Patients' Perceptions of Fatigue in Response to Biochemotherapy for Metastatic Melanoma: A Preliminary Study

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Purpose/Objectives: To explore patients' perceptions of fatigue in response to biochemotherapy treatment for metastatic melanoma.

Design: A descriptive-correlational, cross-sectional study.

Setting: A cancer center in the midwestern United States.

Sample: 12 adult patients between the ages of 28–70 who received at least one cycle of biochemotherapy treatment for metastatic melanoma (stages III and IV) from the inpatient or outpatient services of a midwestern cancer center.

Methods: A demographic data sheet and the Revised Piper Fatigue Scale (PFS) were used to collect data at a single point in time after patients received at least one cycle of biochemotherapy.

Findings: The majority of patients who received biochemotherapy reported severe or moderate fatigue. Female patients' total fatigue scores were higher than those of male patients. Fatigue duration varied from hours to months, with a maximum duration of 12 months after biochemotherapy treatment. All of the patients reported that the most direct causes of their fatigue were metastatic melanoma and biochemotherapy treatment.

Conclusions: Patients who received biochemotherapy treatment for metastatic melanoma reported moderate to severe fatigue. Female patients experienced more intense fatigue than male patients. The findings also supported the multidimensionality of fatigue construct identified in prior fatigue studies. The four dimensions/subscales of fatigue assessed by the Revised PFS were highly correlated to total fatigue scores.

Implications for Nursing: Biochemotherapy is a newer treatment modality for metastatic melanoma. Fatigue, one of the severe toxicities from biochemotherapy treatment, necessitates attention from nurses. The findings will assist nurses in teaching patients about fatigue that may be expected during or after biochemotherapy and about self-care strategies to manage fatigue.

Key Points . . .

- Biochemotherapy refers to the combination of cytokines, particularly interleukin-2 and interferon-alfa, with chemotherapy, specifically cisplatin-based chemotherapy.
- Biochemotherapy is a new but promising treatment modality producing overall response rates of 40%–60% in patients with metastatic melanoma.
- Management of moderate to severe treatment-related fatigue should be a priority during and after biochemotherapy to improve patients' quality of life.

Melanoma is the most serious form of skin cancer. Since the early 1970s, its incidence rate has increased by about 6% per year; about 7,400 deaths will be attributed to melanoma in 2002 (American Cancer Society, 2002). Most cases of early primary melanoma are highly curable. However, once the disease metastasizes to multiple body organs, it is associated with a poor prognosis and a mortality rate of more than 95% (Anderson, Buzaid, Ali-Osman, Braunschweiger, & Grimm, 1997; Atkins et al., 1999). The survival time for patients with multiple organ metastases ranges from 6–9 months (Anderson, Buzaid, & Legha, 1995). Several treatment modalities are available for patients with metastatic melanoma, including single-agent and combination chemotherapy regimens, biologic agents (interleukin-2 [IL-2] and interferon-alfa [IFN-a]), vaccines, and biochemotherapy (Anderson et al., 1995, 1997; Atkins et al.; Cohen & Falkson, 1998; Haigh, Difronzo, Gammon, & Morton, 1999). However, the treatment of metastatic melanoma remains less than satisfactory. A single-agent cytotoxic drug (i.e., dacarbazine) has produced response rates of less than 20% (Anderson et al., 1995; Cohen & Falkson). Combination chemotherapy regimens have response rates of

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25%–40%, but durable complete remissions are rare (Anderson et al., 1995; Atkins et al.; Legha et al., 1998). IFN-a and IL-2 alone have produced response rates of 10%–20% (Anderson et al., 1995; Atkins et al.; Legha et al., 1996). Vaccines have very limited activity in advanced melanoma (Anderson et al., 1995; Atkins et al.; Cohen & Falkson; Legha et al., 1998). Of all the treatment modalities, biochemotherapy, specifically cisplatin-based regimens combined with IFN-a and IL-2, have produced the highest clinical response. Biochemotherapy has produced overall response rates of 40%–60% in patients with metastatic melanoma, with durable complete responses of about 10% (Anderson et al., 1998; Legha et al., 1998). Although fatigue was recognized as a pharmacologic toxicity of biochemotherapy in the medical literature (Legha et al., 1996), the authors of this article found no studies of fatigue experienced by patients who received biochemotherapy treatment for metastatic melanoma. The purpose of this preliminary study was to explore patients' perceptions of fatigue in response to biochemotherapy treatment for metastatic melanoma.

Literature Review

Biochemotherapy

The combination of cytokines, particularly IFN-a and IL-2, with chemotherapy for patients with metastatic melanoma has been a focus of investigation since the early 1990s. Such combination is referred to as biochemotherapy or chemoimmunotherapy (Anderson et al., 1998; Cohen & Falkson, 1998; Legha et al., 1998). The rationale for biochemotherapy is based on the independent antitumor activity of both IL-2 and IFN-a against melanoma and their lack of cross-resistance with cytotoxic chemotherapy (Legha et al., 1997). Among a variety of biochemotherapy regimens, cisplatin-based regimens with both IL-2 and IFN-a have achieved consistently higher response rates (more than 50%) (Anderson et al., 1997; Legha et al., 1998). Although the precise mechanism of antitumor effect of biochemotherapy regimens is unknown, two hypotheses have been proposed based on preclinical data: either chemotherapy enhances the antitumor effect of biologic agents or biologic agents enhance the antitumor cytotoxic effect of chemotherapy (Anderson et al., 1997). Three major biochemotherapy regimens for patients with malignant melanoma currently are being studied.

- Neoadjuvant cisplatin, vinblastine, dacarbazine with IL-2 and IFN-a for patients with stage III melanoma
- A phase II study using cisplatin, temozolomide, IL-2, and IFN-a
- A phase II study using carmustine, dacarbazine, cisplatin, tamoxifen, IL-2, and IFN-a

Toxicities from biochemotherapy include myelosuppression, significant nausea and vomiting, flu-like syndrome (i.e., chills, fever, malaise, and fatigue), and capillary leak syndrome (i.e., shift of intravascular fluid to extravascular spaces resulting in significant hypotension and generalized edema) (Legha et al., 1996, 1998).

Fatigue Definitions

Fatigue as a construct is defined by a variety of disciplines according to the requirements of each domain (Ream & Richardson, 1996). To a physiologist, fatigue is considered a decrease in the capacity to perform work; a pathologist may view fatigue as an indicator of a neuromuscular or metabolic disorder; to a psychologist, fatigue may be a symptom of depression associated with decreased motivation to engage in mental and physical activities (Dalakas, Mock, & Hawkins, 1998). All of those definitions focus on selected dimensions of fatigue, rather than integrating its different dimensions.

Nurse researchers recognize fatigue as a multidimensional construct (Fu, LeMone, McDaniel, & Bausler, 2001; Piper, Lindsey, & Dodd, 1987; Piper, Lindsey, et al., 1989; Ream & Richardson, 1996; Tiesinga, Dassen, & Halfens, 1996). Nurses also realize that the subjective dimension of fatigue provides insightful perceptions because no objective correlates for fatigue have been identified (Crosby, 1991; Schwartz, Jandorf, & Krupp, 1993). The more frequently used definitions include those from the North American Nursing Diagnosis Association (NANDA) (2001), Piper et al. (1987), and Ream and Richardson. NANDA defines fatigue as "an overwhelming sustained sense of exhaustion and decreased capacity for physical and mental work at usual level" (p. 89). Based on their multidimensional fatigue framework, Piper et al. (1987) defined fatigue as "a subjective feeling of tiredness that is influenced by circadian rhythm. It can vary in unpleasantness, duration, and intensity" (p. 19). In a concept analysis of fatigue, Ream and Richardson defined fatigue as "a subjective, unpleasant symptom which incorporates total body feelings ranging from tiredness to exhaustion creating an unrelenting overall condition which interferes with individuals' ability to function to their normal capacity" (p. 527). Tiesinga et al. also identified the multidimensionality of fatigue. They proposed that research models should focus on the subjective dimension because of the subjective nature of fatigue. By validating the defining characteristics of fatigue using a multivariate analysis, Fu et al. also verified the multidimensionality of fatigue construct.

Theoretical Fatigue Framework for Patients With Cancer

In 1987, Piper et al. developed a fatigue framework for patients with cancer centered on the multifactorial causes of fatigue, as well as the subjective (i.e., perceptual) and objective (i.e., physiologic, biochemical, and behavioral) indicators of fatigue. Multifactorial causes of fatigue in patients with cancer include treatment, disease, psychology, environment, and symptom patterns (Piper et al., 1987). Based on the fatigue framework, Piper et al. (1987, 1998) proposed a multidimensional measurement model for subjective and objective manifestations of fatigue. In the model, subjective perception was believed to be key to understanding fatigue. The subjective dimension of fatigue consists of the mental, physical, and emotional symptoms of fatigue (i.e., the sensory dimension); the emotional attributes of fatigue (i.e., the affective dimension); the impact of fatigue on cognition or mood (i.e., the cognitive/mood dimension); and the impact and distress of fatigue on daily living (i.e., the behavior/severity dimension). That theoretical fatigue framework for patients with cancer was employed in this preliminary study as a systematic method to describe the fatigue phenomenon in patients who received biochemotherapy treatment for metastatic melanoma.

Measurements of Fatigue

Researchers from a variety of disciplines have attempted to measure fatigue by assessing observable phenomena, such as changes in adenosine triphosphate, serum lactate, pH levels, and physical ability and strength (Piper, 1997; Tiesinga et al. 1996). However, many researchers consider objective measurements to be inappropriate because of the subjective nature of fatigue and its multidimensionality. Objective and subjective indicators often are not highly correlated (Crosby, 1991; Schwartz et al., 1993). Consequently, using objective measurements may not accurately reflect individuals' perceptions of fatigue.

Self-report instruments that measure individuals' subjective perceptions of fatigue are essential to understanding the phenomenon. Different measures to assess subjective dimensions of fatigue have been developed (Aaronson et al., 1999; Holley, 2000; Piper, Lindsey, et al., 1989; Ream & Richardson, 1996; Schwartz, 1998; Tiesinga et al., 1996). For example, the Piper Fatigue Scale (PFS) was developed to measure subjective multidimensionality of fatigue based on Piper's theoretical framework of fatigue (Piper, Lindsey, et al., 1989). In 1998, Piper et al. revised the PFS into a more concise and user-friendly instrument.

Methods

Design and Sample

This preliminary study was designed using a descriptive-correlational, cross-sectional approach to explore patients' perceptions of fatigue in response to biochemotherapy treatment for stages III and IV metastatic melanoma. All patients diagnosed with metastatic melanoma who received at least one cycle of biochemotherapy over a period of three months at the study site, a midwestern cancer center, were considered potential subjects. To be included in the study, a patient had to be 18 or older, be able to read and write English, and give informed consent. Of 18 eligible patients, 12 agreed to participate.

Procedure

After the institutional review board approved the study, recruitment and data collection were conducted from July through October of 2000. The primary investigator collected data via a survey that was either mailed to the patients or given to them at the cancer center. Each survey package contained a letter from the researcher explaining the purpose of the study, data collection tools, and an envelope with return address and postage. All patients were told that participation in the study was optional and that completion of the survey package would take about 10 minutes. Confidentiality was emphasized. Completion and return of the survey package represented consent to participate in the study. Of the 12 participants, five patients completed the survey package at the cancer center; seven completed it and returned it by mail. Another six patients were contacted by mail twice but did not respond.

Instruments

The **Demographic Data Sheet (DDS)** was used to obtain information about age, gender, years of education, diagnosis of metastatic melanoma, marital status, and confirmation of biochemotherapy received.

The **Revised PFS** (Piper et al., 1998) is a reliable, valid, concise, and user-friendly instrument that measures subjective multidimensions of fatigue. It was developed based on Piper's theoretical framework of fatigue. The instrument consists of 22 items numerically scaled from 0–10 that measure four dimensions of subjective fatigue: sensory (five items), affective (five items), cognitive/mood (six items), and behavior/severity (six items). Five additional items were not used to calculate subscale or total fatigue scores. One assesses duration of fatigue; the other four are open-ended questions that provide qualitative data. The standardized alpha (Cronbach's alpha) for the entire 22-item scale was 0.97. The standardized alphas for subscales were greater than 0.92. Multiple fatigue studies of patients with cancer and healthy women have used PFS as the assessment instrument of choice (Berger, 1998; Berger & Higginbotham, 2000; Fu et al., 2001).

Data Analysis

After data entry, the data file was checked for accuracy. The Statistical Analysis System was used to analyze the data. Descriptive statistical analysis was applied to describe the sample demographic data, as well as patients' total and subscale fatigue scores. Pearson's correlation coefficients were applied to explore the correlative relationship of each individual item and each subscale to the total fatigue score. Content analysis was used to analyze the qualitative data.

Findings

Sample

A sample of 12 patients who received biochemotherapy treatment for metastatic melanoma at a midwestern cancer center was recruited over a three-month period from a population of 18 patients. Five were men and seven were women. The age range of the sample was 28–70 years old with a mean age of 52 years. Ten participants were married, one was single, and one was widowed. Seven participants had earned university degrees, and the remaining five had graduated from high school. All participants received 1–6 biochemotherapy cycles.

Revised PFS

All participants reported having been fatigued after at least one cycle of biochemotherapy treatment. Eight reported that fatigue lasted months, with a maximum of 12 months; two patients reported it lasted weeks; two others said it lasted more than four hours. Patients' perceptions of fatigue were measured by the total and four subscale scores of the Revised PFS. Higher scores reflected more intense fatigue. Fatigue scores, which range from 0–10, were divided arithmetically into categories of low (0–3.3), moderate (3.3–6.7), and severe (6.8–10). The total fatigue mean score for the sample was 6.19, with a range of 1.29–10. Seven patients had total fatigue scores in the severe category, two in the moderate category, and three in the low category. Fatigue scores were highest in the sensory dimension ($\overline{X}$ = 6.62), followed by affective ($\overline{X}$ = 6.4), cognitive/mood ($\overline{X}$ = 6.28), and behavior/severity ($\overline{X}$ = 5.92). The mean total fatigue scores were 6.97 for women and 5.8 for men (see Table 1).

Pearson's correlation coefficients were used to analyze the relationship of each subscale to total fatigue scores. High correlation was found for the dimensions of behavior/severity

Table 1. The Revised Piper Fatigue Scale: Total and Subscale Fatigue Scores

Sample	Behavior/ Severity	Affective	Sensory	Cognitive/ Mood	Total Score
Total					
Minimum	0.00	2.00	2.20	1.83	1.29
Maximum	10.00	10.00	10.00	10.00	10.00
$\bar{X}$	5.92	6.40	6.62	6.28	6.19
SD	3.81	2.52	2.60	2.65	2.85
Female					
$\bar{X}$	6.67	5.95	7.15	7.96	6.97
SD	3.90	3.15	1.69	1.65	2.55
Male					
$\bar{X}$	5.54	6.66	6.35	5.44	5.80
SD	4.02	2.58	3.04	2.59	3.08

(r = 0.98), sensory (r = 0.95), affective (r = 0.94), and cognitive/mood (r = 0.91). Correlations of each individual item to total fatigue scores are presented in Table 2. All items achieved correlation greater than 0.7. Of the 22 items, 12 achieved correlations greater than 0.9.

Open-ended questions were content analyzed. When asked, "Overall, what do you believe is directly contributing to or causing your fatigue?" all 12 patients responded that cancer, particularly metastatic melanoma, and biochemotherapy treatment directly caused their fatigue. In response to the question "Overall, the best thing you have found to relieve your fatigue is:" eight of the participants responded "resting or sleeping"; two patients responded, "Get up and do something"; one patient answered, "Have not found anything to help"; and another said, "Drink a beer." In response to the question "Is there anything else you would like to add that would describe your fatigue better to us?" five patients stated "overwhelming fatigue," "tired," or "no energy"; seven patients said, "No." In response to the question "Are you experiencing any other symptoms right now?" seven patients stated, "No"; five patients specified other symptoms as "nausea/vomiting," "pain," "mental sluggishness," "lack of appetite," and "depression."

Discussion

The findings from this preliminary study revealed that the majority of patients who received biochemotherapy reported that they experienced severe or moderate fatigue. The majority of patients in the study reported having been fatigued after at least one cycle of biochemotherapy treatment; the fatigue lasted for months, with a maximum of 12 months. Thus, for a majority of the patients in this preliminary study, fatigue was a phenomenon of moderate to severe intensity with a duration of months. Female patients' total fatigue scores were higher than those of male patients. A sharp difference was found between women and men in the dimensions of behavior/severity and cognitive/mood. The female sample reported higher fatigue scores in both dimensions, indicating that female patients receiving biochemotherapy might experience more intense fatigue in those dimensions.

The findings also supported the multidimensionality of fatigue. The four dimensions, or subscales, of fatigue assessed by the Revised PFS were highly correlated to total fatigue scores. The behavior/severity dimension had the highest correlation and the cognitive/mood dimension had the lowest correlation. The correlation of each item to total fatigue scores also was high, particularly in regard to behavior/severity—overall interference with enjoyable activities, and fatigue intensity/severity. This might indicate that fatigue was manifested more clearly in the behavior/severity dimension. The lowest correlation of individual items to total fatigue scores was found in the affective dimension—protective/destructive, and positive/negative—and in the dimension of cognitive/mood—ability to concentrate, and ability to remember. These lower correlations might be the result of the ambiguity of the items; people might not consider that fatigue possesses destructive or negative characteristics, and they might not consider the "ability to concentrate or to remember" an aspect of fatigue.

The findings from the qualitative analysis confirmed severe fatigue reported by patients undergoing biochemotherapy. Four patients in the study stated that "overwhelming fatigue," "tired," "no energy," or "long-term fatigue" would describe their fatigue better. The findings also supported Piper's theory of treatment pattern and disease pattern as causes of fatigue. All of the patients reported that the most direct causes of their fatigue were metastatic melanoma and biochemotherapy treatment. The findings also supported Piper's theory of symptom pattern and psychological pattern as causes of fatigue. Five patients in the study reported "other" symptoms while they experienced fatigue, including nausea and vomiting, pain, mental sluggishness, lack of appetite, and depression. The

Table 2. Correlation Between Total Fatigue Scores and Subscales Scores

Subscales and Items	r
Behavior/Severity	0.981
Fatigue distress	0.920
Interference with work/school activities	0.946
Interference with socializing with friends	0.913
Interference with sexual activity	0.949
Overall interference with enjoyable activities	0.964
Fatigue intensity/severity	0.966
Affective Meaning	0.941
Pleasant/unpleasant	0.882
Agreeable/disagreeable	0.876
Protective/destructive	0.748
Positive/negative	0.784
Normal/abnormal	0.929
Sensory	0.949
Strong/weak	0.927
Awake/sleepy	0.930
Lively/listless	0.934
Refreshed/tired	0.804
Energetic/unenergetic	0.829
Cognitive/Mood	0.908
Patient/impatient	0.917
Relaxed/tense	0.916
Exhilarated/depressed	0.858
Ability to concentrate	0.769
Ability to remember	0.725
Ability to think clearly	0.820

majority of patients identified "rest/sleep" and "doing something" as the best interventions to relieve fatigue. These self-care behaviors also were identified in previous studies of fatigue in patients receiving chemotherapy (Graydon, Bubela, Irvine, & Vincent, 1995; Richardson & Ream, 1997; Robinson & Posner, 1992).

Limitations

This preliminary study was exploratory in nature. The small sample size and single-site data collection process restrict its generalizability. Multiple sites to increase sample size and decrease geographic limitation would improve future research. This study also was limited by the data collection process and cross-sectional design. To explore patterns and degrees of fatigue in response to biochemotherapy treatment, future research should employ a longitudinal design and improve the process of data collection by collecting data prior to treatment, as well as according to specific cycles and regimens of biochemotherapy treatment. Finally, this study was limited because it included only biochemotherapy patients. Future studies should provide a comparison of patients who receive biochemotherapy, biotherapy, and chemotherapy for different types of cancer.

Implications for Nursing Research and Practice

Biochemotherapy is a newer treatment modality for patients with metastatic melanoma. The authors found no studies in the nursing literature concerning biochemotherapy and patients with metastatic melanoma. Fatigue, one of the severe toxicities of biochemotherapy treatment, necessitates attention from nurses. Because very few pharmacologic or medical interventions are effective in managing fatigue, nursing plays the most important role in this area (Dalakas et al., 1998). The findings from this preliminary study will help nurses assist patients in developing self-care interventions and coping strategies to manage fatigue during and after receiving biochemotherapy. To apply self-care interventions, an individual first must learn how to recognize a demand or need for actions and then how to perform the actions to meet that demand or need (Orem, 1995). Individuals must have some understanding of the meaning and value of self-care to make rational and reasonable judgments and decisions. Nursing interventions should aim to increase patients' knowledge about the expectation of fatigue from biochemotherapy and decision making about effective self-care interventions. Having realistic expectations may reduce the distress patients experience and enable them to employ self-care interventions and coping strategies.

Nurses should focus on teaching self-care interventions based on the three major strategies proposed by Piper, Rieger, et al. (1989): energy conservation, effective energy use, and energy restoration. Energy conservation focuses on encouraging adequate (not excessive) rest and sleep throughout the day (e.g., planned one-hour naps in mid-morning and early afternoon), delegating housework to others, and permitting others to help (Winningham et al., 1994). Effective energy use encourages prioritizing important tasks and letting go of those that can be delegated or delayed. Energy restoration includes aerobic exercise (MacVicar, Winningham, & Nickel, 1989); scheduled, 10-minute, brisk walks every four hours; maintaining adequate nutrition (Aistars, 1987); progressive muscle relaxation (Frank-Stromborg, 1986), and maintenance of optimal mood. Although patients reported their responses to these self-care interventions, the effectiveness of each individual intervention has not been researched rigorously. Future studies should focus on establishing dosing and schedules for each intervention, as well as their effectiveness.

Fatigue is an overwhelming symptom experienced by a variety of patients with cancer, including patients with melanoma who are undergoing biochemotherapy. Nurses should be educators and supporters throughout the course of treatment and disease. Nursing interventions should include educating patients about fatigue expectation; encouraging exercise; teaching about energy-saving, relaxation, and distraction techniques; relieving other symptoms; modifying dietary needs; and assessing and meeting patients' emotional and spiritual needs. With knowledge provided by nurses, patients may improve their coping abilities to manage fatigue during and after biochemotherapy.

Although fatigue has been studied by many health-related disciplines, its nature and characteristics are not well recognized and widely accepted (Aaronson et al., 1999; Ream & Richardson, 1996; Tiesinga et al., 1996). Nursing research, in collaboration with other disciplines, may lead to better understanding of fatigue. To date, no systematic program exists for management of fatigue as a multidimensional phenomenon. Future fatigue research and practice should focus on providing systematic and integrative management programs based on strategies of energy conservation, effective energy use, and energy restoration (Piper, Rieger, et al., 1989). Such a systematic and integrative program should encompass a variety of interventions, such as scheduling rest and sleep periods during the day, performing aerobic exercise and progressive muscle relaxation, consuming an adequate diet, and assessing and meeting emotional and spiritual needs. Effective intervention programs to manage fatigue will improve the quality of life of patients with metastatic disease.

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For more information . . .

- Archives of cancer-fatigue@listserv.acor.org
  www.listserv.acor.org/archives/cancer-fatigue.html
- Cancer Fatigue
  www.cancerfatigue.org/
- Cancer Care: Managing your fatigue
  www.cancercare.org/managing/fatigue/index.asp

These Web sites are provided for information only. The hosts are responsible for their own content and availability. Links can be found using ONS Online at www.ons.org.