

Review article

Early integration of palliative care in hematology: an urgency for patients, a challenge for physicians

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ABSTRACT

Introduction: Early integration between palliative care and other medical specialties in the care of patients with serious illnesses is consolidating itself as good medical practice, based on scientific and ethical evidence. Despite this, palliative care is still not part of the routine care of patients with hematological diseases, even in specialized centers.

Objective and method: In this article, we review the benefits and the main barriers described in the literature for early integration of hematology and palliative care. We also point out the challenges encountered in clinical practice, such as end-of-life prognosis assessment in patients with hematological diseases and management of the most common symptoms in hematology. Finally, we review models of integration between palliative care and oncology centers in outpatient and inpatient settings.

Results and conclusion: Patients with hematological diseases can greatly benefit from early integration with palliative care, with improvement in symptom control, quality of life, reduction of emotional distress and the development of advanced care directives. It is necessary to make hematologists aware of the benefits of palliative care, provide adequate training for multidisciplinary teams and encourage specific studies of palliative care in patients with hematological diseases.

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Introduction

Concepts of palliative care

Modern palliative care (PC) has been increasingly integrated into the early management of severe illnesses, with well-

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established benefits in clinical practice.¹ Beyond hospice management, which is more associated with end-of-life care, the practice of PC as a medical approach aims to improve the experience of patients and families living with severe illness.² As such, it is becoming consolidated in medical knowledge and has enabled the early integration of curative and palliative approaches.¹

The World Health Organization considers that “palliative care is a global ethical responsibility” and a crucial part of person-centered healthcare for relieving physical, psychological, social and spiritual suffering.³ It is indicated as a complementary approach in oncological diseases, cardiovascular diseases, AIDS, extreme prematurity, genetic malformations and frailty associated with old age. The COVID-19 pandemic particularly reinforced the need for relieving the suffering associated with the end of life and the urgency of qualifying all health professionals in the PC approach.⁴

Approximately 40 million people are estimated to require PC each year and this demand has a strong growth tendency. Almost 80% of this population is concentrated in developing countries. However, less than 14% of these people have access to treatment. The main barriers are the lack of specific public policies for vulnerable populations, absence of health professional training and difficult access to medications to control pain and other clinical symptoms.⁵

The PC is provided by a multidisciplinary team including physicians, nurses, psychologists, physical therapists, social workers and nutritionists. This care primarily aims at symptom control, the integration of psychological and spiritual aspects in patient care and the provision of support to families during illness and mourning periods.⁶ The focus is to improve the quality of life and positively influence the course of the illness, so that the patient lives as actively as possible until death, which is admitted as a natural part of the life process. Thus, the PC is related to life and the alleviation of suffering in the face of serious illness. A multidisciplinary team is indispensable in meeting the complex demands of human suffering in life-threatening diseases.⁵

Palliative care and hematology

Studies with cancer patients admitted early in PC programs have shown evidence that it significantly impacts quality of life, reduces the emotional distress of patients and caregivers, decreases the symptom burden and leads to a less aggressive end of life.⁷ In addition, several scales have been developed as tools to allow for the better prediction of the end-of-life stage of oncologic patients, based on clinical signs, symptoms and laboratory data. These have facilitated the integration of, and gradual transition between, curative and clinical supportive treatment approaches.⁸

Even so, the PC remains on the margin of care for patients with hematologic malignancies. These patients undergo more aggressive end-of-life treatments, are less often referred to hospices in Anglo-Saxon countries and are more likely to die in intensive care units (ICU). Extending the life span is often the focus of hematologic treatment, even in patients with refractory or frankly end-of-life illness.⁹

The hematologists' views on the PC and the main barriers to referral were analyzed by two American studies. Both studies showed that hematologists understand the PC as an end-of-life intervention, refer fewer patients for hospice care and feel less comfortable discussing end-of-life and dying condition preferences.^{10,11}

McCaughan *et al.* studied the barriers noticed by PC physicians in their interaction with hematology teams, including the strong relationship between patients and their hematologists, late discussions about end of life and lack of clear interaction between the two teams of specialists.¹¹ A total of 56% of American hematologists evaluated by Odejide *et al.* reported that, in their own experience, end-of-life discussions happen too late, with health practitioners waiting until death is clearly imminent before approaching the subject.²¹

While oncologists emphasize practical issues in their difficulties with patient referral to the PC, such as structural barriers or limited resources, they are also bound by moral or philosophical concerns.^{9,12,13} These include the view that the PC reduces the hope in, or desire to maintain, the curative treatment and conflicts with care objectives, such as the alleviation of suffering at the expense of curative measures or the adequacy of invasive interventions in critically ill patients.^{11,12} Furthermore, they also tend to prefer to maintain symptom control under their care.^{11,13}

A study performed by the M. D. Anderson Cancer Center showed that having a hematologic neoplasm was the greatest predictor for a poor end-of-life quality.¹³ Hui *et al.*⁹ also showed that being a hematologic malignancy patient is a significant prognostic factor for an aggressive end of life. The chance of dying in the hospital is twice as high for hematologic patients and the chance of receiving the specialized PC is only half as high, compared to oncology patients in general.⁹ Although hospices are the main PC service modality currently offered in the United States, only 2% of patients with hematologic malignancies are referred to them. Fadul *et al.* demonstrated that the mean time between the first PC consultation and death in this group was only 13 days, while in the oncologic disease group, it was 40 days.²²

Le Blanc *et al.*¹³ analyzed the main differences between oncological and hematologic malignancy patients admitted to American hospices between 2008 and 2012. Patients with hematologic malignancies were admitted at very advanced stages of disease, with high mortality rates, at one to seven days after admission, indicating that these patients are referred much later than oncological patients.¹⁰ Another very important difference was the lower propensity to be prescribed opioids in late life than the oncological patients.¹¹ This may be related to different end-of-life symptoms between the groups, with the hematologic population showing higher rates of fatigue and somnolence. It also indicates, however, that hematologists are less likely to prescribe optimized analgesia for them.^{11,14}

El-Jawahri *et al.* analyzed end-of-life data from older patients with acute myeloid leukemia, a subgroup of patients in whom curative approaches are especially limited. They found that 30% of life after diagnosis was spent in hospital stays, more than 80% of the patients were hospitalized in the last 30 days of life and only 20% of the patients had advanced care planning, with the identification of a family member for

the decision-making and the identification of end-of-life preferences.¹⁴ Recent data regarding inpatients with acute myeloid leukemias treatment preferences that are not eligible for intensive treatments suggest that the patients and clinicians have different priorities in the disease journey. While physicians prioritize treatments that aim to increase overall survival, with an increasing risk for hospitalizations and clinical complications, the patients prefer treatments that reduce hospitalization time.¹⁵

An analysis of end-of-life quality in patients with hematological diseases in Germany showed a high rate of chemotherapy, blood transfusion, broad-spectrum antibiotic treatment, ICU admissions and invasive procedures in their last 30 days of life.²⁴

In the context of benign diseases, there are specific studies on the PC for sickle cell disease.^{17,18,19,20} The management of these patients is usually complex and, despite important advances in disease-modifying therapies, there are important losses throughout the life of these patients.¹⁸ The early PC is indicated in this disease, it being a chronic pathology of high impact on functionality and quality of life and for its high load of symptoms.¹⁹ Such integration has potential for more effective symptom control, patient adequacy and rehabilitation in the face of functional losses, family support in the face of illness and bereavement and the elaboration of advanced care planning, in case of severe complications.¹⁹ The proven benefits of the PC in severe and progressive diseases are also likely to be extended to other severe hemoglobinopathies and potentially severe hematologic conditions, such as coagulation disorders.

Challenges of PC practice in hematology

Symptom burden in patients with hematologic neoplasms

Pain, nausea, anorexia and constipation have similar prevalence in oncologic and hematologic patients, but the latter present higher rates of often disabling somnolence and fatigue associated with bone marrow insufficiency symptoms, such as repeated infections and bleeding.¹¹

In 2008, Fadul et al.²³ published a study comparing symptom burden in patients with hematologic neoplasms and oncology patients referred to the Palliative Care Service of the M. D. Anderson Cancer Center in the 12-month period between October 2004 and September 2005. This study showed that both groups presented with a high rate of symptoms, such as pain, dyspnea and constipation, but patients with hematologic neoplasms presented with higher rates of somnolence and delirium, which may be related to being more likely to be close to death.²³

Fatigue and delirium are symptoms that are difficult to manage and require behavioral adjustments, since response to pharmacological treatment is poor.¹ They are also end-of-life symptoms, which shows that patients with hematologic malignancies are lately referred to a specific symptom management program.^{11,13}

Most studies have not evaluated the emotional, religious and spiritual conditions of this population, but evidence points to a worse quality of life during treatment, compared to oncologic patients.¹⁰

Difficult prognostication in hematologic neoplasms

One of the main difficulties identified in the early referral to the PC service is the difficult prognostication in hematologic neoplasms, since they are a heterogeneous group of diseases that vary from very aggressive neoplasms of rapid growth to those of indolent behavior, allowing for years of life.¹⁰ Characteristically, hematological patients experience fluctuations in the trajectory of their disease, importantly delaying the identification and communication of the end-of-life phase and the transition from curative care to exclusive PC.²²

The ability to predict estimated time of life is a powerful tool in ensuring end-of-life quality, since it allows for the reviewing of medical care objectives, adaptation of treatment to the preferences and values of patients and their families and the organization of financial resources for the full care of the complex demands of this scenario.^{5,16} It is important to note that the main studies on both the impact of early PC and predictive signs and symptoms of the end-of-life stage included no patients with hematological diseases, which raises the question whether the clinical behavior of these diseases and the benefit of integrating approaches are supported in this specific population.¹⁶

The first study to evaluate signs and symptoms as prognostic factors of end of life was developed in Italy and published in 2012. Sleepiness was shown as an independent prognostic factor in the survival of hematological malignancy patients.⁹ Button et al.²⁵ conducted a systematic review of the literature in 2017 to identify prognostic factors associated with the end of life in hematologic patients. Not enough evidence was found to associate factors characteristically important in solid tumors with a prognosis of shorter than three months of life in hematologic diseases, such as performance status, disease stage, anorexia-cachexia syndrome, worsening quality of life and symptom burden.²⁵ The main factors found as significant were the presence of sepsis, coagulopathy, renal and hepatic failure, hemodynamic instability and reduced level of consciousness.¹⁰ It is important to note that, of the 28 studies analyzed, 24 included only patients with hematologic malignancies admitted to the ICU, which constitutes an analysis bias, since data collected in this scenario did not include information from outpatients. None of the studies included an assessment of the quality of life, performance status, or clinical prediction (“surprise question”) in the analysis of prognostic factors.²³

Interestingly, Chou et al.²⁶ analyzed if prognostic scales widely validated in the PC practice are accurate in a setting of patients with hematologic malignancies followed up in a PC unit in Taiwan. The 217 patients followed up between the years 2006 and 2012 were categorized by assessment subgroups into the Palliative Prognostic Index (PPI), Charlson Comorbidity Index (CCI) and Glasgow Prognostic Score (GPS) scores and the accuracy of survival estimation was compared between them. The results showed that the PPI, much more than the ICC and GPS, had a significant predictive value for the life expectancy in terminally ill patients with hematologic diseases. The study also showed that the PPI was not able to accurately identify, among hematological patients with a good PPI, those at a higher risk for the end-of-life stage. The

concomitant use of CCI and GPS scores allowed a better discrimination of the survival in patients with the same PPI.²⁵

A German retrospective study conducted by the PC team of the Mannheim University Hospital²⁷ with the 290 patients with hematological neoplasms seen between the years 1998 and 2008 identified other clinical factors with a prognostic impact in this population. These included a performance status assessment by an Eastern Cooperative Oncology Group (ECOG) scale of greater than or equal to three, thrombocytopenia of less than 90 thousand, increased lactate dehydrogenase, use of opioids starting at level three, hypoalbuminemia and a need for red blood cell transfusion. This study classified the estimated survival into three very different groups: high risk (mean survival of ten days), intermediate risk (63 days) and low risk (440 days). Other survival scores used in the PC, such as the PPI, PPS and palliative prognostic (PaP), only proved accurate with regard to estimating 30-day survival. Thus, this was the only study to correlate clinical and laboratory data and transfusion demand with short- and medium-term prognosis, showing great clinical applicability in terms of assisting with the decision to refer patients with hematological diseases to the PC services.²⁷

Challenges of PC practice in Hematology

Early integration studies in bone marrow transplant (BMT) services in which high-risk patients were assessed by a team of pre-transplant PC specialists showed high acceptability, with improved mood and hope, without negative emotional effects.²⁸

A randomized and prospective study evaluated the quality of life, mood, and symptomatology of patients in a bone marrow transplant program after the intervention of regular consultations with specialists in PC twice a week and its results showed a lower decrease in quality of life, lower rates of depression and anxiety after two weeks and higher quality of life and lower rates of depressive symptoms after three months in the group that received the intervention. After a six-month follow-up, the group with PC showed lower rates of post-traumatic stress disorder.²⁷

In view of the increasingly robust evidence that the PC is beneficial when early integrated into the curative approach in hematologic malignancies, the American Society of Hematology (ASH) published recommendations on when to refer patients with hematologic malignancies to PC services in its 2015 Education Book.²⁹ The text considers that patients with hematologic malignancies should be indicated for joint follow-up with PC when they present with high symptom burden, refractory symptoms, prolonged hospitalization, or indications for allogeneic bone marrow transplantation. Other indications would be complex social or family needs, intense emotional suffering, difficulty with understanding the prognosis and, of course, patients with low life expectancy.²⁹

Some North American bone marrow transplant (BMT) services have good examples of early integration with PC, which, at first sight, might seem a paradox, since BMT presupposes intensive care aimed at promoting cure and increased

survival. Precisely in this scenario, with a high burden of symptoms and psychological suffering, early integration has shown to be very beneficial and feasible.^{30,31} The Western Pennsylvania Hospital in Pittsburgh, USA, has a PC team that daily visits the BMT unit. The proximity between teams propitiates the exchange of knowledge and the identification of patients who would benefit from more direct PC action, which from then on performs joint and daily monitoring (301). In the St. Jude Children's Research Hospital, in Memphis, USA, all patients who are scheduled to undergo allogeneic BMT are evaluated before admission by the PC team for a screening and establishment of bond, when the objectives, values, hopes and fears of the patients and their families are identified. From admission, these patients are followed up weekly until discharge and then for every two weeks until the hundredth day after transplantation.³⁰ This early integration system, instituted in 2008, was considered a successful model of care by the institution, as the number of referred patients tripled in the first five years.³⁰ The establishment of triggers, such as refractory symptoms, life-threatening complications and ICU admissions facilitated the identification of patients who would benefit from intensified PC follow-up with directed efforts and resources.²⁹

Practical models of integration between palliative care and hematology teams

The main examples of the integration of outpatient palliative care in patients with serious diseases come from the experience of solid tumors in oncology, a setting in which palliative care is more consolidated in clinical practice,³² and include independent (Figure 1A), co-located palliative care clinic (Figure 1B) and incorporated models (Figure 1C).^{33,34}

Published models of early palliative care in hematologic malignancies are mainly described in an inpatient setting and can be either "trigger-based" or consultative.¹

In the first example, hospitalized patients who present specific criteria, such as a poor prognosis, physical symptoms, or with complex psychosocial needs,^{28, 32} are referred to a multidisciplinary palliative care team and receive follow-up according to their needs during their hospitalization.

In the consultative model, described mainly in the BMT services,^{28, 30, 35} all patients are evaluated by a PC team at the beginning of hospitalization, with patients with greater demand for symptom control or worse prognosis being allocated to evaluation twice a week, until the demand is resolved.²⁹

It is important to emphasize that, in any models of integration between palliative care and hematology, a well-trained and specific multidisciplinary team and transdisciplinary relationships are essential for person-centered care.^{26,28}

The results of integration between palliative care and hematology services are significant, with reduced-length hospital time, increased patient and family satisfaction, reduced conflicts in complex settings and increased advanced planning of care.^{28, 29, 30, 35}

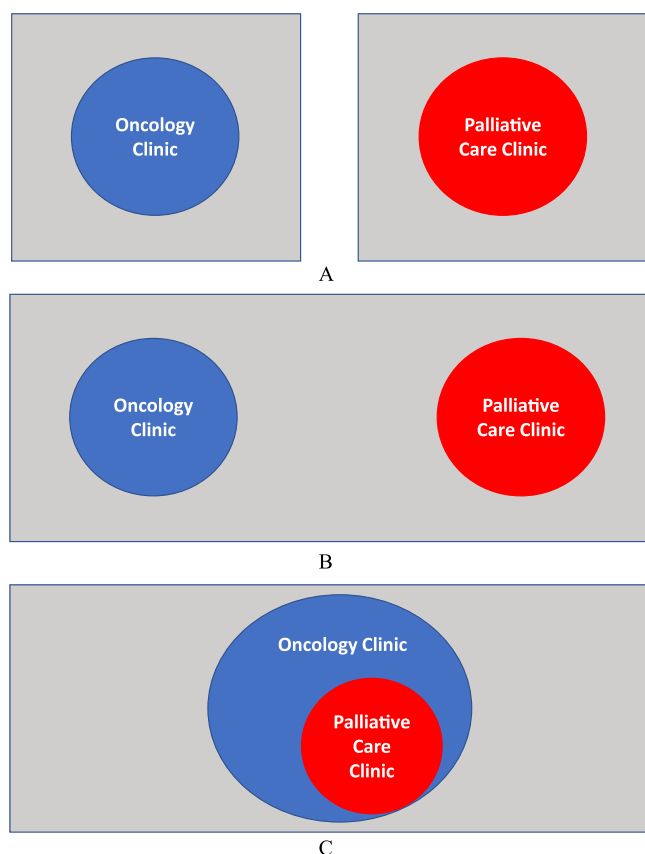


Figure 1 – A: Independent clinic model: the outpatient palliative care clinic has its own space and independently assesses patients, having full control over how and when patients are seen.³³

Figure 1B: A co-located palliative care clinic allows patients to receive palliative care in the same location as their oncologists and at a time coordinated with other appointments.³³

Figure 1C: In a Multidisciplinary Cancer Clinic (embedded model), the palliative care team is one of several specialty teams programmed to serve the patient while receiving cancer care.³³

Conclusions

Hematologic diseases are potentially severe and include a great burden of symptoms, with physical and emotional suffering for patients and their families. The management of these characteristics is especially challenging, even though great advances in curative therapies have been achieved in recent years.

The PC is a powerful tool for improving quality of life and reducing the suffering of experiencing severe hematologic disease, not only for patients and their families, but also for the hematologists. Figure 2 corresponds to the visual diagram containing the main indications, challenges and benefits of PC in hematology.

EARLY INTEGRATION OF PALLIATIVE CARE (PC) IN HEMATOLOGY

An urgency for patients, a challenge for physicians

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WHY INTEGRATE?

- Patients with hematologic malignancies undergo more aggressive end-of-life and have less access to pain control and other symptoms management.
- PC is a powerful tool to improving quality of life and reducing suffering of patients and their families

FOR WHOM TO OFFER PC ?

- Patients with high symptom burden, refractory symptoms, prolonged hospitalization, indication of BMT, intense emotional suffering or low life expectancy.

MAIN CHALLENGES

- Fatigue, somnolence and bone marrow insufficiency symptoms are highly prevalent in hematologic patients and their response to pharmacological treatment are poor.
- Prognosis in hematological diseases is a challenge because they fluctuate in their trajectory and patients can suffer rapid clinical deterioration.

PERSPECTIVES FOR THE FUTURE

The growing early integration between palliative and hematological care will facilitate the investigation of specific prognostic factors for hematological patients and will create their own models of outpatient and inpatient care.

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Figure 2 – Corresponds to the visual diagram containing the main indications, challenges and benefits of PC in hematology.

The main barriers to early PC integration in hematology are a lack of knowledge regarding its benefits on the part of hematologists and the scarcity of specialized PC teams. There is great potential for the development of studies on prognostication and the impact of the PC on time and quality of life in hematologic diseases, both in neoplasms and chronic benign diseases.

The dissemination of knowledge on the best PC practices and on the potential benefits of integrating these specialties among hematologists will impact the assistance given to hematology patients, improving ethical and person-centered care, especially in the uncertain scenario of serious illnesses.

Conflicts of interest

None.

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