despite restricting our study population to patients with either advanced lung or GI cancer, there is likely to be some heterogeneity regarding prognosis and functional status because of different tumor types, concurrent chemotherapies, and disease trajectories. Other limitations include the absence of objective functional outcomes and more accurate measures of lean body mass such as dual-energy x-ray absorptiometry (DEXA) or computed tomography (CT) scan. Although there are no guidelines for selecting the most appropriate modalities to measure body composition, DEXA measurements and single-slice CT scans taken in the third lumber vertebra are more precise and reproducible but are more expensive and invasive than BIA.[27] We did not use these modalities because our patients were no longer undergoing routine CT scans and the potential benefit of using DEXA measurements was outweighed by the additional costs and the patient burden of further tests. Although the accuracy of BIA is poor compared with CT scan and DEXA, BIA does demonstrate good short-term precision (test-retest reliability) in patients with advanced cancer,[28] with a precision error of 1%, and may therefore be useful in measuring changes of body composition over time.[29]

In cachectic patients with advanced lung or GI cancer, oral melatonin 20 mg at night did not improve appetite, weight, or quality of life compared with placebo. More research is required to determine whether melatonin has a role in the supportive care of patients earlier in their disease trajectory.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

AUTHOR CONTRIBUTIONS

Conception and design: Egidio Del Fabbro, Lynn Palmer, Eduardo Bruera
Collection and assembly of data: Egidio Del Fabbro, Rony Dev, David Hui
Data analysis and interpretation: All authors
Manuscript writing: All authors
Final approval of manuscript: All authors

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