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Advancing Palliative Care Integration in Hematology: Building Upon Existing Evidence

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Opinion statement

Patients with hematologic malignancies and their families are among the most distressed of all those with cancer. Despite high palliative care-related needs, the integration of palliative care in hematology is underdeveloped. The evidence is clear that the way forward

includes standard-of-care PC integration into routine hematologic malignancy care to improve patient and caregiver outcomes. As the PC needs for patients with blood cancer vary significantly by disease, a disease-specific PC integration strategy is needed, allowing for serious illness care interventions to be individualized to the specific needs of each patient and situation.

Introduction: what is palliative care?

Palliative care (PC) is defined by the World Health Organization as an "approach that improves the quality-of-life (QOL) of patients and their families facing the problems associated with life-threatening illness, through the prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems, physical, psychosocial, and spiritual" [1]. PC specialists provide complex symptom management and family-centered biopsychosocial assessments with effective communication and focus on QOL [2, 3]. Though PC is often misperceived as end-of-life care, ideal PC is integrated early in the illness trajectory alongside life-prolonging or potentially curative therapies [4]. While PC is sometimes provided by oncologists or other members of the cancer care team, referred to as "primary PC," our use of the term refers to specialty PC services, or those provided by specialized clinicians on an interdisciplinary team.

Specialty palliative care has many benefits

Palliative care has many established benefits for patients with cancer. The 2009 ENABLE II randomized trial paved the way for numerous studies supporting PC integration in cancer care [5]. In 2010, Temel demonstrated that early PC led to improved QOL, improved survival, and decreased the intensity of end-of-life care, among patients with metastatic non-small-cell lung cancer [6]. In 2015, the ENABLE III randomized trial showed that patients receiving earlier, as compared to later, PC had improved one-year survival and reduced family and caregiver burden and depression [7, 8]. Multiple systematic reviews and meta-analyses also demonstrate benefit from PC interventions including improvements in patient QOL, symptom burden, caregiver outcomes, advance care planning, health care utilization, and, often, patient survival [9•, 10, 11]. Resultantly, many organizations have called for the integration of PC into routine comprehensive oncology care [12–15].

Hematologic malignancy patients have high palliative care needs

Patients with HM suffer similar, or sometimes greater, symptom burdens to patients with metastatic solid tumors [4, 19]. Studies show that patients with blood cancers commonly present with distress and numerous physical

and psychological symptoms including fatigue, insomnia, dry mouth, pain, and anxiety [16, 18, 20]. Patients with HM also receive inadequate symptom management, psychological support, and engagement in advance care planning, which all contribute substantially to increased morbidity [21–23]. While survival is improving, approximately 50,000 deaths annually are attributed to hematologic malignancies (HM) [24].

As part of standard HM management, many patients receive intensive treatments, prolonged hospitalization, and oftentimes require life-long suppressive therapies [19]. Patients with HM are more likely than those with solid tumors to receive intensive end-of-life care (e.g., chemotherapy or intensive care at end-of-life) and to die in the hospital [25–27]. Patients with HM are also less likely than solid tumor patients to have documented care preferences such as advance care plans or be referred to hospice [28–30]. Patients referred to hospice tend to experience shorter length of stays, which signals late referrals and limited benefit from hospice care [31, 32]. Patients with HM also experience significant barriers to hospice care including lack of access to blood transfusions for symptom support. Among survivors, symptoms often persist with long-term sequelae and quality-of-life implications. Survivors commonly experience fatigue, pain, neuropathy, cardiomyopathy, neurocognitive deficits, psychological distress, anticipatory grief, fear of recurrence, and post-traumatic stress [33–36].

Barriers to palliative care integration in hematology

While high-quality evidence supports the integration of PC in oncology, many barriers exist [37–40]. Most randomized clinical trials of PC integration have excluded patients with HM. The integration of PC into standard HM care has therefore lagged behind that of solid tumor care [38, 39]. Hematologic malignancy specialists are less likely than solid tumor oncologists to request specialty PC consultation [4, 41–43]. Many also equate PC to end-of-life care and may not recognize the demonstrated benefits of early PC [44–46]. Furthermore, hematologic malignancy specialists may wish to address the primary PC needs of their own patients. Surveys have shown, however, that hematologic malignancy specialists often express discomfort discussing death or hospice referral, as well as a sense of shame that this transition in treatment goals may indicate a personal failure [30, 42, 44, 47].

The treatment trajectories of blood cancers also contribute hurdles for service integration. The possibility of cure is rather unique to HM, especially when compared to most other advanced cancers, and drives aggressive clinical decision-making [39, 48–50]. Patients with HM often have a rapid and unpredictable decline at the end of life, which contributes to prognostic uncertainty and challenges both clinicians and patients; more than half of patients with HM have a different understanding of their prognosis than their hematologist [51, 52]. Prognostic uncertainties and

misperceptions about treatment risks and benefits represent unmet PC needs for patients and families with HM [48, 53–55].

The way forward: disease-specific palliative care integration?

Interest is growing for earlier integration of PC into hematologic malignancy care. Several recent studies demonstrate the benefits of PC integrated into HM care, yet only for some specific HM (ex. acute myeloid leukemia) and care settings (inpatient). HM are a heterogeneous group of diseases, with each patient with HM having unique needs, salient clinical features, treatment paradigms, and expected outcomes. Thus, each major disease group will likely have a different solution to the puzzle of PC-hemato-oncology integration. To follow, we summarize salient features and treatment paradigms for the various major HM disease sub-types. We then examine what is known about the PC needs specific to each disease, detail relevant studies of PC integration, and discuss the anticipated needs of each group, emphasizing areas warranting further study. A summary may be found in Table 1.

Hematologic malignancies: similarities and subtypes

The three main categories of HM include (1) leukemias, (2) lymphomas, and (3) multiple myeloma (MM) [56]. For clarity and completeness, we include further subcategories including acute versus chronic leukemias, myelodysplastic syndromes and myeloproliferative neoplasms, and cellular therapies, including CAR-T therapy and hematopoietic stem cell transplantation (HSCT) (which may be performed in several disease states and have specific PC considerations). While each disease is unique, HM as a group generally share at least one of the following:

1) The need for intensive treatments to achieve remission or cure, which is associated with risk for early mortality and/or treatment toxicity
2) Prognostic uncertainty and unpredictable illness courses, including wide variability in outcomes including possibility of cure
3) Sometimes chronic, indolent, and/or a relapsing and remitting course, requiring indefinite and continuous oral suppressive therapies
4) High patient and caregiving burden (physical, emotional, and/or spiritual), even after treatment completion

Table 1. Treatment paradigms and palliative care integration in various hematologic malignancies sub-types

Hematologic malignancy	Treatment paradigms/ salient features	Symptoms and PC needs	Major PC-hemato-oncology integration randomized trials	Palliative care integration: where next?
Acute leukemia	"High-risk, high-reward" No 'Best' treatment consensus leads to outcome variability Intensive hospitalization	High rates of physical symptoms Significant post-traumatic stress, anxiety and depression High healthcare utilization at the end of life Prognostic uncertainty	El-Jawahri et al. report that integrated PC improved quality of life, depression, anxiety, PTSD, end-of-life discussions, and healthcare utilization at the end of life [102]	Palliative care integration at time of induction chemotherapy Symptom assessment and caregiver support throughout continuum of care Future work is needed for newer, lower-intensity treatment regimens
Chronic leukemias	Slow, indolent disease course Prognosis measured in years "Treatment without end"	High symptom burden due to chronicity and cumulative toxicities, financial distress Anticipatory distress about relapse		Develop psycho-oncologic support interventions for patients and caregivers Research is needed to understand needs and optimal service integration
Lymphoma HL	Curable	Psychological symptoms are common		Future work is needed to guide PC integration in lymphoma care
NHL	Significant variability in aggressiveness and prognosis Sometimes relapsing and remitting disease course	High clinical burden; many physical and psychological symptoms 50% have treatment toxicities Issues of survivorship High end of life utilization		
Multiple myeloma	2nd most common hematologic cancer Chronic survivorship (never off treatment) Survival improving, though remains incurable Cumulative effects of prolonged treatment (unrelenting treatment)	Perhaps worst quality of life compared to other hematologic cancers High physical and psychological symptom burden, financial distress Caregivers experience significant psychological distress		Future work is needed to guide PC integration in MM care Anticipate need for psychosocial support interventions for MM patients and their caregivers

Table 1. (continued)

Hematologic malignancy	Treatment paradigms/ salient features	Symptoms and PC needs	Major PC-hemato-oncology integration randomized trials	Palliative care integration: where next?
Myelodysplastic syndromes Myeloproliferative neoplasms	Wide variability in clinical presentations Need for HSCT or transfusions Many new treatments currently being studied	Dyspnea and fatigue common and debilitating Transfusion dependence limits hospice eligibility Depressive and anxiety symptoms are common High caregiver burden		Future work is needed to guide PC integration in MDS and MPN care At the end of life, we should reconsider transfusion dependence as a hospice exclusion criterion
CAR T cell therapy	"High risk, high reward" Novelty of treatment limits available data	High end of life healthcare utilization High psychological distress among patients Prognostic uncertainty		Psychosocial PC interventions are needed for this population PC integration with CAR T cell therapy has not been studied, but should be designed and implemented
Hematopoietic stem cell transplant	Invasive and morbid (concern for graft vs host disease) Possibly curative Prolonged, isolating index hospitalization Concurrent high-dose chemotherapy	Psychological symptoms including PTSD are common Many physical symptoms Generally low quality of life High caregiver burden	2016 RCT described PC improving psychological well-being and symptom burden (159,160) 2020 RCT examining psychological intervention for HSCT patient caregivers (161)	PC integration at time of HSCT is prudent Future work should be aimed at developing robust psychosocial interventions for HSCT patients and caregivers

Acute leukemias

Treatment paradigms

Leukemias are subdivided into two types: acute or chronic. Acute myeloid leukemia (AML) is the most common in adults followed by acute lymphoid leukemia (ALL). The abrupt presentation and rapidly progressive nature of acute leukemia lends itself to be more responsive to chemotherapy than solid tumors, which means a chance for cure. Cure, however, typically requires higher-dose intensity chemotherapy than typical solid tumor regimens and/or consolidative hematopoietic stem cell transplantation [56]. This establishes a characteristic "high-risk, high-reward" treatment paradigm in acute leukemia care. Patient's will receive intensive chemotherapy regimens, while other non-intensive treatments contributes to wide variability in treatment-associated morbidity and mortality. HSCT is considered for many patients and is discussed in a separate section below.

Symptom burden and palliative care needs

Acute leukemia may be among the most psychologically distressing of all cancers [57]. The intensive treatments for acute leukemias necessitate weeks long and socially isolating hospitalizations [58–61]. Treatments can carry high risk of death and treatment-related toxicities. Physical symptoms may be severe and include fevers, fatigue, mucositis, and other distressing gastrointestinal symptoms [62–64]. Treatment effects may be long-lasting, contributing to emotional and psychological symptoms and worsened QOL [59, 65–67]. A secondary data analysis of 160 patients with AML found that a substantial proportion reported clinically significant post-traumatic stress symptoms one month after intensive chemotherapy [68]. Approximately, a third of patients will report significant depressive or anxiety symptoms. Another one-third experience acute stress reactions from the shock of the diagnosis and unexpected urgent hospitalization [60, 61, 65, 69].

In addition to the high burden of physical and emotional symptoms, patients with acute leukemias have additional unmet PC-related needs. One study revealed that while 86% of AML patients were expected by their oncologists to have a poor prognosis, 74% of these patients reported at least a 50% chance of cure [70]. Older adults with AML over-estimate their prognosis by threefold [55]. This skew towards optimistic prognostication and aggressive care leads to increased healthcare utilization at the end of life. Patients with acute leukemia are more likely to choose aggressive therapies and die in the hospital, while accessing PC services less frequently than those patients with advanced solid tumors [71]. A study of 168 deceased patients with acute leukemia revealed that 66.7% were hospitalized in the last week of life and over half received chemotherapy in the last 30 days of life [72]. Another study of 200 leukemia patients reported the median time from last code status transition to death was only two days. Thirty-two percent (32%) of those code status conversations occurred at the time of clinical deterioration and 39.5%

without the patient present or capable of making their own medical decisions [73]. Thus, there are significant opportunities for improvement in advance care planning and symptom management in acute leukemia care.

Palliative care integration

In 2021, El-Jawahri published a multisite randomized clinical trial of 160 adults with AML undergoing intensive chemotherapy showing that integrated specialty PC significantly improves patient-reported QOL, depression, anxiety, and posttraumatic stress symptoms. Among the patients who died, those receiving integrated PC were more likely to have discussed their end-of-life preferences and less likely to receive chemotherapy at end-of-life [74••, 75]. Smaller studies reinforce the benefits of integrated PC in acute leukemia care, showing increased hospice use and fewer intensive care unit admissions [76].

Next steps

For patients with AML receiving intensive induction chemotherapy, the evidence of benefit of PC integration early in the disease course is clear. PC should be involved at the time of admission for induction chemotherapy or index hospitalization. PC services have much to offer including providing symptom management throughout the hospitalization, caregiver encouragement, support during potential HSCT, and, if needed, end-of-life care [77, 78]. Future work is needed in this area with at least one major clinical trial underway. SPRINT is an active multisite randomized controlled clinical trial examining collaborative palliative and leukemia care versus standard leukemia care alone in patients with AML and high risk MDS receiving non-intensive chemotherapy [79].

Chronic leukemias

Treatment paradigms

In direct contrast with acute leukemias, chronic leukemias often present asymptomatically and have a slow disease course. Chronic myeloid leukemia (CML) and chronic lymphoid leukemia (CLL) are the most common types in adults. In general, prognosis is measured in years, sometimes even decades.

Typical cases of CML are treated with oral tyrosine kinase inhibitors, which typically confer an excellent prognosis and often well-tolerated side effects. While prognosis is good, patients with CML often require indefinite and continuous oral targeted therapy, which has psychological, financial, and other implications. This 'treatment-without-end' paradigm is characteristic of CML care. Atypical cases of CML, such as those with resistant mutations or those that transform to AML, may have shortened survival or experience the effects described previously related to the transformed acute leukemia [56]. Some patients face severe side effects or tolerability issues from their treatment.

CLL is typified by older patient age and a slow-growing, indolent nature, with most patients presenting initially asymptomatic. The default management strategy for those with less aggressive variants is 'active surveillance' without treatment. Sometimes CLL can transform into an aggressive and life-limiting variant or aggressive lymphoma ("Richter's transformation"), which indicates a poor prognosis. Regardless, patients with CLL can face frequent infectious and nosocomial complications, the need for hospitalization or intermittent treatments unpredictably, and, as with other HM, difficult prognostication [80]. Some require indefinite oral therapies, at significant financial cost and sometimes with unfavorable side effect profiles [56].

Symptom burden and palliative care needs

There is marked clinical heterogeneity in how chronic leukemia variants may impacts a patient's life. Patients with chronic leukemias may suffer severe toxicities and symptoms, often related to the chronicity of the illness and/or treatment. An international survey of 1482 patients with CLL found significantly worse emotional well-being in those with CLL than other patients with cancer [80]. Life-long suppressive treatments, uncertainty related to the timing and severity of inevitable relapse, and nosocomial complications all contribute to detriments in physical, emotional, and financial well-being.

Palliative care integration and next steps

While it is recognized that patients with chronic leukemias experience significant symptom burden, often stemming from the cumulative toxicities of decades of continuous oral targeted therapies and recurring relapses, little has been studied regarding PC integration into standard chronic leukemia care. PC specialists could provide an extra layer of support for patients with chronic leukemias, particularly regarding the need for psycho-oncologic support interventions for patients with CLL and enhanced symptom management [80]. Furthermore, there may be opportunity to provide support around the experience of living with a chronic illness, which may be experienced as a sword of Damocles or having the potential for transformation or progression in a manner that is difficult to predict. It is not clear, however, that every patient with a chronic leukemia needs or would benefit from specialist palliative care services. Perhaps those with CLL may do well with geriatrics or social work support with periodic PC consultation for those with specific and challenging PC needs. More research is needed to better understand the needs and the optimal involvement of PC in this population.

Multiple myeloma

Treatment paradigms

MM is the second most common hematologic malignancy. While survival is improving with the advent of new therapies, MM remains generally incurable. The disease course is typified by periods of remission and relapse. The time in remission before relapse varies greatly depending on disease phenotype the clinical aggressiveness of the MM, though in ideal circumstances can last years. Patients often remain on maintenance therapies even when in remission. MM patients commonly are treated with five or more lines of therapy, including HSCT and multidrug regimens [56]. Patients with 'standard risk' MM may be expected to live approximately 5–10 or more years [56].

Symptom burden and palliative care needs

MM patients receive indefinite therapy and must cope with the relapsing and remitting disease course, cumulative toxicities, and chronic survivorship. Symptoms, both physical and psychological, stem from the snowballing effects of treatments, the expectation and timing uncertainty of inevitable relapse, and the need for recurrent treatments [81–83]. Patients with MM have been described as having worse physical function and global mental health than the general population, as well as diminished health-related QOL when compared to those with other HM [83, 84]. Physically, patients experience fatigue, pain, breathlessness, nausea, muscle weakness, and peripheral neuropathy [85–87]. Psychologically, patients report the impact of social isolation, financial stress, relationship strain, anticipatory grief, and the toll of endless and unrelenting treatment. A recent cross-sectional, multisite study of 180 MM patients reported that nearly 25% of patients reported clinically significant depression, anxiety, and post-traumatic stress symptoms [88].

There is growing evidence that the caregivers of patients with MM also struggle with psychological symptoms and could benefit from PC support. A cross-sectional, multisite study of 127 MM caregivers revealed that 44.1% have clinically significant anxiety, while another 24.4% reported post-traumatic stress symptoms. Caregivers reported higher rates of anxiety than the patients with MM themselves [89]. Prognostic misunderstanding and patient–provider communication was thought to be a major contributor of stress for caregivers of patients with MM in this study.

Palliative care integration and next steps

Despite the high illness burden experienced by both MM patients and caregivers, there is a paucity of data on models for PC integration in the care of MM patients. PC integration research is needed in the MM population. During periods of disease progression, the possible benefits of PC involvement seem clear. During the prolonged periods of disease control, however, the ideal

integration and involvement of palliative services is less apparent. We suspect that patients may still benefit from symptom assessments, psychosocial support, and assistance with coping during this period marked by survivorship and the anticipation of inevitable relapse. Assessing for unmet palliative-related needs and consideration of PC involvement is crucial throughout the trajectory of care.

Lymphomas

Treatment paradigms

Lymphomas are a heterogenous group of diseases. Lymphomas are divided into Hodgkin's lymphoma (HL) and non-Hodgkin's lymphoma (NHL). While HL have a chance of cure with intensive chemotherapy and a fair prognosis overall (approximately 90% 5-year survival), NHLs vary in severity, treatment responsiveness, and prognosis [56]. There are over 3 dozen subtypes of NHL with presentations spanning the full range from indolent to aggressive.

Aggressive NHL tends to respond favorably to chemotherapy and may be curable. Diffuse large B cell lymphoma (DLBCL), for example, carries an expected cure rate around 40–50% with multiagent chemotherapies. However, there are genetic and other risk factors, such as relapsed DLBCL, which may confer worse prognosis, especially if unresponsive to initial treatments [56].

Indolent NHL, such as "follicular lymphoma," may be incurable, but often with long expected survival rates. Indolent NHL may be experienced similarly to patients with some chronic leukemias in that the initial discovery of the disease may be met with "active surveillance" and without treatment. In general, the median survival is often greater than ten years. After treatment courses, patients usually experience periods of remission, sometimes lasting years, but disease relapse and progression are inevitable. Over time, multiple relapses and lines of treatment devolve into diminished treatment responsiveness, progressive decline, and steady disease progression. As with chronic leukemias, "transformation" to a phenotypically more aggressive variant with poor prognosis is possible [56].

Symptom burden and palliative care needs

Patients with lymphoma experience high symptom burden and PC-related needs. In HL patients, emotional and physical distress is common [90]. NHL patients experience high rates of financial toxicity and physical symptoms. Fatigue, in particular, can be severe, debilitating, and persistent even in survivorship [91–93]. More than 50% of NHL patients experience substantial treatment toxicities and high care utilization at the end of life [94]. One study of 91 older NHL patients with aggressive disease demonstrated that in the last 30 days of life, 70% were hospitalized, one-third received systemic

therapies, nearly one-quarter underwent admission to an intensive care unit, and more than half died in a healthcare facility. Fewer than half of these patients received PC consultation and even fewer were referred to hospice [95]. As newer treatments bring improved prognosis for both types of lymphoma, patients are increasingly having to contend with issues of survivorship including persistent physical symptoms, post-traumatic stress, and financial toxicity [38].

Palliative care integration and next steps

Robust clinical trials examining PC integration in lymphoma care have not been conducted to date. Further research is needed to identify the optimal approach to PC integration in lymphoma care. We suspect that lymphoma patients may benefit from symptom screening, advance care planning, and an extra layer of support at numerous time points throughout the disease course [38].

Myelodysplastic syndromes and myeloproliferative neoplasms

Treatment paradigms

Myelodysplastic syndromes (MDS) and myeloproliferative neoplasms (MPN) are another widely heterogeneous group of disorders. These disease processes result from mutations occurring in the stem cells of the bone marrow. It is possible, though not necessary, for one patient to have features of both MPN and MDS.

MPN are a sub-type of various HM in which the bone marrow cancerously produces leukocytes, erythrocytes, or platelets, leading to (a) CML (as described previously), (b) polycythemia vera, (c) essential thrombocythemia, or (d) myelofibrosis, respectively.

MDS occurs when the bone marrow fails to produce appropriate quantities of mature and functional blood cells and, instead, produces immature and dysplastic cells. There are several variants of MDS with substantial phenotypic variability. Higher-risk MDS confers a bleak prognosis with rapid disease progression, high risk of transformation to AML, and poor long-term survival. Presently, the only potentially curative therapy for MDS is HSCT, which carries its own risks and associated burden as described in a separate section below. Patients with MDS frequently require blood transfusions and other invasive treatments. While many new targeted therapies are available for other myeloid diseases like AML and CML, there are few approved treatment options for MDS and MPNs [96].

Symptom burden and palliative care needs

MPN and MDS patients experience significantly diminished health-related QOL. Fatigue and dyspnea are common and debilitating physical symptoms [97]. Blood transfusions and HSCT have been found to be helpful in prolonging life and sometimes reducing symptoms of fatigue and dyspnea, though each also impart

their own risks. Blood transfusion dependence is onerous—physically, emotionally, and financially. Patients may also experience unexpected urgent hospitalization for bleeding, complications, infections, or transformation to secondary AML. Psychological symptoms are thought to be common, though data are lacking. Patients with high-risk disease, functional impairment, and transfusion dependence carry higher risks of anxiety and depression. Caregivers may suffer similar to worse mental health outcomes when compared to MDS patients [98, 99].

Palliative care integration and next steps

There have been no randomized trials to systematically study PC interventions in patients with MDS or MPN. We suspect that that patients with MDS and MPNs and their caregivers would benefit from the development of interventions aimed at promoting serious illness conversations, addressing symptom burden, and alleviating psychological distress. At the end of life, one major area of improvement could be addressing transfusion dependence as an exclusion criterion for hospice care, which impedes many MDS and MPN (as well as leukemias and other HM) patients from engaging with and benefiting from these services. Research is needed to implement supportive and psychosocial interventions for these patients and families. Symptom assessment and consideration for palliative care referral should be pursued throughout the continuum of MDS and MPN care.

CAR T cell therapy

Treatment paradigms

Chimeric Antigen Receptor (CAR) T cell therapy is an exciting new treatment which is approved for specific hematologic malignancy management, specifically MM, B cell NHL, or ALL [38]. CAR T cell therapy represents a largely unexplored area of palliative-hemato-oncologic care. Little is known about CAR T cell-associated PC needs. Anecdotally, however, these patients often have advanced disease, a generally poor prognosis, and significant symptoms, while awaiting the receipt of CAR T cell therapy. Yet CAR-T therapy can be highly successful at achieving short-term and even sometimes long-term remissions. Manufacturing turnaround time and arduous cell collection requirements for CAR T cell therapy create significant delays and logistical issues in caring for these patients.

Symptom burden and palliative care needs

CAR T cell therapy carries a risk for cytokine release syndrome, neurotoxicity, and other physical symptoms from treatment including pain, fatigue, and anorexia which may last months after treatment [38, 100]. Early studies of CAR T cell therapy show that these patients experience substantial healthcare utilization, especially at the end-of-life. One study reported that among descendants of CAR T cell therapy, most were hospitalized within 30 days of death, died in a hospital setting, and did not receive PC or hospice services [101]. Furthermore,

a recent study found that CAR T cell therapy patients report overly optimistic prognostic impressions and have high rates of psychological distress [102].

Palliative care integration and next steps

Integration of PC interventions for patients receiving CAR-T lack current evidence, perhaps owing to its novelty. Our clinical experience is that CAR T cell patients have similar health-related experiences to those patients with acute leukemia in that they are experiencing a "high-risk, high-reward" treatment, which is associated with prolonged hospitalizations, iatrogenic symptoms, and the potential for psychological distress. Available, though limited, data suggests a need for psychosocial interventions to support patient coping [102]. Future research integrating PC into CAR T therapy from treatment planning through survivorship or death could help mitigate the substantial burden of treatment toxicity, prognostic uncertainty, and prolonged hospitalization.

Hematopoietic stem cell transplantation

Treatment paradigms

Hematopoietic stem cell transplantation (HSCT) is an intensive and potentially curative treatment for many HM. Between 1957 and 2019, there have been more than 1.5 million HSCT procedures performed worldwide [103, 104]. HSCT requires preparative chemotherapy, which is typically delivered during an often prolonged and intensive index hospitalization. Many patients who undergo the procedure, especially those receiving allogeneic transplants, develop complications including graft-versus-host-disease (GVHD) [105, 106]. Autologous HSCT is less risky and poses no risk of GVHD, but still requires high-dose chemotherapy prior to stem cell rescue. Of the diseases specifically discussed in this article, HSCT is commonly performed for patients with AML, ALL, aggressive lymphomas, MM, or MDS. Autologous HSCT is mostly performed in MM and NHL. We have opted to discuss HSCT separately from these other diseases because these patients have considerable symptoms and specific PC needs. Furthermore, PC integration in stem cell transplant care is an active area of study.

Symptom burden and palliative care needs

Patients undergoing HSCT have unmet PC needs [56]. HSCT is associated with low health-related QOL and high physical and psychological symptom burden [107–110]. Physical symptoms are common and sometimes debilitating, perhaps comparable to patients with acute leukemias undergoing intensive high-dose chemotherapies. Psychologically, patients who undergo HSCT are highly likely to develop post-traumatic stress symptoms due to their treatment experience [60, 84, 111, 112]. The prolonged, socially isolating hospitalizations are associated with decreased patient-reported QOL, elevated levels of anxiety, and depressive symptoms including pronounced anhedonia [113]. Thirty-seven

percent (37%) of HSCT patients meet criteria for clinically significant depressive symptoms the week after transplant [107, 114]. Patients describe feeling trapped, fearful, discouraged, and powerless [115]. Psychological stressors have been linked to higher risks of GVHD and decreased overall survival [116]. Social isolation has only been intensified by the COVID-19 pandemic [117].

We are just beginning to understand the effect of HSCT on patients' families and caregivers. Caregivers of HSCT recipients have prolonged and intensive caregiving burden, which has been shown to negatively impact QOL, physical well-being, and mood [118–120]. Even prior to the procedure, caregivers experience immense anticipatory psychological distress [107, 121, 122]. During HSCT, caregiver distress remains elevated as their loved ones experience treatment toxicities, physical and psychological symptoms, and the prolonged hospitalization and prognostic uncertainty [107, 118, 122, 123].

Palliative care integration and next steps

PC integration into HSCT care is an active area of study. Several randomized clinical trials examined the feasibility and efficacy of PC-HSCT integration. A 2016 trial showed that specialty PC services improve psychological well-being and reduce symptom burdens during HSCT [124••]. Outcomes from the same HSCT cohort six months after transplantation showed longitudinal benefits of PC on QOL, physical symptoms, anxiety, depression, and post-traumatic stress symptoms [124••, 125]. There was also an observed benefit in caregiver QOL and psychosocial outcomes, which prompted a subsequent unblinded, randomized trial conducted in 2020 examining a psychological intervention for caregivers of HSCT patients [126]. A multisite randomized clinical trial of integrated specialist palliative care during the initial transplant hospitalization is ongoing (NCT# NCT03641378).

PC integration at the index hospitalization for HSCT is beneficial and necessary. Future work is needed to improve psychological outcomes in patients who undergo HSCT and their caregivers. While recent small studies have examined various stress management interventions and treatment modalities, we must develop and implement PC interventions traversing the continuum of HSCT care which promote coping, improve QOL, reduce symptom burdens, and alleviate distress in HSCT patients and families [107, 127, 128].

Conclusion: the way forward

Patients with HM undergo intensive and often chronic treatments. They experience prolonged hospitalizations, undergo invasive procedures, and endure toxicities with long-lasting physical and psychological impact. Patients with HM and their families are perhaps the most psychologically distressed of all patients with cancer. Despite the high burden of unmet palliative-related needs, patients with blood cancers are substantially less likely to access PC than are patients with solid tumors.

The evidence is clear that the way forward includes standard-of-care PC integration into routine hematologic malignancy care to improve patient and caregiver outcomes, but this may not be required or helpful for all patients and situations. More research is needed to inform the highest need populations and the highest

impact interventions. As the PC needs for patients with blood cancer vary significantly by disease, a disease-specific PC integration strategy is needed, allowing for serious illness care interventions to be individualized to the specific needs of each patient and situation. As we have outlined throughout this article and summarized in Table 1, we are beginning to see the development of a robust evidence base for the integration of PC into standard practice AML, MM, and HSCT care. On the other hand, evidence has lagged in other hematologic malignancy conditions such as lymphoma, chronic leukemias, and MDS/MPN, despite high symptom burden, psychological distress, and poor QOL among these patients and their families. High-quality randomized clinical trials are needed for these specific patient populations to build upon the existing evidence and guide us forward in the care of these patients with serious illness.

Compliance with Ethical Standards

Conflict of Interest

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This article does not contain any studies with human or animal subjects performed by any of the authors.

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