Strategies for introducing palliative care in the management of relapsed or refractory aggressive lymphomas

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Recent advances in treatment of patients with aggressive lymphomas ranging from chimeric antigen receptor T-cell therapy to combination of antibody–drug conjugates with chemotherapy have improved survival outcomes. Despite these significant advances, patients with relapsed or refractory disease experience high physical and psychological symptom burden, and a substantial proportion still die of their lymphoma. In addition, end-of-life care outcomes are suboptimal with high rates of intensive end-of-life health care use and low rates of timely hospice enrollment. Integrating palliative care concurrently with disease-directed care for this patient population has strong potential to improve their symptom burden, quality of life, and end-of-life care. Multiple factors, including heightened prognostic uncertainty in the setting of relapsed/refractory disease, pose challenges to timely provision of palliative care. This article reviews benefits of primary and specialty palliative care for patients with relapsed/refractory aggressive lymphomas and barriers to such care. It also highlights strategies for effectively integrating palliative care for patients with relapsed/refractory aggressive lymphomas.

LEARNING OBJECTIVES

- Identify barriers to optimal palliative care for patients with relapsed/refractory aggressive lymphomas
- Learn strategies to improve timing and conduct of goals-of-care discussions for patients with aggressive lymphomas
- Identify patients with aggressive lymphomas who may benefit from specialty palliative care

Clinical case

A 66-year-old man presented with bilateral axillary lymphadenopathy, unintentional weight loss, and night sweats. An excisional axillary lymph node biopsy revealed a diagnosis of diffuse large B-cell lymphoma (DLBCL), not otherwise specified. Positron emission tomography (PET) showed enlarged fluorodeoxyglucose-avid lymphadenopathy above and below the diaphragm, as well as liver involvement. The result of his bone marrow biopsy was positive for disease involvement, consistent with stage IV disease. His lactate dehydrogenase level was elevated. He received six cycles of rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone and attained a complete remission. Four months after treatment, he developed fatigue, night sweats, and recurrent axillary lymphadenopathy, which prompted his hematologic oncologist to order a PET scan. This revealed lymphadenopathy above and below the diaphragm along with multiple bony lesions. Biopsy of an enlarged lymph node confirmed relapsed DLBCL. He began second-line chemotherapy with rituximab, ifosfamide, carboplatin, and etoposide. After two cycles, his repeat PET scan demonstrated refractory lymphoma. The patient and his wife met with his hematologic oncologist to discuss next steps in management. The patient reported fatigue and severe bone pain not relieved by the opioid analgesic regimen prescribed by his hematologic oncologist. He also stated, "I am very disappointed that the chemotherapy did not work, but I have learned of a treatment on the internet called chimeric antigen receptor T-cell therapy. Many people describe it as a magic bullet for lymphoma; I hope this will cure my lymphoma."

Introduction

Over 26 000 people are diagnosed with aggressive B- and T-cell lymphomas each year in the United States.[1,2] Despite advances in therapy, a substantial proportion of these patients develop relapsed/refractory disease. These patients

have significant palliative care needs, including high physical and psychological symptom burden and impaired quality of life (QOL).[3-5] In addition, many harbor misunderstandings regarding their prognosis,[6-8] hindering their ability to engage in informed decision making regarding their care and end-of-life (EOL) preferences. Integrating high-quality palliative care is thus essential for this population; yet, existing evidence suggests suboptimal palliative care uptake. In this review, we discuss the benefits of primary and specialty palliative care for patients with relapsed/refractory aggressive lymphomas and barriers to the delivery of such care. We also review approaches to optimize palliative care for this patient population.

Benefits of palliative care

Palliative care is an approach that improves QOL of patients facing life-threatening illness through the prevention and relief of suffering by early identification and impeccable treatment of pain and other physical, psychosocial, and spiritual problems.[9] It includes primary palliative care, such as goals-of-care discussions and basic management of physical (eg, fatigue, pain, neuropathy) and psychological symptoms (eg, anxiety and depression), which can be provided by hematologic oncologists. It also includes specialty palliative care, which is provided by palliative care specialists, and focuses on more complex symptom management, management of psychological distress, and complicated goals-of-care discussions (Figure 1).[10] Several studies have shown that palliative care improves QOL of patients and increases the likelihood of patients receiving care that is aligned with their goals.[11-13] Accordingly, early integration of palliative care concurrent with routine cancer-directed care is recommended.[14,15]

Goals-of-care discussions represent an important archetype of primary palliative care that can be provided by hematologic oncologists. These discussions entail eliciting patients' goals, values, and preferences regarding their treatment and EOL care options. These discussions are ideally conducted in the context of prognostic information to promote informed decision making. Patients who engage in goals-of-care discussions with their hematologic oncologists are more likely to receive care that is consistent with their preferences, to receive specialty palliative care, and to enroll in hospice.[16-18] They are also less likely to experience intensive EOL health care use (eg, multiple hospital admissions, hospital death),[19] with corresponding improvement in QOL, reduced risk of complicated grief for bereaved caregivers, and lower health care costs.[16]

Patients with aggressive lymphomas have substantial palliative care needs, including fatigue, dyspnea, depression, and pain, which typically worsen near the EOL.[3-5] Therefore, in addition to basic symptom management by hematologic oncologists, they stand to benefit from the support of specialty palliative care even when receiving curative intent therapy. In the first randomized controlled trial of specialty palliative care that focused solely on patients with hematologic malignancies (28% of whom had lymphoma), integrating specialty palliative care with hematopoietic stem cell transplant (HSCT) care significantly improved QOL and reduced symptom burden 2 weeks after transplant compared with routine transplant care.[12] Moreover, although the intervention was limited to the transplant admission, patients had sustained improvement in depression symptoms at 6-month follow-up compared with the standard care arm.[20] This study established the benefit of specialty palliative care for patients with lymphoma and illustrates that specialty palliative care can be combined with potentially curative therapy.

Barriers to optimal palliative care for patients with relapsed or refractory lymphoma

Despite increasing recognition of the benefits of palliative care, uptake of primary and specialty palliative care among patients with aggressive lymphoma is low.[19,21-23] With respect to goals-of-care discussions, 56% of hematologic oncologists in a national survey reported that EOL discussions typically occur "too late," and many would wait until death is clearly imminent to initiate discussions regarding resuscitation or hospice preferences.[22] In a study of patients who died of aggressive lymphomas and other hematologic malignancies, the median time from the first documented goals-of-care discussion to death was only 15 days.[19] In addition, symptom management in the primary palliative care

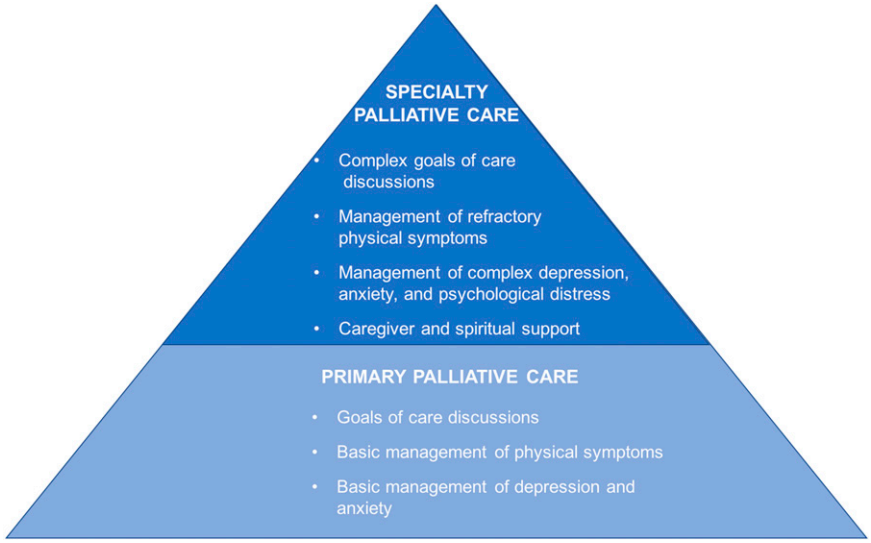

Figure 1. Primary and specialty palliative care.

setting is impeded by lack of systematic screening. Similar to primary palliative care, rates of specialty palliative care consultation are low, ranging from 33% to 40%,[21,24] with a median time between first consultation and death of 12 days,[21] and most occur in the inpatient setting.[23] Such low and untimely referrals preclude patients from fully benefiting from the longitudinal support that specialty palliative care provides. Limited integration of primary and specialty palliative care for patients with aggressive lymphoma contributes to prognostic discordance between patients and hematologic oncologists and impairment in QOL.[7,8]

Among several barriers to palliative care (Table 1), one that is amplified for patients with relapsed/refractory aggressive lymphomas is high prognostic uncertainty, given the potential of cure in relapsed settings and recent treatment advances.[25,26] For example, although the SCHOLAR-1 trial results were sobering with complete response and 24-month overall survival of 7% and 20%, respectively, for patients with refractory DLBCL,[27] complete response ranges from 40% to 58% with chimeric antigen receptor (CAR) T-cell therapy,[25,26] and the estimated 24-month overall survival is 50.5% for axicabtagene ciloleucel.[28] Although CAR T-cell therapy is a success story, a substantial proportion of patients will not experience a durable response, and the trajectory of decline in these patients is often rapid. The likelihood of durable response to treatments for relapsed/refractory aggressive T-cell lymphomas is typically even more dismal than that for B-cell lymphomas, and predictors of sustained response are unclear, highlighting the need for early palliative care.[29] Conducting nuanced goals-of-care conversations that effectively balance the potential promise of intensive disease-directed treatment in the relapsed/refractory setting with the risk of morbidity and mortality is difficult and may contribute to clinicians avoiding these discussions until death is clearly imminent.

With the backdrop of prognostic uncertainty, the effect of other barriers to palliative care (eg, clinician concern about taking away hope, not knowing the right thing to say to patients, misperceptions about specialty palliative care, unrealistic patient and clinician expectations) is compounded.[30-32] For example, prognostic uncertainty coupled with the misperception that specialty palliative care is synonymous with EOL care and needed only when no lymphoma-directed therapy is available[31,32] likely further delays integration of specialty palliative care. Systemic factors, such as limited access to specialty palliative care in some oncology settings and difficulty integrating specialty palliative and oncologic appointments in the same visit, also pose barriers to integration. Despite existing challenges, palliative care remains essential for patients with aggressive lymphomas; accordingly, effective strategies to ensure that patients receive high-quality primary and specialty palliative care are urgently needed.

Table 1. Barriers to primary and specialty palliative care

Disease-related barriers
High prognostic uncertainty
Rapid decline at the end of life
Physician-related barriers
Misperception that palliative care is synonymous with end-of-life care
Unrealistic physician expectations
Not knowing the right thing to say
Concern that the term "palliative care" will decrease patients' hope
Patient-related barriers
Misperceptions about palliative care
Unrealistic patient expectations
System-related barriers
Lack of universal and systematic symptom screening
Lack of universal and standardized training in primary palliative care
Limited access to specialty palliative care in some clinical settings
Difficulty integrating palliative and oncologic appointment schedules for patients

Optimizing goals-of-care discussions for patients with aggressive lymphomas

Patients with aggressive lymphomas desire to have goals-of-care conversations with their hematologic oncologists but seldom feel empowered to bring up these discussions.[6,33] In a study of patients with relapsed/refractory aggressive lymphomas, although 44.4% of patients had thought of their care preferences should they become critically ill, only 11.1% reported that they had the opportunity to discuss those preferences with their hematologic oncologists.[6] Hematologic oncologists thus need to be intentional in allotting time to engage in these discussions. It has been shown that when hematologic oncologists initiate goals-of-care discussions (compared with other clinicians), patients are less likely to die in hospitals and are more likely to enroll in hospice more than 3 days before death.[19] This underscores the powerful role that hematologic oncologists play in goals-of-care discussions and patient decision making. To optimize goals-of-care discussions, it is necessary to identify "when" and "how" to conduct these discussions.

When should goals-of-care discussion occur?

National guidelines recommend that goals-of-care discussions should occur early in the disease course for patients with life-limiting illness.[14] In addition, they should be revisited during the disease course because patients' preferences may evolve.[18] Although early engagement in these discussions is essential, this is difficult to operationalize in real time for patients with aggressive lymphomas. Therefore, practical triggers to conduct these conversations are critical (Table 2). Key transition points at which prognosis changes during the disease course, such as refractory disease or relapsed disease, can be used as triggers for initiating and revisiting goals-of-care discussions. These transition points were identified by lymphoma clinicians in a focus group as important signposts for engaging in goals-of-care discussions.[34] Lymphoma clinicians also identified other triggers for goals-of-care discussions, such as significant worsening of performance status and organ insufficiency, even in the absence of relapse. It is also critical to engage in these discussions with patients who are considering highly intensive therapies such as HSCT or CAR T-cell therapy. Another trigger with high utility is the surprise question, "Would you be surprised if this patient died in the next year?"[35,36] Indeed, this question has been shown to have a positive predictive value of 68.3% among patients with lymphoma and other hematologic malignancies.[36]

How should goals-of-care discussions be conducted?

Communication skills training and guides can equip hematologic oncologists to effectively conduct goals-of-care discussions. Examples of trainings and tools for goals-of-care discussions

Table 2. Triggers for goals-of-care discussions with patients with lymphoma

Relapsed disease
Refractory disease
Worsening performance status
Organ insufficiency
Planned hematopoietic stem cell transplant
Planned chimeric antigen receptor T-cell therapy
Surprise question (You would not be surprised if the patient died in the next 1 y.)

include the VITALTalk courses,[37] the Serious Illness Conversation Guide,[38] and the REMAP (reframe, expect emotion, map out patient values, align with values, and propose a plan) framework (Table 3).[39] These resources share the following best practices for conducting goals-of-care discussions. First, hematologic oncologists should explore the patient's understanding of their illness trajectory at the start of the conversation. This will help to appropriately frame the rest of the conversation on the basis of the patient's level of understanding of their illness and prognosis. Next, hematologic oncologists should provide information regarding their patient's illness and discuss prognosis (what is known of it) tailored to the degree of information the patient desires. This aspect of the conversation often elicits emotions from patients. It is important to acknowledge such emotions; one way to do so is by making reflective statements (eg, "I know this is really difficult news").

After taking the time to respond to emotions, hematologic oncologists can then explore their patient's values and goals in the context of their lymphoma. This part of the conversation may start with a question such as, "What is most important to you, given where things are with your lymphoma?" To have a comprehensive grasp of the patient's goals and values, clinicians will need to elicit the concerns, fears, and trade-offs the patient is willing to make to prolong life. It is important to summarize the goals and values of the patient, repeating them back to him or her to confirm that one's understanding is accurate. Next, if the patient is open to a recommendation, the hematologic oncologist should propose a plan that has the best chance of achieving the patient's goals on the basis of their expressed values and the available medical treatments that might feasibly help. Throughout the conversation, it is vital to affirm commitment to the patient so that he or she does not feel abandoned. It is also critical to engage the patient's loved ones (as preferred by the patient) in these conversations. Finally, documentation in the medical record is essential so that the patient's care preferences are known and honored across care transitions.

Optimizing specialty palliative care integration for patients with aggressive lymphomas

To improve rates and timing of specialty palliative care for patients with relapsed/refractory aggressive lymphomas, it is necessary to conceptualize specialty palliative care as an additional layer of support that is beneficial even when patients are receiving disease-directed care, similar to how other specialties (eg, infectious disease, cardiology) are consulted when there is a need for their expertise during cancer-directed care. With this understanding of specialty palliative care, consultation should be considered for patients with palliative care needs such as high symptom burden (physical or psychological), difficulty coping with illness, complex family dynamics, or complicated goals-of-care discussions (Table 4).[12] Indeed, in a large consensus study of criteria for specialty palliative care referral, there was a greater emphasis on needs-based triggers than on time-/prognosis-based triggers.[40] Specialty palliative care consultation should also be considered for patients undergoing highly intensive therapy with significant morbidity such as HSCT, given high-quality data demonstrating significant and long-lasting benefits of concurrent specialty palliative care in this setting.[12,20] Despite the shortcomings of relying solely on prognosis in the context of prognostic uncertainty to prompt specialty palliative care consultation, the surprise question can be used as a trigger because it is a practical way to identify patients with unmet palliative care needs.[36] Importantly, close collaboration between specialty palliative care teams and hematologic oncologists is vital for seamless and coordinated care provision to patients with relapsed/refractory lymphoma.

Clinical case revisited

Although the hematologic oncologist had previously engaged in goals-of-care discussions with the patient earlier in the disease course, she realized that refractory disease represented a key transition point at which to revisit goals-of-care discussions. The hematologic oncologist thus assessed the patient's understanding of his illness, reviewed prognostic information, and elicited the patient's values and goals. The patient and his wife expressed intense disappointment and sadness at the refractory nature of his

Table 3. Description of the REMAP[39] framework for goals-of-care discussions

REMAP step	Task
Reframe	Assess the patient's understanding of their lymphoma trajectory and, if needed, provide new information. Place the details of the patient's illness in a bigger context, and explain the need to initiate or revisit goals of care.
Expect emotion	Acknowledge the patient's emotion so that he or she can feel heard and supported.
Map out patient values	Explore what matters most to the patient in the context of their lymphoma, their concerns about the future, trade-offs they are willing to make, and their goals.
Align with values	Verbally reflect what is heard from the patient to ensure clear understanding of the patient's values. During this process, one may find that additional clarification of values is needed.
Propose a plan	With permission from the patient, recommend a plan that has the best chance of maximizing the likelihood of meeting the patient's goals using a combination of the patient's values and your knowledge of feasible medical treatments.

REMAP, reframe, expect emotion, map out patient values, align with values, and propose a plan.

Table 4. Triggers for specialty palliative care consultation for patients with lymphoma

High or refractory symptom burden
Psychological distress
Difficulty coping with illness
Misperceptions about illness understanding despite goals-of-care discussions
Complex goals-of-care discussions
Complicated family dynamics
Planned hematopoietic stem cell transplant
Recurrent unplanned hospital admissions
Surprise question (You would not be surprised if the patient died in the next 1 y.)

lymphoma, which the hematologic oncologist acknowledged. The patient noted that one of his goals was to be alive for his youngest daughter's wedding in 6 months and that he would be willing to undergo intensive treatment despite side effects and hospitalizations to try to attain this goal. He also longed for relief from his refractory bony pain. The hematologic oncologist reviewed benefits and risks of CAR T-cell therapy as a potential management option. She also discussed specialty palliative care with the patient for additional management of refractory pain and coping. The patient established care with the specialty palliative care team and decided to pursue CAR T-cell therapy. The palliative care specialist formulated a pain management plan, which led to improvement of bony pain; she also collaborated closely with the patient's oncologist during CAR T-cell admission and subsequent outpatient follow-up to provide additional support to manage the unmet palliative care needs of the patient and his family.

Conclusions

Despite recent treatment advances, patients with relapsed/refractory aggressive B- and T-cell lymphomas experience high symptom burden and many still die of their disease. Timely integration of both primary and specialty palliative care has strong potential to improve QOL for this population; yet, these are underused because of several barriers that are compounded in the context of high prognostic uncertainty. Practical triggers to prompt timely goals-of-care discussions and specialty palliative care consultations, as well as use of communication tools and training, are promising ways to overcome barriers to palliative care integration. Palliative care research for patients with hematologic malignancies has burgeoned in the past few years,[12,41,42] and the time is ripe to better characterize the palliative care needs of patients with lymphoma and develop effective strategies to integrate palliative care for this population.

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