47 Palliative Care in Transplant Patients

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Introduction

Historically transplantation and palliative medicine have been seen on the opposite ends of the spectrum, with transplant medicine focusing on aggressive life prolongation and palliative care being equated with end-of-life care. However, recent trends show that these specialties are not mutually exclusive.

Due to advances in medicine and technology, many more people than ever before are living with chronic and end-stage illness and have the possibility of organ transplantation as a means of potential treatment. Patients with leukemia, multiple myeloma, and some types of lymphoma may now have the option of a bone marrow transplant. However, some patients evaluated for transplant might not be found appropriate candidates due to medical or psychosocial reasons or may pass while awaiting a transplant [1, 2]. Others may not survive the transplant or postoperative period or may have complications which limit their quality of life (QOL) or long-term survival [2]. In addition, patients undergoing transplantation trade one chronic illness for another, as all transplant recipients must take a complicated post-transplant regimen, associated with multiple side effects [3–5].

While successful transplantation may afford a patient another 5 to 20 years of life [6], with the uncertain and tenuous transplant process, it is paramount to shift the focus from quantity to quality of life.

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What Is Palliative Care?

The World Health Organization defines palliative care as "an approach that improves the quality of life of patients and their families facing the problems associated with life-threatening illness through the prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems, physical, psychosocial and spiritual." [7]

Palliative care is medical care provided by an interdisciplinary team including medicine, psychiatry, nursing, social work, chaplaincy, counseling, nursing assistants, and other health professionals, focused on the relief of suffering and support for the best possible QOL for patients facing serious life-threatening illness and their families. Palliative care expands the focus from traditional disease-model medical treatments to include the goals of enhancing QOL, optimizing functioning, and helping with decision-making including decisions regarding end-of-life care [8]. Palliative care includes:

1. The structure and process of care.
2. Physical aspects of care.
3. Psychological and psychiatric aspects of care.
4. Social aspects of care.
5. Spiritual, religious, and existential aspects of care.
6. Cultural aspects of care.
7. Care of the imminently dying patient.
8. Ethical and legal aspects of care.

These core domains of care are used to provide individualized patient- and family-centered care where each patient's and their family's needs are assessed, documented, and addressed individually. Such assessment includes documentation of the disease status, diagnoses, and prognosis, patients' and families' understanding of the disease and prognosis, and patient and family expectations, including goals for care and for living. The palliative care team

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facilitates the documentation of patients' wishes for care along the healthcare continuum via completion of documents such as an advanced care directive or a Physicians Orders for Life-Sustaining Treatment (POLST) [8, 9].

An advanced care directive is a legal document that is completed at any point during the patients' disease process that (1) designates a surrogate decision-maker if a patient becomes unable to make decisions about their own medical care and (2) provides general treatment guidance or instructions in making healthcare decisions (e.g., when to continue, withhold, or withdraw care at the end of life). A POLST is not a legal document and does not designate a surrogate decision-maker. Instead, a POLST is completed when patients are nearing the end of life and are expected to die within a year, and it functions as "portable medical order for specific medical treatments the patient would want tonight" [9] and orders medical personnel to provide specific treatment in an emergency. A POLST contains three major elements including if the patient wishes to receive cardiopulmonary resuscitation if they are nonresponsive, have no pulse, and are not breathing, what type of treatment they wish to receive in an emergency when they have a pulse and are breathing, and if they wish to receive artificial nutrition [9]. After documenting patients' wishes regarding their goals of care, the palliative care team ensures that patients' goals and choices are understood, respected, and implemented within the limits of state and federal law including implementation of do not resuscitate (DNR) orders which instruct medical providers to not provide cardiopulmonary resuscitation if a patient becomes unresponsive, stops breathing, and has no pulse [8, 9].

Aside from assessment, documentation, and implementation of patients' goals for treatment, palliative care can manage symptoms such as pain, shortness of breath, fatigue, nausea, weakness, anorexia, insomnia, anxiety, depression, confusion, and constipation, as well as other symptoms and side effects of the disease process and its treatment. The palliative care team is able to assess and communicate the signs of impending death and care for patients during the dying process and provide grief and bereavement assistance to the patients' families and treatment team [8].

Palliative Care and the Transplant Process

Molmenti and Dunn describe patients eligible for transplants as highly vulnerable physically, socioeconomically, psychologically, and spiritually from the consequences of end-stage organ failure. Their and their families' wishes may evolve over time due to the progression of the underlying disease which changes the goals of care. Once transplanted, patients' and their families' expectations for complete recovery may be incongruent with the nature of their disease, post-transplant complications, age, comorbid medical illness, and previous functional status [10]. The involvement of palliative care in the transplant process has been documented to improve advance care planning and goals of care discussions, increase do not resuscitate (DNR) rates, and decrease length of stay in the hospital, without increasing the rate of mortality. They also decrease the rate and severity of symptoms such as nausea, insomnia, pain, tiredness, constipation, depression, anxiety, anorexia, and dyspnea [1].

The integration of palliative care into the transplant process has been found to be highly effective in supporting patients throughout their disease process [11]. Yet, many misconceptions about palliative care act as barriers to referral [12]. Ouimet Perrin describes key barriers to include the misconception by medical providers, patients, and their families that palliative care is solely appropriate for patients near death and is separate from standard care. Therefore, involvement of palliative care can be seen as undermining the goal of saving the patient's life. Furthermore, the unpredictable disease trajectory of organ failure [1, 13] makes it difficult for clinicians to decide when is the best time to involve palliative care. Santivasi et al. describe the concept of a "therapeutic inertia" where the adherence to a preconceived course of treatment even in the face of new medical problems or risks can prevent the consideration of non-transplant-directed care [14, 15].

The integration of palliative care intro transplant clinics has been discussed in numerous articles and has been increasing over the years. Wentlandt et al. describe the integration of palliative care clinic into the organ transplantation service within the University Health Network's Multi-Organ Transplant Program in Toronto, Canada [13]. They report that since 2011, over 250 patients have been referred to the palliative care clinic. After initial consultation, patients' Edmonton Symptom Distress Score, an assessment of symptom distress in the palliative care setting, improved for pain, tiredness, drowsiness, sleep, cough, depression, and anxiety. Each unique solid organ transplantation program (i.e., heart, lung, kidney, liver, gut) as well as hematopoietic cell transplantation can have their own unique issues, question, and symptom burdens. It is important to address the unique aspects of palliative care in these patient populations separately.

Palliative Care and Heart Failure

Improvements in cardiovascular treatment have led to an increase in those living with heart failure, which is expected to rise to nearly 8 million people by 2030 [16]. With advances in diagnosis and therapy, patients with heart failure have

access to a variety of treatments including (1) medical therapy, (2) electrical therapy, (3) surgery, and (4) combination therapy. For many patients, as their disease progresses, medical therapy is no longer enough, and evaluation for placement of ventricular support devices and heart transplantation becomes an option [17].

In 2017, there were 3244 heart transplants in the United States. Despite this number, there are currently 3956 patients who are currently registered and waiting for a heart transplant with the median waiting time between 70 and 535 days [18]. Due to prolonged waiting times for a heart transplant, patients may experience emotional strain as well as physical decompensation marked by shortness of breath, nausea, dizziness, and edema. At times these symptoms may be intractable [19]. These symptoms interfere with the ability to work or complete daily activities and cause significant psychological distress for both patients and their families [20]. Worsening anxiety, anorexia, and sleep disturbance may not only be immediate issues for the patient but also detrimental to their long-term health and jeopardize their transplant status [19]. Patients who receive heart transplant and are discharged from the hospital have decreased 5-year survival of 76.2–79.2%, compared to the general population [18]. This is of course superior to medical therapy alone with 1-year survival of only 25% [20].

Thus, opportunities for palliative care team to offer their services are ample throughout the continuum of end-stage heart disease. Ideally, the utilization of palliative care should be started at the time of diagnosis when a patient's health is not in crisis and there exists ample opportunity to discuss diagnoses, symptoms, prognosis, treatment options, treatment preferences, and healthcare values. This integration of palliative care into the initial visits with the patient and their family can provide support to the patient and their family during their disease process. The palliative care providers have the ability to assist the heart failure team with treatment of changing physical and emotional symptoms and discussions of changes in goals of care which may occur during the disease trajectory [19].

Schwarz et al. describe a pilot study of palliative care consultation in patients with advanced heart failure referred for cardiac transplantation. In this study, 20 patients received a palliative care consultation with resulting decreased use of opioids, increased clarity about treatment plans, and realignment of goals of care. Of these patients, 30% completed advanced care directives. In addition, both patients and their cardiologists reported that the palliative care consult provided either moderate or significant positive impact on the patient care [4]. Another study demonstrated that integration of palliative care into heart failure treatment increased patients' QOL, improved their symptom burden, and increased advanced care planning [21].

Post-transplant, while patient's QOL improves and caregiver burden decreases, physical symptoms, such as pain, may continue. In addition, patients might experience an increase in emotional and psychosocial-spiritual burden with up to 69% of patients endorsing such symptoms after transplant [20]. Overall, early and continual involvement of palliative care throughout the disease and transplant process can help not only delineate and clarify evolving goals of care but provide treatment of distressing symptoms, improve QOL, and support patients and their families throughout the disease process.

Palliative Care and Ventricular Assist Devices

In recent years, ventricular assist devices (VADs) have been used not only as a bridge to transplants but also as a destination therapy when a patient is not eligible or does not wish to receive a heart transplant [2, 22]. As a result, nearly 150,000 to 250,000 patients annually are eligible for a destination VAD therapy, although the current 1-year mortality rate for destination (DT) left ventricular assist devices (LVAD) is around 20% and the average survival only slightly exceeds 2 years after implantation [22]. As such, the therapy itself may be considered aggressive palliation as the risk of complications remains very high and includes rehospitalization, infection, stroke, device malfunction due to clotting, and progressive right heart failure [22].

Some of the psychosocial problems common among LVAD patients are different from transplant patients. The caregiving for patients with an LVAD is more burdensome than care of heart transplant candidates or recipients and has been found to be comparable to patients receiving mechanical ventilation at home [16]. In 2013, the Joint Commission mandated that all accredited DT-LVAD programs must have a palliative care specialist as part of the treatment team, and this is also consistent with the 2014 recommendations by the Centers for Medicare and Medicaid Services [22]. Integration of the palliative care team at the time of the initial discussion and implantation decision-making can facilitate understanding and documentation of patient's goals, preferences, and values, including completion of associated documents such as advanced care directives ideally done prior to device implantation. Palliative care can also increase in-home support as symptom burden and complications progress [16]. Longitudinal care and involvement by the palliative care team from implantation of the DT-LVAD can help continually assess the patients' and their families' evolving goals of care and facilitate transitions in goals of care, including device deactivation and end-of-life care [22].

Palliative Care and End-Stage Lung Disease

For patients with end-stage lung disease, lung transplant may be the therapy of choice that can improve both survival and QOL [23]. Unfortunately, lung transplantation includes many risks including drug toxicities, infections, and rejection [24]. Survival post-lung transplant remains low with 1-year and 5-year survival of 87–89.1% and 52.2–55.4%, respectively [18]. In addition, improvement in lung transplant recipients' QOL may not be fully evident until 1 year after transplant [2]. Long-term concerns include bronchiolitis obliterans, a progressive, insidious, and often fatal lung alloreaction, which affects 49% and 75% of patients 1 year and 5 years post-transplant, respectively, determining the trajectory and outcomes post-lung transplant and significantly affecting patients' QOL [5]. Thus, lung transplantation may be seen not as a curative therapy but more as a continuation along the spectrum of chronic disease which makes early palliative care interventions desirable and necessary. In addition, both the American Thoracic Society and American College of Chest Physicians support the involvement of palliative care in the care of patients with advanced lung disease [25].

Despite the recommendations for integration of palliative care, few patients get referred to palliative care services after lung transplantation. In a survey of transplant pulmonologists and palliative care clinicians from the major US lung transplant programs with at least 15 lung transplant annual volume, 18 centers out of 27 contacted responded [26]. The survey indicated that on average, less than five patients per year were referred to the palliative care services from each center. Of note, 94% of palliative care referrals were made late in the disease trajectory, with average length of survival being less than 30 days after such referrals. Despite lung transplant clinicians endorsing palliative care in assistance with not only end-of-life discussions but also in providing family support, pain and symptom management, psychological support, and planning of care, 45% of lung transplant recipients still died in the intensive care unit (ICU) [26].

Co-management by palliative care of end-stage lung disease patients, both pre- and post-transplant, has demonstrated a decrease in symptom burden as well as an increase in goals of care discussions. Freeman et al. described that in a co-managed palliative care and lung transplant clinic, patients experienced an improvement in their sleep and cough and a trend toward improvement in pain. Discussion of advance care directives occurred 74% of the time. All patients who were started on opioids pre-transplant for dyspnea and cough by the palliative care service discontinued opioids post-transplant, demonstrating effective management of dyspnea by the palliative care team [27]. Rosenberger et al. suggested that by incorporating both palliative and restorative care as integral parts in a patient's overall treatment, clinicians may better address patients' distressing symptoms, prepare patients for pre- and post-transplant challenges, and address their changing needs throughout the disease trajectory [5].

Palliative Care in Cystic Fibrosis and Lung Transplant

Patients with cystic fibrosis (CF) are unique in that they live with the possibility that they may die young [28]. Improvement in medical care has increased the median survival time in a patient with CF to 47 years of age in 2016 [29]. As a result, among patients with CF, studies show that palliative care is often deferred in lieu of aggressive medical treatments that aim to sustain patients until transplantation [5], although most patients die prior to receiving a transplant [28]. Therefore, patients with CF are more likely to die in ICU without having ever discussed their goals of care [5]. Chapman et al. have demonstrated that due to the unique nature of being diagnosed and living with CF, these patients were comfortable when questions of dying were raised early by medical staff, despite the reluctance of staff to discuss goals of care, deterioration, death, and dying [28]. In addition to questions about death and dying, patients with CF are living longer lives with significant symptom burden. In a palliative care survey completed by patients with CF receiving medical care in a major academic institution, 24% of patients reported chronic pain and nearly one-half of these patients reported that pain interfered with general activity, enjoyment of life, and ability to exercise. Only 31% of patients complaining of chronic pain had a treatment plan for pain. Unsurprisingly, patients reporting worse physical symptoms also had worsening lung function. In addition, 43% of patients reported that they frequently think about the impact of CF on their lives and 33% of patients reported that now or earlier was the ideal time to discuss end-of-life care. Despite the fact that 95% of patients reported that they felt comfortable talking to their CF team about end-of-life care, only 25% had completed a healthcare proxy form, a living will, or other written instructions [30]. The disparity between the high amount of symptom burden and actual treatment of patients' symptoms and discussion about their end-of-life care goals highlights an ample opportunity to improve care for patients living with CF. In addition, the disparity between patients' reported comfort and eagerness for such discussions as compared to providers' discomfort and hesitancy demonstrates the need for increasing providers' education and support regarding such discussions. The integration of palliative and active care throughout the life of a patient with CF would allow the patient, their family, and the team to better adapt to the progression of the disease and to improve QOL in physical, psychological, and spiritual domains across the continuum of the illness experience [28].

Palliative Care and End–Stage Renal Disease

There are four treatment modalities established for the management of end-stage kidney disease: hemodialysis, peritoneal dialysis, transplant, and conservative care defined as management of end-stage renal disease (ESRD) without dialysis [31, 32].

In 2017, there was a total of 18,489 kidney transplant nationwide, with adults over the age of 65 representing the third largest age group receiving a kidney transplant with 3666 transplants [18]. While a kidney transplant greatly reduces morbidity and mortality from ESRD compared to patients on the waiting list, larger benefits were seen for patients who were 20 to 39 years old [33]. Patients over the age of 70 did not achieve equal survival benefit compared to those on the waitlist, until 2 months after transplant. Yet these patients are a growing segment of the population with ESRD. Chen et al. describe that this population has a 5-year mortality rate of 60% post-kidney transplantation [34]. In patients continuing dialysis, the annual mortality rate is between 20 and 25%, and the majority of these patients die in acute care facilities without accessing palliative care services [35].

All patients with ESRD report high symptom burden independent of whether there are receiving dialysis or are transplant patients, and studies have shown that many patients have comparable symptom burden to those of patients with advanced cancer [36]. Despite the high symptom burden and high mortality rate, especially for patients ineligible for transplant, few patients have knowledge regarding their disease trajectory and palliative and hospice care services. In a survey of 584 patients with stage 4 and 5 chronic kidney disease who presented to dialysis, transplantation, or pre-dialysis clinics, only 17.9% felt their health would deteriorate in the next 12 months. Despite 60.7% of dialysis patients regretting their decisions to start dialysis, 83.4% did not know about palliative care. Among these surveyed patients, 65.6% reported being comfortable discussing end-of-life care with their nephrology staff, but only 38.2% had completed an advanced directive [32]. These studies demonstrated the need for integration of palliative care services into the renal clinics to address patients' symptoms, to provide support in decision-making around questions of conservative care versus further treatments such dialysis and transplant, and to complete advanced care planning.

Post-transplant patients may continue to have a significant symptom burden. Afshar et al. described a cross-sectional symptom survey of patients in the United Kingdom who had received a renal transplant 1 year prior to completion of the survey. Of the 110 patients surveyed, seven symptoms affected at least one third of the population examined. These included weakness (55%), difficulty sleeping (45%), dyspnea (42%), anxiety (36%), drowsiness (35%), dissatisfaction with body image (35%), and weight gain (33%) [37].

The Renal Palliative Care Initiative at Baystate Medical Center in collaboration with area dialysis and hospice centers describes an integrated palliative care service which included symptom assessment and management protocols, advance care planning, hospice referral, and bereavement services for all patients with ESRD. They have demonstrated an increase in advanced care directives completion from 6% to 32% [38]. Thus, given the previously described roles of palliative care to address ongoing symptoms pre- and post-transplant, discuss goals of care, and support patients throughout their disease process, the integration of palliative care into renal clinics can allow for better management of symptom burden and delivery of patient- and family-driven care.

Palliative Care and End-Stage Liver Disease

More people are affected by liver disease every year due to increased alcohol consumption, viral hepatitis, and obesity. Twenty percent of patients listed for liver transplant will die before a donor becomes available, and many patients living with cirrhosis are not eligible for transplant. End-stage liver disease (ESLD) represents a major cause of mortality and morbidity with 38,000 patients dying annually and is the seventh leading cause of death in the United States [39]. In terms of QOL, patients with ESLD have a significant symptom burden, suffer many complications, and require management of a complicated medication and nutrition regimen [40]. The complexity of symptom management is particularly highlighted in end-of-life care when patients may experience an average of 14 physical symptoms in the last month of care [41, 42]. In addition, some patients describe significant distress waiting for a liver transplant including difficulty coping, loss of trust in medical personal, and uncertainties about their future [43].

Typically goals of care and prognosis discussions in ESLD occur too late and may not include the patient themselves. As described by Low et al. at a tertiary treatment center in North London, United Kingdom, 77% of the time, the prognosis was discussed with family members, and 53% of such discussions occurred at or less than 34 days before the patient's death. In most cases, the medical team and not the patient or their family members had completed DNR orders. Most patients died in the hospital and were referred to palliative care 5 days before death [41]. This study demonstrated that although patients were clearly in poor health, there were limited discussions to address their QOL, goals of care, and prognosis and that referral to palliative care was done too late in the disease process. Low et al. reported that the liver clinicians engaged in "reactive treatment at the expense of palliative care" and that palliative care was only discussed at the initiation of the patient and not the team [41].

Unfortunately, this is not uncommon as it has frequently been reported that only 0.97–7.1% of patients with ESLD and 11% of patients removed from liver transplant lists received palliative care despite their uncontrolled symptoms [30, 41, 44, 45].

Several reasons for late referral to palliative care in patients with ESLD have been described. One of these is the unpredictable trajectory of liver disease, where patients may have frequent admissions and decompensations but may remain stable in between these exacerbations and only develop symptoms of ESLD abruptly. In addition, physicians' desire for active treatment may be secondary to their own perceptions of patient's expectations, their misunderstanding of palliative care, poor continuity of care, and perceived lack of skill and confidence when discussing prognosis and palliative care with patients and their caregivers. Despite this, early palliative care referral is associated with better QOL and can decrease both patient's affective and physical symptoms.

Waiting for liver transplant and receiving palliative care does not need to be a mutually exclusive process. Rossaro et al. describe a case of a 50-year-old man with ESLD secondary to hepatitis C who successfully received both palliative care services and was listed for a liver transplant [40]. While integration of palliative care into the transplant program was met with patient and family barriers and physician reluctance, this new integrated model improved QOL and prepared the patient for end of life in case of not receiving a liver in time. Rossaro proposes that patients too sick for a liver transplant should be immediately referred to palliative care. Patients with an increasing Model for End-stage Liver Disease (MELD) score, signaling worsening liver disease and increasing symptomatology, should be referred concurrently to palliative care and liver transplant and thus be supported and prepared for any eventual outcome. This was also demonstrated in a study at the University of California in Davis where patients were jointly co-managed by hospice and hepatology and showed improvement in their MELD scores [43].

A study published by Baumann et al. [46] demonstrated that an intervention via incorporation of a longitudinal, multidisciplinary early palliative care into the pre-transplant evaluation at Albert Einstein Medical Center in Philadelphia improved moderate to severe symptoms such pruritus, appetite, and fatigue in 50% of patients. Other improvements that were noted but were not statistically significant included pain, myalgias, sexual dysfunction, sleep disturbance, and dyspnea. In addition, depression symptoms improved in 27.8% [46]. Moreover, 55.6% of patients established new healthcare power of attorneys and 17% completed advanced directives [46]. Other studies have also demonstrated that a palliative intervention for liver transplant patients can improve DNR status clarification from 52% to 81% [44]. Therefore, these studies demonstrate that palliative care interventions in liver transplantation provide improved patient QOL, decreased disease symptomatology, improved education and goals of care discussions, decrease in ICU length of stays, and improved communication and family satisfaction without impacting patient mortality [43].

Palliative Care and Intestinal Transplant

It is estimated that two to three persons per million per year experience intestinal failure (IF), and 15% of them become candidates for intestinal transplant (ITx) [47]. Unique challenges in ITx include the large number of bacteria in the gut increasing the risk for post-transplantation infection and the large number of white cells in the bowel providing a strong stimulus for rejection. Due to these risks, ITx remains the rarest of organ transplants.

For the majority of patients with IF, total parenteral nutrition (TPN) is the preferred treatment as patients can be managed on home TPN for many years, and presently, long-term survival on TPN is superior to intestinal transplant for short bowel syndrome. In the first 1–2 years, the data varies on TPN's superiority to ITx. While earlier studies showed promising short-term (1-year) patient survival after isolated intestinal transplantation of 88–92%, which is similar to survival on TPN, later studies reported more discouraging statistics of 77% 1-year survival [48–50]. Long-term survival after ITx is consistently found to be lower compared to TPN over the same time frame. The International Intestinal Transplant Registry in 1997 reported that a 5-year patient survival is only 50% after ITx, compared with 60%–80% 5-year survival on TPN [51]. A review article by DeLegge in 2007 reported a 5-year patient survival similarly at 49% [50]. Due to improved survival on TPN compared to intestinal transplant, ITx is not currently indicated for patients dependent on TPN who are not experiencing complications.

For those experiencing complications on long-term TPN, intestinal transplant can be a life-saving procedure and is the only long-term solution. Additionally, ITx does provide a marked improvement in QOL with most patients consuming all their calories orally or via tube feedings and the majority returning to school and work. TPN is time-consuming, taking 10–16 h and up to 24 h to administer with the need for attachment to an intravenous pump. Not surprisingly, long-term TPN affects one's ability to work and maintain usual activities [52].

Due to its comparative infrequency to other organ transplants, studies looking at palliative care interventions and needs specific to the intestinal transplant patient are lacking. The challenges faced by ITx candidates and recipients over-

lap with the broader challenges of transplant patients magnified by the unique challenges of the gut. Pre-transplant, ITx candidates have the highest mortality for those awaiting transplantation. The US Scientific Registry of Transplant Recipient Data reported mortality rates of 16% per year. Adults aged 35–65 awaiting small bowel and liver transplantation have a mortality rate three to six times that of patients awaiting liver transplantation alone [53].

Additionally, there is not the same degree of conflict between QOL and maintaining optimal physical condition in patients awaiting ITx as compared to patients waiting for another solid organ transplant (SOT). TPN management, associated with such QOL concerns as complexity of catheter care and duration of administration, is critical in optimizing physical strength and resiliency for survival and recuperation from transplant surgery. This is in marked contrast to symptoms like air hunger seen in lung transplant candidates where palliative sedation with opioids can reduce this highly distressing symptom but also decrease level of activity or may even not be compatible with transplant listing. Due to these issues, referral to palliative care is a realistic and needed consult starting with the initial ITx evaluation.

Post-transplant, ITx patients need more intense immunosuppressive protocols than other SOT patients due to large size of the graft and the strong evoked immune response. Thus, opportunistic infections and neoplastic diseases are seen more commonly in ITx recipients compared to other SOT. Graft versus host disease (GVHD) is also more common in ITx than in other SOT due to the large size of the transplanted tissue creating a strong stimulus for an immune response [54]. The heavy immunosuppressant burden needed to prevent GVHD in turn leads to sepsis, the leading cause of death following intestinal transplant. Acute rejection is seen in 50–75% of patients, and chronic rejection occurs in up to 10–15% of recipients [47, 55]. With longer survival, post-transplant lymphoproliferative disease (PTLD) becomes a risk from prolonged immunosuppression and is a leading cause of death long-term in intestinal transplant recipients [56]. Thus, while quality of post-transplant life is markedly high with approximately 80% of surviving patients fully independent of TPN [48] and with a high rate of reduction in narcotic needs, transplant recipients still must deal with a chronic disease process with heavy immunosuppression therapy, multiple complications, and hospitalizations and a gradual deterioration in health over time. With all these challenges, palliative care can provide an invaluable service for both the pre- and post-ITx patients in understanding their illness trajectory, clarification of the uncertainty around the relapsing and remitting course of the disease process, and assisting patients and families with planning around an intervention with low long-term survival rates [47, 48, 50, 56–58].

Palliative Care in Hematopoietic Cell Transplantation

Hematopoietic cell transplantation (HCT) is a potentially life-saving and curative intervention with high recovery rates. Bush et al. found that 1–4 years after HCT, 73% to 81% of survivors rated their overall QOL as good to excellent. By 2 years after transplantation, 71% of survivors reported that they had recovered from their transplantation, up from 41% at 6 months and 66% at 1 year [59]. At the same time, HCT still carries significant risk for acute complications and late effects including GVHD, organ toxicity, osteoporosis, infections, cataracts, secondary cancers, and infertility. In the case of hematological malignancies, patients also experience the side effects from high doses of chemotherapy including nausea, fatigue, mouth sores, extreme weakness, diarrhea, or constipation. HCT procedure requires patients to spend several weeks in the hospital to help protect against increased susceptibility to infections, possible need for blood transfusions, and monitoring/treatment for possible complications. Even after hospital discharge, the recovery process can take several more months before the individual is able to engage fully in life activities prior to the transplant. Additionally, despite the advancements in treating hematological malignancies, the threat of relapsed disease, progression of symptoms, and eventual mortality remain. For all these factors, the involvement of palliative care both pre- and post-HCT and ongoing and active evaluations of one's QOL are a vital part of management in patients undergoing HCT.

While one of the barriers in consulting and benefitting from palliative care has been its equation with end-of-life and hospice care, the concurrent involvement of palliative care with active treatment shows improved outcomes, including decreased symptom burden during hospitalization and increased mood and overall QOL [60]. A randomized control trial in 160 enrolled patients by El-Jawahri et al. had palliative care provide guidelines for addressing nausea, pain, diarrhea, constipation, fatigue, insomnia, anxiety, and depression as well as meeting with the patient for at least four visits during the course of their hospitalization with two of the visits in the first 2 weeks of care. Palliative care involvement was associated with less decline in overall QOL and some improvements in depression and anxiety. Caregivers of patients who had been followed by palliative care reported better coping, improvement in administrative and financial QOL, and fewer depressive symptoms [61].

Currently palliative care services are elicited less frequently in HCT and patients with hematological malignancies as compared to SOT and other oncologies [66]. Howell demonstrated that patients with hematological malignancies were far less likely to receive care from palliative or hospice services compared to other cancers [62]. For the United States

specifically, the proportion of patients with all cancers receiving input from palliative care team is 59% versus 21% in specifically hematological cancers. Similarly, a US retrospective study by Cheng et al. showed that 11% of hematological patients accessed palliative care compared to 89% of patient with solid tumors [63].

The causes for the lower rates of palliative care involvement in hematological malignancies vary considerably and reflect the heterogeneity in the indications for HCT. Factors like the belief that symptom burden in hemato-oncological patient is less than other oncological patients have not stood up in studies with hematological patients who experienced similar levels of pain and more drowsiness and delirium than other oncological patients [64]. The chronic trajectory of the illness with intermittent acuity creates strong bonds over a long duration of care with the hematology team. This may lead the patient and family to look to the hematology care team for both active treatment and palliative care needs and may reduce the hematology teams' readiness to involve another specialty, particularly if referral to palliative care may signal too starkly the transition to terminal care. Alternatively, once advanced disease is identified, the rapid mortality of the condition compared to solid tumors may prevent enough time to involve the palliative care team. Fadul et al. determined time from palliative care referral to death in hematological patients was 13 days as compared to 46 days in patients with solid tumors [64]. Given this rapid mortality of hematological malignancies, earlier involvement of palliative care can ease the transition from active treatment to end-of-life care, provide education on clinical indicators of the dying process, and help patients and families better recognize imminent death risk. Hematological patients are also more likely to die in the hospital setting which can be an added strain for patients and their families. End-of-life care in the home environment can be comparatively more complex as terminal patients may require frequent transfusions. However, these challenges highlight the utility of palliative care involvement. Interventions such as transfusions can be performed in prearranged home visits rather than defaulting to day units. For those who have been mostly cared in the acute hospital but wish to pass at home, early involvement with palliative care can provide a much-needed familiarity and connection.

Given that the transition point between life-prolonging care and palliative phases of the disease can be difficult to predict or define, the focus on palliative care as distinct from end-of-life and hospice care in HCT patients is imperative.

Conclusions

Early palliative care involvement in the transplant evaluation and treatment process provides numerous advantages to patients, families, and care teams. In the transplant process, palliative care teams can reduce symptom burden, improve caregiver support, offer education, clarify goals of care, and provide clear healthcare directives for loved ones and the care team. Even more importantly, early palliative care involvement has demonstrated a survival advantage of 2.7 months for individuals with similar level of disease burden [65].

In contrast to common misperceptions among medical personnel, studies repeatedly have shown that patients welcome honest and early discussions around mortality and disease prognosis. Given the high morbidity and mortality for organ and bone marrow transplant, the discussion of end-of-life care is a realistic and needed part of the care plan and often comes too late in the disease process. When the goals of care change, palliative care can assist in the transition from active to comfort care while maximizing quality of life in the process. Studies have found no disadvantage or harm with involvement of palliative care [39], although limitations like cost remain a potential barrier, as the cost-effectiveness for palliative care involvement has not been adequately explored. However, palliative care services are available at most major institutions where transplants are offered, making the barriers for early involvement of palliative care low compared to the strong benefits this service provides. The support for early and continuous involvement of palliative care throughout the transplant process is strong from many providers and continues to grow.

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