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Symptom burden and supportive care in patients with acute leukemia

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Abstract

We examined the symptoms and referral rates to specialized palliative care and psychosocial oncology services of patients with acute leukemia. The Memorial Symptom Assessment Scale (MSAS) was completed by 249 adult patients with acute leukemia. Patients reported a median of 9 physical and 2 psychological symptoms, and those with intense lack of energy, difficulty sleeping and pain were more likely to report intense worrying/sadness ($P < 0.001$). No patients with moderate-severe pain were referred for specialized symptom control and only 13% of those with severe worrying/sadness were referred to psychiatry/psychology within one month of the

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Conflict of interest

The authors have declared no conflicts of interest. The authors have no financial or personal relationship with individuals, organizations or companies that might be perceived to bias the work.

assessment. Patients in this population have a substantial symptom burden; further research is needed to determine the benefit of early referral to specialized supportive care services.

Keywords

Leukemia; Symptom assessment; Pain; Palliative care; Supportive care; Psychosocial oncology

1. Introduction

The disease process in acute leukemia and the intensive treatment regimens that are typically employed can result in substantial symptom burden. However, while there has been extensive study of the symptom burden in patients with solid tumor cancers [1–3], there has been little systematic study of symptoms in patients with acute leukemia. Retrospective studies in patients with leukemia and other hematological malignancies have revealed that in the last month of life, pain is reported by 27–76% [4,5], shortness of breath by 44–50% [4–6], and fatigue by 88% [6]. However, these studies did not document symptoms earlier in the course of disease [5,6] and were not limited to patients with acute leukemia.

Few prospective studies have documented symptoms in patients with hematological diseases early in the disease course and even fewer specifically in patients with acute leukemia. In a prospective study of 180 patients with hematological malignancies, a mean of 8.8 symptoms was reported, with fatigue being most prominent. However, this study included only 19 patients with acute leukemia, with most patients having a diagnosis of myeloma or lymphoma [7]. Another prospective study examined symptoms using the EORTC-QLQ C-30 questionnaire during an outpatient management program for 60 patients with acute leukemia who were receiving intensive chemotherapy, and found that high infectious comorbidity significantly reduced physical functioning [8]. In a recent prospective study of 53 patients with newly-diagnosed acute leukemia, median scores of 0/10 for dyspnea and nausea, 1/10 for pain, depression, anxiety and appetite, and 3/10 for fatigue were reported on the Edmonton Symptom Assessment System (ESAS) [9]. However, the ESAS has severity ratings for only nine symptoms, and does not measure symptom distress or frequency.

There has been recent acknowledgment of the relevance of palliative care for patients with hematological malignancies [10], and accumulating evidence of the benefit of palliative care when provided concurrently with curative or life-prolonging treatment [11–15]. However, there have been no prospective studies assessing referral to palliative care and psychosocial services for patients with acute leukemia and correlating these data with symptom severity. Palliative care referral tends to occur late in the course of disease for patients with cancer [16], particularly for those with hematological malignancies [17–19]. Retrospective studies have found that for patients with hematological malignancies palliative care referral tends to occur within approximately 2 weeks of patient death, compared to approximately two months in patients with solid tumors, despite similar symptom severity [18,19]. However, these studies assessed symptoms at the time of referral to palliative care services, rather than at diagnosis or relapse, and did not specifically assess patients with acute leukemia.

In order to identify better the symptom control and psychosocial needs of patients with acute leukemia, we assessed comprehensively and systematically the symptom burden experienced by patients with newly-diagnosed or recently-relapsed disease, as well as their referral rates to palliative care, psychiatry/psychology and social work services.

2. Materials and methods

2.1. Setting and procedures

The study took place at the Princess Margaret Cancer Centre, University Health Network, Toronto, Canada. Patients were recruited on a 35-bed specialized leukemia unit and in a hematology outpatient clinic. The unit and clinic represent a tertiary referral center for leukemia and are staffed by nurses, physicians and social workers with expertise in the care of patients with leukemia. Routine prophylactic and therapeutic medications are given for nausea, pain, sleeplessness and other symptoms, as required. On referral, specialized palliative care and psychiatry/psychology services offer pain and symptom management, advance care planning, counseling and treatment.

This study was approved by the University Health Network Research Ethics Board (REB); all participants provided informed written consent. Eligible participants were at least 18 years old, had a new diagnosis or relapse of acute leukemia within the past 8 weeks (at the time of completion of forms), had sufficient English literacy to provide informed consent and complete study questionnaires, and obtained a score of 20 or more on the Short Orientation-Memory-Concentration (SOMC) [20] test of cognitive functioning administered by research staff at the time of recruitment.

Patients were approached between January 30, 2008 and February 22, 2012 on the inpatient leukemia unit or in the hematology outpatient clinic, within one month of hospital admission for treatment. Patients were asked to fill out the questionnaire package and return it within 2 weeks. Outpatients mailed back the questionnaires in the stamped and addressed envelope that was provided; research staff collected inpatients' questionnaires once they had been completed, and provided assistance, if required.

2.2. Measures

Participant and disease characteristics were obtained from patients and from their medical charts. These included: age, gender, marital status, living arrangements, country of birth, education, employment status, average family income, past psychiatric history, disease type, disease status, duration of illness, type and intensity of treatment received, number of days hospitalized until time of study assessment, and days since starting chemotherapy until time of study assessment.

Physical functioning was assessed using the Karnofsky Performance Status index (KPS) [21], a widely-used observer-rated measure of patient autonomy in carrying out normal activities and self-care [22,23]. Scores range from 100 (normal, no signs or symptoms of disease) downwards in decrements of 10 to 0 (death).

Symptom burden was assessed using the 32-item Memorial Symptom Assessment Scale (MSAS) [2], a well-validated multidimensional self-report scale that assesses, during the preceding week, the prevalence, frequency, severity, and distress associated with 26 physical and six psychological cancer symptoms [2]. The physical symptom subscale score (PHYS) is the average of the frequency, severity and distress associated with 12 prevalent physical symptoms (lack of appetite, lack of energy, pain, feeling drowsy, constipation, dry mouth, nausea, vomiting, change in taste, weight loss, feeling bloated, and dizziness). The psychological symptom sub-scale score (PSYCH) is the average of the frequency, severity and distress associated with six prevalent psychological symptoms (worrying, feeling sad, feeling nervous, difficulty sleeping, feeling irritable, and difficulty concentrating) [2].

The total MSAS score (TMSAS) is the average symptom score of all 32 MSAS symptoms; each symptom score is the average of its two or three associated dimensions. The global distress index (GDI) measures overall symptom distress, which is calculated from the average of the frequency of four psychological symptoms (worrying, feeling sad, feeling irritable, and feeling nervous), and the distress associated with six physical symptoms (lack of appetite, lack of energy, pain, feeling drowsy, constipation, and dry mouth) [24].

Treatment intensity was categorized into groups based on the chemotherapy regimens received by the participants: (1) none (not receiving or had not yet started chemotherapy at the time of assessment); (2) low (hydroxyurea, etoposide-only, clinical trial single agent or low-dose cytarabine); (3) moderate (daunorubicin + cytarabine 3 + 7 induction [+/− tretinoin, midostaurin or gemtuzumab], amsacrine + cytarabine induction [+/− tretinoin], A-NOVE, ALL DFCI [25] [+/− imatinib] or hyper-CVAD induction) [26]; and (4) High (NOVE-HiDAC [27] or MEC [28]).

Days since starting chemotherapy was categorized because toxicity generally peaks and then subsides. The following groups were used, based on the number of days from starting chemotherapy until the time of study assessment: no chemotherapy (not yet started or none given); 1–7 days; 8–14 days; 15–21 days; 22–28 days; 29–35 days; and >35 days. The chemotherapy regimens used were typically between 5 and 7 days in duration.

Incidence and reasons for referrals to palliative care, psychiatry/psychology and social work were determined from the Palliative Care and Psychosocial Oncology clinical databases for a period of 6 months from the symptom assessment.

Time to death was determined by calculating the time between completion of questionnaires and death. Death dates were collected from medical charts for all patients up to 6 months following the time of assessment.

2.3. Statistical analyses

Data were analyzed using the Statistical Package for the Social Sciences (SPSS), version 19.0 (IBM SPSS, Chicago, IL). An examination of missing data did not reveal any systematic or nonrandom patterns across all measures. For those with missing data, scores were pro-rated if 75% or more of the items in a given measure had been answered. Multivariable regression models were used to evaluate the relationship between validated

MSAS subscales and study variables. Symptom intensity was defined as a combined ranking across frequency, severity and distress subscales, with symptoms that ranked highest on all subscales rated as the most intense. For the three most intense symptoms, the relative risks of having other associated intense symptoms (rated ≥2 in frequency, severity and distress) were calculated, similar to studies in other populations [24,29]. The Bonferroni correction was used to adjust for multiple comparisons, resulting in a level of significance of $P < 0.0016$. The GDI, PHYS and PSYCH subscale scores were compared using *t*-tests, between patients who died within 6 months and those who survived; and between patients referred, or not, to palliative care and psychosocial services within one month of the assessment.

3. Results

3.1. Sample

Of the 580 eligible patients approached for this study, 358 (62%) consented to participate and 272 (47%) returned completed assessments. Of the 222 (38%) who refused, 96 were not interested, 74 felt too unwell, and 27 cited the time required as the reason for declining. Of those who consented, 80 withdrew and 6 died before completing the questionnaires. Of the 272 who completed the assessment, 23 did so more than 8 weeks after their diagnosis/relapse and were therefore excluded. The present analyses included responses from a final sample of 249 participants.

Patients who refused to participate ($n = 222$) or who did not complete measures ($n = 86$) did not differ from those who completed measures, in terms of leukemia type, age, or gender (the only data available for comparison due to REB guidelines). Of 249 participants, 224 (90%) were in hospital at the time of assessment and 213 (86%) were receiving induction chemotherapy. The majority (78%; 193/249) had acute myeloid leukemia (AML) and the mean time since diagnosis or relapse was less than one month (Table 1).

3.2. Symptom burden

Participants reported a median of 9 physical (range 0–22) and 2 psychological (range 0–6) symptoms (Table 2). Two hundred and twenty-six participants (91%) reported >5 concurrent physical and psychological symptoms and 151 (61%) reported >10 concurrent symptoms. The most prevalent physical symptoms were lack of energy (79%), drowsiness (56%), dry mouth (54%) and weight loss (54%); pain was present in 49% (Table 3). The most prevalent psychological symptoms were difficulty sleeping (55%), worrying (43%), difficulty concentrating (39%), and feeling sad (36%). Lack of energy, difficulty sleeping and pain were the most intense symptoms, with the highest combined ratings of severity, frequency and distress. Regarding symptom severity, the numbers of patients reporting slight, moderate, or severe symptoms were as follows: lack of energy, slight, 46 (18%); moderate, 94 (38%); severe, 48 (19%); difficulty sleeping, slight, 20 (8%); moderate, 66 (27%); severe, 43 (17%); and pain, slight, 20 (8%); moderate, 61 (25%); severe, 41 (16%).

Multivariable regression analyses revealed that PHYS was associated with poorer functional status ($P < 0.0001$; $\beta = -0.247$); PSYCH was associated with past psychiatric history ($P = 0.007$; $\beta = 0.194$) and acute lymphocytic leukemia (ALL) disease type ($P = 0.013$; $\beta =$

−0.177); GDI was associated with worse functional status ($P = 0.005$; $\beta = -0.178$) and past psychiatric history ($P = 0.028$; $\beta = .139$); and TMSAS was associated with female gender ($P = .046$; $\beta = 0.123$), past psychiatric history ($P = 0.033$; $\beta = 0.132$) and worse functional status ($P < 0.0001$; $\beta = -0.226$). Of note, disease status, days since starting chemotherapy, relapsed versus newly diagnosed disease, and intensity of the chemotherapy regimen were not significant predictors of the TMSAS score or the MSAS subscale scores.

3.3. Relative risk of experiencing simultaneous intense symptoms

Patients with intense pain had an increased relative risk of having other intense physical symptoms, including lack of energy, nausea, mouth sores and lack of appetite (Table 4). They also had greater difficulty sleeping and more than a three-fold relative risk of sadness, worrying and difficulty concentrating. Intense lack of energy was associated with intense pain, nausea, weight loss and lack of appetite, and with all six MSAS psychological symptoms. Intense difficulty sleeping was associated with pain, sweats, lack of energy, drowsiness, lack of sexual interest/activity, sadness, worrying and nervousness.

3.4. Referral to palliative care/psychosocial oncology services

Within one month of the symptom assessment, 0.8% (2/249) of patients were referred to palliative care and 8% (19/249) were referred to psychiatry or psychology; 2% (5/249) and 14% (34/249), respectively, were referred within 6 months of the assessment. There was no difference in GDI, PHYS or PSYCH subscale scores between those who were or were not referred to palliative care or psychiatry/psychology within one month of the assessment. Of those with moderate-severe pain, none (0/102) were referred to palliative care for symptom control within one month of the assessment; 13% (11/82) of those with severe worrying or sadness were referred to psychiatry/psychology services. Most patients (78%; 193/249) had contact with a social worker on the leukemia team, with discharge planning, transportation, accommodation, community resources, drug coverage, and/or financial difficulties as the reasons documented for this referral.

3.5. Subsample of deceased patients

Of the 249 patients, 35 (14%) died within the 6-month follow-up period, with a mean time to death of 3 ± 1.4 months from the assessment (Table 5). Almost all had AML (97%), and 83% were newly-diagnosed. All patients receiving supportive care, 71% of those participating in clinical trials, 19% undergoing re-induction, and 10% undergoing induction died within 6 months.

Of the 35 patients who died, 2 (6%) were referred to palliative care, with a mean time of 6 days from referral to death. Of these patients, one was receiving induction treatment at the time of the assessment and one was participating in a clinical trial. There was no significant difference in GDI, PSYCH and PHYS subscale scores between patients who died within 6 months and those who survived beyond the 6-month period.

4. Discussion

We investigated systematically the prevalence of physical and psychological symptoms in patients with newly-diagnosed or recently-relapsed acute leukemia and the referral of such patients for specialized psychosocial and palliative care services. Most of these patients were hospitalized with recently-diagnosed acute leukemia, and were receiving intensive treatment. The symptom burden was high, with patients reporting a median of 9 physical and 2 psychological symptoms, and 61% reporting 10 or more concurrent symptoms. The mean scores on measures of physical, psychological and global distress were even higher than those reported in two studies of inpatients and outpatients with solid tumors [1,24]. Most patients received social work assistance, as is routine for newly-diagnosed patients at the study center. Referral for specialized palliative care was rare, even in those who died, and only a small minority of those with severe worrying or sadness were referred to psychiatry or psychology for psychological treatment and/or medication.

The most problematic symptoms, as reflected in combined rankings of severity, frequency, and distress, were lack of energy, difficulty sleeping and pain. Lack of energy and difficulty sleeping were particularly prominent, both reported in more than half of the study sample. Although fatigue may eventually improve in patients with AML who live longer than 6 months [30,31], it may be associated with considerable distress. Difficulty sleeping might have been accentuated by the inpatient environment, and by the psychological distress associated with a recent diagnosis of acute leukemia. Both fatigue and difficulty sleeping were correlated with a number of other physical and psychological symptoms. In addition to screening for and treating such associated symptoms, exercise programs are being evaluated to ameliorate fatigue in hospitalized patients and outpatients with acute leukemia, including those receiving chemotherapy [32–35].

Forty-one percent of patients rated their pain as moderate to severe despite the frequent use of opioid analgesics at the study center; none of these were referred to the palliative care service within one month of the assessment. Intense pain was associated with lack of appetite, fatigue, nausea and psychological distress, as in patients with solid tumors [3,24,29,36]. The additional association of pain with mouth sores and changes in taste may be due either to gum disease from the leukemia itself or to mucositis from its treatment. Longitudinal studies are necessary to understand better the nature and course of the pain experienced by patients with acute leukemia and its response to treatment, with or without involvement of a specialized pain management/palliative care team.

Severe sadness and worrying were reported by more than 20% of the sample, which is consistent with our recent observation that full syndrome or subsyndromal acute stress disorder is present in approximately one third of patients with newly-diagnosed acute leukemia [37]. These patients received support from the treatment team, and the majority also had social work consultations. However, only 13% of patients with severe sadness or worrying were referred to psychology or psychiatry services within one month of the assessment. Routine distress screening may help to identify symptoms that are clinically significant and that may benefit from timely referral to specialized psychosocial services [38].

The rate of referral to palliative care was extremely low, even for those who died, and did not correlate with symptom severity. Previous retrospective studies have found similarly low rates of referral to palliative care in patients with hematological malignancies [6,17,39]. The interval of 6 days between referral and death in this sample of patients with acute leukemia is similar to that reported in retrospective studies of patients with hematological malignancies, which have reported intervals between referral and death of 2 weeks or less [18,19]. There is increasing evidence of the benefit of early palliative care in patients with metastatic cancer [11–15]. Models of palliative and supportive care, designed specifically for patients with acute leukemia, may be useful to support patients through the symptoms and distress associated with intensive treatment, and potentially to the end of life. Further research in this area is needed.

Limitations of this study include its cross-sectional nature, the exclusion of patients who were not fluent in English, and the possibility that participants may differ in undetected ways from nonparticipants. Incidence of referrals to palliative care and psychosocial services did not take into account those who were offered referral but refused. Patients diagnosed with acute leukemia are treated as soon as possible, and for most patients it was therefore not possible to obtain symptom assessments before treatment. However, neither time from start of chemotherapy nor regimen intensity was a significant predictor of symptom severity.

The results of this prospective study in patients with acute leukemia reveal a high burden of physical and psychological symptoms, with a low rate of referral to psychiatry/psychology or palliative care services. Further research is needed to examine longitudinal symptom trends and to determine the benefit of early referral to specialized supportive care services.

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Table 1

Participant and disease characteristics.

Variable	No.	%	Range
Age (years), mean (SD)	49.8	(16.0)	18.3–86.1
Male	143	57.4	
Married/common law	174	69.9	
Living alone[a]	29	11.6	
Canadian born	148	59.4	
Ethnicity (white)	163	65.5	
College/university education[b]	173	69.5	
Employment status[c]			
Employed	126	50.6	
Student/retired	83	33.3	
Unemployed/on disability	39	15.7	
Mean family income			
≤$29,999	31	12.4	
$30,000–$59,999	58	23.3	
≥$60,000	107	43.0	
Not answered	53	21.3	
Past psychiatric history	22	8.8	
Karnofsky performance status, mean (SD)	72.2	(10.7)	40–100
Disease type			
Acute myeloid leukemia	193	77.5	
Acute lymphocytic leukemia	56	22.5	
Time from diagnosis or relapse until assessment (months), mean (SD)	0.9	(0.4)	0–2
Disease status			
New onset	220	88.4	
Recently-relapsed	29	11.6	
Treatment type			
Induction	213	85.5	
Re-induction	26	10.4	
Clinical trial	7	2.8	
Supportive care	3	1.2	
Hospital status (at recruitment)			
Inpatient	231	92.8	
Outpatient	18	7.2	
Hospital status (at time of assessment)[d]			
Inpatient	224	90.0	
Outpatient	25	10.0	
Time from starting chemotherapy until assessment[e] (in days)			
$n = 239$, mean (SD)	17.1	(10.9)	0–55

Variable	No.	%	Range
0 (not yet started)	11	4.6	
1–7	36	15.1	
8–14	60	25.1	
15–21	66	27.6	
22–28	34	14.2	
29–35	14	5.9	
>35	18	7.5	
Treatment intensity			
Not yet started at time of assessment	11	4.4	
No treatment	1	0.4	
Low	10	4.0	
Moderate	207	83.1	
High	20	8.0	

[a] Living situation: missing data for one study participant.

[b] Education: missing data for one study participant.

[c] Employment status: missing data for one study participant.

[d] Hospital status: 17 patients were recruited as inpatients but completed questionnaires as outpatients (after being discharged after treatment), 7 patients were never admitted and 10 were recruited as outpatients but completed questionnaires as inpatients (after being admitted for treatment).

[e] Time from starting chemotherapy until assessment: 10 patients who were receiving supportive care or were participating in clinical trials were not included as dates were not available. Usual duration of induction/re-induction chemotherapy regimens was 5–7 days.

Table 2

Memorial Symptom Assessment Scale subscale scores.

	Mean	Standard deviation	Range	Scale range
Number of physical symptoms				
Mean	8.8	3.9	0–22	0–26
Median	9.0			
Number of psychological symptoms				
Mean	2.2	1.9	0–6	0–6
Median	2.0			
Physical symptom frequency, *n* = 239	2.4	0.5	1–4	1–4
Physical symptom severity, *n* = 247	2.0	0.5	1–4	1–4
Physical symptom distress, *n* = 239	1.5	0.8	0–4	0–4
PHYS, *n* = 246	1.9	0.6	0.5–3.3	0–4
PSYCH, *n* = 188	2.0	0.6	0.7–3.7	0–4
GDI, *n* = 244	1.5	0.9	0–4	0–4
TMSAS, *n* = 248	1.9	0.5	0.5–3.2	0–4

Abbreviations: PHYS, physical symptom subscale (12 items); PSYCH, psychological symptom subscale (6 items); GDI, global distress index (10 items); TMSAS, total MSAS score (32 items).

Table 3

Prevalence, frequency, severity and distress of symptoms reported by study participants (n = 249).

Symptom	Overall prevalence (%)	Severity (%)[a]	Frequency (%)[b]	Distress (%)[c]
Psychological group				
Difficulty sleeping	55.2	44.0**	30.2**	20.0**
Worrying	43.2	28.0	15.3	8.4
Difficulty concentrating	39.2	20.0	11.1	7.2
Feeling sad	35.6	22.4	8.5	9.2
Feeling nervous	30.8	20.8	9.8	10.0
Feeling irritable	20.0	10.8	5.5	4.0
Physical group				
Lack of energy*	79.2	57.2**	43.8**	19.6**
Feeling drowsy*	56.4	37.6**	18.3	4.0
Dry mouth*	54.0	35.2	31.5**	12.0**
Weight loss*	53.6	31.6	*NE*	4.0
Lack of appetite*	52.0	39.2**	31.9**	9.2
Change in taste of food*	51.2	37.2	*NE*	12.4
Pain*	49.2	40.8**	19.6**	21.2**
Nausea*	44.8	29.6	14.0	14.0**
Changes in skin	42.2	31.2	*NE*	9.2
Hair loss	39.6	33.2	*NE*	6.8
Sweats	38.0	25.6	12.3	8.8
Diarrhea	32.0	22.8	16.2	9.6
Mouth sores	31.6	25.2	*NE*	10.8
Constipation*	26.4	20.4	*NE*	8.4
Itching	25.2	19.6	11.9	6.0
Cough	24.4	11.2	3.8	3.2
Vomiting*	24.0	16.8	3.0	7.6
‘I don’t look like myself’	22.4	14.4	*NE*	6.8
Feeling bloated*	20.4	12.8	6.0	3.2
Shortness of breath	20.4	13.2	4.3	5.6
Dizziness*	20.0	11.2	3.8	3.2
Numbness or tingling in hands/feet	18.0	9.2	8.9	2.0
Swelling of arms and legs	16.4	12.0	*NE*	4.8
Difficulty swallowing	16.0	12.0	8.1	6.0
Problems with sexual interest/activity	12.8	10.0	10.6	3.6
Problems with urination	7.6	6.4	5.5	4.0

Symptoms are derived from the 32-item Memorial Symptom Assessment Scale (MSAS); *NE*, MSAS does not evaluate this dimension for these symptoms.

*Items included in the 12-item PHYS subscale. All 6 psychological symptoms listed make up the PSYCH subscale.

** Items ranking in the top 5 of ratings for frequency, severity and distress, respectively.

[a] Severity: percentage rated moderate to very severe.

[b] Frequency: percentage rated frequently to almost constantly.

[c] Distress: percentage rated quite a bit to very much.

Table 4

Relative risks of intense symptoms associated with intense pain, lack of energy or difficulty sleeping.

Symptoms rated moderately to severely intense	Pain	Lack of energy	Difficulty sleeping
	Relative risk (95% CI)	Relative risk (95% CI)	Relative risk (95% CI)
Psychological symptoms			
Difficulty sleeping	**1.8 (1.3–2.6)**[a]	**2.4 (1.7–3.4)**[a]	–
Worrying	**3.3 (2.0–5.6)**[a]	**4.5 (2.6–8.0)**[a]	**3.5 (2.0–6.0)**[a]
Difficulty concentrating	**4.7 (2.2–9.9)**[a]	**15.8 (4.9–51.0)**[a]	2.6 (1.3–5.2)
Feeling sad	3.4 (1.9–6.2)[a]	**3.7 (2.0–6.8)**[a]	**2.7 (1.5–4.9)**[a]
Feeling nervous	1.7 (0.9–3.1)	**4.0 (2.1–7.5)**[a]	**4.7 (2.4–9.0)**[a]
Feeling irritable	3.8 (1.6–8.8)	**8.4 (2.9–24.2)**[a]	3.3 (1.4–7.7)
Physical symptoms			
Lack of energy	**2.6 (1.8–3.6)**[a]	–	**2.4 (1.7–3.3)**[a]
Feeling drowsy	2.3(1.34.1)	**6.4 (3.1–12.8)**[a]	**2.8 (1.6–5.1)**[a]
Dry mouth	1.9 (1.2–3.1)	2.2 (1.4–3.7)	2.0 (1.2–3.2)
Weight loss	3.0 (1.4–6.6)	**4.5 (1.9–10.6)**[a]	1.9 (0.9–4.1)
Lack of appetite	**3.8 (2.2–6.4)**[a]	**6.5 (3.5–12.1)**[a]	2.3 (1.4–3.8)
Change in taste of food	**2.7 (1.7–4.2)**[a]	**2.5 (1.6–3.9)**[a]	1.4 (0.9–2.3)
Pain	–	2.8 (1.9–4.1)[a]	**1.9 (1.3–2.7)**[a]
Nausea	**3.4 (2.1–5.6)**[a]	2.5 (1.5–4.0)[a]	1.8 (1.1–2.8)
Changes in skin	1.6 (1.0–2.7)	2.2 (1.3–3.7)	2.1 (1.2–3.5)
Hair loss	2.8 (1.5–5.3)	**3.0 (1.6–5.8)**[a]	2.2 (1.2–4.1)
Sweats	3.1 (1.5–6.3)	2.0 (1.0–4.0)	**3.7 (1.8–7.6)**[a]
Diarrhea	2.5 (1.3–4.8)	2.7 (1.4–5.3)	1.9 (1.0–3.7)
Mouth sores	**2.9 (1.7–4.8)**[a]	1.1 (0.7–1.9)	1.2 (0.7–2.0)
Constipation	1.6 (0.8–3.1)	2.3 (1.2–4.4)	2.3 (1.2–4.6)
Itching	1.5 (0.8–2.9)	1.4 (0.7–2.8)	2.2 (1.1–4.2)
Cough	2.3 (0.9–6.4)	3.6 (1.2–10.3)	1.5 (0.6–4.3)
Vomiting	3.7 (1.5–9.1)	3.1 (1.3–7.7)	2.6 (1.1–6.3)
‘I don’t look like myself’	1.8 (0.7–4.0)	**4.9 (2.0–12.3)**[a]	**5.1 (2.1–12.7)**[a]
Feeling bloated	3.5 (1.5–8.2)	3.0 (1.3–7.0)	1.1 (0.5–2.7)
Shortness of breath	1.3 (0.5–3.0)	3.7 (1.5–8.9)	1.7 (0.7–3.9)
Dizziness	1.5 (0.5–4.3)	4.5 (1.4–14.0)	1.8 (0.6–5.1)
Numbness or tingling in hands/feet	1.2 (0.4–3.8)	1.4 (0.5–4.3)	1.0 (0.3–3.3)
Swelling of arms and legs	1.7 (0.7–4.0)	1.4 (0.6–3.4)	1.5 (0.6–3.6)
Difficulty swallowing	2.3 (1.0–5.4)	1.1 (0.4–2.6)	1.4 (0.6–3.2)
Problems with sexual interest/activity	1.0 (0.4–3.0)	2.5 (1.0–6.6)	**6.1 (2.0–18.5)**[a]
Problems with urination	0.6 (0.2–2.2)	2.6 (0.9–7.3)	1.5 (0.6–4.3)

[a] Intense symptoms (rated ≥2 in severity, frequency and distress) with a significant relative risk of association with intense pain, lack of energy or difficulty sleeping ($P < 0.001$).

Table 5

Disease characteristics at time of assessment and referral rates of deceased patients.

	Death/total deceased[a]		Death/total category[b]	
	f/*n*	%	*f*/*n*	%
Disease type				
AML	34/35	97.1	34/193	17.6
ALL	1/35	2.9	1/56	1.8
Disease status				
New onset	29/35	82.9	29/220	13.2
Recently-relapsed	6/35	17.1	6/29	20.7
Treatment type				
Induction	22/35	62.9	22/213	10.3
Re-induction	5/35	14.3	5/26	19.2
Clinical trials	5/35	14.3	5/7	71.4
Supportive care	3/35	8.6	3/3	100.0
Hospital admission status (at assessment)				
Inpatient	27/35	77.0	27/224	12.1
Outpatient	8/35	23.0	8/25	32.0
Treatment intensity				
Not yet started at time of assessment	1/35	2.9	1/11	9.1
No treatment (supportive care only)	1/35	2.9	1/1	100.0
Low	7/35	20.0	7/10	70.0
Moderate	20/35	57.1	20/207	9.7
High	6/35	17.1	6/20	30.0
Referrals				
Palliative care	2/35	5.7	2/5	40.0
Psychiatry/psychology	0/35	0.0	0/34	0.0
Social work	24/35	68.6	24/193	12.4

All disease characteristics were collected at the time of assessment; the evaluation period for dates of death was 6 months (180 days) after completion of measures, as 6-month follow-up was available for all participants. Abbreviations: *f*/*n*, frequency/number.

[a]Death/total deceased: proportion is based on the number of deaths in a given category over the total number of deaths in the sample ($n = 35$).

[b]Death/total category: proportion is based on the number of deaths in a given category over the total sample in each category.