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Early Palliative Care for Patients with Hematologic Malignancies: Is It Really so Difficult to Achieve?

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Abstract Evidence points to many benefits of "early palliative care," the provision of specialist palliative care services upstream from the end of life, to improve patients' quality of life while living with a serious illness. Yet most trials of early palliative care have not included patients with hematologic malignancies. Unfortunately, patients with hematologic malignancies are also known to have substantial illness burden, poor quality of life, and aggressive care at the end of life, including a greater likelihood of dying in the hospital, receiving chemotherapy at the end of life, and low hospice utilization, compared to patients with solid tumors. Given these unmet needs, one must wonder, why is palliative care so underutilized in this population? In this article, we discuss barriers to palliative care integration in hematology, highlight several reports of successful integration, and suggest specific indications for involving palliative care in the management of hematologic malignancy patients.

Keywords Palliative care · Hematologic malignancies · Health services · Quality measures · End-of-life care

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Introduction

Evidence continues to mount in support of the many benefits of "early palliative care" in oncology [1]. Here, early palliative care refers to specialist palliative care services provided upstream during the illness course, concurrently with active cancer treatment, to improve patients' lived experiences with serious illness. Many benefits of early palliative care are reported in published trials, including improved symptom management [2, 3•], quality of life [2–7], mood [4, 6], distress [3•], satisfaction with care [2], healthcare utilization [4], improved caregiver outcomes [8, 9], reductions in aggressive care at the end of life [4], and in some cases even survival (as summarized in Table 1) [4, 10]. Collectively, no palliative care study to date has shown harm. While the quality of this evidence is high, most randomized trials of early palliative care have not included patients with hematologic malignancies. Furthermore, evidence also suggests that patients with hematologic malignancies are under-utilizers of palliative care services overall, compared to patients with solid tumors, and that they are more likely to receive aggressive care at the end-of-life (EOL) [11–13]. In this paper, we will review the evidence about palliative care use in hematologic malignancies, discuss factors that have limited its expansion, and highlight a path forward, by discussing emerging data, models for early palliative care integration, and specific populations in need of interventions.

The Status Quo

The National Quality Forum (NQF) endorses several key quality measures relating to optimizing palliative and end of life care among patients with cancer [14]. Metrics that are indicative of poor quality EOL care include (1) receipt of chemotherapy in the last 14 days of life, (2) more than one

Table 1 Randomized trials of early palliative care in patients with cancer

Trial	Design	Population and setting	Intervention	Outcome improvements
Bakitas (ENABLE II) [7]	Randomized controlled trial (RCT)	Advanced breast, lung, GI, or GU cancer (newly diagnosed, with <1 year prognosis); rural and urban areas of New Hampshire	Telephone-based nurse-administered psychoeducational intervention	Improved quality of life (QoL), less depression (at 1 year from enrollment, or last observed value)
Temel [4]	RCT	Metastatic non-small-cell lung cancer (NSCLC; newly diagnosed); academic center in urban New England	Integrated specialist outpatient consultative palliative care, with monthly clinic visits at minimum	Improved QoL, improved mood (12 weeks); also less aggressive care at end of life, improved prognostic understanding, prolonged survival
Zimmermann [2]	Cluster randomized trial	Advanced solid tumors of various types (stage III/IV, with expected prognosis 6–24 months); comprehensive cancer center in an urban setting in Canada	Specialty palliative care consultation, with at least monthly outpatient follow-up	Improved symptoms, improved QoL, improved satisfaction with care, improved spiritual well-being, improved QoL at the end of life (at 4 months)
Bakitas (ENABLE III) [10], and Dionne-Odom (caregiver intervention) [8]	RCT (of early versus. later palliative care)	Advanced cancer (including hematology patients) with expected 6–24 month prognosis; rural and urban areas of New Hampshire	In-person palliative care consultation, followed by telephone-based nurse-administered psychoeducational intervention, with an additional caregiver-focused intervention	Prolonged survival (at 1 year), less caregiver depression (at 3 months)
Grudzen [5]	RCT	Advanced cancer; emergency department in New York City	Specialty palliative care consult in the emergency department, and outpatient palliative care follow-up	Improved QoL (at 12 weeks)
El-Jawahri [3•]	RCT	Patients admitted to the hospital for stem cell transplantation	Inpatient specialist consultative palliative care, with minimum of twice weekly visits while hospitalized	Improved symptom management, better QoL, less anxiety/depression, less caregiver depression (at 2 weeks)
Temel [6]	RCT	Incurable NSCLC or non-colorectal GI cancers; academic center in urban New England	Integrated specialist outpatient consultative palliative care, with monthly clinic visits at minimum	Improved QoL, less depression (at 24 weeks); dying patients also more likely to discuss their wishes

emergency department visit in the last days of life, (3) use of intensive care unit services in the last 30 days of life, and (4) suboptimal use of hospice services, defined as use of hospice care services for less than 3 days (or not at all). Several large, well-designed studies demonstrate that patients with hematologic malignancies experience poor quality EOL care, based on these metrics. For example, a systematic review by Howell shows that patients with hematologic malignancies are much more likely to die in the hospital [15]. Another systematic review shows that this population is less likely to use palliative care services of any type [16].

Similarly, a large study done at the MD Anderson Cancer Center points to poor EOL care, with hematologic malignancy patients being more likely to receive chemotherapy at EOL, have emergency room visits, multiple hospital admissions, intensive care unit stays, and significant time spent in the hospital near the EOL (>14 days) [17]. Another MD Anderson study among patients who died in the hospital suggests that having a hematologic malignancy is one of the major predictors of not receiving palliative care services [18]. In addition, a large hospice research network study shows that patients with hematologic malignancies have a much shorter average length of stay on hospice compared to patients with solid tumors, are that they are much more likely to die within 3 days of enrollment, or even within 24 h of enrollment [19]. Another study in patients with myelodysplastic syndromes (MDS) points to low use of hospice care services therein, along with a high rate of aggressive EOL care, including frequent intensive care unit utilization [20]. Furthermore, a SEER database analysis of lymphoma patients also demonstrates low hospice use in this population [21]. Lastly, a study of healthcare utilization among older patients with acute myeloid leukemia demonstrates that these patients spend a significant proportion of their lives in the hospital near EOL, and most end up dying in the hospital [22].

However, palliative care is not just about EOL care, rather, it increasingly focuses on providing an extra layer of support to improve patients' experiences living with (and being treated for) serious illnesses, like hematologic malignancies [23•]. Despite the under-utilization of palliative care services in hematologic malignancies, it is clear that these patients have significant unmet needs in domains that are very likely to be improved via palliative care services, far upstream even from the EOL care setting. For example, studies of symptom burden demonstrate that patients with hematologic malignancies face a symptom burden at least as severe (if not more) as that of patients with advanced solid tumors [24]. Similarly, data suggest that leukemia patients have marked distress [25, 26]. Furthermore, patients undergoing stem cell transplantation are known to have marked symptom distress and quality of life impairments [27]. Given these marked unmet needs, and poor performance on the NQF quality measures for palliative and EOL care in oncology, one must wonder, why is palliative care not more routinely deployed in patients with hematologic malignancies?

Factors Influencing the Provision of Palliative Care in Hematologic Malignancies

Several factors have limited the expansion of palliative care more readily into blood cancer care, including: (1) misperceptions equating "palliative care" with EOL care, (2) lack of a clear transition between curative and palliative phase of therapy (due to the extent of prognostic uncertainty in many hematologic malignancies), and (3) reimbursement and policy challenges (which particularly impact the provision of high-quality EOL care, such as via hospice) [11–13, 23•].

Misunderstanding Palliative Care as Just EOL Care Palliative care has experienced immense growth in the last decade. Although only recently becoming a board-certified subspecialty, there are now over 100 fellowship training programs and most hospitals of 300 beds or more have available specialist palliative care clinicians [28]. Twenty years ago, hospice care was the primary modality of palliative care provision available in the USA. There were no palliative care specialists, per se. While more modern conceptions of palliative care have moved far upstream from the EOL, it therefore makes sense that many clinicians' views and knowledge about palliative care and its scope have yet to catch up to these relatively recent and rapid developments in the field's evidence base and scope of practice.

When palliative care is thought of as a euphemism for care of the dying, it is not surprising that it might not be incorporated until very late in the course of illness, if at all. Indeed, evidence suggests that hematologists view palliative care in this regard, and that they do so more often than solid tumor specialists [29]. And if palliative care is thought of as a service one invokes only when a patient is dying, or a clinical team that is appropriate only when no therapeutic options remain, then the notion of early palliative care becomes nonsensical. This gap in knowledge about the scope of modern palliative care likely explains the quality measures gap in hematology, at least in part. The referral gap is likely also compounded by a bias among hematologic malignancy specialists towards more aggressive care, their tendency to be less comfortable discussing EOL issues, and their higher likelihood of experiencing a sense of defeat upon disease relapse or progression [30]. While this is a sensitive topic that can be difficult to discuss, it is also an assertion that is supported by data. It is also quite understandable, as it is much more common to see relapsed or refractory hematologic malignancy patients end up being cured with aggressive, last-ditch therapies compared to patients with solid tumors. Until palliative care is more universally recognized as being appropriate along with active cancer treatments, it will remain difficult to integrate.

Prognostic Uncertainty Prognostic uncertainty makes the palliative care referral quandary even more complicated in hematology. Hematologic malignancies in themselves are often more treatable than solid tumors, especially those diseases with poor long-term prognoses, such as acute myeloid leukemia in an older patient [31]. While the long-term prognosis is poor, shorter-term remissions are more likely than with many solid tumors [31]. In addition, a small proportion of these patients are indeed cured with aggressive therapy, though many do also die in pursuit of a cure. Therefore, if palliative care is misconstrued as requiring a patient to be near the EOL, or to have no active therapeutic options, it is not surprising that referrals occur late, or less often at all. Evidence from interview studies as well as national survey data from hematologists supports this perception [32]. For example, several practicing hematologists in a focus group noted the difficulty of knowing when to engage hospice care services due to challenges inherent in prognostication, and in trying to identify the EOL phase of many patients with hematologic malignancies [32]. Until palliative care is conceptualized as an “extra layer of support” for patients and caregivers in addition to standard cancer care, offered along with active treatments, this referral problem will persist. The appropriateness and provision of palliative care therefore cannot be dependent upon a particular prognosis; as long as it is viewed as such, we will continue to see late or absent referrals of hematologic malignancy patients to palliative care and poor EOL quality outcomes.

Reimbursement and Policy Challenges Policy and reimbursement considerations compound the palliative care referral issue as well, though more specifically regarding EOL care via hospice than for upstream concurrent palliative care [33]. For patients with solid tumors, the transition to hospice care is much less uncertain than it is in hematology. For instance, when facing a patient with a solid tumor that is refractory to multiple lines of chemotherapy, or who has become too frail to tolerate cancer-directed therapy, hospice care is often the clear next step. In a setting like this, cure is no longer possible, and amid progressive decline and difficult symptoms from treatment and disease alike, families are often ready for this transition by that point. On the other hand, for patients with relapsed/refractory hematologic malignancies, meaningful responses are common. The treatment goal may even remain cure in these refractory settings, if stem cell transplantation is an option, yet the longer-term prognosis may remain statistically quite poor. As such, these patients often continue to receive aggressive disease-directed therapies until the very end. Transitioning to hospice care, which requires a person to forego further disease-modifying therapy, or even beneficial palliative treatments like transfusions, precludes any such possibility in patients like this. Yet evidence suggests that home transfusion programs are feasible, and may even be cost-saving in comparison to hospitalizations, while allowing patients to spend more time at home with loved ones [34, 35]. To our knowledge, such interventions have yet to be meaningfully tested in the USA, and they pose hospice benefit reimbursement challenges that have not been remedied [33].

Many patients with hematologic malignancies may derive palliative benefits from receiving transfusion support, to help manage fatigue, dyspnea, or reduce serious bleeding events [36, 37]. They may also benefit from cancer-directed therapies for palliative purposes, such as chemotherapy, despite a limited prognosis. One typical example is the use of low-dose cytarabine or hypomethylating therapy in older patients with acute myeloid leukemia [38, 39]. While transient remissions are possible with these therapies, cure is not; rather, they can help patients achieve important goals by improving longevity, reducing transfusion needs or symptoms by improving blood counts, and improving quality of life [40]. Typically, the receipt of such disease-directed therapies is not allowed under hospice care. Until we develop a way to provide meaningful palliative care services at home, concurrent with active cancer therapies, hematologic malignancy patients will continue to suffer from late referrals to high-quality EOL care services like hospice.

In this section, we have highlighted three main barriers to palliative care in hematology. It is important to recognize that none of these issues should preclude earlier, more upstream, concurrent palliative care, which can be provided independent of prognosis, and which does not require patients to forego helpful therapies. As such, we contend that barriers to early palliative care are largely philosophical and educational ones. These should be more readily fixable, compared to the policy solutions required to address barriers to hospice care in hematology.

Overcoming Barriers to Early Palliative Care in Hematologic Malignancies

Above, we have highlighted three primary categories of barriers to palliative care in hematology—misunderstandings about palliative care, prognostic uncertainty, and barriers to high-quality EOL care due to reimbursement/policy—that collectively are unique to the practice of caring for patients with hematologic malignancies. Addressing these barriers will require targeted efforts in three specific areas.

Education Educational outreach is needed. This is not only true for clinicians of all types (e.g., physicians, nurse practitioners, physician assistants, social workers, etc.), but also for the lay public. Public opinion polling data suggest that once people learn about palliative care, they are interested in these services; [41] however, conflicting evidence suggests that the word "palliative" itself may be polarizing or traumatizing, for patients, caregivers, and clinicians alike [42, 43]. Special emphasis must be placed on the modern definitions and evidence of early palliative care, in contrast to outdated views that palliative care is synonymous with EOL care. Of note, educational interventions should help address prognosis-related barriers to early palliative care as well, as these barriers are dependent upon an outdated perception of palliative care as requiring a certain prognosis. Moreover, education is required to reduce the stigma. Some have gone so far as to recommend consideration of a name change to "supportive care." While some data suggest this may reduce clinician barriers to referral [43], it is not clear that this strategy is necessarily better than education. At a minimum, targeted educational efforts are needed for clinicians, such as continuing medical education events, along with layperson campaigns to improve public perceptions about palliative care. Additional interventions to address misconceptions among hospital administrators, payers, and policy makers may also be helpful.

Research While early palliative care is shown to improve various patient-centered outcomes in oncology, the evidence in hematology specifically is much less developed. If we are to encourage earlier, concurrent palliative care in hematology, it is necessary to better understand the scenarios in which it is of clear benefit, along with the most optimal methods to provide it. Emerging evidence suggests there may be differential effects of early palliative care on different solid tumor populations [6]; this may also be true in hematologic malignancies, and we will only clarify this through rigorous, prospective trials.

Changes in Policy Lastly, policy solutions are needed to improve financial coverage for clearly beneficial treatments and services among patients with hematologic malignancies near EOL and/or with a poor prognosis. Forcing patients, caregivers, and clinicians to choose between palliative therapies and transfusions versus high-quality hospice care is frankly unacceptable. Hospice care has many benefits, including caregiver support, decreasing hospital admissions, and aggressive symptom management, among others. Similarly, palliative cancer therapies can help improve quality of life and longevity, while allowing patients to achieve important life goals while their time is short. No one should have to choose between these two services. Of note, several outcome improvements associated with early palliative care relate to health care utilization and goal-concordant care at the end of life. As such, in the current economic climate wherein "high-value care" is increasingly a focus of policy propositions, palliative care is particularly noteworthy, and may be a key part of proposed solutions. By promoting goal concordance, palliative care helps to ensure that patients get the care they want when they want it, and that they receive less aggressive care at the end of life, when it is unlikely to be helpful.

Models for Early Palliative Care in Hematologic Malignancies

As barriers to palliative are addressed, it will increasingly be important to ascertain the most effective methods of providing early palliative care for patients with hematologic malignancies. While hematology presents some unique challenges, it is certainly not impossible. In fact, several vanguard initiatives demonstrate that is it feasible, acceptable to both patients and clinicians, and likely to improve outcomes. Here we will review published examples of successful early palliative care interventions, in hematology to demonstrate that it is indeed possible to implement in various ways depending on salient features such as the local clinical context, disease focus, and perception of needs. Published models include those that are more "trigger-based," such as at time of hospital admission for stem cell transplant, or those that are more consultative, as described below.

At the Massachusetts General Hospital, investigators randomized 160 consecutive stem cell transplantation patients to early concurrent palliative care versus usual oncology care [3•]. In this study, patients were randomized at time of admission to the hospital for the transplant process. Those randomized to early palliative care received a specialist palliative care consult and a minimum of two visits per week. This intervention was not heavily manualized, but early palliative care clinicians received training in what to expect regarding symptom, quality of life, and mood/distress derangements in this population, and were advised to focus on symptom management and coping as essential components of the intervention. The primary outcome measure was the change in overall quality of life by the "Functional Assessment of Cancer Therapy—Bone Marrow Transplant" (FACT-BMT) scale, from baseline to day 14 post-transplant; secondary outcomes included rates of depression by the "Hospital Anxiety and Depression Scale" (HADS) and "Patient Health Questionnaire-9" (PHQ-9) scale, among other outcomes. This intervention led to clinically meaningful and statistically significant improvements in overall quality of life, symptom burden, depression, and anxiety during the hospitalization for stem cell transplantation. While the intervention itself was only administered during the inpatient phase of the transplant process, patients experienced sustained effects from this relatively "low-dose" early palliative care intervention, which demonstrated less anxiety/depression and less post-traumatic stress at 3 months. This study clearly demonstrates the benefits and feasibility of a trigger-based early palliative care model in stem cell transplantation, which occurred at the initiation of the transplant itself.

Another example, from the University of Washington Fred Hutchinson Cancer Research Center, by Loggers and colleagues, evaluated the acceptability of pre-transplant early palliative care consultation among patients at high risk for adverse transplant outcomes (those with a Hematologic Cell Transplantation comorbidity index (HCT-CI) of > = 3, relapse risk >25%, or planned human leukocyte antigen-mismatched transplant) [44]. Participants received an outpatient palliative care consult before admission for the transplant, and had at least monthly visits thereafter with palliative care. Feasibility was demonstrated, with nearly 70% (22 of 32) of eligible subjects consenting to participate, 82% of which felt very comfortable with palliative care, and did not report any negative effects on mood or hope at a median of 3 months follow-up. This pilot study suggests that early palliative care prior to admission for stem cell transplantation is feasible and acceptable; further testing of this intervention is planned.

At the University of California San Diego (UCSD), the inpatient palliative care service was first established on the stem cell transplant unit. This experience is described in a series of papers highlighting lessons learned in this novel collaborative effort [45•, 46, 47]. In the initial years of this model (2005 and 2006), just over 100 transplants were performed annually at UCSD. In the first 6 months of the palliative care service, 136 encounters were completed, such that more than half of stem cell transplant patients treated at UCSD during that time received a palliative care consult. By 2014, there were 143 annual transplants and 585 palliative care encounters, with an increase seen in consults for anxiety or depression issues (*n* = 144 or 25% of encounters). These results point to increased uptake and satisfaction with the palliative care integrated care delivery model, perhaps driven by positive reinforcement with each palliative care consultation.

Similarly, Selvaggi describes an embedded palliative care service on the bone marrow transplant unit of the Western Pennsylvania Hospital in Pittsburgh [48]. Therein, Selvaggi and colleagues carried out a quality improvement initiative to raise awareness about unmet palliative care needs in stem cell transplant patients, and demonstrated the value of consultative palliative care in the management of this population. This was ultimately a quality improvement intervention, which involved an initial needs assessment of unit staff, including semi-structured interviews and informal conversations, followed by targeted didactic education. Data were collected about the reason for the consult, pain scores, goals of care conversations, hospice enrollment, and satisfaction surveys. In a published report, Selvaggi describes the results of nearly 400 consultations to over 250 unique patients. Here, palliative

Table 2 Several potential triggers for early palliative care involvement

Hematologic malignancy patients who can benefit from additional support via palliative care	Rationale
Patients with significant symptom burden and/or refractory symptoms	Early palliative care improves symptom control and quality of life
Patients with chronic symptom challenges, or symptom distress from novel therapies (e.g., CML, myeloma, CLL)	Early palliative care improves symptom control and quality of life
Patients hospitalized for stem cell transplantation	Early palliative care improves symptom control and provides additional psychological support
Patients with chronic graft-versus-host disease	Early palliative care improves symptom control and quality of life
Patients with significant psychological distress (especially at time of diagnosis/relapse)	Early palliative care reduces psychological distress
Patients with difficulty coping with their illness	Early palliative care enhances patients' coping strategies and provides additional psychological support
Patients with complex family and psychosocial needs	Early palliative care improves family caregivers' mood, provides additional support, and addresses patients' social needs
Patients with significant and/or persistent misperceptions about their illness trajectory and overall prognosis	Early palliative care enhances patients' prognostic understanding
Patients who may have a poor prognosis and limited life expectancy *(i.e., you would not be surprised if they die within a year)*, or significant health problems that might portend a poor outcome (e.g. geriatric patients with multiple comorbidities)	Early palliative care facilitates EOL care planning, and prepares patients emotionally and psychologically for the EOL

Adapted from LeBlanc and El-Jawahri, American Society of Hematology Education Book chapter on palliative care in hematologic malignancies [23•]

care clinicians were the first clinicians to document goals of care for 67% of the patients evaluated. Furthermore, while many consults were for refractory pain management, overall pain scores were reduced to acceptable levels within 48 h of consultation in approximately two-thirds of cases. Hospice referral increased as well, from 5 to 41% (67 of 165 patients who died during the study) and oncologists reported high satisfaction with the program.

Other promising models of early palliative care have been described in solid tumor settings, but not yet in hematology. For example, the solid tumor inpatient service at the Duke University Hospital employs a "co-rounding model," wherein a medical oncologist and a palliative care physician round together on the same service, with one of the two serving as the attending physician of record for each given patient; those patients with more palliative needs are managed by the palliative care physician, while those receiving chemotherapy or having more cancer-related needs are managed by the oncologist [49]. This model is associated with clinically and statistically significant reductions in hospital length of stay, and trends in reduced intensive care unit transfers as well as increased hospice utilization. It has also led to enhanced collaboration between oncologists and palliative care physicians and improved multidisciplinary education on the ward. Satisfaction among attending oncologists and staff nurses has been very high [50].

Other data suggest that trigger-based models may be impactful. For example, at Mount Sinai Hospital a set of standardized triggers was developed and implemented for patients with advanced solid tumors. Those patients meeting trigger criteria received a palliative care consultation. This simple intervention led to significant improvements in 30-day readmission rates, reductions in EOL chemotherapy, and improved hospice referral rates after hospital discharge [51]. This type of model could readily be implemented in hematology; however, the relevant triggers may be different. This idea should be explored and further tested in hematologic malignancies, given its impact on EOL quality measures in the solid tumor population.

Targets for Intervention (and Further Study)

As we consider how to implement early palliative care in hematologic malignancies, it is important to recognize that not every patient with a hematologic malignancy can see a palliative care specialist. Workforce challenges are significant in palliative care [28]. This makes it even more imperative that we identify high-risk patients and/or clinical scenarios, and rationally target the application of palliative care services amid this scarcity. While the state of the science remains in its infancy, regarding testing the efficacy of early palliative care interventions in hematology, data describing unmet palliative care needs is robust. Based on our review of this available evidence regarding unmet palliative care needs, we suggest several potential triggers for early palliative care involvement in this population, which we have updated and adopted from our earlier recommendations (Table 2) [23•].

We developed this list of triggers on a rational basis, extrapolating from two important sources of data: (1) the evidence base for which domains are improved via early palliative care involvement in other cancer populations and (2) data pointing to unmet needs in hematologic malignancy patients. Overall, however, much more empirical work must be done in this area to develop and test appropriate triggers, and early palliative care interventions, in the remarkably diverse group of patients with hematologic malignancies. We are currently testing an early concurrent palliative care intervention among patients with high-risk acute myeloid leukemia at time of admission for induction chemotherapy. Many more studies like this are needed, in different hematology populations, to test the efficacy of novel interventions to improve the experience of patients and caregivers.

Conclusion

While a growing literature demonstrates many benefits of early palliative care in oncology, its benefits in hematologic malignancies require further testing. Yet the evidence is clear in indicating poor EOL quality outcomes in hematology patients, and in significant unmet palliative care needs in this population. While palliative care is underutilized in blood cancers, the barriers to earlier and more effective palliative care integration are achievable, and several vanguard practices have already demonstrated the feasibility and benefits of early palliative care in this setting. We believe that efforts to improve education, evidence, and policy will improve the integration of palliative care into hematologic malignancies care, as a standard practice to improve the lives of patients and caregivers facing these serious illnesses.

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Compliance with Ethical Standards

Conflict of Interest Eric Roeland and Areej El-Jawahri each declare no potential conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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