Identification of Latent Classes in Patients Who Are Receiving Biotherapy Based on Symptom Experience and Its Effect on Functional Status and Quality of Life

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Purpose/Objectives: To identify subgroups of patients receiving biotherapy with pain, fatigue, sleep disturbance, and depression and to determine functional status and quality of life differences between subgroups.

Design: A descriptive, prospective, cohort study design.

Setting: Internet-based survey.

Sample: 187 patients with cancer receiving biotherapy.

Methods: Pain intensity, Piper Fatigue Scale, General Sleep Disturbance Scale, Center for Epidemiological Studies–Depression, Karnofsky Performance Scale, and the Multidimensional Quality of Life Scale–Cancer were used at two time points one month apart (T1 and T2). Latent profile analysis identified subgroups.

Main Research Variables: Biotherapy, symptoms, functional status, and quality of life.

Findings: At T1 (N = 187), five patient subgroups were identified, ranging from subgroup 1 (mild fatigue and sleep disturbance) to subgroup 5 (severe on all four symptoms). At T2 (N = 114), three patient subgroups were identified, ranging from subgroup 1 (mild pain, fatigue, and sleep disturbance without depression) to subgroup 3 (mild pain, moderate fatigue, and sleep disturbance with severe depression). At each time point, the patient subgroup with the most severe symptoms showed significantly lower functional status and quality of life.

Conclusions: As with other cancer treatments, biotherapy can be divided into similar patient subgroups with four prevalent symptoms. Subgroups of patients differ in functional status and quality of life as a result of symptom severity.

Implications for Nursing: Clinicians should assess and identify patients with severe levels of the four prevalent symptoms and offer appropriate interventions. Future study is needed to investigate the factors that contribute to symptom severity and to examine the occurrence of symptom clusters that may place patients at increased risk for poorer outcomes.

The majority of research on symptoms in patients with cancer is focused on the characteristics of a single symptom (e.g., pain, fatigue) or an association between symptoms (e.g., depression, anxiety). Although this approach advances the understanding of some symptoms, the findings are not very helpful when clinicians need to manage a patient with multiple, concurrent symptoms. In response to this lack of knowledge, a growing body of oncology research has examined the occurrence of symptom clusters and their effect on patient outcomes. A symptom cluster is defined as three or more concurrent symptoms that are related to each other (Dodd, Miaskowski, & Paul, 2001). In addition, Dodd, Dibble, et al. (2001) proposed that symptom clusters have adverse effects on patient outcomes. Since the concept of a symptom cluster in patients with cancer was proposed in 2001, researchers have endeavored to understand this complex issue. A literature search on PubMed using the keywords *symptom cluster* and *cancer* yielded more than 100 citations. Numerous studies have used the conceptual approach of grouping of symptoms to create symptom clusters (Chen & Tseng, 2006; Chow et al., 2008; Cleeland et al., 2000; Gift, Jablonski, Stommel, & Given, 2004; Gift, Stommel, Jablonski, & Given, 2003; Gleason et al., 2007; Kim et al., 2009; Kim, Barsevick, Tulman, & McDermott, 2008; Tseng, Cleeland, Wang, & Lin, 2008; Wang et al., 2003, 2006; Wang, Tsai, Chen, Lin, & Lin, 2008); however, only three studies have used the conceptual approach of grouping individuals by similar symptom experiences. These three studies have identified four distinct subgroups of patients with cancer based on their experiences with four preselected symptoms: pain, fatigue, sleep disturbance, and depression (Dodd, Cho, Cooper, & Miaskowski, 2009; Miaskowski et al., 2006; Pud et al., 2008). These preselected symptoms are not only highly prevalent and distressing, but they also are known to be related to each other (Barsevick, 2007; Dodd et al., 2009). The reason findings from the current study will be compared to these three studies is threefold: (a) the same conceptual approach is used (grouping of individuals), (b) the same preselected symptoms are used, and (c) with fulfillment of the previous two conditions, comparison of symptom clusters between biotherapy and other cancer treatments is possible.

In a cross-sectional study with a heterogeneous sample of 191 outpatients with cancer receiving active treatment (Miaskowski et al., 2006), four relatively distinct subgroups were identified: patients with low levels of all four symptoms, patients with high fatigue and low pain, patients with low fatigue and high pain, and patients with high levels of all four symptoms. No differences were found among the four subgroups in any demographic characteristics except age and marital status. The subgroup reporting high levels of all four symptoms were significantly younger ($p = 0.04$) and were less likely to be married or partnered ($p = 0.007$) than patients in the subgroup reporting low levels of all four symptoms. No differences were found among the four subgroups in any disease or treatment characteristics. The subgroup reporting low levels of all four symptoms had significantly better functional or performance status and quality of life (QOL) than the subgroup reporting high levels of all four symptoms.

In a study of 228 outpatients with mixed types of cancer who were receiving active treatment (Pud et al., 2008), cluster analysis was used to identify subgroups based on their experiences with the same four symptoms. Again, four distinct subgroups were identified: low levels of all four symptoms, high fatigue and low pain, moderate fatigue and high pain, and high levels of all four symptoms. No differences were found among the four subgroups on any demographic, disease, or treatment characteristics. The group that reported high levels of all four symptoms had significantly poorer functional status and QOL than the other three groups. The findings replicated those reported in Miaskowski et al. (2006).

In the third study (Dodd et al., 2009), the only longitudinal study, 112 women with breast cancer were recruited at the time of their initial cycle of chemotherapy. Cluster analysis identified four relatively distinct subgroups of patients based on their symptom experiences at both the beginning of chemotherapy and at the end of treatment. Three distinct subgroups were identified approximately one year after the patients' chemotherapy began. Again, the subgroup with high levels of all four symptoms had significantly lower functional status and QOL scores at T2 and T3. Conversely, patients with low levels of all four symptoms had significantly higher functional status and QOL. These findings corroborate with the cross-sectional studies (Miaskowski et al., 2006; Pud et al., 2008) and suggest that these patient subgroups persist over time.

Although the three previous studies recruited patients on active treatment, the number of patients receiving biotherapy was very low, ranging from virtually none to 5% (Dodd et al., 2009; Miaskowski et al., 2006) and 11% (Pud et al., 2008). In addition, a thorough search of the cancer literature using the key terms of *biotherapy and symptom cluster*, *monoclonal and symptom cluster*, *Herceptin®* (trastuzumab, Genentech) *and symptom cluster*, *interferon and symptom cluster*, *BCG* (Bacillus Calmette-Guérin) *and symptom cluster*, and *biological therapy and symptom cluster* yielded no citations. Therefore, by recognizing this gap in the literature, the goals of this current study were to identify subgroups of patients receiving biotherapy based on their experiences with the symptoms of pain, sleep disturbance, fatigue, and depression, and describe whether these subgroups differed on functional status and QOL.

Methods

Participants and Setting

A descriptive, prospective, cohort study design was used for this Internet-based survey. Patients completed online questionnaires on the symptoms of pain, fatigue, sleep disturbance, depression, and selected patient outcomes (i.e., functional status, QOL) after receiving the first dose of biotherapy (T1) and again one month later (T2). The rationale for selecting T1 was to understand the severity and nature of the symptoms at the initiation of biotherapy treatment.

To compare studies, the time frame of a one-month follow-up approximates the data collection times from the other studies (Dodd et al., 2009; Miaskowski et al., 2006; Pud et al., 2008).

A healthcare education and information company, NexCura (Seattle, WA), was the site of data collection. The majority of NexCura's patients have given permission for NexCura to contact them via e-mail for subsequent studies and relevant information about their condition. This contact opportunity was used by the authors to recruit study participants.

The study was approved by the University of California, San Francisco, Committee on Human Research. All patients electronically signed a written, informed consent through NexCura. Patients had to be receiving biotherapy defined as "treatment to boost or restore the ability of the immune system to fight cancer, infections, and other diseases" (National Cancer Institute, 2009). The specific biotherapies administered to patients in this study included trastuzumab for breast cancer; BCG vaccine for bladder cancer; aldesleukin or interferon gamma for kidney cancer; and interferon alfa-2b, ibritumomab tiuxetan, tositumomab, or rituximab for non-Hodgkin lymphoma. A total of 934 patients responded to the NexCura registration, and 187 completed the online survey at T1. The primary reasons for failure to complete the questionnaires at T1 were not receiving biotherapy ($n = 235$), would receive biotherapy later ($n = 60$), did not want to participate ($n = 44$), did not have cancer ($n = 30$), or were receiving multiple types of biotherapy ($n = 10$). An additional 367 did not complete the T1 online survey. One month later (T2), 114 completed the second part of the online survey. Seventy-three patients did not respond to the reminder for reasons unknown.

Instruments

A demographic questionnaire was completed at T1 and provided information on age, ethnicity, gender, marital status, years of education, and current employment.

The **Karnofsky Performance Status (KPS)** (Karnofsky, 1977), completed at T1, measures the physical abilities of the patient based on the definitions provided on a 0%–100% scale. The scale is used extensively in oncology to evaluate performance status. A score of 100% indicates that the individual is able to carry on normal activities. A score of 30% indicates that the individual is severely disabled and needs to be hospitalized. The KPS has well-established interrater reliability, concurrent validity, and criterion validity (Hyde, Wolf, McCracken, & Yesner, 1973; Karnofsky, 1977; Mor, Laliberte, Morris, & Wiemann, 1984; Schag, Heinrich, & Ganz, 1984). In clinical trials, pretreatment KPS score was a good predictor of response to cancer treatment (Dodd, 1988).

The **medical history form**, completed at T1, obtained information on cancer diagnosis, stage of disease, type of initial cancer therapy, and current therapy. In addition, patients used a "yes or no" format to indicate the presence of 24 comorbid conditions.

The **worst pain intensity scale**, a single-item scale completed at T1 and T2, is a numeric rating scale with the descriptive anchors of 0 (no pain) to 10 (worst pain imaginable) that asked patients to rate their worst pain in the prior 24 hours. A descriptive numeric rating scale is a valid and reliable measure of pain intensity (Jensen, 2003).

The **Piper Fatigue Scale (PFS)** (Piper et al., 1998), completed at T1 and T2, consists of 22 items and four subscales: behavior and severity, affective and meaning, sensory, and cognitive and mood. Each item was rated on a numeric rating scale that ranged from 0 (none) to 10 (a great deal). The average total fatigue score is calculated by summing participants' responses and then dividing by the number of items. The PFS is a standardized scale that has excellent reliability and validity (Winningham, 1998; Young-McCaughan & Sexton, 1991). In the current study, Cronbach alpha for the PFS was 0.97.

The **General Sleep Disturbance Scale (GSDS)** (Lee, 1992), completed at T1 and T2, consists of 21 items that evaluate various aspects of sleep disturbance (quality and quantity of sleep, sleep latency, waking up during sleep, daytime sleepiness, and medication use). Items are rated from 0 (never) to 7 (every day) to yield a total score that can range from 0 (no disturbance) to 147 (extreme disturbance). A score higher than 43 reflects sleep disturbance in the general population (Lee & Gay, 2004). The GSDS has well-established validity and reliability (Dodd et al., 2009; Lee & DeJoseph, 1992; Lee, Portillo, & Miramontes, 1999; Miaskowski et al., 2006; Miaskowski & Lee, 1999; Pud et al., 2008). In the current study, Cronbach alpha for the GSDS was 0.87.

The **Center for Epidemiological Studies–Depression (CES-D)** scale (Radloff, 1977), completed at T1 and T2, is a 20-item self-report instrument that measures the clinical symptoms of depression. Each item is rated on a four-point scale (0–3) that describes its frequency of occurrence in the previous week (Radloff, 1977). Scores can range from 0–60, with higher scores reflecting more depression. A score of 16 or higher indicates a need for a clinical follow-up assessment. The CES-D has well-established reliability and validity estimates across samples of patients with cancer (Dodd et al., 2009; Dodd, Miaskowski,

Table 1. Demographic and Clinical Characteristics of Participants and Nonparticipants

	Time 1		Time 2			
	Participants (N = 187)		Participants (N = 114)		Nonparticipants (N = 73)	
Characteristic	$\bar{X}$	SD	$\bar{X}$	SD	$\bar{X}$	SD
Age (years)	52	11	54	11	49	9
Characteristic	**n**	**%**	**n**	**%**	**n**	**%**
Gender						
Male	31	17	20	18	11	15
Female	154	82	94	83	61	84
Missing	2	1	–	–	1	1
Education						
High school or higher	187	100	114	100	73	100
Ethnicity						
Caucasian	173	93	106	93	67	92
Marital status						
Married	139	76	86	78	53	74
Employment						
Full- or part-time	101	54	61	54	40	55
Diagnosis and treatment						
Breast	128	68	79	69	50	68
• Trastuzumab	110	–	59	–	50	–
Lymphoma	29	16	16	14	13	18
• Rituximab	26	–	12	–	13	–
Bladder	26	14	16	14	10	14
• Bacillus Calmette-Guérin	24	–	15	–	10	–
Kidney	4	2	3	3	1	1
• Interleukin-2	2	–	–	–	–	–
Concurrent chemotherapy	140	75	84	74	56	77
State						
California	25	13	14	12	11	15
Ohio	11	6	8	7	–	–
Pennsylvania	–	–	–	–	5	7
Florida	10	5	7	6	–	–
Illinois	–	–	–	–	4	5
Other	141	75	85	74	53	73

Note. Sample size varies from incomplete data. Because of rounding, not all percentages total 100.

Table 2. Fit Indices of Latent Profile Analyses in Patients Receiving Biotherapy at Time 1 and Time 2

	Time 1				Time 2		
Fit Indices	**Class 2**	**Class 3**	**Class 4**	**Class 5[a,b]**	**Class 2**	**Class 3[a,b]**	**Class 4**
Parameter estimates	19	24	29	34	19	24	29
Loglikelihood	–2,180.65	–2,167.76	–2,155.7	–2,140.39	–1,386.65	–1,377.84	–1,369.18
AIC	4,399.3	4,383.52	4,369.39	4,348.78	2,811.29	2,803.68	2,796.37
BIC	4,460.69	4,461.06	4,463.1	4,458.64	2,863.28	2,869.35	2,875.72
BLRT p value	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01	0.07	0.09

[a] Latent profile analyses were conducted to create subgroups based on patients' ratings of pain, fatigue, sleep disturbances, and depression.
[b] Best-fitting model based on fit indices
AIC—Akaike Information Criteria; BIC—Bayesian Information Criterion; BLRT—Bootstrapped Likelihood Ratio Test

et al., 2001; Miaskowski et al., 2006; Pud et al., 2008). In the current study, Cronbach alpha for the CES-D was 0.92.

The **Multidimensional QOL Scale–Cancer (MQOLS-CA)** (Ferrell, Wisdom, & Wenzl, 1989) is a 33-item instrument completed at T1 and T2 that measures five dimensions of QOL (physical well-being, psychological well-being, nutrition, symptom distress, and interpersonal well-being). Items are rated on a 0 (not at all) to 10 (extremely positive) numeric rating scale. The average total QOL score is calculated by summing participants' responses and then dividing by the number of items. Higher scores indicate better QOL. No cutoff score is available for better or worse QOL. The MQOLS-CA has well-established construct validity and test-retest reliability coefficient (Dibble, Padilla, Dodd, & Miaskowski, 1998; Dodd, Dibble, et al., 2001; Pinar, 2004). In the current study, Cronbach alpha ranged from 0.94–0.95.

Statistical Analyses

Data were analyzed using SPSS®, version 15.0, and Mplus, version 5.1. Descriptive statistics and frequency distributions were generated on the sample characteristics. One-way analysis of variance (ANOVA) was used to test for differences among patient subgroups at each time point in demographic characteristics, symptom scores, and outcome measures (i.e., functional status and QOL). If significant differences among subgroups were found, post-hoc contrasts were done using the Bonferroni procedure to control the overall alpha level for the family of pairwise contrasts at 0.05.

Latent profile analysis was used to classify patients into subgroups based on their experiences with pain, fatigue, sleep disturbance, and depression. Latent profile analysis is conceptually similar to cluster analysis (Nylund, Asparouhov, & Muthén, 2007) in that it identifies latent classes (subgroups) based on an observed response pattern (Clogg, 1988; Nylund, Bellmore, Nishina, & Graham, 2007). According to Nylund, Asparouhov, et al. (2007), as an analytic approach, latent profile analysis has several advantages over cluster analysis: latent profile analysis is model-based and it generates probabilities for group membership. Statistical fit indices can be used to assess model fit and help to determine the optimal number of latent classes (subgroups). Usually, the final number of latent classes (subgroups) is identified by evaluating the Bayesian Information Criterion (BIC) and the parametric bootstrapped likelihood ratio test (BLRT). Among the competing models, the model that fits the data best has the lowest BIC as well as a BLRT that shows that the estimated model is better than the model with one fewer class (subgroup). In addition, well-fitting models have loglikelihood values that are replicated in analyses with multiple "random starts," indicating that the solution is not based on a local maximum for the loglikelihood. Finally, well-fitting models are conceptually congruent, and the various patient classes or subgroups differ as expected on variables not used in generating the model at each time (Nylund, Asparouhov, et al., 2007).

Results

Demographic Characteristics

The sample was recruited from 43 states, had a mean age of 52 years, and was mostly female (82%) and Caucasian (93%) (see Table 1). All of the participants had at least a high school education, 76% were married, and 68% were women with breast cancer. No significant differences in demographic characteristics were found between those who did and did not complete (39%) the T2 survey.

Results of Latent Profile Analysis at Time 1 and Time 2

To name the various subgroups identified using latent profile analysis at each time point, mild, moderate, and severe cut points were defined for pain and fatigue symptoms: pain scores of 1–4 were mild, 5–6 were moderate, and 7–10 were considered severe (Beck, Dudley, & Barsevick, 2005); fatigue scores of 1–3 were mild, 4–6 were moderate, and 7–10 were considered severe (Piper et al., 1998); sleep disturbance scores of 43 or higher were categorized as having sleep disturbance (Lee & Gay, 2004);

and depression scores of 16 or higher were considered as having depressive symptoms (Radloff, 1977). T1 and T2 were treated cross-sectionally; therefore, subgroups at each time point were not compared over time.

At T1, the BIC and BLRT indicated that a five-subgroup model best fit the data (see Table 2). At T2, the BIC and BLRT indicated that a two-subgroup model best fit the data. However, an examination of the three-subgroup solution indicated that the sample size–adjusted BIC was smaller for the three-subgroup solution, the significance level for the BLRT was 0.07, and the entropy for the three-subgroup solution was the same as for the two-subgroup solution. In addition, the new subgroup clearly differed from the other members of the subgroup it was separated from, with very high CES-D scores compared to the originating subgroup. Therefore, the three-subgroup solution was selected over the two-subgroup solution on a substantive basis, together with BIC and BLRT values that were only marginally larger with entropy for classification that was identical.

As shown in Table 3, using the symptom severity cut points, the five patient subgroups at T1 were named based on their experience with the prespecified symptom cluster. Subgroup 1 included 104 patients (56%) with mild fatigue and sleep disturbance; subgroup 2 included 20 patients (11%) with mild fatigue and moderate pain; subgroup 3 included 21 patients (12%) with mild pain and sleep disturbance, moderate fatigue, and depression; subgroup 4 included 28 patients (15%) with moderate pain, fatigue, sleep disturbance, and depression; and, lastly, subgroup 5 included 13 patients (7%) who reported high severity scores on all four symptoms.

As shown in Table 4, three subgroups were identified at T2. Subgroup 1 included 64 patients (56%) with mild pain, fatigue, and sleep disturbance, but no depression. Subgroup 2 included 38 patients (33%) with moderate pain, fatigue, sleep disturbance, and depression. Subgroup 3 included 12 patients (11%) with mild pain, moderate fatigue, as well as sleep disturbance and depression.

Differences in Characteristics and Symptom Severity Scores Among Subgroups

Time 1: As shown in Table 5, no differences were found at T1 among the patient subgroups on any demographic characteristics, except gender ($p = 0.05$). Patients in subgroup 5 were all women who reported high levels of all four symptoms and tended to be younger ($\bar{X} = 46.9$, $SD = 9.1$) than the other subgroups (range 50.1–54.1, $p = 0.09$). The majority of patients (69%–80%) in each subgroup were married or partnered. About 50% of the patients in each subgroup had full- or part-time employment. No differences were found among the patient subgroups on cancer diagnosis (breast cancer versus other types of cancer) or types of biotherapies.

Table 3. Mean Symptom Severity Scores and Differences in Symptom Severity Scores Among Patient Subgroups for the Five Class Solution at Time 1

	Total (N = 187)		Subgroup 1			Subgroup 2			Subgroup 3			Subgroup 4			Subgroup 5			
Symptom	$\bar{X}$	SD	n	$\bar{X}$	SD	n	$\bar{X}$	SD	n	$\bar{X}$	SD	n	$\bar{X}$	SD	n	$\bar{X}$	SD	Statistics
Pain	2.72	2.69	101	0.92	1	20	4.75	0.72	21	1.67	1	28	6.57	1.5	12	7.33	1.3	$F_{4,177} = 233.27$; $p < 0.0001$ $1 < 2, 4, 5$; $p < 0.001$ $3 < 4, 5$; $p < 0.001$ $1 < 3$; $p = 0.05$
Fatigue	3.75	2.49	102	2.62	1.95	19	2.02	1.6	22	5.66	1.56	27	5.81	1.39	13	7.66	1.14	$F_{4,182} = 47.07$; $p < 0.0001$ $1, 2 < 3, 4, 5$; $p < 0.0001$ $3, 4 < 5$; $p < 0.05$
Sleep disturbance	53.23	23.87	101	44.43	20.74	20	40.39	15.12	22	61.94	17.18	27	69.67	16.61	13	92.42	15.72	$F_{4,178} = 27.97$; $p < 0.001$ $1, 2 < 3, 4, 5$; $p \leq 0.003$ $3, 4 < 5$; $p \leq 0.005$
Depression	13.02	10.4	104	7.42	4.82	20	5.29	3.68	22	25.39	6.19	28	18.84	4.53	13	36.23	5.4	$F_{4,182} = 164.46$; $p < 0.0001$ $1, 2 < 3, 4, 5$; $p < 0.001$ $3 < 4, 5$; $p < 0.001$ $4 < 5$; $p < 0.001$

Note. Because of missing data, sample size for empirical means varied.

Table 4. Mean Symptom Severity Scores and Differences in Symptom Severity Scores Among Patient Subgroups for the Three Class Solution at Time 2

	Total (N = 114)		Subgroup 1 (N = 64)		Subgroup 2 (N = 38)		Subgroup 3 (N = 12)		
Symptom	$\bar{X}$	SD	$\bar{X}$	SD	$\bar{X}$	SD	$\bar{X}$	SD	Statistics
Pain	3.04	2.78	1.42	1.38	6.42	1.41	1	1.6	$F_{2, 111} = 163.81$; $p < 0.0001$ $1 < 2, 2 > 3$; $p < 0.001$
Fatigue	3.93	2.45	3.16	2.17	4.63	2.49	5.83	2.2	$F_{2,111} = 9.56$; $p < 0.0001$ $1 < 2, 3$; $p \leq 0.006$
Sleep disturbance	54.8	22.84	48.67	21.08	63.99	22.09	58.38	25.54	$F_{2,111} = 6.02$; $p = 0.003$ $1 < 2$; $p < 0.003$
Depression	14.04	11.42	9.41	8.31	16.14	10.87	32.08	7.13	$F_{2,111} = 32.55$; $p < 0.001$ $1 < 2 < 3$; $p < 0.001$

Patients (n = 104) in subgroup 1 reported mild fatigue and sleep disturbance. This subgroup experienced significantly lower pain, fatigue, sleep disturbance, and depression scores than subgroups 3, 4, and 5 (all $p < 0.05$).

Patients in subgroup 2 (n = 20) experienced moderate pain and mild fatigue. The pain scores for this group were significantly higher than subgroups 1 and 3, but lower than subgroups 4 and 5. Subgroup 2 patients experienced significantly lower fatigue, sleep disturbance, and depression than subgroups 3, 4, and 5 (all $p < 0.003$).

Patients in subgroup 3 (n = 22) experienced mild pain and sleep disturbance, moderate fatigue, and severe depression. Pain was significantly lower in this group than in subgroups 2, 4, and 5 ($p < 0.001$), but higher than subgroup 1 ($p = 0.5$). Fatigue, sleep disturbance, and depression scores were significantly higher in this group than subgroups 1 and 2 ($p < 0.003$), and lower than subgroup 5 ($p < 0.01$). Significant differences were noted in the depression scores between subgroups 3 and 4 ($p < 0.001$).

Patients in subgroup 4 (n = 28) experienced moderate fatigue, sleep disturbance, depression, and severe pain. Pain, fatigue, and sleep disturbance were significantly higher in this group than subgroups 1 and 2 ($p < 0.001$). One of the distinctions between subgroups 3 and 4 was pain and depression scores. Subgroup 4 had significantly higher pain ($p < 0.001$), but lower depression scores than subgroup 3 ($p < 0.001$). Subgroup 4 had significantly lower fatigue, sleep disturbance, and depression scores than subgroup 5 ($p < 0.05$).

Patients in subgroup 5 (n = 13) reported high severity scores for all four symptoms. Only a small percentage of patients (7%) were categorized in this subgroup. Pain, fatigue, sleep disturbance, and depression were significantly higher than subgroups 1, 2, and 3 ($p < 0.01$). Three symptoms (i.e., fatigue, sleep disturbance, and depression) were significantly higher in subgroup 5 than subgroup 4 ($p < 0.05$).

Time 2: No significant differences were found in any demographic or clinical characteristics among the three subgroups at T2 (see Table 6). However, significant between-subgroup differences were found in symptom severity scores.

Patients in subgroup 1 reported mild pain, fatigue, and sleep disturbance, all of which were significantly lower than subgroup 2 and 3 ($p < 0.006$). No depression was reported in subgroup 1.

Patients in subgroup 2 experienced moderate pain and fatigue, as well as sleep disturbance and depression. Pain intensity was significantly higher in this subgroup than the other two subgroups ($p < 0.001$). Fatigue and sleep disturbance were significantly higher in this subgroup than subgroup 1 ($p < 0.006$). Depression was significantly higher in this subgroup than subgroup 1, but lower than subgroup 3 ($p < 0.001$).

Patients in subgroup 3 experienced mild pain, moderate fatigue, as well as sleep disturbance and depression. Depression was significantly higher than in subgroups 1 and 2 ($p < 0.001$).

Differences in Functional Status and Quality of Life Among Patient Subgroups

Functional status: Significant differences were found in KPS scores among the five patient subgroups at T1 ($F_{4,182} = 29.8$, $p < 0.001$). Post-hoc contrasts revealed that subgroup 5 had significantly lower functional status scores ($\bar{X} = 64.6$, SD = 16.1) than the other four subgroups (all $p < 0.001$). In addition, patients in subgroup 4 reported lower functional status scores ($\bar{X} = 78.2$, SD = 8.6) than patients in subgroups 1, 2, and 3 (all $p < 0.001$). No significant differences in functional status were found among subgroups 1, 2, or 3. At T2, subgroup 1 had a higher functional score ($\bar{X} = 87.3$, SD = 10), but was not significantly different from subgroup 3 ($\bar{X} = 81.7$, SD = 13.4) although it was significantly different from subgroup 2 ($\bar{X} = 80$, SD = 11.2, $p = 0.003$).

Quality of life: Significant differences in QOL scores were found at T1 among the patient subgroups ($F_{4,182}$ = 48.2, $p < 0.0001$). Post-hoc contrasts revealed that patients in subgroup 5 reported significantly lower QOL scores ($\bar{X}$ = 3.4, SD = 1, $p < 0.001$) than the other four subgroups. Subgroups 1 ($\bar{X}$ = 7.6, SD = 1.4) and 2 ($\bar{X}$ = 7.9, SD = 1.1) had similar QOL scores, and subgroups 3 ($\bar{X}$ = 5.8, SD = 1) and 4 ($\bar{X}$ = 5.5, SD = 1.4) had lower QOL scores than subgroups 1 and 2 (both $p < 0.001$). At T2, significant differences in QOL scores were found among the three subgroups ($F_{2,111}$ = 18.8, $p < 0.0001$). Subgroup 3 reported a significantly lower QOL score ($\bar{X}$ = 5.2, SD = 1.4) than subgroup 1 ($\bar{X}$ = 7.6, SD = 1.4), but not subgroup 2 ($\bar{X}$ = 6.3, SD = 1.7).

Discussion

To the best of the authors' knowledge, this study is the first to describe distinct subgroups of patients based on their experience with four highly prevalent symptoms at the time of their first biologic therapy treatment and one month later, and to determine whether patients in these subgroups differed on functional status and QOL.

At the beginning of the biotherapy (T1), 56% of patients reported mild fatigue and sleep disturbance without pain and depression, and 7% of patients reported high levels of all four symptoms. One month later (T2), 56% were classified with mild levels of pain, fatigue, and sleep disturbance, but no depression. Approximately 73% were in subgroup 1 at both time points. This finding suggests relative stability in subgroup membership in patients who report relatively low levels of symptom severity for the cluster of pain, fatigue, sleep disturbance, and depression.

In this study, at T1, the patient subgroup with high levels of all four symptoms (subgroup 5) had the worst functional status scores of all five subgroups. A comparison of the KPS scores for subgroups 1 and 5 demonstrated a difference of 2.17 SD units at T1. At T2, the subgroup reporting low levels of all four symptoms (subgroup 1) showed a higher functional status score than the other two subgroups, which represented a difference of 0.7 SD units and 0.5 SD units. The differences are consistent with previous reports (Dodd et al., 2009; Miaskowski et al., 2006; Pud et al., 2008) that showed differences of 0.8–2.9 SD units in functional status scores between subgroups of patients with relatively high levels compared to relatively low levels of all four symptoms. A clinical meaningful difference is considered to be a 0.5 SD for assessment scores in the same patient population (Dodd et al., 2009; Sloan et al., 2003, 2006). In this study, at T1 and T2, the SD clearly showed the clinical meaningful differences among the subgroups.

The patient subgroups with high symptom severity had significantly lower QOL at the beginning of biologic

Table 5. Differences in Selected Demographic Characteristics Among Patient Subgroups at Time 1

	Total (N = 187)		Subgroup 1 (N = 104)		Subgroup 2 (N = 20)		Subgroup 3 (N = 22)		Subgroup 4 (N = 28)		Subgroup 5 (N = 13)		
Characteristic	$\bar{X}$	SD	$\bar{X}$	SD	$\bar{X}$	SD	$\bar{X}$	SD	$\bar{X}$	SD	$\bar{X}$	SD	**Statistics**
Age (years)	52.4	10.6	54.1	11.5	51.2	8.6	51.2	8.9	50.1	9.3	46.9	9.1	$F_{4,182}$ = 2.05, p = 0.09
Characteristic	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**Statistics**
Marital status													
Married	139	76	77	76	16	80	17	77	20	74	9	69	χ^2 = 0.56, p = 0.97
Gender													
Female	154	83	83	54	13	65	20	91	28	89	13	100	χ^2 = 9.3, p = 0.05
Education													
More than high school	171	92	96	93	18	90	22	100	24	86	11	85	High school versus more than high school χ^2 = 4.66, p = 0.32
Employment													
Full- or part-time	101	54	55	53	12	60	16	73	13	46	5	39	χ^2 = 5.34, p = 0.25
Cancer type													
Breast	128	68	75	72	10	50	16	73	19	68	8	62	Breast cancer versus others χ^2 = 4.3, p = 0.4
Lymphoma	29	16	13	13	2	10	3	14	7	25	4	31	
Bladder	26	14	16	15	6	25	2	9	2	7	1	8	
Kidney	4	2	–	–	3	15	1	5	–	–	–	–	

Note. Because of rounding, not all percentages total 100.

Table 6. Differences in Selected Demographic Characteristics Among Patient Subgroups at Time 2

	Total (N = 114)		Subgroup 1 (N = 64)		Subgroup 2 (N = 38)		Subgroup 3 (N = 12)		
Characteristic	$\bar{X}$	**SD**	$\bar{X}$	**SD**	$\bar{X}$	**SD**	$\bar{X}$	**SD**	**Statistics**
Age (years)	54.4	10.8	55.1	12.4	53.2	7.9	55	10.1	$F_{2,111} = 0.36$, $p = 0.7$
Characteristic	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**Statistics**
Marital status									
Married	86	78	47	76	31	84	8	67	$\chi^2 = 1.75$, $p = 0.42$
Gender									
Female	94	83	50	78	34	90	10	83	$\chi^2 = 2.13$, $p = 0.35$
Education									
More than high school	103	91	56	89	35	92	12	100	High school versus more than high school $\chi^2 = 1.61$, $p = 4.5$
Employment									
Full- or part-time	61	54	35	55	20	53	6	50	$\chi^2 = 0.11$, $p = 0.95$
Cancer type									
Breast	79	69	42	66	28	74	9	69	Breast cancer versus others
Lymphoma	16	14	11	17	4	11	10	14	$\chi^2 = 0.93$, $p = 0.63$
Bladder	16	14	10	16	5	13	1	14	
Kidney	3	3	1	2	1	3	1	3	

Note. Because of rounding, not all percentages total 100.

therapy. One month later, the subgroup 2 patients (moderate pain and fatigue, as well as sleep disturbance and depression) and the subgroup 3 patients (mild pain, moderate fatigue, as well as sleep disturbance and depression) reported lower QOL than subgroup 1. Although fatigue and sleep disturbance were not significantly different in subgroups 2 and 3, a notable distinction was seen in pain and depression; subgroup 2 had a significantly higher score of pain, whereas subgroup 3 had a significantly higher score of depression.

Minimum criteria of 0.2–0.5 SD units have been shown to be not only statistically significant but also clinically meaningful in QOL studies (Guyatt, Osoba, Wu, Wyrwich, & Norman, 2002; Norman, Sloan, & Wyrwich, 2003; Osoba, Rodrigues, Myles, Zee, & Pater, 1998). Previous studies (Miaskowski et al., 2006; Pud et al., 2008) found 1.7–2 SD units differences in QOL scores between their subgroups with low levels compared to high levels of all four symptoms, which were similar to the current study sample at T1. Dodd et al. (2009) showed a range of effect sizes between 1.51–3.53 SD units during and after cancer treatment. At T2 in the current study, differences in QOL scores between subgroup 1 (mild symptoms on pain, fatigue, and sleep disturbance) and subgroup 2 and subgroup 3 demonstrated statistically and clinically meaningful differences.

Notably, the subgroups of patients with more severe symptom scores (i.e., subgroups 4 and 5) at T1 (the beginning of their biotherapy) reported higher fatigue, sleep disturbance, and depression scores than the most severe subgroup of patients (i.e., subgroup 3) at T2 (one month later). Clearly, these patients experienced remarkable symptom morbidity at the initiation of their biotherapy. T1 scores could be, in part, from preexisting symptoms and the result of side effects of biotherapy. What proportion each part contributed to symptom morbidity cannot be discerned. This finding warrants further investigation to determine what factors contributed to the development of these symptoms. In addition, whether the patients' symptoms or other factors precluded them from completing the study questionnaires at T2 is unclear. The percentage not responding and subgroup affiliation of these 73 nonresponders at T1 were: subgroup 1 (39%), subgroup 2 (55%), subgroup 3 (32%), subgroup 4 (32%), and subgroup 5 (46%). Unfortunately, participants who did not complete the study could not be contacted to determine reasons for nonparticipation.

This study extends the authors' previous work on the identification of subgroups of patients who report different experiences with four common and deleterious symptoms. Importantly, this study showed relatively consistent patient subgroups, particularly subgroups who reported low and high levels of all four symptoms. Notably, in both Miaskowski et al. (2006) and Pud et al. (2008), patients in the subgroup reporting high levels of all four symptoms reported higher pain intensity scores ($\bar{X} = 8.3$, SD = 1.1, and $\bar{X} = 9.1$, SD = 1.1, respectively) than in the Dodd et al. (2009) study ($\bar{X} = 6.9$, SD = 2.1) and in the current study ($\bar{X} = 7.3$, SD = 1.3). The majority of patients in all four studies experienced mild to moderate levels of fatigue. All four studies found severe sleep disturbance in the subgroup reporting high levels of all four symptoms. A final comparison revealed that, in all four studies, severe depression was reported in the subgroup reporting high levels of all four symptoms. These findings suggest that the symptom

experiences are remarkably similar in patients receiving either outpatient chemotherapy or biologic therapy, particularly at the more severe level of symptoms. If the authors included symptoms more in keeping with flu-like symptoms (e.g., chills or generalized whole body aching), the two treatment regimens could have subgroups that may differ on functional status or quality of life.

Observing that the more severe symptom subgroups had significantly lower functional status and QOL has importance for the identification of patients in greater need of immediate targeted interventions. As Fox, Lyon, and Farace (2007) stated, "If symptom cluster research is to become useful in practice, an important focus is to assess, both clinically and through research, the interventions that most effectively target all the symptoms in a cluster or the most powerful in adversely affecting outcomes such as functional status and QOL" (p. 66).

Limitations

Several study limitations need to be acknowledged, particularly related to the use of an Internet survey. Internet users may be better educated, have a higher socioeconomic status, and be predominantly Caucasian (Eysenbach, 2005). These characteristics were observed in the current study's participants, which points to selection bias as one of the study's major limitations. Another limitation is that demographic and clinical data (e.g., treatment regimen) could not be verified. Also, exactly how soon participants completed the first online survey after having received their initial biotherapy treatment is unknown. Although response rates and loss to follow-up are frequent limitations of Internet-based studies (Im & Chee, 2004a, 2004b), in the current study only 5% of the pool of potential study participants who met the study selection criteria declined to participate, with 39% lost to follow-up at T2. Despite these limitations, the fact that the participants were recruited from 43 states in the United States is considered a strength. However, the merits of this wide recruitment are somewhat diminished by the selection bias of Internet users as previously discussed.

Conclusion

The use of Internet-based surveys is popular and useful in clinical cancer research despite existing limitations. The four symptoms that commonly co-occur in patients with cancer receiving chemotherapy also were present in patients receiving biotherapy with similar severity levels of symptoms. Latent profile analysis, like cluster analysis, was useful to differentiate the patient subgroups by severity of symptoms. Distinct patient subgroups emerged at the beginning of biotherapy and one month from the initial treatment, but characteristics and severity of patient subgroups varied at each time point. Findings of this study showed that symptom experiences with pain, fatigue, sleep disturbance, and depression are remarkably similar in patients receiving either outpatient chemotherapy or biologic therapy, particularly at the more severe level of symptoms. Clinicians should assess and identify patients with severe levels of these four prevalent symptoms and offer appropriate interventions.

However, research on symptom clusters in patients with cancer is still in its infancy (Miaskowski, Dodd, & Lee, 2004). Additional investigation is warranted to explore why different patient subgroups formed despite no significant differences in demographic or clinical characteristics and which factors contribute to the severity of symptoms at the beginning of biotherapy as well as one month later. To diminish the adverse effect on patient outcomes and translate existing findings to clinical applications, additional studies on symptom clusters are needed.

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