Advances and Controversies in Hematopoietic Transplantation and Cell Therapy
Series Editors: Syed A. Abutalib · James O. Armitage

Laura Finn
Alva R. Roche Green *Editors*

Supportive Care Strategies

Optimizing Transplant Care

Springer

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1 Introduction to First Edition: Progress in Supportive Care Medicine and Hematopoietic Cell Transplant and Cellular Therapy

Laura Finn and Alva Roche Green

Hematologists are tasked with treating and potentially curing patients with terminal cancers through the constantly evolving field of hematopoietic cell transplant. Transplant has progressed dramatically over the past decade(s) with an enduring increase in the number of hematopoietic cell transplants performed, an increase in patient populations offered transplant, and an expansion of the variety of sources of CD34+ cells donated for transplant. Patient outcomes during and after transplant have improved during this evolution through changes in patient selection and greater improvements in supportive care. Supportive care has improved through understanding and management of complications and side effects, immune suppression, and infection control, though the need for improvement remains in areas of mental health, patient and caregiver quality of life, management of refractory transplant complications, and long-term survivorship concerns. As the process of transplant continues to advance, hematopoietic cell transplant and cellular therapy programs have begun to foster relationships with palliative medicine to strengthen their comprehensive patient care and further improve the hematopoietic cell transplant trajectory. This relationship may seem counter-intuitive, but the affiliation upon appraisal is natural for both services and advantageous to patients and their families.

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Palliative medicine is specialized care of patients living with serious illness including advanced cancer focusing on alleviating the burden of disease, treating refractory symptoms, and improving patient quality of life. It is appropriate for any age and any stage of any serious illness and is ideally provided concurrently with curative and life-prolonging treatments including hematopoietic cell transplant (Center to Advance Palliative Care and National Palliative Care Research Center 2015). Palliative medicine specialists work alongside the patient's multidisciplinary team to provide symptom and communication expertise, emotional support, and assistance with medical decision making. Despite the obvious harmony between the hematopoietic cell transplant population and the goals of palliative medicine, frankly, palliative medicine is at present grossly under-utilized in the field of hematology and transplant.

A variety of barriers may antagonize the relationship between hematology and palliative medicine. There is a reported perception that hematologist/oncologists may be reluctant to access palliative medicine services due to the misconception that palliative medicine is associated with end-of-life care and lack of knowledge regarding the spectrum of palliative care services (Cherny 2009). One simple but effective measure to divest this stigma is simply adding "supportive care" to the name of palliative medicine practices (Roeland and Ku 2015). "Palliative Medicine and Supportive Care" teams have established connections with hematologists and hematopoietic cell transplant services. Another approach is direct education of hematologist and oncologists to improve awareness of the range of potential partnerships with palliative medicine and roles of primary and secondary palliative care providers (Selvaggi et al. 2014).

Hematologists are primary palliative care providers. During the hematopoietic cell transplant trajectory, hematologists provide the primary management of pain and non-pain symptoms, often from the time of cancer diagnosis, through cancer treatments including transplant, to the time of cancer survivorship. This primary palliative care involves the entire transplant team and sub-specialists. Palliative medicine experts deliver specialized secondary palliative care treating refractory symptoms and pain, addressing all forms of patient distress, deliver caregiver and family stewardship, and often provide an opportunity for patients to convey their goals for advance care planning (Hui 2014). Palliative medicine becomes an additional tier to the multidisciplinary transplant care team.

This guide to supportive care during hematopoietic cell transplant is the *first book* to discuss palliative medicine as a coexisting specialty with transplant. There is limited but expanding research on the involvement and delivery of palliative medicine during transplant. This volume explores that research and describes the experience of experts in the fields of palliative medicine and hematopoietic cell transplant and cellular therapy. The goal of this volume is to demystify the field of hematopoietic cell transplant for palliative medicine providers and to outline the opportunities for palliative medicine integration for hematologists.

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Palliative Care for the Hematopoietic Cell Transplant and Cellular Therapy Clinician

2

Winnie Wang, Eric Roeland, Thomas LeBlanc, and Areej El-Jawahri

2.1 Introduction

Palliative care is a multidisciplinary model of medical care that aims to improve quality of life for patients and families facing serious illness. Palliative care focuses on assessing and treating physical, psychosocial, and spiritual suffering. Following the 2010 study by Temel and colleagues that demonstrated its clear benefits for patients with advanced cancer, and other key randomized controlled trials (Temel et al. 2010; Bakitas et al. 2009), the American Society of Clinical Oncology (ASCO) released a provisional clinical opinion in 2012, recommending that palliative care be delivered concurrently with usual oncology care early in the course of illness for all patients with metastatic disease and/or in patients with high symptom burden (Smith et al. 2012). Based on subsequent studies, ASCO issued an updated provisional clinical opinion in 2016, extending the recommendation for early concurrent palliative care for all patients with advanced cancer and their caregivers—with

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advanced cancer more clearly defined as one that is life-limiting or late-stage, with distant metastasis, and/or a prognosis of 6–24 months (Ferrell et al. 2017). Despite evolving clinical guidelines and immense unmet symptomatic burden, patients with hematologic malignancies infrequently receive palliative care services (Manitta et al. 2011; Epstein et al. 2012). Yet, there are many reasons to think these patients stand to benefit. To inform oncologists' clinical practice in this regard, this chapter will review the evidence of unmet palliative care needs in hematology, describe and define the scope of palliative care, discuss the challenges to its integration in hematology, and provide a model for care moving forward.

2.2 Unmet Palliative Care Needs in Patients with Hematologic Malignancies

Hematologic malignancy patients experience a substantial symptom burden that is equal to or possibly greater than non-hematologic malignancies (Manitta et al. 2011; Fadul et al. 2008; LeBlanc et al. 2015a). This symptom burden is attributable to both disease and its treatments; however, little is known about how symptoms differ across disease types or specific treatment regimens (LeBlanc and Abernethy 2013). Frequent physical symptoms include pain, mucositis, dyspnea, depression, fatigue, nausea, constipation, diarrhea, anorexia, and delirium (Epstein et al. 2012; LeBlanc et al. 2015a; Roeland et al. 2010a). In a study of 180 patients with hematologic malignancies, patients reported a mean of 8.8 physical and psychological symptoms (Manitta et al. 2011). Risk factors for a higher number of symptoms included active treatment, poor performance status, hospitalization, and more advanced disease (Manitta et al. 2011).

Patients with hematologic malignancies often undergo hematopoietic cell transplant, a highly intensive and potentially curative therapy. There has been a recent rise in the use of transplant for the treatment of hematologic malignancies due to data demonstrating its efficacy for new disease indications and acceptable safety profile for older patients, particularly with the advent of reduced-intensity conditioning regimens. Hematologic malignancy patients undergoing transplant experience substantial physical symptoms due to chemotherapy-induced toxicities and early post-transplant complications. Studies show that 50–70% of patients who undergo transplant report moderate-to-severe nausea, vomiting, diarrhea, pain, insomnia, and fatigue. These symptoms, along with the physical isolation patients experience during their often-prolonged transplant hospitalization, contribute to a rapid and dramatic deterioration in their quality of life and mood (El-Jawahri et al. 2015a). Notably, 40% of patients report clinically significant depression and anxiety symptoms during their transplant hospitalization (El-Jawahri et al. 2015a).

The psychological impact of having a hematologic cancer is also daunting for patients and their caregivers and can persist for years regardless of the outcome (McGrath 2001, 2002; Nissim et al. 2013; Goetzmann et al. 2008). Psychosocial stressors include the disease itself, as well as related treatments and side effects,

worry about treatment success, financial burden, family-related stress, and difficulty understanding and processing information from clinicians (Heinonen et al. 2005; LeBlanc et al. 2017). Patients struggle with symptoms of depression, anxiety, grief/loss, demoralization, and anger while caregivers can experience decreased quality of life and increased depression (El-Jawahri et al. 2015a; Roeland et al. 2010b; Nipp et al. 2016a).

As increasing numbers of patients survive hematopoietic cell transplant, there is a growing recognition of survivorship needs of these patients and their caregivers (Bevans et al. 2017). Many consider these to be unmet palliative care needs. While the majority of patients return to pre-transplant conditions within the first year, a significant number of patients report residual physical and psychosocial distress after the first year of transplant. Notably, studies show 10–50% of patients have ongoing physical symptoms like pain, fatigue, sleep disturbance, physical debility, and sexual dysfunction, while 5–60% of patients have persistent psychological symptoms including emotional distress, depression, post-traumatic stress, and cognitive dysfunction (Mosher et al. 2009). Financial burden/toxicity is also substantial, impacting up to 73% of patients (Khera et al. 2014). Risk factors predicting residual effects and decrease in quality of life include poor pre-transplant health, history of depression, reduced social support, being female, and active chronic graft-versus-host disease, the latter of which is the strongest predictor of negative long-term outcomes (Syrjala et al. 2004; Fraser et al. 2006; Fiuza-Luces et al. 2016). Chronic graft-versus-host disease, which occurs when donor T lymphocytes attack the host cells of the immunocompromised recipient, is a relatively common complication of long-term transplant survivors, with an incidence of 40–70% (Socie et al. 2003). Graft-versus-host disease is a major and often lethal complication with a host of complex symptoms related to involved organ systems including the skin, liver, lungs, eyes, and gastrointestinal tract (Socie et al. 2003). As such, we contend that patients with chronic graft-versus-host disease have marked unmet palliative care needs.

In addition to the palliative care needs of patients during and after hematopoietic cell transplant, patients with hematologic malignancies have substantial unmet palliative care needs at the end of life. Symptom trajectory at the end of life in this population has been poorly studied. However, data suggest that hematologic malignancy patients may not receive high quality end-of-life care (Hui et al. 2014; El-Jawahri et al. 2015b; Mannis et al. 2016). In the last 30 days of life, these patients are more likely to receive active cancer treatment, to be hospitalized, and to die in the acute care setting (Hui et al. 2014; El-Jawahri et al. 2015b; Howell et al. 2011, 2013, 2017). Transplant clinicians also recognize that end-of-life discussions may be occurring too late, with many clinicians waiting until death is imminent before initiating advance care planning or end-of-life discussions (Odejide et al. 2016a; Wang et al. 2016a). Despite significant unmet palliative care needs, these patients rarely utilize palliative care and hospice services before death, or enroll in hospice too late to obtain meaningful benefit (El-Jawahri et al. 2015b; Howell et al. 2011; Odejide et al. 2016b; LeBlanc et al. 2015b).

2.3 Defining Palliative Care

Many health organizations, including the World Health Organization (WHO), National Comprehensive Cancer Network (NCCN), and Oncology Nursing Society (ONS), have published official definitions of palliative care. We prefer the iteration issued by the Center to Advance Palliative Care, as follows:

> Palliative care is specialized medical care for people with serious illness. This type of care is focused on providing patients with relief from the symptoms, pain, and stress of a serious illness—whatever the diagnosis. The goal is to improve quality of life for both the patient and the family. Palliative care is provided by a team of doctors, nurses, and other specialists who work with patients' other doctors to provide an extra layer of support. Palliative care is appropriate at any age and at any stage in a serious illness, and can be provided together with curative treatment (CAPC 2011).

This definition emphasizes that palliative care is prognosis independent. Although palliative care is frequently misunderstood by patients and blood cancer specialists as equivalent to end-of-life or hospice care (LeBlanc et al. 2015c; Odejide et al. 2014; Hui et al. 2015), palliative care is appropriate at any point, even concurrent with curative-intent treatment (Fig. 2.1) (Ferrell et al. 2017; El-Jawahri et al. 2016a). End-of-life care is just one aspect of palliative care, while hospice is just one type of end-of-life care (Fig. 2.2). The Center to Advance Palliative Care definition also highlights the multidisciplinary collaboration necessary between palliative care specialists and various medical specialties to provide comprehensive palliative care for all patients. Oncology clinicians often provide what is called "primary palliative care," by managing basic symptoms and engaging in discussions about prognosis and advanced care planning (Quill and Abernethy 2013). In cases where patients and families may need additional support in managing complex symptoms and psychosocial burden of illness, "secondary palliative care," also known as "specialist palliative care," offers an additional layer of support and expertise—just as an infectious disease specialist supports the hematopoietic cell transplant team in challenging cases of unusual or refractory infections (Quill and Abernethy 2013). Studies of early palliative care offered concurrently with active cancer therapy support this distinction, demonstrating that palliative care clinicians focus on different issues

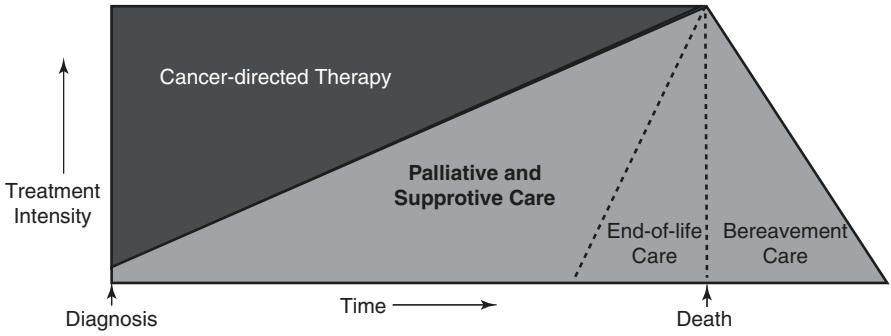

Fig. 2.1 Concurrent palliative care timeline

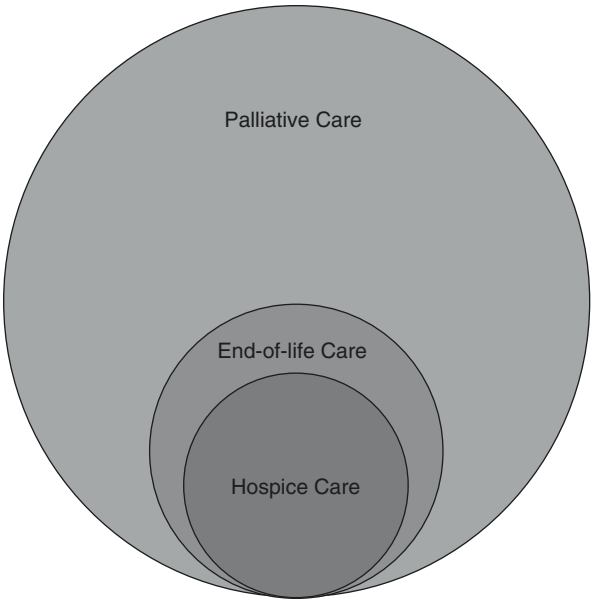

Fig. 2.2 Palliative care-related terms

than oncologists, thereby providing an extra layer of much needed support (Back et al. 2014; Yoong et al. 2013). Patients may focus on their cancer with their oncologist while they discuss their symptoms with palliative care specialists (LeBlanc and El-Jawahri 2015). Integrated palliative and oncology care collectively provides enhanced care and more support to patients and caregivers facing serious illness.

2.4 The Benefits of Palliative Care

The benefit of early palliative care integration is well established in solid tumor patients, as demonstrated in a series of well-designed randomized control trials (Table 2.1). In ENABLE II, the first of these studies, 322 patients with advanced solid tumors were randomized to a palliative care intervention versus usual oncology care (Bakitas et al. 2009). The intervention was a manualized, psychoeducational, telephone-based palliative care–focused intervention delivered by palliative care advanced practice nurse practitioners (with no integration of specialty palliative care clinicians otherwise). Intervention patients reported better quality of life and mood, with a trend toward less symptom burden. In a randomized control study by Temel and colleagues, 150 patients with newly diagnosed metastatic non-small-cell lung cancer were randomized to receive early integrated palliative and oncology care versus usual oncology care alone. The intervention entailed at least monthly outpatient palliative care visits from the time of diagnosis until death (Temel et al. 2010). Palliative care visits were not manualized or scripted, but they followed guidelines published by the National Consensus Project for Quality Palliative Care (Temel et al. 2010). Intervention patients reported better quality of life and mood and better prognostic awareness, and received less aggressive end-of-life care

Table 2.1 Key randomized controlled trials for benefits of early palliative care in solid tumors (LeBlanc and El-Jawahri 2015; Ferrell et al. 2017)

Reference	Setting	Population	Intervention	Control	Duration	Improved QOL/mood	Reduced healthcare utilization	Improved survival	Improved caregiver outcomes
Bakitas et al. (2009) ENABLE II study	Rural New Hampshire and Vermont at cancer centers, VA medical centers, community clinics	Patients with advanced stage solid tumor with prognosis 1 year	*n* = 161 Telephone-based, manualized, nursing-led multicomponent psychoeducational intervention	*n* = 161 Usual care	11/2003–12/2007	Yes	No	No	[a]
Temel et al. (2010)	Academic hospital	Patients with newly diagnosed metastatic lung cancer	*n* = 77 Early integrated PC with monthly outpatient PC clinic visits	*n* = 74 Usual care	6/2006–7/2009	Yes	Yes	Yes	[a]
Zimmermann et al. (2014)	Cluster RCT, Canadian comprehensive care center	Patients with stage III/IV lung, GI, GU, gynecologic cancer with prognosis 6–24 months	*n* = 228 PC consultation and at least monthly follow-up in PC clinic	*n* = 233 Usual care	12/2006–2/2011	Yes	Yes	[a]	[a]
Bakitas et al. (2015) ENABLE III study	Rural New Hampshire and Vermont at cancer centers, VA medical centers, community clinics	Patients with advanced stage solid tumor or hematologic malignancy (*n* = 10, 4.8%) with prognosis 6–24 months	*n* = 104 Early initiation of PC (within 30–60 days of diagnosis) Involving outpatient in-person PC consult, 6 weekly telephone coaching session by advanced practice nurse using manual	*n* = 103 Delayed initiation of PC (3 months of diagnosis)	10/2010–3/2013	No	No	One-year survival: Yes Overall survival: No	[a]

Dionne-Odom et al. (2015) ENABLE III study	Rural New Hampshire and Vermont at cancer centers, VA medical centers, community clinics	Caregivers of patients with new diagnosis, recurrence, or progression of advanced-stage solid tumor or hematologic malignancy (n = 7, 3.4%) with prognosis 6–24 months	n = 61 Early initiation of PC (within 30–60 days of diagnosis) Telephone-based, manualized, nursing-led coaching for caregiver	n = 61 Delayed initiation of PC (3 months of diagnosis)	10/2010–3/2013	[a]	[a]	[a]	Yes
Grudzen et al. (2016)	Urban, academic emergency department at a quaternary care referral center	Patients with advanced stage solid tumor	n = 69 PC consultation by inpatient team; refer to outpatient PC clinic if appropriate	n = 67 Usual care	6/2011–4/2014	Yes	No	No	*
El-Jawahri et al. (2016a, b)	Academic hospital	Caregivers of patients with new diagnosis of incurable lung or non-colorectal GI cancer	n = 137 PC visit for patient within 4 weeks of enrollment and at least monthly until death. Caregivers encouraged, but not required to attend	n = 138 Usual care	5/2011–7/2015	[a]	[a]	[a]	Week 12: Yes (improved caregivers' total distress, depression, but not anxiety or QOL) Week 24: No (no differences in caregivers' outcomes)

(continued)

Table 2.1 (continued)

Reference	Setting	Population	Intervention	Control	Duration	Improved QOL/mood	Reduced healthcare utilization	Improved survival	Improved caregiver outcomes
Temel et al. (2017)	Academic hospital	Patients with newly diagnosed incurable lung or noncolorectal GI cancer	*n* = 175 Early integrated PC with monthly outpatient PC clinic visits	*n* = 175 Usual care	5/2011–7/2015	(varied by cancer type) Lung cancer: Intervention patients with improved QOL and depression at 12 and 24 weeks, usual care patients reported deterioration GI cancer: Both study groups reported improvements in QOL and mood by week 12	[a]	[a]	[a]

QOL quality of life, *PC* palliative care
[a]Not studied

compared to those receiving usual oncology care. Aggressive end–of-life care was defined as receiving chemotherapy within 14 days of death, lack of hospice care, or admission to hospice within 3 days of death. Interestingly, patients randomized to palliative care also had a better overall survival compared to those receiving oncology care without palliative care. These two studies provided the rationale for ASCO's 2012 provisional clinical opinion recommending concurrent palliative care from the time of diagnosis for all patients with metastatic cancer and/or in patients with high symptom burden (Smith et al. 2012).

Subsequent studies have explored the effects of palliative care across different diseases, care settings, and delivery models and investigated the components of palliative care that impact patient outcomes. In a cluster randomized trial of 461 patients with advanced solid tumors and a prognosis of 6–24 months, Zimmerman and colleagues randomized patients to receive early palliative care versus usual oncology care (Zimmermann et al. 2014). Patients in the intervention arm, who received outpatient palliative care consultation and monthly follow-up, reported better quality of life and less symptom burden at 4 months. Although this data is promising, much more work is needed to understand which patients benefit most from concurrent palliative care. For example, a recent randomized control trial of early palliative care in patients with advanced lung or non-colorectal gastrointestinal cancers suggests there may be differential effects of early palliative care in different cancer populations (Temel et al. 2017). Palliative care has also been tested in the emergency department setting (Grudzen et al. 2016). In a randomized control trial by Grudzen and colleagues, 136 patients with advanced cancer presenting to the emergency department at an academic, urban care center were randomized to receive a palliative care consultation versus usual care (Grudzen et al. 2016). Patients in the intervention arm received palliative care consultation with comprehensive evaluation, daily follow-up upon admission, and outpatient follow-up upon discharge, if indicated. These patients reported improvement in their quality of life at 12 weeks, despite this relatively low "dosage" of palliative care intervention. Median survival increased, but this difference was not statistically significant. Rates of healthcare and hospice use were unchanged.

ENABLE III tested the timing of palliative care: 207 advanced cancer patients (including 4.8% patients with advance hematologic malignancies) were randomized to early versus delayed palliative care. While all patients received the ENABLE intervention, which involved one initial in-person palliative care consultation followed by nurse-led telephone coaching, patients were randomly assigned to receive the ENABLE intervention early (within 30–60 days of diagnosis) or delayed (3 months after diagnosis). Those randomized to early palliative care were more likely to live 1 year compared to patients that received delayed palliative care (Bakitas et al. 2015). Although this trial did not demonstrate a benefit in patient-reported outcomes, this study had limited power and half of the patients in the delayed group actually received palliative care consults earlier than what was specified in the protocol. Together these trials provide growing evidence that early palliative care improves quality of life, mood, symptoms, delivery of end-of-life care, and satisfaction with care, with no adverse outcomes reported.

Additionally, recent trials have studied the effects of palliative care on caregivers (i.e., family and close friends), with encouraging findings. As part of the ENABLE III study, caregivers of advanced cancer patients were randomly assigned to a caregiver-directed palliative care-based psychoeducational intervention consisting of early versus delayed telephone-based caregiver intervention. Caregivers who received the early intervention had improved mood and less stress (Dionne-Odom et al. 2015). Moreover, a recent randomized control trials of caregivers of patients with advanced lung and gastrointestinal cancers randomized to early subspecialty palliative care involvement reported improvement in caregiver psychological distress (El-Jawahri et al. 2016b), while a recent cluster-randomized study of caregivers of patients with advanced lung, gastrointestinal, genitourinary, breast, and gynecological cancers randomized to early palliative care reported increased caregiver satisfaction with care (McDonald et al. 2017). In light of these new studies, ASCO issued an updated provisional clinical opinion in 2016, extending the recommendation for early palliative care concurrent with treatment to all patients with advance cancer, and additional consideration for referring caregivers of patients with early or advance cancer to palliative care services (Ferrell et al. 2017).

Despite clear evidence of these benefits among patients with advance solid tumors, patients with hematologic malignancies have largely been excluded from these studies. The ENABLE III study is the only early palliative care trial that included any patients with hematologic malignancies, and there were only 10 such patients randomized, wherein 5 received early palliative care and 5 delayed palliative care (Bakitas et al. 2015). But new data suggest that the integration of palliative care concurrently with usual transplant care for hematologic malignancy patients may indeed improve their outcomes. In a recent single-center randomized control trial by El-Jawahri and colleagues, 160 patients with hematologic malignancies were randomized to early inpatient palliative care integrated with transplant care versus usual transplant care during hospitalization for hematopoietic cell transplant (El-Jawahri et al. 2016a). Recipients of the palliative care intervention were seen by palliative care clinicians at least twice a week during transplant hospitalization; the palliative intervention was focused on symptom management and psychological support. At week 2 of follow-up, intervention recipients reported better quality of life and less depression, anxiety, and symptom burden compared to controls. Three months after hematopoietic cell transplant, intervention recipients continued to report better quality of life, and less depression compared to controls. Additionally, they reported less post-traumatic stress symptoms at 3 months post-transplant, compared to those receiving usual care. Although this study was underpowered to examine caregiver outcomes, the palliative care intervention also led to improvements in caregivers' coping and depression symptoms at 2 weeks, suggesting that modifying patients' experiences during transplant may have positive effects on aspects of caregivers' well-being as well. This is the first randomized control trial to demonstrate feasibility and efficacy of early concurrent palliative care in patients with hematologic malignancies, and the first clinical trial to show benefit of palliative care in the curative setting. A similar multi-site randomized control trial of early concurrent palliative care is underway among patients with high-risk acute myeloid leukemia hospitalized for intensive induction chemotherapy (El-Jawahri 2016).

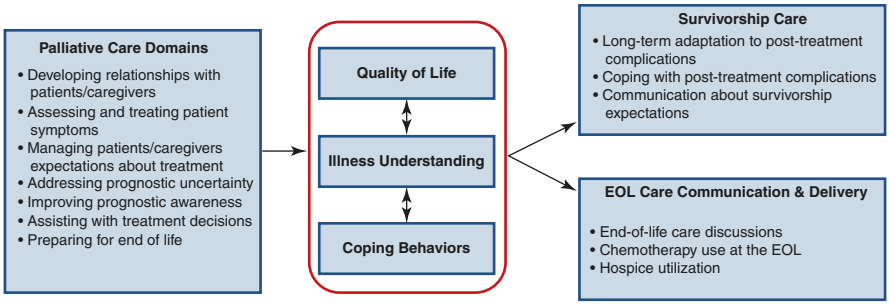

Fig. 2.3 Conceptual model of integrated palliative care's impact on patients with hematologic malignancies and their caregivers

2.5 Conceptual Model of Palliative Care in Hematologic Malignancies

Figure 2.3 depicts our conceptual model for palliative care integration in hematologic malignancies, which is adapted from our conceptual model for the early integration of outpatient palliative care for patients with solid tumors (Irwin et al. 2013). This model depicts the mechanism by which early integration of palliative and oncology care in patients with hematologic malignancies is thought to improve patients' and caregivers' quality of life, illness understanding, and coping behaviors. By enhancing patients' and caregivers' illness understanding and coping behaviors, the integrated palliative care in oncology model has the potential to improve both long-term adaptation to illness and survivorship care and end-of-life communication and delivery. Of note, the potential impact of palliative care integration may extend to all individuals interacting with palliative care and thus may impact outcomes among both patients and caregivers.

2.6 Barriers to Palliative Care Integration in Hematologic Malignancies

Despite the mounting evidence of palliative care's benefits in oncology, there remains a lack of integration of palliative care in neoplastic hematology, primarily due to illness-specific factors that are reinforced by misconceptions about the appropriate timing of palliative care consultation (Manitta et al. 2011; Epstein et al. 2012). Patients with hematologic malignancies have a unique set of care needs. Unlike the solid tumor setting, for example, where palliation is the main goal in advance disease, hematopoietic cell transplant offers the chance of cure for those with hematologic malignancies, even in advance stage of the disease. A short and rapid decline near death and the lack of a clear demarcation between curative and palliative stages of illness make it difficult to identify when a patient is approaching the end of life and when to stop treatment (Odejide et al. 2014; LeBlanc 2014). Prognostication is further confounded by recent studies demonstrating encouraging survival rates in

this patient population even when admitted to the intensive care unit (Azoulay et al. 2013, 2014; Pene et al. 2008). Thus, if hematologist-oncologists misunderstand palliative care as being only end–of-life care (LeBlanc et al. 2015c; Odejide et al. 2014; Hui et al. 2015), patients are then referred to palliative care when they are actively dying, when it is often too late for the patient to fully benefit from palliative care services, rather than facilitating upstream, concurrent palliative care independent of prognosis (LeBlanc 2014).

In addition, many clinicians are not aware of the benefits that palliative care can offer to their patients. In a recent survey of hematologic oncologists, the most commonly reported barrier to high-quality end-of-life care was "unrealistic patient expectations" (Odejide et al. 2016c). Palliative care specialists are trained to facilitate effective advance care planning discussions and prognostic communication, and can help patients gain improved understanding of their illness. However, many hematologists are perhaps unaware of this observation. In the same study, the second highest-ranked perceived barrier to end-of-life care was "clinician concern about taking away hope" (Odejide et al. 2016c). Although oncologists may feel that talking about poor prognosis or end-of-life issues will dash their patients' hopes, patients report desiring detailed, honest disclosure of their prognosis for better understanding and realistic planning (El-Jawahri et al. 2014, 2015c). In fact, studies suggest that early palliative care can facilitate better prognostic understanding without increasing anxiety or depression (Temel et al. 2010).

There are also system-based issues unique to hematologic malignancies that pose barriers for hospice access, further challenging the ability to provide high-quality end-of-life care for this population. Hospice agencies are currently ill-equipped to manage the complex symptom burden of patients with hematologic malignancies, including infections, bleeding, and graft-versus-host disease. For example, patients with hematologic malignancies frequently experience bleeding complications at end of life, sometimes necessitating palliative transfusions (Odejide et al. 2014). Because of the low per-diem reimbursement rate for a patient receiving hospice care, hospice agencies are frequently unable to provide blood transfusions due to their cost. Thus, patients and their clinicians are left to choose between hospice care and hospital care (LeBlanc 2014; Wang et al. 2016a, 2016b). Moving forward, we must develop hospice reimbursement models that account for and address the hematology population's unique needs at end of life. We also must study and more fully understand the unique needs faced by these patients, their caregivers, and their clinicians at end-of-life.

2.7 Strategies to Optimize Integration/Expert Point of View

While the recent trial of early integrated palliative care in hematopoietic cell transplant and cellular therapy offers encouraging evidence of the benefits of palliative care for patients with hematologic malignancies (El-Jawahri et al. 2016a), it also underscores the need for further research. There is a great need for rigorous studies that comprehensively assess the needs of patients with hematologic malignancies,

while fully acknowledging that these needs may differ across cancer type, disease risk, and illness trajectory. There is also a great need for studies of different modalities for providing palliative care to the hematology population. Since recent data suggest that the benefits of palliative care may differ across cancer populations (Temel et al. 2017), future palliative care intervention studies should target the specialized needs of particular populations with an eye toward better understanding of the expected trajectory of their patient-reported outcomes. This includes those with hematologic malignancies, among others.

Amid a workforce shortage in palliative care, future studies must also identify high-risk populations that may benefit from palliative care at particular points in their illness. Additionally, we must develop a more comprehensive understanding of the potential mediators and moderators of the effect of palliative care interventions, to better elucidate the benefits of the integrated care model and guide its implementation across different populations. This will allow for the development and dissemination of personalized integrated palliative care models that are best equipped to address the specialized and evolving needs of patients with hematologic malignancies. Lastly, we must develop and test primary palliative care models that address the unique needs of patients with hematologic malignancies within the cancer care team, separate from specialist involvement. Together, these strategize will help us enhance the quality of life and delivery of care for all patients with hematologic malignancies, and their families.

Promoting palliative care research and educational outreach is critical to overcome misperceptions about palliative care, and allowing for more successful integration with hematologic malignancies. These studies create opportunities for collaboration between palliative care and transplant clinicians, or non-transplant hematologists, thereby building trust while encouraging bidirectional education. While future palliative care research efforts should also focus on improving the delivery of end-of-life care for patients with hematologic malignancies, studies that focus on the potential benefits of palliative care for patients receiving curative therapy can help overcome the substantial misconceptions that exist in hematology, which equate palliative care with end-of-life care (LeBlanc et al. 2015c; Hui et al. 2015).

2.8 Future Directions

Amid growing evidence as to the many benefits of early, concurrent palliative care among patients with serious illness, now is the time to explore the integration of palliative care in hematology. Patients with blood cancers have unique needs, requiring unique approaches and necessitating further research in a few key areas (Temel et al. 2010): clarifying the role of early palliative care in hematology (Bakitas et al. 2009); identification of high-risk patients who would most benefit (Smith et al. 2012); and evaluating the specialized needs of these patients at key points in their illness trajectory. Just as solid tumor patients can have different palliative care needs depending on cancer type, age, and sex (Nipp et al. 2016b; Greer et al. 2016), it is likely that

patients with blood cancers have different needs depending on the type of malignancy, stage of disease, and/or treatment regimen. Ongoing palliative care research combined with continued education on the role of palliative care, and exposure to helpful palliative care specialists, will form a base for collaboration moving forward. Additional efforts are needed to improve available modalities for providing end-of-life care to patients with blood cancers, which will likely require reimbursement and policy solutions. Lastly, further studies are needed to improve understanding of the end-of-life trajectory of hematology patients, to enable us to best optimize end-of-life care outcomes by matching patients with available services. Innovative end-of-life care delivery models are sorely needed to target this patient population, given their unique end-of-life needs, including palliative transfusions, infectious complications, and graft-versus-host disease, which currently preclude most patients with blood cancers from receiving high-quality end-of-life care and access to hospice care services (Hui et al. 2014; El-Jawahri et al. 2015b; Mannis et al. 2016).

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