

Mini Review

Early Palliative Care in Hematologic Malignancies a Review of Current Knowledge

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Abstract

Background: Hematology patients present a significant symptom burden and are more likely to receive aggressive care near the end of life. Palliative care in hematology is largely focused on end-of-life care, whereas it is increasingly recognized that the early integration of palliative care tends to improve quality of life in chronic disease.

Objectives: The goal of this review is to describe the barriers between early integration of palliative care and hematologic malignancies and discuss the potential contribution of early palliative care to hematology patients.

Methods: We conducted a narrative literature review by keywords in the Pubmed and Clinical Trials databases and with no time limitation. We also selected relevant articles in french papers and books on palliative care and hematology.

Results: Our review identified four main groups of symptoms of discomfort: physical, psychological, social, and medullary-related. We found a number of barriers hindering early integration of palliative care in hematology, chiefly the difficulty establishing prognosis, the clinical course features, and the clinicians themselves. A growing literature has shown that in other specialties such as oncology, cardiology or neurology, the early integration of palliative care has brought real benefit for quality of life and even overall survival. However, there is only a tiny handful of prospective studies currently ongoing to evaluate the benefit of palliative care integration in hematologic malignancies.

Conclusion: Early integration of palliative care tends to improve patient quality of life in other specialties, but the benefits have yet to be demonstrated in hematology.

Keywords: Quality of life, Hematological malignancies, Palliative and supportive care, Symptoms of discomfort

Abbreviations

EIPC: Early Integration of Palliative Care; QoL: Quality of Life; ASCO: American Society of Clinical Oncology; HM: Hematologic Malignancies; HP: Hematology Patients; PC: Palliative Care; EoLC: End-of-Life Care; HO: Hematologic Oncologists; PTSD: Post-Traumatic Stress Disorder

Introduction

A growing literature shows that Early Integration of Palliative Care (EIPC) in standard care brings real benefits to patients with life-limiting illnesses. EIPC leads to better Quality of Life (QoL) [1–4] and mood [1], a decrease in pain and, to a larger extent, better management of discomfort symptoms [2,3]. Tailored management of these symptoms even improves the overall survival of patients with advanced cancer [1]. This data has prompted authorities such as the American Society of Clinical Oncology (ASCO) to issue recommendations on solid tumors that underline the importance of early management of discomfort symptoms [5,6]. Hematologic Malignancies (HM) are rare diseases yet still account for 10% of new cancer cases in France [7]. Hematology Patients (HP) present

a high symptom burden early in the course of illness and are more likely to receive aggressive care near the end of life [8,9]. Palliative Care (PC) is increasingly being recommended early in solid tumor oncology and non-oncology diseases but remains largely focused on End-of-Life Care (EoLC) in HM. Even though solid tumors and HM are both cancers, their medical care patterns share a number of key differences, both in disease evolution and in patient and clinician profiles. Here we describe the barriers between EIPC and HM and discuss their potential contribution to HP.

The Barriers to Integration of Palliative Care in Hematologic Malignancies

HP are less likely to be referred for palliative care compared to solid cancers [8–16]. Several hypotheses have been put forward to explain this fact, most of which are drawn from observations of routine clinical practice. First, Hematologic Oncologists (HO) experience difficulty establishing a prognosis for HM and determining early when PC should begin [9,17], as clinical course is more uncertain with HM than solid tumors. Cancer patients present an initially slow pattern of decline that accelerates in the last months of life [18]. This “cancer trajectory” leaves the time needed

to refer to the palliative team [19]. However, HP can either follow an “aggressive HM trajectory” marked by significant functional impairment at diagnosis that can be improved by treatment leading to a durable remission or else sudden unexpected dramatically life-threatening complications like septic shock or uncontrolled bleeding causing death, or a “chronic HM trajectory” defined as a slow decline with intermittent life-threatening complications [12]. In both cases, patient prognosis is unpredictable [20] and triggers a sudden transition between curative care and PC. Furthermore, hematology is a medical specialty in which therapeutic innovations have been known to bring dramatic improvement [21]. These new target molecules bring a degree of optimism [22], but further complicate the task of establishing a prognosis and determining timely referral to PC when relapse occurs. Thus, in this context of advanced disease, patients, caregivers and doctors face an impossible dilemma between access to a new drug through a research protocol, and palliative care. In these situations, consideration as to the place of PC is very limited and comes too late. Patients and caregivers are caught up in a spiral of hard choices between inclusion in an early clinical trial and preparing for a peaceful end of life, between hope and distress, between ‘fighting’ disease or quiet rest. Second, there is both a lack of knowledge between the two specialties and acknowledgement between the two teams [23]. HO have misperceptions of PC. They see PC as EoLC or as “an alternative philosophy of care” [24] and take the stance that their cancer-related treatment goals are incompatible with PC. On the PC side, PC teams often underappreciate the uncertainty involved in hematological prognosis, as HP may respond to treatment even in advanced stages [13], and they tend to underestimate HP needs, such as the transfusions required until late in illness course, taking the stance that these therapies are futile and inappropriate. The difficulty organizing transfusions in hospice services may also be a barrier to referral for PC. Furthermore, there is no evidence in the literature on the benefit of EIPC in HM, which is not the case with solid tumors [8], and in this context a majority of HO wants to maintain care for all aspects of the disease, and thus prefer to provide PC themselves [25], whereas HP experience similar symptoms and physical decline patterns to solid-tumor patients in the last 3 months of life, which suggests they have similar EoLC needs [26,27]. The past few decades have seen HM become chronic diseases with long follow-up promoting tight relationship between HO and their HP. Third, the severity of the disease can require aggressive curative treatments like induction chemotherapy or hematopoietic stem cell transplantation that lead to a hugely uncomfortable life, with side effects that carry severe morbidity and risks of death. After such huge emotional investment to fight the disease together, the transition from curative intervention to PC may be especially difficult [28]. This maximal effort already invested by HP, caregivers and clinicians leads to an “escalation of commitment” where HO are tempted to suggest treatment with curative intent while the chances of response are known to be low [29]. This strong link may also explain why HO are reluctant to integrate other clinicians into patient care, which they feel would be disruptive [13,25] and a sign of failure in the relationship right at the toughest time. Furthermore, HO prefer to keep patients’ hopes up rather than talk about the poor prognosis or end-of-life issues [13], even though patients want to know clearly their prognosis is. Unfortunately, in particular cases such as stem cell transplantation, the patient’s understanding of prognosis is sometimes associated with

poor QoL, increased depression and symptoms of discomfort [30], which may strengthen HO belief that it is better for HP to keep hold of a mistaken vision of their prognosis. Note too that some HO report being uncomfortable starting the conversation about end-of-life issues, possibly due to this strong link with HP or to a lack of training on the requisite communication skills [31]. For all these reasons, the discussion about end-of-life issues occurs too late [14,32]. The pattern to date is that without early anticipation, a late sudden transition from curative to PC leaves little time for appropriate PC [10].

The Contribution of EIPC in Other Specialties

To date, several prospective trials of EIPC have been published in both oncology and non-oncology diseases such as heart failure. Despite different interventions and different methods, all confirm the absence of negative impact of EIPC. Several studies, particularly in oncology [1,3,4,33], have even shown a real benefit of EIPC, prompting authorities like ASCO to recommend bringing EIPC into standard oncology care [5,6]. The main benefits of EIPC are improved QoL, decreased discomfort symptoms and increased patient satisfaction [34]. Experience in solid tumor settings shows that EIPC does not alter the relationship between the solid tumor oncologists and patients. In fact PC is complementary to routine clinical care and both are valuable allies to assist solid tumor oncologists in managing symptoms or psychosocial distress [35]. Pain management seems to be different between solid tumors oncologists and PC staff. PC team appears to employ different pain management practices, with a noticeably higher use of opioids. EIPC reduces the risk of suffering from severe pain [36]. Successful management of discomfort symptoms and the external position of PC creates a climate of trust between palliative caregiver and patient, thus facilitating difficult discussions concerning non-physical issues. Unlike oncologists, the PC team is not engaged in the curative effort to fight the disease, and so HP find it easier to discuss to PC staff than with their HO or their family. PC team may allow to engage the patient in “emotional work to facilitate coping, accepting and planning” [35] and to increase prognosis awareness [35]. Patients receiving EIPC who clearly understand their poor prognosis are less likely to receive intravenous chemotherapy near the end of life, whereas understanding of prognosis does not correlate with chemotherapy administration near the end of life for patients receiving standard care [37]. PC could provide keys to enable informed decision-making. Conversion about end-of-life issues is also associated with a decrease in aggressive EoLC, such as a lower rates of ventilation, resuscitation and intensive care unit admissions [38]. Although the prime vocation of PC is not to prolong patient survival, several studies have assessed the impact of EIPC on overall survival, and it has been found that contrary to common belief, patients receiving EIPC do not have higher mortality [34] indeed, several studies have even demonstrated significantly better survival with EIPC [1,33,39,40]. The reason for this survival benefit is probably multifactorial: QoL improvement, decrease in depressive mood, better social support leading to optimal personal care, better understanding of illness prognosis leading to less aggressive care at end of life [41]. Other factors may play a more subjective role, such as patients in PC regaining control of their existence [12]. In addition to the benefit for patients with life-limiting illness, EIPC contributes

Table 1: Ongoing Trials.

STUDY TYPE	PRIMARY ENDPOINT	TIME FRAME	INTERVENTION	TESTS	PATIENTS	DISEASE	STATUS
Interventional	Successful enrollment of 30 patient care giver pairs	Baseline to 3 months	Care management by oncology nurses before or after regularly-scheduled oncology clinic visits		80	Refractory or recurrent hematologic malignancy	Recruiting
Interventional Randomized	Measure of quality of life	12 weeks	Supportive /palliative care intervention at least once a month until the 12 th week, more if needed.	FACTLeu	80	Acute leukemia in relapse	Recruiting
Interventional Randomized	Comparison of the change in patients' FACT Anemia score	Baseline to 6 months	Standard hematology care vs. collaborative palliative and hematology care	Fact-An	140	At the time of diagnosis for myeloid acute leukemia, myelodysplastic syndrome and DLBCL in relapse	Recruiting
Interventional Randomized	Comparison of the change in patients' FACT Leukemia score	2 weeks	Standard leukemia care vs. collaborative palliative and oncology care	FACTLeu	160	High-risk acute myeloid leukemia	Recruiting

to caregiver satisfaction. However, the benefit of EIPC on QoL, mood and emotional burden of caregivers varies between studies [34]. The impact of EIPC on resource use and expenditures is also unclear, and requires more investigation [12].

Symptom Burden by Patients with Hematologic Malignancies

Despite the therapeutic improvement, many HP present a high symptom burden, with a mean of 8.8 symptoms [42] since diagnosis [43]. The most frequent symptoms are fatigue, sleep disorders, drowsiness and dry mouth [42]. Fatigue seems to be a multidimensional symptom, and is not exclusively correlated with hemoglobin level [44]. Pain management remains an important issue, with a high prevalence from diagnosis until end of life, especially in certain pathologies like multiple myeloma. For example, 49% of patients with acute leukemia present pain early in the disease course, of which 41% report moderate to severe pain intensity [45]. During the last 3 months of life, more than 83% of patients with lymphoma, leukemia or myeloma present pain, of which 63% describe the pain as distressing [46]. Over the illness course, prevalence of psychological symptoms over the full illness course is high [42,43,45] and may lead to Post-Traumatic Stress Disorder (PTSD) [47,48]. For patients with acute leukemia, depressive symptoms seem to be associated with the symptom burden whereas hopelessness is associated with older age and lower self-esteem [49]. A third of newly-diagnosed acute leukemia patients present a full syndrome or subsyndromal acute stress disorder [50]. Six months after stem cell transplantation, 28% of patients meet criteria for PTSD and 43% suffer from depression. For stem cell transplanted patients, decline of QoL and increase in depressive symptoms are correlated with occurrence of PTSD [47]. In addition, pre-transplantation depression is associated with lower overall survival and higher risk of complications [51]. Another study found that 17% of HM survivors met criteria for PTSD and that fear of recurrence was significantly associated with PTSD occurrence [48]. Patients need honest and comprehensive discussion about their prognosis, and a majority expect the doctor to start the conversation about advance care planning and end-of-life preferences [52]. Very often, it is difficult to explain the reality of prognosis. Indeed, some

patients may arrive near death and yet the first round of treatment transforms them and even improves their QoL [53,54]. Despite relapses, they think that treatment will succeed like it did the first time, and so they hold on to an optimistic picture of their prognosis [55]. In this context, patients with HM are more likely to receive invasive or clinical research care near the end of life even if the prognosis is known to be limited [8,56]. HP are referred to hospice services late in the illness course, and are already in poor general condition [57].

The New Clinical Trials in Hematologic Malignancies

A robust literature has highlighted the significant symptom burden in HP. PC teams have strong experience in managing these symptoms (pain, psychological distress) and in improving QoL and prognosis awareness. Early collaboration between PC team and HO, as recently experimented in solid tumors, is entirely viable in HM, especially as the specificities of HM require the experience of a HO and may require the expertise of a PC team. In fact, a few clinical trials have set out to evaluate this strategy. Roeland et al, reported their experience of EIPC for SCT patients. The most common reasons for consultation with PC remained symptom management and psychological distress. Interestingly, SCT patients tended to under-report their symptoms for fear of being undertreated or for fear of disappointing their SCT team and family caregivers. The separation between symptoms management team and SCT team could help overcome patients' reluctance to express their symptoms of discomfort [58]. Loggers et al, studied the impact of pre-transplantation supportive and PC consultation for patients with high-risk SCT and found no negative impact on hope or mood. Furthermore, a significant number of patients declined to participate, citing "feeling overwhelmed with the pre-transplantation process or the topic of the study or feeling that extra support was not necessary". In addition, agreement to participate was improved by using the word "supportive" instead of "palliative", which further confirms the misperceptions by patients and families about PC [59]. There are a tiny handful of prospective trials currently recruiting patients in order to determine the impact of EIPC in HP [60,61] (Table 1).

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