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ORIGINAL ARTICLE

Pain in patients with newly diagnosed or relapsed acute leukemia

Adir Shaulov[1,2] · Gary Rodin[1,3] · Gordana Popovic[1] · Valerie B. Caraiscos[1,4] · Lisa W. Le[5] · Anne Rydall[1] · Aaron D. Schimmer[6,7] · Camilla Zimmermann[1,3,8]

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Abstract

Purpose Acute leukemia (AL) is associated with substantial morbidity and mortality. We assessed the prevalence and correlates of pain in patients with newly diagnosed or relapsed AL.

Methods Patients with newly diagnosed or relapsed AL admitted to a comprehensive cancer center completed the Memorial Symptom Assessment Scale (MSAS), which assesses prevalence, severity, and distress associated with pain and other symptoms. Factors associated with severe pain were assessed using logistic regression. Two raters completed chart reviews in duplicate for patients with severe pain (MSAS severity ≥ 3/4) to determine the site of pain.

Results Three hundred eighteen patients were recruited from January 2008 to October 2013: 245 (77.0%) had acute myeloid or acute promyelocytic leukemia (AML/APL) and 73 (23.0%) had acute lymphoblastic leukemia (ALL); 289 (90.9%) were newly diagnosed and 29 (9.1%) had relapsed disease. Pain was reported in 156/318 (49.2%), of whom 55/156 (35.3%) reported severe pain (≥ 3/4). Pain was associated with all psychological symptoms (all $p < 0.005$) and some physical symptoms. Severe pain was associated with younger age ($p = 0.02$), worse performance status ($p = 0.04$), ALL diagnosis ($p = 0.04$), and time from onset of chemotherapy ($p = 0.03$), with pain peaking at 4 weeks after chemotherapy initiation. The most common sites of severe pain were oropharynx (22; 40%), head (12; 21.8%), and abdomen (11; 20%). Only 3 patients (0.9%) were referred to the symptom control/palliative care team during the month prior to or following assessment.

Conclusions Pain is frequent, distressing, and predictable in patients undergoing induction chemotherapy for AL. Further research is needed to assess the efficacy of early supportive care in this population.

Keywords Cancer · Oncology · Hematology · Acute leukemia · Pain

Introduction

Acute leukemia (AL) is a malignant disorder of hematopoietic stem cells that is usually treated with aggressive chemotherapy [1]. AL includes two distinct disease entities, acute myeloid leukemia (AML) and acute lymphoblastic leukemia (ALL), which differ in cell of origin, clinical course, and treatment. AML is primarily a disease of the bone marrow that is treated with induction chemotherapy—classically the "7+3" protocol (7 days of continuous cytarabine with 3 days of anthracycline)—and then consolidation with either chemotherapy or allogeneic bone marrow transplantation [1]. Acute

✉ Camilla Zimmermann
camilla.zimmermann@uhn.ca

[1] Department of Supportive Care, Princess Margaret Cancer Centre, University Health Network, 610 University Ave., 16-712, Toronto, Ontario M5G 2M9, Canada

[2] Department of Hematology, Hadassah-Hebrew University Medical Center, Jerusalem, Israel

[3] Department of Psychiatry, University of Toronto, Toronto, Ontario, Canada

[4] Freeman Centre for the Advancement of Palliative Care, North York General Hospital, Toronto, Ontario, Canada

[5] Department of Biostatistics, Princess Margaret Cancer Centre, University Health Network, Toronto, Ontario, Canada

[6] Department of Medical Oncology and Hematology, Princess Margaret Cancer Centre, University Health Network, Toronto, Ontario, Canada

[7] Department of Medical Biophysics, University of Toronto, Toronto, Ontario, Canada

[8] Department of Medicine, University of Toronto, Toronto, Ontario, Canada

promyelocytic leukemia (APL) is a subtype of AML, characterized by the presence of the PML-RARA gene translocation, life-threatening disseminated intravascular coagulopathy at onset, and good overall prognosis [2]. ALL is a disease of the bone marrow and the lymphatic system, with a higher degree of organ invasion and central nervous system involvement. Treatment involves continuous courses of induction, consolidation, and maintenance chemotherapy (systemic and intrathecal) for a prolonged period of up to 2 years [3]. Both the disease process and the intense treatment regimens provided for AL can result in substantial morbidity and mortality, but there is limited literature on the prevalence and correlates of pain in this population.

Data from small prospective studies in end-of-life settings suggest that pain is a prominent symptom in patients with AL late in the disease course [4–7]. However, there is limited research on pain in newly diagnosed patients receiving induction chemotherapy [8]. Our group has previously reported a high physical and psychological symptom burden in newly diagnosed and relapsed patients with AL [9–11]. We now report data on pain prevalence and characteristics in a large cohort of patients receiving induction chemotherapy for AL and report on predictors and sites of pain in this population.

Methods

Setting and procedures

Patients with newly diagnosed or relapsed AL were recruited from a tertiary referral center for leukemia at the Princess Margaret Cancer Centre, University Health Network, Toronto, Canada, from January 2008 to October 2013. The leukemia service includes a 35-bed specialized inpatient leukemia unit and an outpatient clinic. Routine prophylactic and therapeutic medications are administered by hematology staff for nausea, pain, difficulty sleeping, and other symptoms, as required. Symptoms are managed using maximal medical therapy by the leukemia team. On referral, specialized palliative care and psychiatry/psychology/social work services offer additional services including specialized pain and symptom management, advance care planning, and counseling.

Eligible participants were at least 18 years of age, had a new diagnosis or relapse of AL within the past 10 weeks, and had begun aggressive chemotherapy treatment with intention of cure within the past 46 days. Participants 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) [12] screening test of cognitive functioning, which was administered by research staff at the time of recruitment. Patients were asked to fill out the questionnaire package and return it within 2 weeks. Research staff provided assistance with completion of questionnaires, if required, and collected inpatients' questionnaires once they had been completed. This study was approved by the University Health Network Research Ethics Board (REB); all participants provided informed written consent.

Measures

Participant and disease characteristics were obtained from patients and from their medical charts. These included age, sex, marital status, living arrangements, education, employment status, average family income, past psychiatric history, disease type, disease status, functional status, type of treatment received, and number of days from treatment until time of study assessment. Performance status was assessed using the Karnofsky Performance Status (KPS) index [13]. Treatment intensity of AML/APL was categorized into three groups based on the chemotherapy regimens received by the participants: (1) therapies based on continuous infusion cytarabine and an anthracycline ("7+3" regimen ± midostaurin/gemtuzumab/tretinoin) [14], (2) other intensive chemotherapy (NOVE-HIDAC [15], MEC [16], FLAG ± idarubicin, [17] high-dose cytarabine + etoposide/idarubicin/amsacrine) usually used in a relapse setting, and (3) patients receiving non-standard chemotherapy regimens (cytarabine only or daunorubicin only). Patients receiving non-intensive treatment (palliative chemotherapy or all-trans retinoic acid with arsenic trioxide) were excluded from this study.

Symptom burden was assessed using the 32-item Memorial Symptom Assessment Scale (MSAS). This is a well-validated multidimensional self-report scale that assesses pain, 25 other physical symptoms, and six psychological symptoms in cancer according to subscales of prevalence, frequency, severity, and distress. Respondents first indicate whether or not they have had a symptom during the previous week. If present, frequency is categorized as 1 = rarely, 2 = occasionally, 3 = frequently, 4 = almost constantly; severity is categorized as 1 = slight, 2 = moderate, 3 = severe, 4 = very severe; distress is categorized as 0 = not at all, 1 = a little bit, 2 = somewhat, 3 = quite a bit, 4 = very much [18]. Dates of death were collected from medical charts for all patients and obituary searches were performed for those lost to follow-up.

For patients reporting severe pain (MSAS severity scores 3–4), two investigators (AS and GP) conducted

chart reviews to document the site(s) of pain recorded in the patient's medical chart for the week prior to including the day of MSAS completion. The chart reviews were performed independently; in case of disagreement, both investigators reassessed the chart and a consensus was reached.

Statistical analyses

Patient demographics and disease characteristics were summarized using descriptive statistics. Prevalence of physical and psychological symptoms was documented according to level of pain severity, and their associations with pain level were tested using the Cochran-Armitage trend test with Bonferroni correction for multiple testing. Univariable and multivariable logistic regression models were used to evaluate the factors associated with the presence of severe pain. Factors with $p < 0.25$ on univariable logistic regression were entered to a stepwise variable selection process, and those with $p < 0.10$ was retained in the multivariable analysis. Analysis was performed using SAS (v9.4, Cary, NC).

Results

Three hundred eighteen patients with AL were recruited (Table 1); 289 (90.9%) had new onset disease, while 29 (9.1%) had relapsed disease. A total of 213 (67.0%) patients had AML, 32 (10.0%) had APL, and 73 (23.0%) had ALL. All patients with ALL were treated with the Dana Farber protocol [19]; 209 (85.3%) of AML patients received the "7+3" regimen, while 36 (14.7%) received other induction chemotherapy. Study questionnaires were completed during the first week after chemotherapy by 46 participants (14.5%), during the second week by 79 (24.9%), during the third week by 101 (31.9%), during the fourth week by 63 (19.9%), and from 28 to 46 days after treatment by 28 (8.8%). Within 46 days of treatment initiation, 7/318 (2.2%) patients died, and 3 were referred to palliative care.

A total of 156 (49.2%) patients reported having pain, and 55 (35.3%) of these reported their pain to be severe to very severe (MSAS severity ≥ 3/4) (Table 2). Pain prevalence was associated with all measured psychological symptoms, including difficulty sleeping, worrying, difficulty concentrating, and feeling sad, nervous, or irritable, with a consistent trend for more severe pain to be associated with increased psychological symptoms. For example, the prevalence of difficulty sleeping was 41% in patients with no pain, 60% in those with pain that was not severe (MSAS

Table 1 Summary of demographics and clinical outcomes for all patients ($n = 318$)

Variables	Number (%)
Age in years, Mean ± SD; Median (Range)	49.1 ± 15.8; 50.7 (18.3 - 86.1)
Male	172 (54.1%)
Married/common law	225 (70.8%)
Living alone	37 (11.7%)
College/university education	227 (71.8%)
Employment status	
Employed	164 (51.7%)
Student/retired	104 (32.8%)
Unemployed/disability	49 (15.5%)
Mean household income	
≤ 29,999$	35 (14.3%)
30–59,999$	74 (30.3%)
≥ 60,000$	135 (55.3%)
Disease type	
AML	213 (67.0%)
ALL	73 (23.0%)
APL	32 (10.0%)
Disease status	
New onset	289 (90.9%)
Relapsed	29 (9.1%)
Chemotherapy protocol	
ALL	73 (23.0%)
AML/APL intense	33 (10.4%)
AML/APL standard (7+3)	209 (65.7%)
AML/APL others	3 (0.9%)
KPS	
≤ 50	6 (1.9%)
60	60 (18.9%)
70	161 (50.6%)
80	62 (19.5%)
≥ 90	29 (9.1%)
Time from chemotherapy to assessment (days)	
0–7	46 (14.5%)
8–14	79 (24.9%)
15–21	101 (31.9%)
22–28	63 (19.9%)
29–46	28 (8.8%)

ALL acute lymphoblastic leukemia, *AML* acute myeloid leukemia, *APL* acute promyelocytic leukemia, *KPS* Karnofsky performance scale

Missing data on employment status in 1 patient; missing data on household income in 74 patients

Table 2 Pain frequency, severity and distress

	Frequency		Severity		Distress	
	n	%	*n*	%	*n*	%
0	161	50.8	161	51.3	169	53.8
1	31	9.8	26	8.3	37	11.8
2	59	18.6	72	22.9	37	11.8
3	42	13.3	42	13.4	36	11.5
4	24	7.6	13	4.1	35	11.2

For frequency, 0 = did not have, 1 = rarely, 2 = occasionally, 3 = frequently, 4 = almost constantly. For severity, 0 = did not have, 1 = slight, 2 = moderate, 3 = severe, 4 = very severe. For distress, 0 = not at all or did not have, 1 = a little bit, 2 = somewhat, 3 = quite a bit, 4 = very much

Missing data: frequency, 1 patient; severity, 4 patients; distress, 4 patients

severity ≤ 2), and 71% in those with severe pain (≥ 3/4). Some physical symptoms were also correlated with pain, including lack of energy, hair loss, sweats, mouth sores, bloating, numbness/tingling in hands and/or feet, and difficulty swallowing (Table 3).

On univariable analysis (Table 4), severe pain was associated with younger age (OR 0.98, 95% CI 0.96–0.99, severe pain vs not severe or no pain, $p = 0.01$), worse KPS performance status (OR 0.96, 95% CI 0.93–0.99, $p = 0.01$), ALL (OR 2.46, 95% CI 1.32–4.59, $p = 0.005$), ALL chemotherapy protocol (OR 2.47, 95% CI 1.30–4.68, $p = 0.02$), and longer time from chemotherapy initiation to study assessment (OR 1.25, 95% CI 1.01–1.54, $p = 0.04$). On multivariable analysis (Table 4), severe pain was associated with younger age (OR 0.98, 95% CI 0.96–0.996, $p = 0.02$), worse performance status (OR 0.96, 95% CI, 0.93–0.998, $p = 0.04$), ALL (OR 2.05, 95% CI 1.05–4.00, $p = 0.04$), and longer time from chemotherapy start to assessment (OR 1.28, 95% CI 1.02–1.61, $p = 0.03$). In both AML and ALL, average pain increased sharply from two to 4–5 weeks after initiation of chemotherapy, and then subsided (Fig. 1).

For patients with severe pain ($n = 55$), pain was localized to the following areas: oropharynx in 22 (40%), head in 12 (21.8%), abdomen in 11 (20%), musculoskeletal in 9 (16.4%), rectal in 5 (9.1%), chest in 2 (3.6%), and other sites in 7 (12.7%) (Fig. 2). Ten (18%) patients reported severe pain in more than one site. In two cases, the site of pain could not be identified from the chart review. There was no significant association between the site of pain and disease type or time from chemotherapy; however, there was a trend for headache and oropharyngeal pain to be more common in patients with ALL and rectal pain to be more common in patients with AML.

Discussion

In this cohort of patients with AL undergoing induction chemotherapy, pain was a frequent symptom, reported by 49.2% overall; of these, 35.3% reported their pain as severe to very severe. Pain was associated with several other physical symptoms and with all psychological symptoms assessed, including difficulty sleeping, worrying, difficulty concentrating, and feeling sad, nervous, or irritable. Severe pain was associated with younger age, poorer performance status, a diagnosis of ALL, and time from onset of chemotherapy, with pain increasing sharply from 2 to 4–5 weeks after initiation of chemotherapy. The most common sites of severe pain were oropharynx, head, and abdomen.

Pain was prevalent in our cohort despite maximal inpatient treatment by the leukemia team. The prevalence of pain in approximately half of the sample was higher than that reported by patients with stage 1–3 solid tumors, though not as high as that of hospitalized patients with advanced cancer [20]. The association between pain and time from chemotherapy onset suggests that, in contrast with other malignancies, pain in patients with AL results mainly from the treatment and its complications, rather than from the disease process itself. Indeed, the prevalence of severe pain over time in our cohort mirrors the decrease in blood counts, which reach their nadir during the second and third weeks from initiation of chemotherapy. Chemotherapy-induced cytopenias may result in bleeding and localized infections, which in addition to chemotherapy-induced mucositis, may be the primary cause of pain during leukemia induction therapy. Indeed, all of the physical symptoms associated with severe pain in our study may be complications of chemotherapy treatment, including lack of energy, hair loss, sweats, mouth sores, bloating, numbness/tingling in the hands or feet, and difficulty swallowing. The rapid appearance of severe pain in opioid-naïve patients with AL is challenging, as medications such as opioid medications and neuropathic agents require titration in order to avoid adverse side effects, particularly in this population of fragile patients [21].

ALL was associated with a higher prevalence of severe pain, which was particularly prominent in the head and oropharynx; the abdomen was also a frequent site for severe pain in both AML and ALL. Oropharyngeal and

Table 3 Psychological and physical symptoms associated with severity of pain

Symptoms	*n*	Pain severity[a]			*p* value[b]
	Total *n* = 318	No pain *n* = 161	Not severe *n* = 98	Severe *n* = 55	
Psychological symptoms					
Difficulty sleeping	164 (52.2%)	66 (41.0%)	59 (60.2%)	39 (70.9%)	*< 0.0001*
Worrying	132 (42.0%)	55 (34.2%)	42 (42.9%)	35 (63.6%)	*0.0002*
Difficulty concentrating	125 (39.8%)	48 (29.8%)	41 (41.8%)	36 (65.5%)	*< 0.0001*
Feeling sad	122 (38.9%)	48 (29.8%)	44 (44.9%)	30 (54.5%)	*0.0004*
Feeling nervous	96 (30.6%)	37 (23.0%)	34 (34.7%)	25 (45.5%)	*0.001*
Feeling irritable	68 (21.8%)	23 (14.4%)	24 (24.7%)	21 (38.2%)	*0.0002*
Physical symptoms					
Lack of energy	253 (80.6%)	114 (70.8%)	88 (89.8%)	51 (92.7%)	*< 0.0001*
Feeling drowsy	175 (55.7%)	78 (48.4%)	60 (61.2%)	37 (67.3%)	0.007
Dry mouth	167 (53.2%)	78 (48.4%)	59 (60.2%)	30 (54.5%)	0.21
Weight loss	171 (54.8%)	75 (46.9%)	61 (62.9%)	35 (63.6%)	0.009
Lack of appetite	166 (53.2%)	76 (47.5%)	56 (57.7%)	34 (61.8%)	0.04
Change in the way food tastes	159 (51.0%)	75 (46.9%)	49 (50.5%)	35 (63.6%)	0.04
Nausea	156 (49.7%)	71 (44.1%)	49 (50.0%)	36 (65.5%)	0.009
Changes in skin	145 (46.5%)	67 (41.9%)	45 (46.4%)	33 (60.0%)	0.03
Hair loss	140 (44.9%)	59 (36.9%)	47 (48.5%)	34 (61.8%)	*0.0009*
Sweats	127 (40.4%)	47 (29.2%)	52 (53.1%)	28 (50.9%)	*0.0003*
Diarrhea	101 (32.2%)	48 (29.8%)	35 (35.7%)	18 (32.7%)	0.51
Mouth sores	102 (32.7%)	37 (23.1%)	38 (39.2%)	27 (49.1%)	*0.0001*
Constipation	81 (26.0%)	38 (23.8%)	24 (24.7%)	19 (34.5%)	0.16
Itching	85 (27.2%)	36 (22.5%)	34 (35.1%)	15 (27.3%)	0.20
Cough	84 (26.8%)	39 (24.2%)	32 (32.7%)	13 (23.6%)	0.69
Vomiting	81 (25.8%)	33 (20.5%)	26 (26.5%)	22 (40.0%)	0.005
"I don't look like myself"	73 (23.4%)	30 (18.8%)	22 (22.7%)	21 (38.2%)	0.006
Feeling bloated	67 (21.3%)	19 (11.8%)	30 (30.6%)	18 (32.7%)	*< 0.0001*
Shortness of breath	60 (19.1%)	22 (13.7%)	22 (22.4%)	16 (29.1%)	0.007
Dizziness	63 (20.2%)	23 (14.4%)	25 (25.8%)	15 (27.3%)	0.01
Numbness/tingling in hands/feet	46 (14.6%)	15 (9.3%)	16 (16.3%)	15 (27.3%)	*0.001*
Swelling of arms and legs	54 (17.3%)	25 (15.6%)	18 (18.6%)	11 (20.0%)	0.41
Difficulty swallowing	48 (15.4%)	15 (9.4%)	17 (17.5%)	16 (29.1%)	*0.0004*
Problems with sexual interest or activity	33 (10.5%)	12 (7.5%)	17 (17.3%)	4 (7.3%)	0.45
Problems with urination	17 (5.4%)	7 (4.3%)	6 (6.1%)	4 (7.3%)	0.37

[a] Categories of "slight" and "moderate" were classified as "not severe"; categories of "severe" and "very severe" were classified as "severe." Missing data on 6 patients in feeling irritable, weight loss, lack of appetite, change in the way food tastes, changes in skin, hair loss, mouth sores, constipation, itching, "I don't look like myself," dizziness, swelling of arms and legs, and difficulty swallowing; missing 4 patients in all other items

[b] With Bonferroni correction, a value is $a/n = a/31 = 0.05/31 = 0.002$; symptoms reaching this level of significance ($p < 0.002$) are in italics

abdominal pain are most likely the result of mucositis and typhlitis, while headaches may be secondary to lumbar puncture, brain and leptomeningeal spread of disease, anemia, or cranial hemorrhage secondary to thrombocytopenia. ALL induction chemotherapy includes multiple intrathecal treatments which may cause chemical meningitis

Table 4 Factors associated with severe pain ($n = 318$)

Variable	Univariable analysis		Multivariable analysis	
	Severe vs. not severe/no pain		Severe vs. not severe/no pain	
	OR (95% CI)	p value[d]	OR (95% CI)	p value[d]
Age, years	0.98 (0.96–0.99)	*0.01*	0.98 (0.96–0.996)	*0.02*
KPS	0.96 (0.93–0.99)	*0.01*	0.96 (0.93–0.998)	*0.04*
OS time, per 100 days[a]	1.50 (0.59–1.01)	0.39		
Female	1.42 (0.79–2.54)	0.24		
Married/common law	0.66 (0.36–1.22)	0.19		
College education	0.93 (0.49–1.77)	0.83		
Employment		0.07		0.09
Employed	0.41 (0.19–0.88)	0.06	0.41 (0.18–0.90)	0.06
Student/retired	0.54 (0.24–1.21)	0.60	0.54 (0.23–1.25)	0.61
Unemployed/disability	–	–	–	–
Avg. household income[b]	0.81(0.61–1.08)	0.16		
ALL vs. AML/APL	2.46 (1.32–4.59)	*0.005*	2.05 (1.05–4.00)	*0.04*
New onset	1.93 (0.56–6.63)	0.29		
Psychiatric history	1.82 (0.80–4.16)	0.15		
Chemotherapy protocol		*0.02*		
ALL	2.47 (1.30–4.68)	0.02		
AML/APL intense	–	–		
AML/APL less intensive	1.09 (0.39–3.05)	0.46		
AML/APL others[c]	NA	NA		
Weeks from chemotherapy	1.25 (1.01–1.54)	*0.04*	1.28 (1.02–1.61)	*0.03*

OS overall survival, *KPS* Karnofsky performance scale, *ALL* acute lymphoblastic leukemia, *AML* acute myeloid leukemia, *APL* acute promyelocytic leukemia

[a] OS time was calculated up to last known alive date for alive patient; [b] excluded from variable selection for MV analysis due to a high percentage of missing; [c] excluded from UV analysis due to small count ($n = 3$); [d] italics designate a significant p value (<0.05)

and post-lumbar puncture headache, which may account for the trend for increased headache in ALL in comparison with AML. As well, ALL may be associated with more pain as a result of central nervous system involvement or mass effect secondary to lymphadenopathy or hepatosplenomegaly, which are more prominent in ALL.

The tendency for severe pain to be more common in younger patients has also been observed in other studies of patients with cancer [22–25]. This may in part be due to an age-related "response shift" in the perception of pain, whereby the pain experience in older patients is reconceptualized based on the previous experience of pain associated with chronic medical conditions [26]. In addition, lower doses of chemotherapy are commonly utilized in older patients [27, 28], which may result in decreased toxicity to mucosa [29, 30], fewer infections [28, 30], and therefore less pain. Correspondingly, chemotherapy-induced mucositis pain has previously been reported as more prevalent in younger patients with cancer [31].

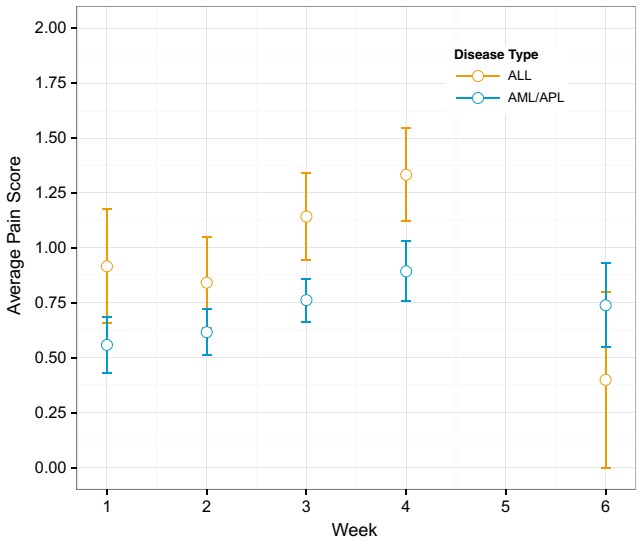

Fig. 1 Average pain score by week from chemotherapy ($n = 318$)

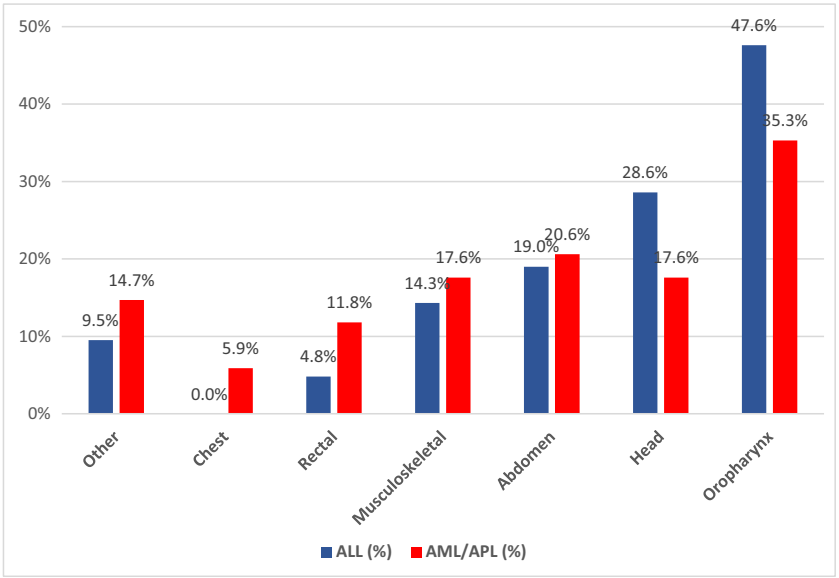

Fig. 2 Site of pain for patients reporting severe pain and percentage of patients reporting severe pain (AML/APL $n = 34$; ALL $n = 21$; total $n = 55$)

In our cohort of patients with AL receiving aggressive induction chemotherapy, less than 1% of patients were referred to palliative care, despite a high pain burden and a median survival of 30.9 months. Despite the high prevalence of pain and other distressing symptoms in patients with AL, they are less likely to be referred to palliative care and are referred later in their disease trajectory relative to patients with other malignancies [32–34]. In comparison with solid tumor oncologists, hemato-oncologists are more likely to favor aggressive therapy even when the chance of survival is low [35] and generally equate palliative care with end of life care [36]. In patients undergoing hematopoietic stem cell transplantation, early palliative care intervention has been shown to improve pain and other symptoms [37]. Given the predictable appearance of pain following chemotherapy in patients with AL, early palliative care may be able to attenuate pain, resulting in improved long-term effects, regardless of prognosis [38, 39].

Our study has several limitations. Although we collected patient-reported information on prevalence, severity, and distress associated with pain, we did not collect information on the site of pain, which was gathered from chart review. The assessment of differences in sites of pain in AML and ALL is limited in this regard as well as due to the small sample size for this comparison. Symptoms in AL may change rapidly, and our cross-sectional results do not allow for an evaluation of the pain trajectory over the period of induction chemotherapy. Results from our longitudinal study of pain and other symptoms over time will add to knowledge in this regard.

Although treatment protocols for AL have changed little over the past 30 years, patient survival has improved substantially as a result of improvements in treatment of severely neutropenic patients with new antibacterial and antifungal agents and because of new imaging modalities [40]. However, it is unclear whether there has been concomitant improvement in quality of life in these patients. The high prevalence and predictable trajectory of pain in our study highlight the need for further research into the trajectory of symptoms and interventions to alleviate them. This may entail approaches for early diagnosis of pain syndromes specific to AL as well as rapid and aggressive pain control. Early palliative care interventions may play a role in this regard and should be tested in this patient population.

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Administrative support: AR.
Provision of study materials or patients: ADS.
Study implementation, acquisition and/or assembly of data: AS, GP, VBC, AR.
Analysis and interpretation of data: LWL, AS, ADS, CZ, GR.
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funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Compliance with ethical standards

This study received approval from the University Health Network (UHN) Research Ethics Board (REB #06-0387-CE). All study participants provided written informed consent.

Conflict of interest A.D. Schimmer reports personal fees and grants outside this submitted work from Novartis, Takeda Pharmaceuticals, Aeglea Pharmaceuticals, and Trillium Therapeutics. The remaining authors declare no conflicts of interest.

Prior presentation Findings were presented in part at the Multinational Association of Supportive Care in Cancer (MASCC)/ISOO 2017 Annual Meeting on Supportive Care in Cancer, Washington, DC, USA, June 22–24, 2017 (e-poster presentation); early/preliminary findings were presented at the 20th International Congress on Palliative Care, Montreal, Quebec, Canada, September 9–12, 2014 (poster presentation); the MASCC/ISOO 2014 Annual Meeting on Supportive Care in Cancer, Miami, Florida, United States, June 26–28, 2014 (oral presentation); the Hospice Palliative Care Ontario Annual Conference, Toronto, Ontario, Canada, April 27–29, 2014 (oral presentation); and the 9th Annual Advanced Learning in Palliative Medicine Conference, Vancouver, British Columbia, Canada, June 13–15, 2013 (oral presentation).

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