Symptom Management and Supportive Care

Factors Associated with Response to Methylphenidate in Advanced Cancer Patients

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LEARNING OBJECTIVES

After completing this course, the reader will be able to:

1. Identify the specific patient characteristics associated with response to methylphenidate as treatment for cancer-related fatigue.
2. Compare day 1 patient response to methylphenidate to day 8 response and evaluate as a predictor of long-term improvement.

This article is available for continuing medical education credit at CME.TheOncologist.com.

ABSTRACT

Background. There has been increasing interest in the use of methylphenidate for cancer-related fatigue (CRF) in patients with advanced cancer. However, there is limited literature on the specific patient characteristics associated with response to methylphenidate. Our objective of this study was to identify the specific patient characteristics associated with response to methylphenidate and to compare day 1 response with day 8 response.

Methods. We retrospectively reviewed the records of

patients in two prospective controlled clinical trials that we had conducted who had received methylphenidate for cancer-related fatigue. Baseline patient characteristics, symptoms (as assessed by the Edmonton Symptom Assessment System [ESAS] and Functional Assessment of Chronic Illness Therapy-Fatigue [FACIT-F]), and response (change in fatigue) at the end of day 1 treatment were analyzed to determine their association with response to methylphenidate on day 8.

Results. A total of 82 patients with advanced cancer

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who received methylphenidate for CRF were included in our review. The median age was 55 years, 66% were female, 74% were white, and the most common cancer type was breast (37%). Fifty out of 82 patients (61%) responded to methylphenidate (≥ 7 points in FACIT-F). The intensity of baseline fatigue positively correlated with the response to methylphenidate ($p < .001$). Change in fatigue in response to methylphenidate was not associated with intensity of baseline depression, anxiety, drowsiness, or daily opioid dose. Better improvement of fatigue after treat-

ment on day 1 was associated with more improvement with fatigue on day 8 as assessed by FACIT-F ($p = .0004$) and ESAS ($p = .0001$). Day 1 response as a predictor of day 8 response had a sensitivity of 0.84, a positive predictive value of 0.67, and specificity of 0.6.

Conclusions. Response to methylphenidate is associated with higher baseline fatigue but not with higher baseline depression or sedation. Additionally, day 1 improvement is highly sensitive as a predictor of long-term improvement. *The Oncologist* 2011;16:246–253

INTRODUCTION

Cancer-related fatigue (CRF) is the most common symptom reported in patients with advanced cancer [1, 2]. CRF is defined as “a distressing persistent, subjective sense of tiredness or exhaustion related to cancer or cancer treatment that is not proportional to recent activity and interferes with usual functioning” [3]. CRF is different from the fatigue of everyday life in that it does not usually resolve with rest. It is estimated that CRF is present in about 60% to 90% of patients with advanced cancer [4, 5]. CRF is a multidimensional syndrome that is very likely to interfere with physical and social activities [6, 7].

As a result of the complex etiology of CRF, multiple therapeutic approaches have been investigated to treat this very distressful condition symptomatically. On the basis of recent studies and meta-analysis [8–17], methylphenidate is the most studied pharmacological agent for CRF and preliminary evidence points to it as an effective treatment that is well tolerated in patients with various types of cancer. However, randomized controlled trials showed mixed results [9]. Hence, there is need to understand whether patient-related characteristics have a role in response to treatment with methylphenidate for cancer-related fatigue. This understanding would enable us to personalize the use of methylphenidate to only the patients who respond to this treatment. Methylphenidate has also been found effective in the management of opioid-induced sedation [12, 14] and depression [13]. As both of these conditions are associated with CRF, it could be that the observed benefits of methylphenidate in CRF patients are secondary to an improvement in sedation or mood in these patients.

The objectives of this study were to determine whether specific patient characteristics were associated with response to methylphenidate used for the treatment of cancer-related fatigue. We also examined whether day 8 response could be predicted based upon day 1 response.

MATERIALS AND METHODS

Study Design

The study design and patient recruitment method have been described previously [16, 17]. Briefly, we accessed the original baseline data from two previously conducted prospective clinical trials [16, 17]. We reviewed the demographic information (such as age, gender, ethnicity, cancer diagnoses), Edmonton Symptom Assessment System (ESAS), Mini-Mental State Examination (MMSE), and Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) scores at baseline, CAGE questionnaire (screening tool for alcoholism), treatment history assessment (including morphine equivalent daily dose at baseline), and performance status (using a Zubrod scale) recorded for these patients. We included patients in the study that had received methylphenidate as an intervention for the treatment of CRF after baseline assessments. Of 82 patients identified, 52 had participated in “Patient-controlled methylphenidate for cancer fatigue: a double-blind, randomized, placebo-controlled trial” (Protocol 1: 2003-0537; time period: July 29, 2003 through February 24, 2005) and 30 in “Patient-controlled methylphenidate for the management of fatigue in patients with advanced cancer: a preliminary report” (Protocol 2: ID02-166; time period: August 19, 2002 through March 12, 2003).

In both the studies, patients who agreed to participate in the study were given a 7-day supply of 5-mg methylphenidate tablets. They were directed to use one 5-mg tablet as needed every 2 hours for patient-described significant fatigue. Patients were allowed to take a maximum of 4 tablets per day.

We received approval from The University of Texas MD Anderson Cancer Center Institutional Review Board for the present study and all patients provided written informed consent at the time of their initial enrollments. Due diligence was taken to protect the patients' confidentiality.

Patients

We recruited patients who were seen by the physicians in the Palliative Care Outpatient Clinic, the Pain Clinic, or the Breast Center at MD Anderson Cancer Center or by the oncologists at Lyndon B. Johnson General Hospital to participate in our original studies [16, 17]. Inclusion criteria for the current study included the following: a fatigue score ≥ 4 on a scale of 0–10 (0 = no fatigue, 10 = worst possible fatigue) during the previous 24 hours and lasting for a minimum of 4 days; a normal MMSE score (that is, a score ≥ 24); and a hemoglobin level ≥ 10 g/dL within 2 weeks of enrollment in the study to rule out anemia. Exclusion criteria were the following: a history of tachycardia or uncontrolled hypertension; presence of glaucoma, a severe anxiety disorder, or substance abuse; current use of monoamine oxidase inhibitors, tricyclic antidepressants, clonidine, psychostimulants, steroids, or other medications specifically for fatigue; a history of seizures or uncontrolled central nervous system disease; and clinically significant hepatic or renal dysfunction.

Assessment Tools

Edmonton Symptom Assessment System (ESAS)

We previously designed the ESAS to assess 10 symptoms commonly experienced by cancer patients during the previous 24 hours: pain, fatigue, nausea, depression, anxiety, drowsiness, dyspnea, anorexia, sleep disturbance, and feelings of well-being [18]. The severity of each symptom is rated on a numerical scale of 0–10 (0 = no symptom, 10 = worst possible severity). The ESAS is both valid and reliable in the assessment of the intensity of symptoms in cancer patients [19].

Mini-Mental State Examination (MMSE)

The MMSE is one of the screening tools most widely used by health care providers to evaluate a patient's cognitive status [20]. The MMSE is easy to administer and requires less time to assess a patient's cognitive status than other mental status or neuropsychological tests [20, 21].

Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F)

The FACIT-F 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 4 domains (physical, social, emotional, and functional), plus a 13-item fatigue subscore [22]. This 13-item fatigue subscore was the primary outcome of our study. The patient rates the intensity of fatigue and its related symptoms on a scale of 0–4. The total score ranged

between 0 and 52, with higher scores denoting less fatigue. According to the scoring manual, the negatively worded items on the FACIT-F are reverse-scored so that the higher scores indicate more positive health states. Test-retest reliability coefficients for the FACIT-F subscale have ranged from 0.84 to 0.90 [22]. This scale has been shown to have strong internal consistency ($\alpha = 0.93$ – 0.95) [22–24]. It has a sensitivity of 0.92 and specificity of 0.69 [22–24].

Statistical Analysis

Pooled analysis of patients in two prospective controlled clinical trials who had received methylphenidate for cancer-related fatigue were included [16, 17]. We analyzed the associations between change in FACIT-F fatigue scale score, change in ESAS fatigue item score, and (a) the baseline scores of the symptoms on ESAS and FACIT-F, (b) subsets of FACT scale (physical well-being, functional well-being, social well-being, and emotional well-being), and (c) demographic characteristics, baseline Zubrod performance status, cancer diagnoses, CAGE (alcoholism), and treatment history assessment, including morphine equivalent daily dose at baseline. Spearman correlation coefficients were used when testing for associations between difference scores (change in FACIT-F subscale) and all continuous variables; Wilcoxon rank-sum test was used when testing for associations between difference scores and categorical variables.

Day 8 response was defined as ≥ 7 points change in the FACIT-F score on day 8 of the study. Day 1 response was defined as ≥ 1 point change as assessed by the ESAS fatigue scale after 1 day of methylphenidate treatment.

For the analysis of responses over time, sensitivity was defined as the proportion calculated as the number of patients who were day 1 and day 8 responders (True positive) divided by the number of True positive plus False negative [day 8 responders but day 1 nonresponders]. Specificity was defined as the proportion calculated as the number of True negative patients [day 8 and day 1 nonresponders] divided by the True negative patients plus False negative patients.

Sensitivity, specificity, positive predictive value, and negative predictive value of whether a single question about fatigue intensity rated on a 0–10 scale is equivalent to using a longer, 13-item scale for comparisons of methylphenidate effects on fatigue in people with advanced cancer were calculated. To analyze sensitivity, specificity, positive predictive value, and negative predictive value, we defined response using FACIT-F subscale as a change in FACIT-F subscale scores from baseline to day 8 of ≥ 7 points; response using ESAS fatigue was defined as a decrease of ≥ 2 points.

Table 1a. Patient characteristics (<i>N</i> = 82)	
Characteristic	Frequency (%)
Gender	
Female	54 (66)
Male	28 (34)
Ethnicity	
White	61 (74)
Hispanic	11 (13)
Black	7 (9)
Asian	3 (4)
Primary cancer diagnosis	
Lung	5 (6)
Breast	30 (36)
Gastrointestinal	4 (5)
Genitourinary	5 (6)
Melanoma	1 (1)
Hematologic	10 (12)
Gynecologic	5 (6)
Head and neck cancer	12 (16)
Other ^a	10 (12)
Education	
Less than 6th grade	3 (4)
Less than 12th grade	9 (11)
High school graduate	27 (33)
College or higher	43 (52)

^aSarcoma, brain, skin, unknown primary cancer.

RESULTS

Of the total of 82 advanced cancer patients who received methylphenidate, the median age was 55 years, with 66% being female, 74% being white, and the most common cancer type being breast (37%) (Tables 1a and 1b). There was no significant difference between the two studies based on any demographic characteristics, including percentage of females ($p = .95$), race (white to nonwhite, $p = .59$), and college-educated participants ($p = .24$), with the exception that protocol 1 had a higher number of breast cancer patients at 54% (28 out of 52) than did protocol 2 at 10% (3 out of 30).

The mean ($\pm$ SD) of the daily capsules of methylphenidate taken by patient between day 1 and day 8 (study period) was 2.3 ($\pm$ 1.0) in protocol 1 and 2.3 ($\pm$ 1.2) in protocol 2.

In both protocols 1 and 2, methylphenidate was well tolerated. There was no patient withdrawal due to drug toxicity and no serious adverse events related to methylphenidate. In protocol 1, 1 patient reported slurred speech, 11 patients reported restlessness, 8 reported behavioral

Table 1b. Patient responses (<i>N</i> = 82)		
Variables	Mean (SD)	Median
ESAS items		
Pain	4.64 (2.56)	5
Fatigue	7.46 (1.84)	8
Nausea	1.86 (2.43)	1
Depression	3.67 (3.07)	3
Anxiety	3.35 (3.10)	2
Drowsiness	4.12 (3)	4
Shortness of breath	2.37 (2.58)	2
Appetite	4.27 (3)	4
Sleep disturbance	4.86 (2.81)	5
Well-being	5.14 (2.34)	5
FACT subscales		
Physical	13.48 (5.72)	13
Social	21.79 (5.16)	23
Emotional	15.76 (5.31)	16
Function	13.3 (5.82)	13
Morphine equivalent daily dose (in mg)	152 (280)	47

change, 3 reported skin rash, 7 reported vertigo, 2 reported tachycardia, 17 reported insomnia, and 12 reported anorexia. In protocol 2, 2 patients reported increased restlessness, 1 patient reported increased dizziness, 2 patients reported increased anorexia, 1 patient reported a 2-day self-resolved skin rash, 1 patient reported intermittent vertigo for 2 days, and 1 patient reported self-resolved tachycardia for 3 days.

There was no significant difference (defined as $p < .05$) between the two studies based on the intensity of symptoms at baseline in any group as measured by FACIT-F and ESAS.

For 61% (50 out of 82 patients) of methylphenidate day 8 responders, there were no significant differences by the responder rate in protocols 1 and 2 ($p = .15$).

The intensity of baseline fatigue correlated positively with the response to methylphenidate ($p < .001$; Tables 4, 5, and 6). Change in fatigue in response to methylphenidate was not associated with intensity of baseline depression, anxiety, drowsiness, or daily opioid dose (morphine equivalent daily dose).

There was no association of FACIT-F change and patient characteristics and treatment (Tables 5 and 6).

On the basis of multivariate analysis, baseline ESAS fatigue score was a significant predictor of ESAS fatigue ($p = .02$) at day 8, after drowsiness and depression were controlled for in the model. However, baseline FACIT-F score

Table 2. Functional Assessment of Chronic Illness Therapy-Fatigue subscale and fatigue (Edmonton Symptom Assessment Scale) scores over time

Variable (N = 82)	Mean	SD	Median
Baseline FACIT-F	17.1	9.25	17
Day 8 FACIT-F	29.4	10.75	29
FACIT-F change ^a	12.3	12.0	9
Baseline fatigue (ESAS)	7.4	1.84	8
Day 8 fatigue (ESAS)	4.2	2.43	4
Fatigue (ESAS) change ^b	-3.3	2.6	-3

Effect size: ^a1.235; ^b1.3.

was not a significant predictor of FACIT fatigue ($p = .08$) at day 8 (although there was a trend for significance), after drowsiness and depression were controlled for in the model.

Better improvement of fatigue after methylphenidate treatment at day 1 was associated with better improvement of fatigue at day 8 as assessed by FACIT-F ($p = .0004$) and ESAS ($p = .0001$). In addition, of the 63 of 82 (77%) who responded after 1 day of treatment, 67% (42 out of 63 patients) demonstrated continued response at day 8 ($r = 0.47$, $p = .03$). Day 1 response as a predictor of day 8 response had a sensitivity of 0.84, a positive predictive value of 0.67, and a specificity of 0.6.

The sensitivity of the single-item ESAS fatigue question on a 0–10 scale as an equivalent for the 13-item scale FACIT-F subscale for the comparison of the effects on fatigue in patients with advanced cancer is 45 out of 50, or 90%, the specificity is 16 out of 32, or 50%, the positive predictive value is 74%, and the negative predictive value is 76%.

DISCUSSION

Our main finding was that CRF response to methylphenidate in patients with advanced cancer was associated with a higher intensity of baseline fatigue but not with higher levels of baseline depression or sedation. Improvement in CRF after 1 day of treatment with methylphenidate is highly sensitive for long-term improvement.

The intensity of baseline fatigue correlated positively with the response to methylphenidate. This finding is important because prior studies have shown that the mean score for fatigue in patients presenting to the palliative care center in ambulatory settings is 6 on an ESAS scale of 0–10 (median of 5, SD = 2.91) [15, 25]. However, there was a difference in the prognostic ability of the baseline FACIT-F subscale score ($p = .08$) as compared with baseline ESAS fatigue score ($p = .02$) as a predictor of fatigue at day 8 of

treatment. This may be due to the fact that FACIT-F subscale score refers to fatigue in the last 1 week and ESAS fatigue item score refers to fatigue in the last 24 hours. Hence, methylphenidate may be of particular benefit to the most distressed palliative care population. Future research should address whether such improvement in fatigue leads to increased function and improved adherence to cancer treatment in the subgroup of severely fatigued patients.

Change in fatigue in response to methylphenidate treatment was not related to intensity of baseline depression, anxiety, or drowsiness. Our findings suggest that, in patients with severe fatigue, methylphenidate results in an improvement independent of the severity of baseline depression or drowsiness. An improvement in fatigue has been noticed in prior studies when methylphenidate was used to reduce opioid-induced sedation [9, 12–14].

Better response to methylphenidate after day 1 was associated with better improvement of fatigue as assessed by FACIT-F day 8 ($p = .0004$) and ESAS ($p = .0001$). Day 1 response also has been used in the past as a predictor of response to treatment with methylphenidate in attention deficit hyperactivity disorder [27]. These results confirm that methylphenidate is an attractive option in the palliative care population since its rapid effects will provide immediate relief in a severely distressed population with a short expected life span. The prediction after a single day of treatment of longer-term efficacy is also important because of concerns regarding cost, addictiveness, and side effects with methylphenidate that have been reported in prior attention deficit hyperactivity disorder and CRF studies (side effects can include insomnia, tachycardia, dizziness, restlessness, and anorexia) [8, 27].

Our findings suggest that ESAS fatigue rated on a 0–10 scale is highly sensitive (90%) to detect responses to therapeutic fatigue interventions, when using FACIT-F subscale as a gold standard. However, our findings are highly preliminary due to the small sample size and should be confirmed by larger studies.

Our study has a number of limitations. The variability in the responses of different patients treated with methylphenidate may be caused by the complex multidimensional pathophysiology of fatigue, which results from multiple biological, psychological, and physiological factors, along with the possibility of a placebo effect. These factors may respond to a combined multidisciplinary multidimensional approach such as using combinations of methylphenidate with exercise and/or cognitive behavioral therapy. Future large prospective well-designed studies should be considered to investigate the multimodal approach for the treatment of CRF bias of response to nonspecific treatment in protocol 2 due to lack of placebo despite adequate correc-

Table 3. Associations between changes in FACIT-F fatigue subscale and ESAS fatigue with ESAS baseline symptoms, $N = 82$

ESAS symptom ^a	Spearman correlation coefficient (r), significance (p)	
	FACIT-F fatigue subscale ^b	ESAS fatigue
Pain	$r = 0.12, p = .25$	$r = -0.11, p = .33$
Fatigue	$r = 0.36, p = .0009$	$r = -0.40, p = .0002$
Nausea	$r = -0.05, p = .67$	$r = 0.09, p = .43$
Depression	$r = 0.08, p = .45$	$r = -0.03, p = .79$
Anxiety	$r = 0.07, p < .51$	$r = -0.05, p = .67$
Drowsiness	$r = -0.03, p = .79$	$r = -0.01, p = .95$
Dyspnea	$r = -0.07, p = .55$	$r = 0.03, p = .81$
Anorexia	$r = -0.007, p = .94$	$r = 0.09, p = .45$
Insomnia	$r = 0.001, p = .98$	$r = -0.11, p = .32$
Feeling of well-being	$r = -0.13, p = .24$	$r = 0.16, p = .14$

^aEdmonton Symptom Assessment Scale.
^bFunctional Assessment of Chronic Illness Therapy-Fatigue subscale.

Table 4. Associations between change in FACIT-F Subscale, ESAS fatigue and baseline FACT-G subscales, daily opioid use, and day 1 response

	Spearman correlation coefficient (r), significance (p)	
	FACIT-F subscale	ESAS fatigue
FACT-Physical	$r = -0.12, p = .28$	$r = 0.01, p = .89$
FACT-Social	$r = 0.13, p = .24$	$r = -0.08, p = .49$
FACT-Emotional	$r = -0.07, p = .54$	$r = -0.06, p = .58$
FACT-Function	$r = -0.065, p = .56$	$r = -0.03, p = .78$
FACIT-F subscale	$r = -0.475, p < .0001$	$r = 0.22, p = .048$
Daily opioid use [MEDD ^a]	$r = 0.13, p = .24$	$r = -0.16, p = .16$
Day 1 ESAS response	$r = -0.39, p = .0004$	$r = 0.47, p < .0001$

^aMorphine equivalent daily dose.

tion in calculation of minimal clinical important difference in statistical analyses. Differences in the pharmacogenetic profiles of patients may also have contributed to the variable response to methylphenidate, so future studies to explore possible genetic predictors of response to methylphenidate may further enable clinicians to tailor treatment to the patients most likely to benefit. The anchors used for the assessment of intensity of fatigue as assessed by ESAS is to rate how they have felt on average over the past 24 days, whereas using FACIT-F they rate how they have felt on average over the past 7 days. Hence, comparison of these tools requires caution as the time anchors for the questions are different (24 hours versus 7 days). As cancer-related fatigue is a chronic syndrome, it is likely the impact will be minimal. However, further research is needed.

Methylphenidate is the most comprehensively studied pharmacological agent for the treatment of CRF. We found response to treatment with methylphenidate to be associated with higher intensity of baseline fatigue but not with higher baseline depression or sedation. Day 1 improvement of CRF was highly sensitive for predicting longer-term (day 8) improvement. However, further validation studies are needed.

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Table 5. Change in FACIT-F subscale and change in ESAS fatigue according to patient characteristics

Patient variables	N	Mean (SD)	Median (interquartile)	FACIT-F change ^a (p)	ESAS change (p)
Gender					
Male	27	8.5 (12.1)	8 (1–16)	.06	.16
Female	55	14.2 (11.6)	11 (5–25)		
Race					
White	60	12.8 (12)	11 (4.5–20.5)	.43	.96
Nonwhite	22	11.6 (12.1)	9 (3–20)		
Education					
College education	39	14.2 (12)	14 (6–25)	.10	.14
No college education	42	10.6 (12)	6.5 (3–18)		
Marital status					
Married	58	12.4 (12)	10 (4–21)	.68	.86
Not married	24	12 (12.2)	8 (4–17)		
Zubrod scale					
0,1	25	10 (10)	9 (4–16)	.92	.82
2,3,4	31	10.2 (10.1)	9 (3–14)		
CAGE status					
0	79	12.6 (11.6)	9 (4–20)	.71	.20
1+	3	5.6 (22.1)	9 (–18 to 26)		

^a≥7 points change in the FACIT-F score on day 8 of the study.

Table 6. Change in FACIT-F subscale and ESAS fatigue according to treatment

Treatment	N	Mean SD	Median (interquartile)	FACIT-F change ^a (p)	ESAS change (p)
Chemotherapy					
No	6	7.3 (12.7)	5.5 (–1 to 17)	.23	.17
Yes	76	12.7 (12.1)	10 (4–23)		
Radiotherapy					
No	19	8.5 (9.6)	7 (3–11)	.09	.08
Yes	63	13.5 (12.4)	12 (5–25)		
Surgery			4 (1–8)		
No	5	5.8 (6.5)		.16	.12
Yes	77	12.8 (12.1)	11 (4–21)		
Hormonal					
No	69	12.8 (12.3)	9 (4–21)	.49	.48
Yes	13	9.7 (10)	6 (5–14)		

^a≥7 points change in the FACIT-F score on day 8 of the study.

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AUTHOR CONTRIBUTIONS

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