

Signs, Symptoms, and Characteristics Associated With End of Life in People With a Hematologic Malignancy: A Review of the Literature

Elise Button, RN, MAdPrac (Hons), BN, GCertPC, Raymond Chan, RN, PhD, MAppSc, BN, FACN, Shirley Chambers, PhD, BHlthSc (Hons), Jason Butler, MBBS (Qld), MMedSc (ClinEpid), FRACP, FRCPA, and Patsy Yates, RN, PhD, MSocSc, DipAppSc, BA

Button is an acting nurse researcher in Cancer Care Services at Royal Brisbane and Women's Hospital and a doctoral candidate in the School of Nursing at the Queensland University of Technology; Chan is an associate professor in the Cancer Nursing Professorial Precinct at Royal Brisbane and Women's Hospital and the Queensland University of Technology; Chambers is a research fellow in the Institute of Health and Biomedical Innovation at the Queensland University of Technology; Butler is a senior staff specialist in the Haematology and Bone Marrow Transplant Unit at Royal Brisbane and Women's Hospital; and Yates is head of the School of Nursing at the Queensland University of Technology, all in Brisbane, Australia.

Button was supported by the National Health and Medical Research Council Centre of Research Excellence in End of Life Care Scholarship, the Queensland University of Technology Health Top-Up Scholarship, and Royal Brisbane and Women's Hospital Postgraduate Scholarship.

Button, Chan, Chambers, and Yates contributed to the conceptualization and design and provided the analysis. Button completed the data collection. All authors contributed to the manuscript preparation.

Button can be reached at elise.button@student.qut.edu.au, with copy to editor at ONFEditor@ons.org.

Submitted July 2015. Accepted for publication December 23, 2015.

Key words: hematologic malignancies; identification; end of life; transition

ONF, 43(5), E178-E187.

doi: 10.1188/16.ONF.E178-E187

Problem Identification: Identifying people with hematologic cancer who are at risk of deteriorating and dying is essential to enable open, honest discussions, leading to appropriate decision making and effective end-of-life care.

Literature Search: PubMed, CINAHL®, PsycINFO, and the Cochrane Central Register of Controlled Trials were searched from January 2005 to December 2015 for descriptive observational studies.

Data Evaluation: Critique of the studies was guided by the Critical Appraisal Skills Programme Cohort Study Checklist.

Synthesis: Twelve studies were included. The majority of studies ($n = 8$) sampled patients from palliative populations, and most were retrospective ($n = 11$). A number of signs, symptoms, and characteristics associated with end of life in people with a hematologic malignancy were identified, including pain, hematopoietic dysfunction, dyspnea, and reduced oral intake.

Conclusions: The studies described a clinical scenario of deterioration, largely in a palliative population. Findings indicate that people with a hematologic malignancy share certain clinical signs of deterioration with other populations and receive a high level of medical interventions at the end of life.

Implications for Practice: Nurses are well positioned to identify many of the signs, symptoms, and characteristics found in this review and can play a key role in identifying when a person is nearing the end of life.

Hematologic malignancies include leukemia, lymphoma, multiple myeloma, myeloproliferative neoplasms, and myelodysplastic syndromes (Swerdlow et al., 2008). These malignancies differ from solid tumors, most notably in the involvement of the bone marrow, leading to issues such as bleeding, infection, and anemia (Pallister & Watson, 2011). The clinical course and prognosis for people with a hematologic malignancy vary significantly depending on many factors, including the type and specific subtype of the disease, response to treatment, and personal characteristics of the patient (Hung et al., 2013; Pallister & Watson, 2011). Certain diseases, such as acute leukemia, advance rapidly and are imminently fatal (Pallister & Watson, 2011), whereas other malignancies, such as low-grade lymphoma, often follow an indolent illness trajectory (Matasar & Zelenetz, 2008). Aggressive treatment often holds dual potential for cure and mortality (Ezzone & Schmit-Pokorny, 2007).

The illness trajectory of a person with a hematologic malignancy differs from that of a person with solid tumors (Auret, Bulsara, & Joske, 2003; Maddocks, Bentley, & Sheedy, 1994) and shares more similarities with the illness trajectory of a person with organ failure (i.e., heart and lung failure) in the context of

progressive chronic illness (Murray, Kendall, Boyd, & Sheikh, 2005). People with a hematologic malignancy characteristically experience acute deteriorations. However, they may recover from near-to-death deterioration, and life-threatening disease may respond well to treatment; neither scenario is uncommon (Hung et al., 2013; Manitta, Philip, & Cole-Sinclair, 2010). Because the illness trajectory is unpredictable and people often deteriorate rapidly to a terminal event, significant difficulties exist in prognosticating for this group of patients (Manitta et al., 2010). This has been reported to be a key barrier to the integration of timely palliative care (Manitta et al., 2010).

The transition from receiving aggressive treatment to terminal care is complex and can occur rapidly for people with a hematologic malignancy (Hung et al., 2013; Maddocks et al., 1994; Manitta et al., 2010). In certain situations, the goals of care can change from cure to comfort within hours (Button, Gavin, & Keogh, 2014). Identification and explicit communication with patients who are at high risk of dying, as well as their families, are necessary for ensuring appropriate decision making and best practices in end-of-life care (Dalgaard, Thorsell, & Delmar, 2010). The nature of a person's care at the end of life can have a significant impact on his or her quality of life and on his or her loved ones' grief (Wright et al., 2008). Recognition of people who are likely to be in their final months of life can prompt clinicians to reassess the goals of care, focus on holistic needs, and share decision making about end-of-life care. It can also facilitate engagement in advance care planning and involvement in specialist palliative care services (Hight, Crawford, Murray, & Boyd, 2013; Orosz et al., 2014). Open, honest communication about end-of-life issues that is sensitive to the concept of hope is reported to increase people's autonomy, satisfaction with care, and ability to plan for the future (Nightingale, Monsell, Wong, & Cheung, 2011).

Identifying people who are likely to be in the final year of life has become a key strategic policy for healthcare services in many countries (Hight et al., 2013). Several clinical tools exist to predict palliative care needs by systematically identifying people who are approaching the end of life or are at risk of dying (Maas, Murray, Engels, & Campbell, 2013). These tools have been developed and tested on people with incurable chronic illness and solid cancers (Maas et al., 2013) and may not be applicable to people with a hematologic malignancy. Integration of palliative care is recommended alongside treatment of curative or life-prolonging intent for all people with life-threatening illness, and it is particularly relevant for people with a hematologic malignancy because of their illness trajectory (National Institute for Health and Clinical

Excellence, 2003). Knowing when this integration should occur is often difficult. However, clinician identification of the signs of deterioration that may lead to death is vital (Maas et al., 2013), particularly for people with a hematologic malignancy who have a unique disease profile compared to people with solid tumors or chronic illness (Maddocks et al., 1994; McGrath & Holewa, 2007). An understanding of the nature of deteriorating and dying for people with a hematologic malignancy is also needed to provide individualized palliative care specific to the needs of the patient. A thorough review of the literature regarding identifying deteriorating and dying for people with a hematologic malignancy returned no relevant studies.

The aim of this review was to identify research-based evidence regarding the signs, symptoms, and characteristics that are associated with the end of life in people with a hematologic malignancy. A search of the literature was conducted of descriptive observational studies that explored the signs, symptoms, and characteristics present in the final three months of life for this group of patients. These factors are not prognostic of mortality but instead describe a clinical scenario of deterioration in people with a hematologic malignancy. The rationale for this review was to provide clinicians with an overview of current evidence to facilitate better palliative care integration for this population and guide future research on the topic.

Methods

This literature review was conducted and reported in accordance with PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) checklists (Moher, Liberati, Tetzlaff, & Altman, 2009). According to a priori protocol, a comprehensive search was performed across the following electronic databases: PubMed, CINAHL[®], PsycINFO, and Cochrane Central Register of Controlled Trials. The protocol was not registered because the review did not meet the criteria of a systematic review. ProQuest's dissertations and theses database was searched to identify grey literature, and the World Health Organization's clinical trial search portal (www.who.int/trialsearch) was searched to identify relevant studies that are underway or have recently been completed. Reference lists and citations of relevant papers and those included in the review were screened to ensure that no relevant study was missed. Key words included *hematological malignancy*; *signs, symptoms, characteristics*; and *deteriorating and dying*. Related synonyms and MeSH (medical subject headings) terms were used in the search for these words.

Screening of search results and articles was undertaken by a single person. Inclusion criteria were (a)

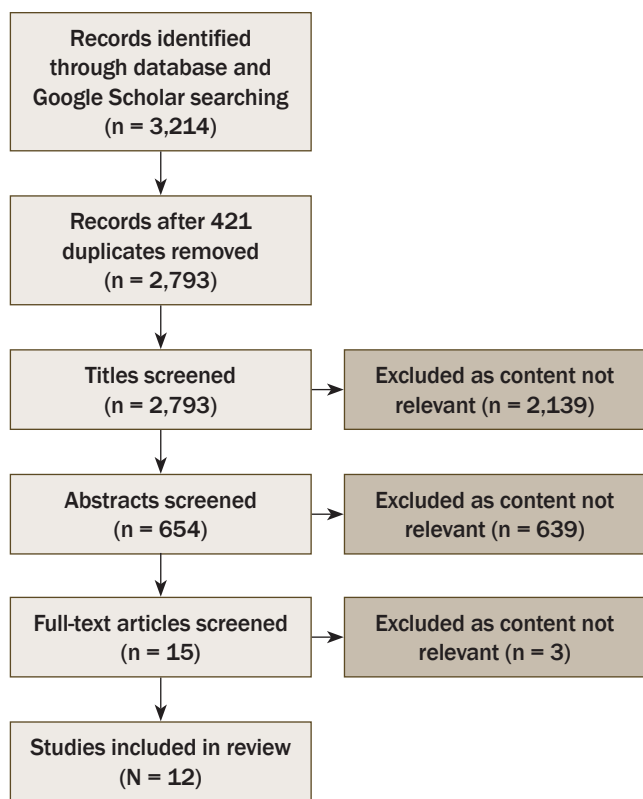


FIGURE 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses Flow Diagram for Inclusion of Studies

English language; (b) participants with a hematologic malignancy (greater than 50% of study sample or data analyzed independently, as in comparison studies [i.e., solid tumor and hematologic malignancy comparisons]); (c) adult patients (aged older than 18 years); (d) primary research; (e) published online or in print from January 2004 to September 2014; (f) median survival of less than three months; and (g) descriptive, observational studies of signs, symptoms, and characteristics. Exclusion criteria were (a) editorials and letters, (b) discussion or expert opinion papers, (c) non-peer reviewed articles, (d) single case studies, (e) qualitative research, and (f) systematic reviews. Challenging decisions regarding the inclusion of a paper were discussed with a second member of the research team.

Studies that met the inclusion criteria were read in full, in chronological order, and summarized. A single researcher extracted data according to the Matrix Method process (Garrard, 2014). Specific variables of interest extracted on a specially designed data tool were country, methodology, purpose, survival times, sampling frame, characteristics of participants, primary outcome(s) measured, results and key findings, limitations, and implications for practice. Because of a wide variation of methodologies and samples of

the included papers, meta-analysis was unable to be performed, and data were analyzed using a narrative synthesis approach. Extracted data were subjected to an iterative process of data comparison, examining patterns, themes, contrasts, and relationships (Garrard, 2014).

The search strategy was systematic in nature; however, formal quality appraisal was unable to be performed on study designs that were noninterventive and purely descriptive as found in this review. To enhance the rigor of the approach, the Critical Appraisal Skills Programme ([CASP], 2013) Cohort Study Checklist was used to guide critique of the studies. This checklist contained the main features of appraisal of descriptive cohort studies, including consideration of selection bias, follow-up of final outcomes, and measurement of misclassification of bias (National Health and Medical Research Council, 2000).

Results

A search of the literature across the aforementioned databases returned 3,214 articles. After duplicates were removed and titles and abstracts were screened against selection criteria, 15 articles were read in full, and 12 articles were deemed relevant for inclusion (see Figure 1).

Study Characteristics

All of the 12 included studies used a descriptive cohort design reporting on the incidence or prevalence of signs, symptoms, or characteristics of people with a hematologic malignancy with a survival time of three months or less. A summary of study characteristics and findings are presented in Table 1. The majority of studies ($n = 11$) were retrospective and set in a single center (Brück et al., 2012; Button et al., 2014; Cartoni et al., 2009; Cheng, Li, et al., 2015; Cheng, Sham, Chan, Li, & Au, 2015; Corbett, Johnstone, Trauer, & Spruyt, 2013; Fadul, El Osta, Dalal, Poulter, & Bruera, 2008; Holler et al., 2009; Hui et al., 2014; Hung et al., 2013; LeBlanc, Abernethy, & Casarett, 2015). Country of publication varied, as did survival times, ranging from 7 days (Brück et al., 2012; Cheng, Sham, et al., 2015) to 72 days (Cartoni et al., 2009; Niscola et al., 2007). The size of the study samples ranged from 21 (Cheng, Sham, et al., 2015) to 3,518 (LeBlanc et al., 2015). The majority of studies ($n = 9$) sampled patients from what is considered to be a palliative population (i.e., referred or admitted to a specialist palliative care service or unit, or had advanced disease with a life expectancy of six months or less). No studies compared the epidemiology of symptoms or complications experienced by people with a hematologic malignancy

TABLE 1. Summary of Study Characteristics (N = 12)

Study (Country)	Methods, Aim, and Sampling Frame	Sample and Instrument	Survival Times	Findings
Nicola et al., 2007 ^a (Italy)	<ul style="list-style-type: none"> • Prospective, longitudinal • To describe epidemiology of pain in homecare service • Homecare service 	Patients with advanced hematologic disease with estimated survival time of less than three months (N = 469) Numeric analog scale; Karnofsky Performance Scale	Median of 72 days (IQR = 1–1,132 days)	Fifty-two percent of participants experienced pain (31% mild to moderate, 69% moderate to severe); the median Karnofsky Performance Scale score was 50 (range = 10–70).
Fadul et al., 2008 (USA)	<ul style="list-style-type: none"> • Retrospective, cross-sectional • To compare symptom burden of patients with a hematologic malignancy to those with a solid tumor at the time of referral to specialist palliative care service • Palliative care service (inpatient and outpatient) 	Patients with hematologic malignancy referred to specialist palliative care service (N = 125) Edmonton Symptoms Assessment System	Median of 13 days (95% confidence interval [8, 17])	The median symptom severity score was 7 for drowsiness (IQR = 5–10), 6 for fatigue (IQR = 6–7), and 4 for pain (IQR = 3–5). Forty-one percent of participants experienced delirium.
Cartoni et al., 2009 ^a (Italy)	<ul style="list-style-type: none"> • Retrospective, longitudinal • To describe epidemiology of hemorrhage in homecare service • Homecare service 	Patients with advanced hematologic disease with estimated survival time of less than three months (N = 469) World Health Organization Bleeding Severity Score	Median of 72 days (IQR = 1–1,132 days)	Twenty-six percent of participants experienced bleeding complications. A higher incidence was noted in patients with acute myeloid leukemia or in blast crisis.
Holler et al., 2009 (Europe)	<ul style="list-style-type: none"> • Retrospective, longitudinal • To describe epidemiology of hemorrhage in hospital • Hospital (inpatient) 	Patients who had undergone hematopoietic stem cell transplantation, experienced organ failure because of severe sepsis or graft-versus-host disease, and had a bleeding event (N = 160)	Mortality was 53% at 28 days and 66% at 100 days.	Twenty percent of participants experienced bleeding events (75% serious, 20% life-threatening, 20% fatal), and 92% received transfusions (platelets or blood). In addition, 66% had white blood cell counts of less than $1 \times 10^9/L$.
Brück et al., 2012 (Germany)	<ul style="list-style-type: none"> • Retrospective, longitudinal • To describe treatment characteristics at end of life in the hospital • Hospital (hematology unit and ICU) 	Patients who died on a hematology unit and patients with a hematologic malignancy who died in the ICU (N = 172)	Focus on last seven days of life	Ninety-four percent of participants experienced pain, and 88% received transfusions (platelets or blood).
Corbett et al., 2013 (Australia)	<ul style="list-style-type: none"> • Retrospective, cross-sectional • To describe epidemiology of symptoms at time of referral to specialist palliative care service • Palliative care service (inpatient and outpatient) 	Patients with a hematologic malignancy referred to specialist palliative care service (N = 276) Edmonton Symptoms Assessment System	Median of 34 days (IQR = 9–144 days)	Eighty-eight percent of participants experienced fatigue, and 80% experienced pain. The median symptom severity score was 5 (IQR = 2–8). Also, 66% experienced reduced appetite, and 39%–47% experienced anxiety. <i>(Continued on the next page)</i>

^a Nicola et al. (2007) and Cartoni et al. (2009) used the same patient sample in their studies.

^b Other symptoms included nausea, vomiting, anorexia, itch or irritation, constipation, diarrhea, wound, incontinence, fatigue, dyspnea, edema, and delirium.

ICU—intensive care unit; IQR—interquartile range

Note. All studies, with the exception of Cheng, Li, et al. (2015), had a mixed patient population consisting of patients with all hematologic malignancies.

TABLE 1. Summary of Study Characteristics (N = 12) (Continued)

Study (Country)	Methods, Aim, and Sampling Frame	Sample and Instrument	Survival Times	Findings
Hung et al., 2013 (Taiwan)	<ul style="list-style-type: none"> Retrospective, cross-sectional To compare symptom burden of patients with a hematologic malignancy to those with a solid tumor at the time of referral to specialist palliative care service Palliative care service 	Patients referred to specialist palliative care service with estimated survival time of less than six months (N = 124) Eastern Cooperative Oncology Group Performance Status	Median of 16 days (IQR = 3–49 days)	Fifty-one percent of participants experienced dyspnea, 48% experienced pain, and 48% experienced fatigue. In addition, 26% had an Eastern Cooperative Oncology Group Performance Status score of 3, and 48% had a score of 4.
Button et al., 2014 (Australia)	<ul style="list-style-type: none"> Retrospective, longitudinal To describe palliative care integration and end-of-life care Hospital (inpatient) 	Patients relapsed from allogeneic hematopoietic stem cell transplantation (N = 30) Palliative Care Problem Severity Score	Terminal admission; median of 18 days (IQR = 1–91 days)	Ninety percent of participants experienced other symptoms ^b (19% mild, 33% moderate, 48% severe), and 67% experienced some form of pain (25% mild, 35% moderate, 40% severe).
Hui et al., 2014 (USA)	<ul style="list-style-type: none"> Retrospective, longitudinal To describe end-of-life care in all settings Cancer center (inpatient and outpatient) 	Patients with advanced disease (N = 113)	Focus on last 30 days of life	Eighty-one percent of participants were admitted to the hospital, and 54% presented to the emergency department.
Cheng, Li, et al., 2015 (China)	<ul style="list-style-type: none"> Retrospective, longitudinal To describe complications at end of life in the hospital Hospital (inpatient and outpatient) 	Patients with acute myeloid leukemia aged older than 60 years who had been referred to a specialist palliative care service (N = 43)	Focus on last 30 days of life	Fourteen percent of participants experienced fatal bleeding events, 51% experienced sepsis, and 51% spent the last 30 days of life as inpatients.
Cheng, Sham, et al., 2015 (China)	<ul style="list-style-type: none"> Retrospective, longitudinal To describe treatment characteristics at end of life in the hospital Palliative care unit (inpatient) 	Deaths in palliative care unit (N = 21)	Focus on last seven days of life	Ninety-one percent of participants required antibiotics, 48% received platelet transfusions, 33% received red blood cell transfusions, 14% received total parenteral nutrition, and 23% received granulocyte-colony-stimulating factor.
LeBlanc et al., 2015 (USA)	<ul style="list-style-type: none"> Retrospective, cross-sectional To compare symptom burden of patients with a hematologic malignancy to those with a solid tumor at the time of referral to specialist palliative care service Palliative care service (inpatient and outpatient) 	Patients admitted to hospice network (N = 3,518) Palliative Performance Scale	Median of 11 days (IQR = 4–38 days)	Twenty-nine percent of participants were prescribed an opiate for dyspnea or pain, and 21% received artificial feeding. On the Palliative Performance Scale, 33% scored less than 40, and 49% scored from 40–60.

^a Niscola et al. (2007) and Cartoni et al. (2009) used the same patient sample in their studies.

^b Other symptoms included nausea, vomiting, anorexia, itch or irritation, constipation, diarrhea, wound, incontinence, fatigue, dyspnea, edema, and delirium.

ICU—intensive care unit; IQR—interquartile range

Note. All studies, with the exception of Cheng, Li, et al. (2015), had a mixed patient population consisting of patients with all hematologic malignancies.

with survival times of less than three months against those with survival times of more than three months. Five studies compared differences between people with a hematologic malignancy and those with a solid tumor; however, only data from the previous group were extracted (Corbett et al., 2013; Fadul et al., 2008; Hui et al., 2014; Hung et al., 2013; LeBlanc et al., 2015).

Patient Characteristics

Most of the studies included patients with any type of hematologic malignancy, including acute leukemia, chronic leukemia, Hodgkin lymphoma, non-Hodgkin lymphoma, multiple myeloma, and myelodysplastic syndromes. One study included only patients with acute myeloid leukemia (Cheng, Li, et al., 2015). Of the six studies that reported on a single population (those that were not comparison studies), only one included people with solid tumors in the sample (12%) (Brück et al., 2012). Therefore, 96% of the included study sample had a hematologic malignancy. The median age of the combined population was 63 years. The youngest group of participants had a median age of 44.15 years (interquartile range [IQR] = 19–65 years) (Holler et al., 2009), and the oldest group had a median age of 78 years (IQR = 68–85 years) (LeBlanc et al., 2015). Collectively, the study participants were predominantly male (59%), ranging from 52% (Hui et al., 2014) to 64% (Button et al., 2014; Fadul et al., 2008) of samples. This aligns with international data that report that men are diagnosed slightly more often than women (Smith, Howell, Patmore, Jack, & Roman, 2011) with certain hematologic malignancies.

Measurement of Signs, Symptoms, and Characteristics

A range of variables were reported collectively in the 12 studies. These variables were defined and measured in a different way in each of the studies, preventing meta-analysis. The majority of studies (n = 6) that examined symptom burden did so by reporting the frequency and severity as per the participants' account (Cartoni et al., 2009; Corbett et al., 2013; Fadul et al., 2008; Hung et al., 2013; LeBlanc et al., 2015; Niscola et al., 2007). Two retrospective studies reported symptoms as per healthcare professionals' clinical documentation, leading to potential bias (Brück et al., 2012; Button et al., 2014). The presence of symptoms and their severity were measured using various symptom assessment scales, such as the Edmonton Symptoms Assessment System and the World Health Organization Bleeding Severity Score.

Signs, Symptoms, and Characteristics Identified

Regardless of disease type or setting, the four most common signs, symptoms, or characteristics

reported were pain, hematopoietic dysfunction, dyspnea, and reduced oral intake. Pain was most consistently rated as a significant symptom, with varying results. Seven of the studies reported on its prevalence. In Niscola et al.'s (2007) study of patients with advanced disease who were supported in the community by a specialized hematology palliative care homecare service, 52% (n = 244) experienced some form of pain. In contrast, in Brück et al.'s (2012) study of patients in the inpatient setting receiving treatment of palliative or curative intent, 94% (n = 163) of participants experienced pain. Drawing conclusions from the latter study is difficult because pain intensity scores were not provided and pain ratings were gathered from documentation in medical notes, not directly from patients' reports. The differences in pain incidence between the two populations may indicate that pain is worse for patients who are unwell in the hospital setting and for those receiving more aggressive treatment as compared to patients on a palliative trajectory in the outpatient setting.

Hematopoietic dysfunction was also identified as commonly occurring in six of the included studies (Brück et al., 2012; Cartoni et al., 2009; Cheng, Li, et al., 2015; Cheng, Sham, et al., 2015; Holler et al., 2009; Hung et al., 2013). For the purposes of this review, hematopoietic dysfunction was defined as anemia, hemorrhage, leukopenia, infection, or fever. Common signs of hematopoietic dysfunction at the end of life included the presence of (a) anemia and/or thrombocytopenia, leading to blood product transfusions; (b) leukopenia or neutropenia, requiring administration of hematopoietic growth factors; and (c) sepsis or fever and administration of IV antibiotics. The need for blood product transfusions, hematopoietic growth factors, and antibiotics cannot be considered to be associated with increased risk of deteriorating and dying. Among the studies, variation was likely to exist in individual practice of the prescribing clinician and routine practice in the clinical setting. Although hematopoietic dysfunction can be a sign of bone marrow suppression caused by treatment, in this population, it was likely indicative of bone marrow failure from advancing disease (Pallister & Watson, 2011).

The presence of dyspnea was reported in five studies. Despite significant variation across study populations and the methods of assessment, results indicated that dyspnea is commonly present in the final three months of life for people with a hematologic malignancy. Decreased appetite also was reported in five studies as a common symptom present in the final months of life for people with a hematologic malignancy. The presence of nausea was explored in four studies, but intensity of this symptom was not assessed, and one study combined it with other

symptoms in a broader symptom category. The findings indicated that nausea is common in this population near the end of life.

Other signs, symptoms, or characteristics that were also reported in the included studies were drowsiness ($n = 3$), delirium ($n = 3$), fatigue ($n = 4$), decreased performance status ($n = 3$), psychosocial or spiritual distress ($n = 3$), and depression and anxiety ($n = 3$). Although some of these factors were identified less often, this may not mean that they are less significant indicators that a person with a hematologic malignancy is nearing the end of his or her life. Certain signs, symptoms, and characteristics may be reported more commonly in the literature for various reasons. In this review, the ability to measure the factor retrospectively may have also affected the number of studies that investigated it because most studies were retrospective ($n = 11$).

The presence of advanced or relapsed disease also seemed to be a common characteristic of people with a hematologic malignancy in the final three months of life. This may be partially because of the bias associated with the sampling approaches used in this field, with the majority of studies undertaken in palliative care settings. No clear definition exists for what constitutes advanced disease in the hematology setting, and definitions of advanced disease for solid tumors are not applicable because they focus on metastatic disease (American Cancer Society, 2014).

Discussion

Identifying people at risk of dying is a largely unexplored topic in the hematology setting. This review identified a number of signs, symptoms, and characteristics present in the last three months of life for people with a hematologic malignancy. Methodologic weaknesses of included studies and a lack of literature in this area have led to ambiguous findings. What remains unclear is whether the signs, symptoms, and characteristics identified are unique or are increasingly found when patients near the end of life and, therefore, have the potential to be associated with an increased risk of mortality. Many of the issues identified, such as anemia, thrombocytopenia, and neutropenia, are related to bone marrow suppression and are present in people who are newly diagnosed, recently relapsed, or at other stages in the illness trajectory (e.g., receiving chemotherapy) (Pallister & Watson, 2011). A similar symptom burden profile has been reported in groups of patients newly diagnosed, recently relapsed, or at any stage in their illness trajectory (Manitta, Zordan, Cole-Sinclair, Nandurkar, & Philip, 2011; Møller et al., 2012; Zimmermann et al., 2013). In the included studies, no comparison

was made with people at other stages in their illness trajectory regarding signs, symptoms, and characteristics experienced. Despite the reported challenges in prognosticating for people with a hematologic malignancy (Auret et al., 2003), little evidence exists to assist clinicians with identifying when this cohort is in the final months of life. This review will begin to address this large gap in the literature; however, much more work is needed in this area.

Comparison to the Literature

The findings of this review are corroborated by a study by Chou et al. (2015) regarding prognosticating at the end of life, a similar yet subtly different concept to identifying the risk of deteriorating and dying. Chou et al. (2015) reported that the Palliative Prognostic Index (PPI) was a useful prognosticator of life expectancy in terminally ill people with a hematologic malignancy receiving palliative care (median survival of 16 days, IQR = 4–47.5 days). The core components of the PPI were identified in this review (performance status, dyspnea, delirium, oral intake), with the exception of edema (Chou et al., 2015). This review expands on Chou et al.'s (2015) study; a number of other factors identified are not included in the PPI, such as advanced or relapsed disease, hematopoietic dysfunction, and the presence of many other symptoms. Much more research is needed in a wider population of people with a hematologic malignancy (e.g., people receiving care of palliative, life-prolonging, or curative intent) to identify and explore what clinical indicators signal they may be nearing the end of life.

Comparison to Other Patient Populations

The findings of this review indicate that some people with a hematologic malignancy share a clinical profile of deterioration that is similar to the clinical profile of people with other types of illnesses. Many of the signs, symptoms, and characteristics identified in this review are markers of general deterioration in the broader population, such as declining performance, increased symptom burden, and weight loss (Highet et al., 2013). These factors are commonly included in tools, such as the Supportive and Palliative Care Indicators Tool (SPCIT), to identify when a person with a progressive incurable illness is likely to be in the final year of life and may have palliative care needs (Highet et al., 2013; Maas et al., 2013). Current tools to identify risk of deteriorating and dying, such as the SPCIT, are likely useful in the hematology setting for people on a palliative trajectory who have progressive incurable illness, as described in this review. More research is required to establish this. The presence of chronic illness or multiple comorbidities, residence in a nursing home, or increased care requirements, which are

included in these tools as clinical indicators, were not identified in this review as being indicative of the risk of deteriorating and dying in patients with advanced hematologic malignancies (Boyd & Murray, 2010; Highet et al., 2013). This may be reflective of the unique illness trajectory of hematologic malignancies. Chou et al.'s (2015) study found that the Charlson Comorbidity Index was not predictive of death in the final weeks of life for people with a hematologic malignancy. Understanding the complex differences between the broader population and those with a hematologic malignancy is needed to understand how current knowledge can be more widely applied in the hematology setting.

Intense End-of-Life Care

Signs, symptoms, and characteristics identified in this review describe deteriorating people who receive high levels of medical care at the end of life, specifically for hematopoietic dysfunction. Healthcare professionals are likely to have frequent contact with this cohort in acute care settings. Frequent contact allows for the development or continuation of close therapeutic relationships with patients and their families, a key concept in the hematology setting because of the lengthy and intensive treatment regimens (Brück et al., 2012). Having a good relationship with a clinician is reported to lead to greater patient satisfaction when engaging in difficult conversations about the end of life (Clayton, Butow, & Tattersall, 2005). However, lengthy patient–physician relationships are also reported to be associated with overly optimistic estimations of life expectancy (Christakis & Lamont, 2000). Care must be taken by all clinicians to avoid this. In addition, this review highlights that people with a hematologic malignancy require care to be tailored to their specific needs at the end of life because they are likely to require hospital admissions, blood product transfusions, antibiotics, and administration of hematopoietic growth factors (Button & Chan, 2014). Specialist palliative care services must consider if they are well equipped to care for people with a hematologic malignancy at the end of life.

Limitations

The literature provides scant evidence of the signs, symptoms, and characteristics present in the final three months of life for people with a hematologic malignancy. Variations in study designs, participants, settings, intent of care, definitions of advanced disease, and referral patterns to specialist palliative care services has made drawing conclusions and generalizing results difficult. Differing time frames for survival may explain some variation in the signs, symptoms, and characteristics identified. Signs and symptoms

Knowledge Translation

- Certain similarities but also key differences existed for people with a hematologic malignancy compared to those with other illnesses, substantiating reports of a unique illness trajectory in the hematology setting.
- Nurses are in a unique position to identify many of the signs, symptoms, and characteristics associated with the end of life in people with a hematologic malignancy; in addition, they can play a key role in helping to transition people to the end of life.
- General signs of deterioration may be useful to identify when a person with a hematologic malignancy treated with palliative intent is nearing the end of life; however, more research is needed.

experienced in the terminal phase are often quite different from those in the weeks or days preceding the terminal phase (Hauser, Stockler, & Tattersall, 2006).

The methodologic quality of studies in this review was poor. Because the majority of studies employed a retrospective design, results were dependent on the quality of documentation in patient records, and the data collected were restricted by availability. All but two studies were conducted in a single center (Cheng, Li, et al., 2015; LeBlanc et al., 2015), and half of the studies ($n = 6$) had sample sizes of fewer than 150 participants. Most of the studies did not provide adequate description of variables measured and were exposed to subjective bias of the researcher.

The studies focused largely on patients on a palliative trajectory, limiting the generalizability of findings to the broader population of people with a hematologic malignancy. Studies that included people who experienced medical emergencies or were admitted to the intensive care unit, despite this group of patients having high rates of mortality, were not located (Naeem et al., 2006; Yang et al., 2007; Yeo et al., 2012).

Implications for Research

Knowledge regarding the signs, symptoms, and characteristics that indicate a person with a hematologic malignancy is nearing the end of life is needed. The review identified a weak body of literature and a lack of studies of people who are not referred to specialist palliative care services or hospices, as well as those who are not considered to have advanced disease. A gap exists in the literature regarding people who are treated aggressively, experience treatment-related mortality, or die in the intensive care unit. Large, prospective, multisite studies that compare signs, symptoms, and characteristics present at different times in a patient's illness trajectory would greatly

add to this limited knowledge base. This knowledge is vital to understanding when a person is at risk of deteriorating and dying and may benefit from integration of palliative care, prior to sudden deterioration and death. This knowledge is also critical for developing nursing interventions that will address the holistic needs of the patient and his or her family as they transition to the end of life.

To expand on the findings of this literature review, one of the authors conducted a systematic review exploring prognostic factors associated with mortality in the final three months of life for people with a hematologic malignancy. The results of this review will be published separately.

Implications for Practice

Within the specialty of hematology, an overwhelming focus is on cure (Dalgaard et al., 2010; Manitta et al., 2010). In previous research, hematology nurses have reported that they are supportive of a palliative approach and believe they are well positioned to identify when patients are nearing the end of life and are appropriate for palliative care integration (Button, 2013; McGrath & Holewa, 2007). The large amount of time spent at patient bedsides means that nurses are able to assess patients for many of the factors identified in this review, such as physical and psychosocial symptoms and declining performance status. Nurses have the ability to play a key role in identifying when a person is at high risk of deteriorating and dying and has potential palliative care needs. Dalgaard et al. (2010) has reported that medical staff often focus on treatment and objective facts, whereas nursing assessment places more emphasis on the patient's general condition and overall quality of life. The holistic focus of nursing allows nurses to assist in meeting the needs of the patient and his or her family as they make the difficult transition to the end of life. However, during a busy day, nurses may have difficulty discussing subtle signs of illness progression or deterioration with medical staff or with the patient and his or her family (Dalgaard et al., 2010). Cooperation and communication is needed between nursing and medical staff regarding the risk of deterioration and dying to allow for assessing palliative care needs and transitioning to the end of life (Dalgaard et al., 2010).

Conclusion

Identifying people who are likely to be in their final months of life is a largely unexplored topic in the hematology setting, which may explain some of the ongoing challenges with integration of palliative care for this population (Manitta et al., 2010). The gaps in the lit-

erature highlighted in this review can serve as a guide for future research. The range of signs, symptoms, and characteristics highlighted can assist clinicians to identify people with a hematologic malignancy who are likely to be nearing the end of their life and may, therefore, benefit from palliative care integration. However, more research is needed to explore this further.

References

- American Cancer Society. (2014). What is advanced cancer? Retrieved from http://www.cancer.org/treatment/understanding_yourdiagnosis/advancedcancer/advanced-cancer-what-is
- Auret, K., Bulsara, C., & Joske, D. (2003). Australasian haematologist referral patterns to palliative care: Lack of consensus on when and why. *Internal Medicine Journal*, *33*, 566–571. doi:10.1111/j.1445-5994.2003.00490
- Boyd, K., & Murray, S.A. (2010). Recognising and managing key transitions in end of life care. *BMJ*, *341*, c5897.
- Brück, P., Pierzchlewska, M., Kaluzna-Oleksy, M., Ramos Lopez, M.E., Rummel, M., Hoelzer, D., & Böhme, A. (2012). Dying of hematologic patients—Treatment characteristics in a German university hospital. *Supportive Care in Cancer*, *20*, 2895–2902. doi:10.1007/s00520-012-1417-8
- Button, E. (2013). *Exploring palliative care provision for patients that relapse following haematopoietic stem cell transplantation* (Unpublished master's thesis). Griffith University, Brisbane.
- Button, E., & Chan, R.J. (2014). Palliative care provision for patients with a hematological malignancy: Can we do more? *Cancer Nursing*, *37*, 239–240. doi:10.1097/NCC.0000000000000164
- Button, E.B., Gavin, N.C., & Keogh, S.J. (2014). Exploring palliative care provision for recipients of allogeneic hematopoietic stem cell transplantation who relapsed. *Oncology Nursing Forum*, *41*, 370–381. doi:10.1188/14.ONF.370-381
- Cartoni, C., Niscola, P., Breccia, M., Brunetti, G., D'Elia, G.M., Giovannini, M., . . . Mandelli, F. (2009). Hemorrhagic complications in patients with advanced hematological malignancies followed at home: An Italian experience. *Leukemia and Lymphoma*, *50*, 387–391. doi:10.1080/10428190802714024
- Cheng, B.H., Sham, M.M., Chan, K.Y., Li, C.W., & Au, H.Y. (2015). Intensive palliative care for patients with hematological cancer dying in hospice: Analysis of the level of medical care in the final week of life. *American Journal of Hospice and Palliative Care*, *32*, 221–225. doi:10.1177/1049909113512412
- Cheng, H.W., Li, C.W., Chan, K.Y., Au, H.Y., Chan, P.F., Sin, Y.C., . . . Sham, M.K. (2015). End-of-life characteristics and palliative care provision for elderly patients suffering from acute myeloid leukemia. *Supportive Care in Cancer*, *23*, 111–116. doi:10.1007/s00520-014-2333-x
- Chou, W.C., Kao, C.Y., Wang, P.N., Chang, H., Wang, H.M., Chang, P.H., . . . Hung, Y.S. (2015). The application of the Palliative Prognostic Index, Charlson Comorbidity Index, and Glasgow Prognostic Score in predicting the life expectancy of patients with hematologic malignancies under palliative care. *BMC Palliative Care*, *14*, 18. doi:10.1186/s12904-015-0011-5
- Christakis, N.A., & Lamont, E.B. (2000). Extent and determinants of error in doctors' prognoses in terminally ill patients: Prospective cohort study. *BMJ*, *320*, 469–472. doi:10.1136/bmj.320.7233.469
- Clayton, J.M., Butow, P.N., & Tattersall, M.H. (2005). When and how to initiate discussion about prognosis and end-of-life issues with terminally ill patients. *Journal of Pain and Symptom Management*, *30*, 132–144. doi:10.1016/j.jpainsymman.2005.02.014
- Corbett, C.L., Johnstone, M., Trauer, J.M., & Spruyt, O. (2013). Palliative care and hematological malignancies: Increased referrals

- at a comprehensive cancer centre. *Journal of Palliative Medicine*, 16, 537–542. doi:10.1089/jpm.2012.0377
- Critical Appraisal Skills Programme. (2013). CASP checklists. Retrieved from <http://www.casp-uk.net/#/checklists/cb36>
- Dalgaard, K.M., Thorsell, G., & Delmar, C. (2010). Identifying transitions in terminal illness trajectories: A critical factor in hospital-based palliative care. *International Journal of Palliative Nursing*, 16, 87–92. doi:10.12968/ijpn.2010.16.2.46754
- Ezzone, S., & Schmit-Pokorny, K. (2007). *Blood and marrow stem cell transplantation: Principles, practice, and nursing insights* (3rd ed.). Sudbury, MA: Jones and Bartlett Learning.
- Fadul, N.A., El Osta, B., Dalal, S., Poulter, V.A., & Bruera, E. (2008). Comparison of symptom burden among patients referred to palliative care with hematologic malignancies versus those with solid tumours. *Journal of Palliative Medicine*, 11, 422–427. doi:10.1089/jpm.2007.0184
- Garrard, J. (2014). *Health sciences literature review made easy: The Matrix Method* (4th ed.). Burlington, MA: Jones and Bartlett Learning.
- Hauser, C.A., Stockler, M.R., & Tattersall, M.H. (2006). Prognostic factors in patients with recently diagnosed incurable cancer: A systematic review. *Supportive Care in Cancer*, 14, 999–1011. doi:10.1007/s00520-006-0079-9
- Highet, G., Crawford, D., Murray, S., & Boyd, K. (2013). Development and evaluation of the Supportive and Palliative Care Indicators Tool (SPICT): A mixed-methods study. *BMJ Supportive and Palliative Care*, 4, 285–290. doi:10.1136/bmjspcare-2013-000488
- Holler, E., Kolb, H.J., Greinix, H., Perrotin, D., Campilho, F., Aversa, F., . . . Rustige, J. (2009). Bleeding events and mortality in SCT patients: A retrospective study of hematopoietic SCT patients with organ dysfunctions due to severe sepsis or GVHD. *Bone Marrow Transplantation*, 43, 491–497. doi:10.1038/bmt.2008.337
- Hui, D., Didwaniya, N., Vidal, M., Shin, S.H., Chisholm, G., Roquemore, J., & Bruera, E. (2014). Quality of end-of-life care in patients with hematologic malignancies: A retrospective cohort study. *Cancer*, 120, 1572–1578. doi:10.1002/cncr.28614
- Hung, Y.S., Wu, J.H., Chang, H., Wang, P.N., Kao, C.Y., Wang, H.M., . . . Chou, W.C. (2013). Characteristics of patients with hematologic malignancies who received palliative care consultation services in a medical center. *American Journal of Hospice and Palliative Care*, 30, 773–780. doi:10.1177/1049909112471423
- LeBlanc, T., Abernethy, A.P., & Casarett, D.J. (2015). What is different about patients with hematologic malignancies? A retrospective cohort study of cancer patients referred to a hospice research network. *Journal of Pain and Symptom Management*, 49, 505–512. doi:10.1016/j.jpainsymman.2014.07.003
- Maas, E.A., Murray, S.A., Engels, Y., & Campbell, C. (2013). What tools are available to identify patients with palliative care needs in primary care: A systematic literature review and survey of European practice. *BMJ Supportive and Palliative Care*, 3, 444–451. doi:10.1136/bmjspcare-2013-000527
- Maddocks, I., Bentley, L., & Sheedy, J. (1994). Quality of life issues in patients dying from haematological diseases. *Annals of the Academy of Medicine, Singapore*, 23, 244–248.
- Manitta, V., Zordan, R., Cole-Sinclair, M., Nandurkar, H., & Philip, J. (2011). The symptom burden of patients with hematological malignancy: A cross-sectional observational study. *Journal of Pain and Symptom Management*, 42, 432–442. doi:10.1016/j.jpainsymman.2010.12.008
- Manitta, V.J., Philip, J.A., & Cole-Sinclair, M.F. (2010). Palliative care and the hemato-oncological patient: Can we live together? A review of the literature. *Journal of Palliative Medicine*, 13, 1021–1025. doi:10.1089/jpm.2009.0267
- Matasar, M.J., & Zelenetz, A.D. (2008). Overview of lymphoma diagnosis and management. *Radiologic Clinics of North America*, 46, 175–198. doi:10.1016/j.rcl.2008.03.005
- McGrath, P., & Holewa, H. (2007). Special considerations for haematology patients in relation to end-of-life care: Australian findings. *European Journal of Cancer Care*, 16, 164–171. doi:10.1111/j.1365-2354.2006.00745.x
- Moher, D., Liberati, A., Tetzlaff, J., & Altman, D.G. (2009). Preferred reporting items for systematic reviews and meta analyses: The PRISMA statement. *PLOS Medicine*, 6, e1000097. doi:10.1371/journal.pmed.1000097
- Møller, T., Adamsen, L., Appel, C., Welinder, P., Stage, M., Jarden, M., . . . Kjeldsen, L. (2012). Health related quality of life and impact of infectious comorbidity in outpatient management of patients with acute leukemia. *Leukemia and Lymphoma*, 53, 1896–1904. doi:10.3109/10428194.2012.676169
- Murray, S.A., Kendall, M., Boyd, K., & Sheikh, A. (2005). Illness trajectories and palliative care. *BMJ*, 330, 1007–1011. doi:10.1136/bmj.330.7498.1007
- Naeem, N., Eyzaguirre, A., Kern, J.A., Lazarus, H.M., Hejal, R.B., Laughlin, M.J., & Kern, E.F. (2006). Outcome of adult umbilical cord blood transplant patients admitted to a medical intensive care unit. *Bone Marrow Transplantation*, 38, 733–738. doi:10.1038/sj.bmt.1705502
- National Health and Medical Research Council. (2000). *How to review the evidence: Systematic identification and review of the scientific literature*. Canberra, Australia: Author.
- National Institute for Health and Clinical Excellence. (2003). *Improving outcomes in haematological cancers: The manual*. London, UK: Author.
- Nightingale, L., Monsell, M., Wong, W.K., & Cheung, C.C. (2011). How to give haematology patients better end-of-life care. *European Journal of Palliative Care*, 18, 114–117.
- Nicola, P., Cartoni, C., Romani, C., Brunetti, G.A., D'Elia, G.M., Cupelli, L., . . . Foà, R. (2007). Epidemiology, features and outcome of pain in patients with advanced hematological malignancies followed in a home care program: An Italian survey. *Annals of Hematology*, 86, 671–676. doi:10.1007/s00277-007-0296-4
- Orosz, J., Bailey, M., Bohensky, M., Gold, M., Zalstein, S., & Pilcher, D. (2014). Deteriorating patients managed with end-of-life care following Medical Emergency Team calls. *Internal Medicine Journal*, 44, 246–254. doi:10.1111/imj.12350
- Pallister, C.J., & Watson, M.S. (2011). *Haematology* (2nd ed.). Banbury, UK: Scion.
- Smith, A., Howell, D., Patmore, R., Jack, A., & Roman, E. (2011). Incidence of haematological malignancy by sub-type: A report from the Haematological Malignancy Research Network. *British Journal of Cancer*, 105, 1684–1692. doi:10.1038/bjc.2011.450
- Swerdlow, S.H., Campo, E., Harris, N.L., Jaffe, E.S., Pileri, S.A., Stein, H., . . . Vardiman, J.W. (Eds.). (2008). *WHO classification of tumours of haematopoietic and lymphoid tissues*. Lyon, France: IARC Press.
- Wright, A.A., Zhang, B., Ray, A., Mack, J.W., Trice, E., Balboni, T., . . . Prigerson, H.G. (2008). Associations between end-of-life discussions, patient mental health, medical care near death, and caregiver bereavement adjustment. *JAMA*, 300, 1665–1673. doi:10.1001/jama.300.14.1665
- Yang, T.M., Wang, P.N., Kao, K.C., Huang, C.C., Tsai, Y.H., & Hsieh, M.J. (2007). Outcome of hematopoietic stem cell recipients who were mechanically ventilated and admitted to intensive care units. *Journal of the Formosan Medical Association*, 106, 295–301. doi:10.1016/s0929-6646(09)60255-2
- Yeo, C.D., Kim, J.W., Kim, S.C., Kim, Y.K., Kim, K.H., Kim, H.J., . . . Rhee, C.K. (2012). Prognostic factors in critically ill patients with hematologic malignancies admitted to the intensive care unit. *Journal of Critical Care*, 27, 739.e1–745.e6. doi:10.1016/j.jcrc.2012.07.014
- Zimmermann, C., Yuena, D., Mischitelle, A., Minden, M.D., Brandwein, J.M., Schimmer, A., . . . Rodin, G. (2013). Symptom burden and supportive care in patients with acute leukaemia. *Leukemia Research*, 37, 731–736. doi:10.1016/j.leukres.2013.02.009