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REVIEW

Early integration of palliative care for patients with haematological malignancies

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Summary

Early palliative care (EPC) significantly improves quality of life, symptoms, and satisfaction with care for patients with advanced cancer. International organizations have recognized and promoted the role of palliative care as a distinct specialty, advocating its involvement throughout the cancer trajectory. Although patients with haematologic malignancies (HMs) have a comparable symptom burden to patients with solid tumours, they face multiple barriers to EPC integration. In this review, we discuss these barriers, present updated evidence from clinical trials of EPC in HMs and propose models to support EPC integration into care for patients with HMs.

KEYWORDS
cancer, delivery of health care, haematologic oncology, haematology, oncology, palliative care

INTRODUCTION

Palliative care (PC) originated from the modern hospice movement in the 1960s, which aimed to provide end-of-life (EOL) care for patients with terminal illnesses. In the following decades, PC evolved from providing exclusively EOL care to proactively supporting patients and caregivers facing a life-threatening disease from the time of diagnosis.[1] Extensive evidence has shown that early palliative intervention significantly improves quality of life, symptoms and satisfaction for patients with advanced cancer and may even prolong survival.[2,3] As a result, international cancer organizations have recognized and promoted the role of PC as a distinct specialty, advocating its involvement throughout the cancer trajectory.[4–7] The World Health Organization now defines PC as "*an approach that improves the quality of life of patients and their families facing the problem 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.*"[8] This definition emphasizes a holistic approach to prevent and manage clinical complications from the disease and its treatments, and is equally applicable to patients with solid tumours as well as haematological malignancies (HMs).

Unlike patients with solid tumours, for whom PC is increasingly integrated early in the disease course, referrals to specialized PC for patients with HMs typically occur late in the disease course.[9–11] However, the symptom burden experienced in these diseases is similar to that of solid tumours, and patients and their caregivers experience substantial psychosocial distress, as well as needs related to navigating the complexities of the health care system and advance care planning.[12–14] Thus, patients with HM could benefit greatly from the interdisciplinary approach offered by PC, which is focused on improving symptoms, communication, shared decision making, psychosocial support, community care resources, advance care planning, and caregiver support.[15,16] Moreover, there is emerging evidence that supports early specialized PC in HM.[17–19]

In this narrative review, we discuss the PC needs of patients with HMs as well as barriers that prevent access to specialized PC for this population. We also present recent evidence from clinical trials demonstrating benefits from the early integration of PC for patients with HM and discuss potential models for early integration.

PC IN HM

Domains of PC and levels of care

PC is provided by interdisciplinary teams, which allows for the delivery of multidimensional care.[20,21] PC addresses multiple domains, including not only physical symptoms but psychosocial, spiritual and EOL care as well as ethical, structural and cultural issues.[22] A popular conceptual model classifies PC into primary, secondary and tertiary PC, according to who delivers the care (Figure 1).[23] Primary PC is delivered in the community by primary care clinicians with general knowledge about PC. Accordingly, all clinicians should have basic training in the principles and practice of PC (i.e., basic pain relief, nausea, mood disorders). Secondary PC is provided in hospitals by specialists who have general knowledge about PC for their specialty. Thus, all oncologists, including haemato-oncologists, should have basic PC training, resulting in a good understanding of symptom management, psychosocial care and advance care planning for patients with HMs.[6] Lastly, tertiary (specialized) PC is provided by PC consultants, who may be consulted to provide specialized PC for more complex situations such as refractory symptoms, severe psychosocial distress or family conflict.

PC syndromes in HMs

In contrast with HMs, the trajectory of disease in solid tumours is relatively predictable, with metastasis generally heralding incurability and a steady downward trajectory (Figure 2). Previous publications have described the characteristics of various types of HM with respect to PC needs.[24,25] We find it helpful to divide HMs into three main groups based on the trajectory of disease, setting of care and challenges to PC delivery. These are described briefly below and are depicted in Figure 2B–D.

Aggressive HMs – "The rollercoaster"

The first group of HM diseases includes aggressive life-threatening diseases with a high risk of harm alongside a realistic possibility for long-term cure (Figure 2B). This group includes acute leukaemias, aggressive lymphomas, stem cell transplantation and acute graft-vs.-host disease. The razor-edge character of these diseases make prognostication difficult until late in the course of disease. Often cure may still

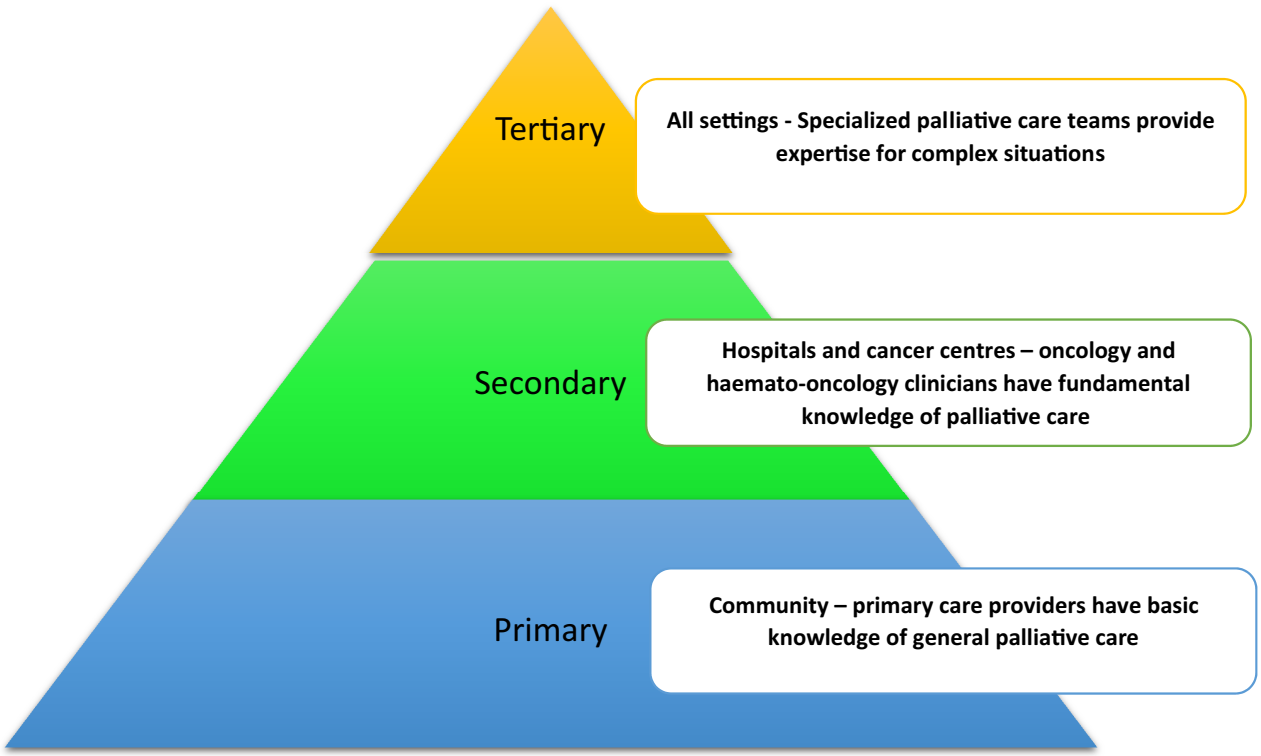


FIGURE 1 A conceptual model of PC delivery based on setting and provider.[Adapted with permission from Kaasa S, Loge JH, Aapro M, Albreht T, Anderson R, Bruera E, et al. Integration of oncology and palliative care: a Lancet Oncology Commission. *Lancet Oncol*. 2018 Nov;19 (11):e588–653]

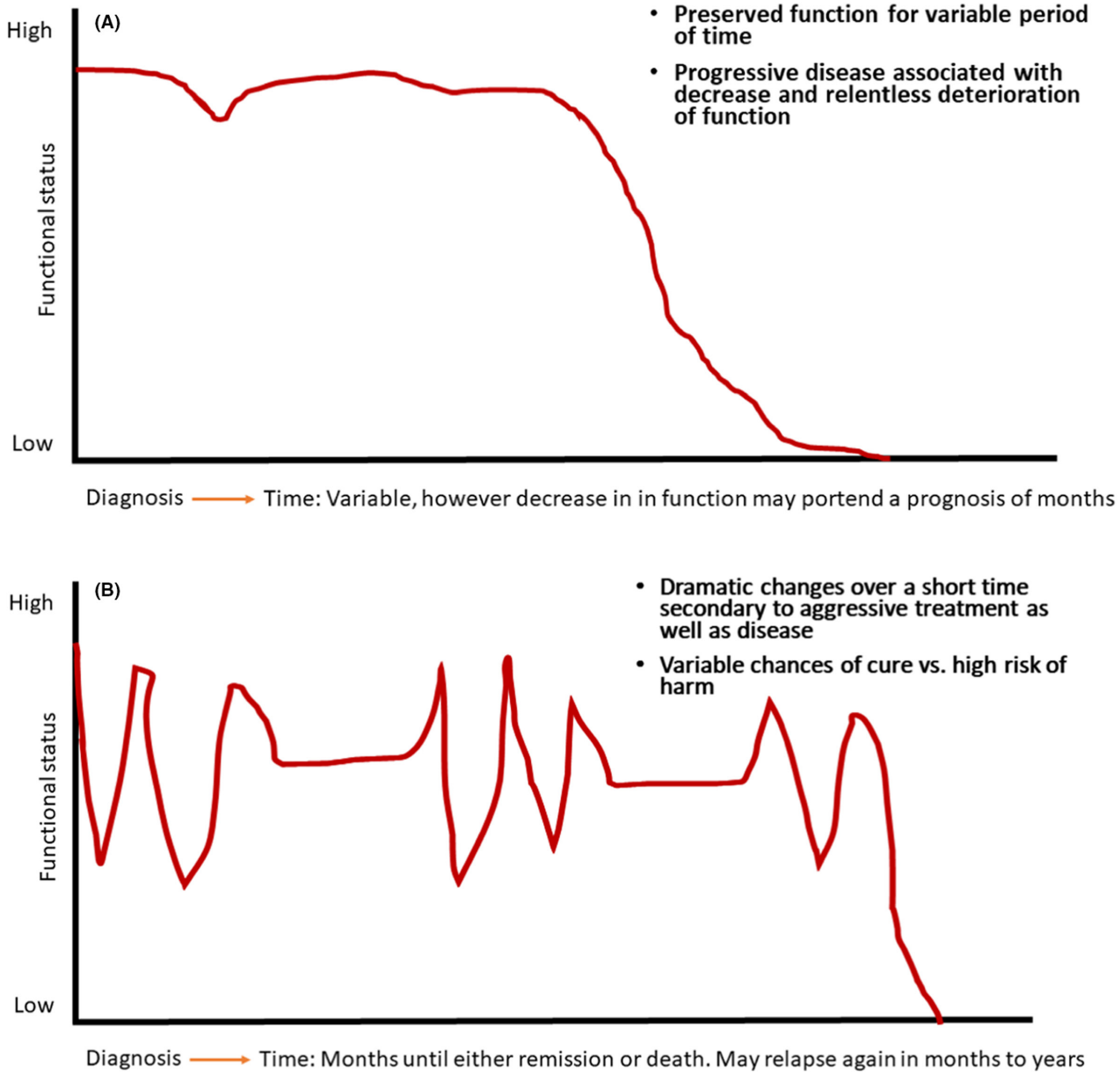


FIGURE 2 (A) Solid malignancy trajectory.[Adapted with permission from Murray SA, Kendall M, Boyd K, Sheikh A. Illness trajectories and Palliative Care. *BMJ*. 2005 Apr 28;330(7498):1007–11. (B) Aggressive HM trajectory – "The rollercoaster": acute leukaemia, aggressive lymphoma, stem cell transplantation, acute graft-vs.-host disease [developed by the authors]. (C) Indolent HM trajectory – "The war of attrition": indolent lymphoma, multiple myeloma, chronic lymphocytic lymphoma [developed by the authors]. (D) Bone marrow failure "the transfusion tether": myelodysplasia, myelofibrosis [developed by the authors]

be a reasonable and achievable goal until days before death. For example, life threatening sepsis during nadir of salvage chemotherapy for refractory double-hit diffuse large B-cell lymphoma may be seen as a terminal event; however, within days, the reversal of neutropenia may find a patient not only recovering from sepsis but indeed in complete remission. Conversely, the decline before death in such scenarios may be very rapid which may be a barrier to transition to hospice care in a timely manner.

The rollercoaster nature of life in the context of these diseases also presents unique challenges, both physical and psychological. While leukaemias do not commonly present as a compressive mass or nerve infiltration, pain is a prominent symptom due to multiple causes related to neutropenia and infection (e.g., perianal pain) as well as the result of treatment (e.g., mucositis, lumbar puncture).[26] Patients with acute leukaemia report multiple burdensome physical and psychological symptoms, including lack of energy, drowsiness, dry mouth, pain, weight loss, difficulty sleeping, worrying, difficulty concentrating and feeling sad. Uncertainty and psychological distress are also prominent in patients with these diseases. For example, the acute onset of leukaemia coupled with uncertainty regarding prognosis as well as high rates of morbidity and mortality may have a

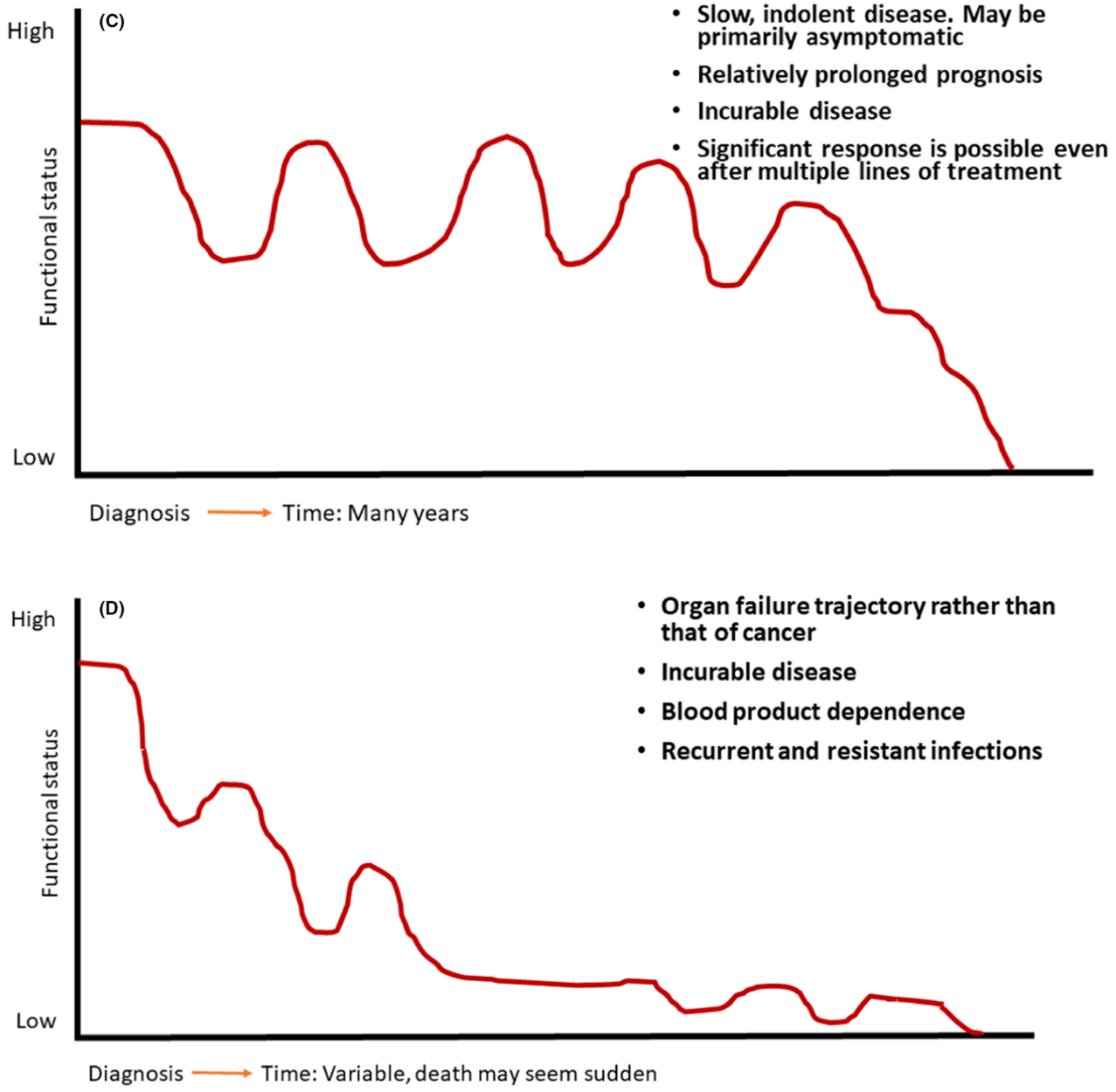


FIGURE 2 (Continued)

devastating psychological effect.[13] Patients referred to specialist care for acute leukaemia may undergo multiple blood tests, bone marrow biopsy, PICC line insertion, whole body imaging, cardiac imaging and fertility preservation followed by intensive inpatient continuous chemotherapy all within days. Illness understanding in patients with acute leukaemia is severely affected by the sheer volume of information they are asked to process over a short period of time, further compromising their ability to effectively participate in decision making.[27]

Weeks of neutropenia are often complicated by infection and mucositis, leading to mortality risk and increasing uncertainty. Mood and hope vary with fluctuations of daily blood counts, while increasing white blood cell counts may either bring the consolation of resolving neutropenia or the harbinger of relapse and increased blast count. It is therefore unsurprising that 32% of acute leukaemia patients suffer from syndromal or subsyndromal acute stress disorder over the course of their disease[14,28,29] and 17% suffer from depressive symptoms.[30,31]

Indolent HMs – "The war of attrition"

The second group includes more indolent diseases such as chronic lymphocytic leukaemia (CLL), indolent lymphomas and many cases of multiple myeloma (Figure 2C). Although these diseases are incurable, prognosis may be prolonged, with episodes of decreased function due to multiple relapses entailing multiple and ever-expanding lines of treatment,

alongside prolonged remissions with excellent function. As increasingly more novel drugs have been found to be effective in the treatment of these diseases, clinically significant remissions can be achieved even in advanced disease. Prognostication may therefore be difficult. More importantly, it is difficult to decide whether further treatment may be efficacious or detrimental to quality of life. Even advanced stage disease after multiple lines of therapy may have a significant response to seemingly over-aggressive treatments. For example, over the past eight years, the FDA has approved five new drugs for the treatment of CLL. Each new approval opens the door for single drug treatment as well as combinations with other novel agents and with chemotherapy, creating an exponential amount of treatment possibilities. Stem cell transplantation, a severely debilitating and dangerous intervention, can attain long term remission and even cure in a significant minority of patients and thus persists as a wild card treatment option in the eyes of both patients and clinicians. CAR-T cell therapy is an additional treatment modality with activity in indolent as well as aggressive HMs and data as to quality of life at the EOL with these treatments is only beginning to emerge.[32]

Physical and psychological challenges are prominent in this group as well. Multiple myeloma is notorious for causing bone pain and spontaneous fractures[33] while lymphomas may behave as solid tumours compressing adjacent organs or nerves causing a variety of symptoms.[34] Moreover, various HMs, as well as the drugs used to treat them, may cause debilitating peripheral neuropathy.[35]

Indolent diseases, such as multiple myeloma, are also associated with psychological distress for patients and families, including anxiety and depression associated with fear of inevitable relapse.[36,37] Of particular interest are indolent, asymptomatic and premalignant conditions, which need no treatment but may portend future symptomatic disease, such as monoclonal gammopathy of unknown significance. The 'watch and wait' approach taken with these patients is in itself a source of psychological distress and decreased quality of life similar to that of multiple myeloma.[38,39]

Bone marrow failure – the 'transfusion tether'

The third group is characterized by bone marrow failure resulting in cytopenias (Figure 2D). This group includes the myelodysplastic syndromes, myelofibrosis, aplastic anaemia and end-stage HM with spent marrow due to infiltration by disease or aplasia from treatment. Profound anaemia causes dependence on blood transfusions for improvement of symptoms such as fatigue, dyspnea, chest pain and more. Severe thrombocytopenia may result in haemorrhage ranging from mild but unsettling mucocutaneous bleeding, which may also exacerbate anaemia, to life-threatening gastrointestinal or intracranial bleeding. These may be partially avoided by regular platelet transfusions. Most importantly, severe neutropenia in the setting of chronic progressive bone marrow failure results in recurrent bacterial and invasive fungal infections. These infections are both life threatening and debilitating, with no ready solution in the form of transfusion. Treating these infections effectively may entail both identification of the cause of infection using cultures, imaging and invasive procedures, as well as the use of broad-spectrum antibiotics. Thus, the commonly used term, the 'transfusion tether', is but one of many tethers tying these patients to the hospital bed.[40] Despite the low risk of transfusion in a home setting[41,42] and many patients' wish to receive transfusions at home,[43,44] transfusions are not readily available in home or hospice settings, mostly due to cost and regulation. In this group, prognostication is again a challenge, as death is the result of acute complications of cytopenias rather than disease progression.

Although the three groups mentioned provide a useful framework to understand the complexities of these diseases, the behaviour of various HMs is heterogeneous and does not adhere rigidly to this categorization. HMs can also transform from one group to another; for example, low grade lymphoma or CLL can transform to aggressive lymphoma and MDS can transform to acute leukaemia. Even without overt morphological transformation, HMs can shift their behaviour in surprising ways whether due to treatment or intrinsic biology, thus aggressive diseases may behave as indolent ones and vice versa, further complicating prognostication.

CURRENT STATE OF PC NEEDS IN HMS

Patients suffering from HMs have an overwhelming symptom burden, with a burden of pain, dyspnea, nausea and anorexia similar to that of solid tumour malignancies.[12,45] However, the overall spectrum of symptoms and their causes may differ from solid tumours, and a deeper understanding of these nuances (which may also be disease-related) may be beneficial for the care of these patients. For example, some symptoms, such as drowsiness, delirium, fatigue and loss of appetite, may be more prevalent in HM patients.[12,45,46]

Despite extensive physical and psychological symptoms, referral to PC remains inadequate in HM patients,[9–11,47] and despite the high incidence of traumatic stress, only a small proportion of these patients are referred to psychology or psychiatry.[48] In one study, 30% of haemato-oncologists reported never referring to PC while all solid tumour oncologists had previously referred to PC.[49] Patients with HM have consistently been shown to have decreased referral rates to PC services as well as hospice care compared to patients with solid tumours.[9,50,51] Patients with HM are less likely to complete advance directives or DNR orders.[11] In comparison with solid tumour malignancies, patients with HM have an increased incidence of emergency room visits, hospital admissions and ICU admissions as well as use of chemotherapy and targeted therapy at the EOL.[10,52–55] In the opinion of most haemato-oncologists, EOL discussions occur too late,[56]

and PC is often discussed only when death is imminent. Further, patients with HM are less likely to have a preexisting opioid prescription upon admission to hospice indicating that symptom management may not be adequate.[11]

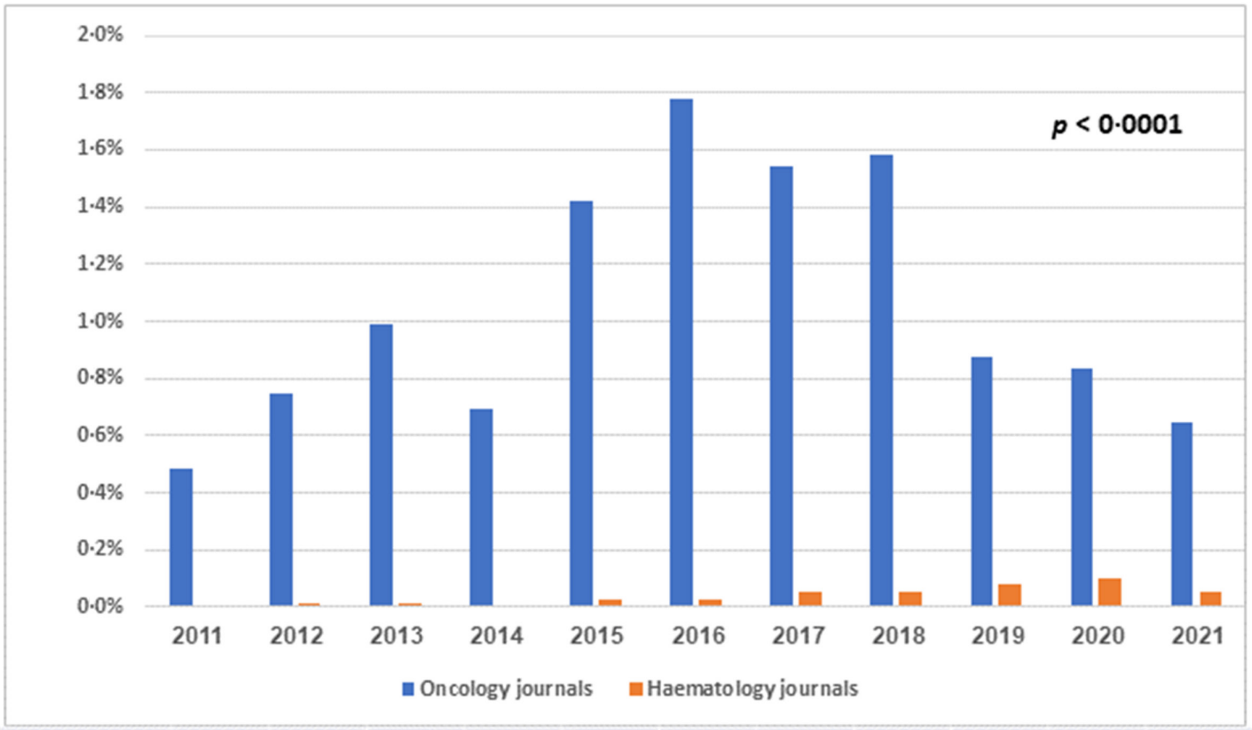
Haemato-oncologists are more likely than solid tumour oncologists to equate PC with EOL care.[31] Not only is the EOL more complex to predict in haemato-oncology; even when death becomes a reasonable scenario, haematologists often feel less comfortable discussing death and dying or referring to hospice and are more likely to feel a sense of failure when disease progresses.[57] A previous review reported a large difference in the number of published studies regarding palliative care in solid tumours compared with haematological malignancies.[24] We performed a focused search for the terms 'palliate', 'palliation' or 'palliative' in article titles of the five leading journals in haemato-oncology and medical oncology, as ranked by journal citation reports, is illustrative of this point (Figure 3). Although the number of publications on PC in leading oncology journals has fluctuated, the percentage of PC publications in these journals has consistently been more than ten-fold higher than in leading haematology journals.

BARRIERS TO THE INTEGRATION OF PC IN HM

Difficulties with prognostication

The relative predictability of prognosis in advanced solid tumour malignancies, particularly when combined with prognostic markers such as performance status,[58] has made it possible to routinely implement models of early PC, including involving PC teams in the outpatient setting at the diagnosis of advanced cancer. This steady decline is in contrast to the highly unpredictable course of most HMs, as described above.

A systematic review of the literature failed to find effective prognostic factors in HM beyond imminently life-threatening events such as multiorgan failure.[59] Factors associated with prognosis in solid tumour malignancies such as level of performance status, symptom burden, cachexia and comorbidities are not as strongly correlated with prognosis in HM patients.[60] Nonetheless, consensus may be found among haemato-oncologists as to potential signals for transition to the EOL phase of disease which



JOURNAL	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021
Oncology	0·48%	0·75%	0·99%	0·69%	1·42%	1·78%	1·54%	1·58%	0·88%	0·83%	0·65%
Haematology	0%	0·01%	0·02%	0·00%	0·03%	0·03%	0·05%	0·06%	0·08%	0·10%	0·05%

FIGURE 3 Comparison of the percentage of publications including the keywords 'palliative', 'palliate' or 'palliation' in the article title, in five leading haematology journals versus oncology journals over the years 2011–2021.The leading journals in heamatology and medical oncology were selected by the yearly impact factor designated by Journal Citation Reports. Haematology journals without an oncology focus were not included (i.e., Circulation, Circulation Research). Within each journal, a search for the terms 'palliate' 'palliation' or 'palliative' within the article title, including meeting abstracts, was conducted using the Web of Science database. Oncology journals included were: *CA: A Cancer Journal for Clinicians, Nature Reviews Clinical Oncology, Nature Reviews Cancer, Journal of Clinical Oncology* and *Lancet Oncology*. Haematology journals included were: *Blood, Lancet Haematology* (from 2014), *Journal of Haematology and Oncology, Blood Cancer Journal* and *Leukaemia*. Mann–Whitney–Wilcoxon test was used to compare the two groups ($p < 0.0001$)

may indicate the need for integration of PC. These include refractory disease, CNS involvement, and worsening performance status.[61] It is clear, however, that prognostication is not the sole barrier to quality EOL care in HM patients. Further barriers will be described in the following sections.

Attitudinal barriers

Haemato-oncologists are more likely than oncologists to prescribe systemic therapy with moderate toxicity and no survival benefit for patients with a severely impaired performance status and an expected survival of 1 month.[57] PC providers may see this as resistance of haemato-oncologists to the core tenets of PC while haemato-oncologists may see the benefit in these therapies in the palliation of symptoms and complications. This attitude is best expressed in the saying by haemato-oncologists that 'the best palliation for HM is chemotherapy'. For example, the presence of severe neutropenia would pose a contraindication for chemotherapy in solid tumour patients, however in the setting of bone marrow infiltrated by HM, chemotherapy may be fully indicated. While some have described the approach of haemato-oncologists as technical rather than holistic,[62] haemato-oncologists may see this as evidence of the inability of other specialties to comprehend the intricacies of HM. Similarly, accepted EOL quality measures such as admission to hospice or time from last chemotherapy to death are often incompatible with the needs of HM patients and may not be appropriate in the haematology setting.[63,64]

The differing characteristics of disease may also have a varying effect on the doctor-patient relationship. While oncologists may see their patients every 3 months, the dynamic character of many HM necessitate visits at shorter time intervals as well as treatment of multiple acute life-threatening events, commonly with prolonged periods of inpatient treatment. It may be argued that this intense and intimate relationship may result in difficulty for both patient and haemato-oncologist in referral to PC.[24,49] Therefore, haemato-oncologists may be more inclined to refer to PC if they can maintain clinic visits with their patients.[65]

Policy barriers and efforts to overcome them

Hospice criteria may exclude patients with HM by limiting access to therapies that may improve their quality of life.[66] PC services have not been traditionally formed to accommodate the more intensive needs of haematology patients at EOL. Real world experience shows that even within a PC unit the needs of HM patients far exceed that expected including the use of broad spectrum antibiotics and blood products in most patients as well as parenteral nutrition and intravascular devices in many.[67] Home PC services are not generally able to administer wide spectrum antibiotics and blood products, and inpatient hospice rarely have the financial ability or philosophy of care to allow for such treatment.[61,68] Many have advocated for policy change including the American Society of Haematology[69] and legislation has recently been introduced to enable administration of blood products in the hospice setting in the US.[70]

EVIDENCE FOR BENEFITS OF PC

Evidence in patients with solid tumours

The benefits of early specialized PC were originally demonstrated in randomized controlled trials conducted in patients with advanced solid tumours (Table 1).[71–79] Most of these trials were conducted in the outpatient setting, with interventions of either free-standing[71] or embedded[72,73] PC clinics. A study in Canada demonstrated that compared to patients who received standard oncologic care alone, those referred early to a free-standing specialized PC clinic experienced better quality of life, symptom control and satisfaction with care.[71] Other trials in the USA and Italy showed that early specialized PC provided by a PC physician or advanced practice nurse embedded in an outpatient cancer clinic improved quality of life, mood, aggressiveness of EOL care, and survival.[72–74]

Evidence in patients with HMs

Although the symptom burden of patients with HMs is equivalent or higher than that for patients with solid tumours, the evidence from randomized trials studying the effect of early PC interventions for HM patients is only currently emerging.[17–19,75,80,81] Unlike the trials in patients with solid tumours, most trials in patients with HM have been conducted entirely or almost entirely in the inpatient setting. Some early trials in the emergency and outpatient setting that included mainly patients with solid tumours also included patients with HMs,[75,82] but results are difficult to interpret given the heterogeneity of the patient population and the very small percentage of patients with HMs (less than 5%) in these trials.

More recently, PC interventions including exclusively patients with HM have provided conclusive evidence for this population in the inpatient setting (Table 2).[17–19,32,80,81] In a randomized controlled trial in patients with HM who underwent allogeneic or autologous stem cell transplantation, patients assigned to the intervention arm received specialized PC within 72 hours of hospital admission and twice weekly as inpatients.[17] Anxiety was reduced and quality of life improved for patients in the intervention arm after 2 weeks of enrolment. Moreover, both patients and caregivers had reduced levels of depression. The benefit in patient quality of life was sustained after 3 months, and at 6 months, there was a positive impact on post-traumatic stress disorder (PTSD)

TABLE 1 Early palliative care clinical trials including only patients with advanced solid tumours

			Intervention				
Setting	**Study/year**	**Cancer diagnosis**	**Clinician providing palliative care**	**Timing of early palliative care**	**Control group**	**Favoured PC arm**	**Did not differ**
Outpatient: free-standing	Zimmermann 2014 McDonald 2017[71,95]	Advanced lung, GI, GU, Gyn, breast.	Specialized PC physician and nurse	Estimated survival 6–24 months	Standard care with referral on request	QOL, symptoms, patient and caregiver satisfaction with care	Caregiver QOL
	Maltoni 2016, Maltoni 2016[74,96]	Nonresectable or metastatic pancreatic cancer	PC physician	Within 8 weeks of diagnosis and no prior chemotherapy	Standard care with referral on request	QOL, aggressiveness at the EOL	Survival, anxiety, depression
	Scarpi 2019[76]	Locally advanced or metastatic gastric cancer	PC physician	Within 8 weeks of diagnosis and no prior chemotherapy	Standard care with referral on request		QOL at 3 months, survival, aggressiveness at the EOL
Outpatient: embedded	Temel 2010, Greer 2012 Temel 2011[72,97,98]	Metastatic NSCLC	Palliative care physician and APN	Within 8–12 weeks of diagnosis	Standard care with referral on request	QOL, mood, communication, less aggressive EOLc, survival	
	Temel 2016 El-Jawahri 2017[73,99]	Incurable lung or non-colorectal GI cancer	Palliative care physician and APN	Within 8 weeks of diagnosis	Standard care with referral on request	QOL, mood, decision making, coping, EOLc discussions, caregiver distress	Illness understanding, caregiver anxiety, QOL at week 12
Mixed inpatient and outpatient	Vanbutsele 2018 Vanbutsele 2020[77,100]	Incurable solid tumour	Specialized PC nurse with PC physician referral if required	Prognosis ≤1 year, and within 12 weeks of diagnosis or progression	Multidisciplinary care with nurse specialist, psychologist and dietitian. PC referral on request	QOL at 3 months	Survival, anxiety, depression, symptoms, health care utilization, aggressiveness at the EOL
	Franciosi 2019[78]	NSCLC (no EGFR), pancreatic, gastric, or biliary tract cancer	Oncologist specialized in PC and PC nurse	Within 8 weeks of diagnosis	Standard care with referral on request		QOL at 3 months, health care utilization
Mixed face to face and telephone	Groenvold 2017[79]	Stage IV lung, GI, breast, other with at least one PC need and 4 symptoms on EORTC-QLQ-C30	Multidisciplinary team (doctor, nurse, psychologist, among others)	Timing not specified	Standard care with referral on request	Nausea/vomiting	QOL, depression, survival
Telehealth	Bakitas 2009[75]	Lung, GI,GU, breast	APN with PC specialty training	Prognosis ≤1 year and within 8 weeks of diagnosis	Standard oncology and supportive care	QOL, mood	Symptom intensity, Resource use

Abbreviations: EOLc, end-of-life care; EOL, end-of-life; QOL, quality of life; GI, gastrointestinal; GU, genitourinary; APN, advance practice nurse; NSCLC, non-small cell lung cancer; PC, palliative care.

TABLE 2 Early palliative care clinical trials including patients with haematological malignancies

Type according to setting	Study/year	Cancer diagnosis	Intervention		Comparison group	Favours PC arm	Did not differ
			Clinician providing multidisciplinary PC and SC	Timing of early palliative care			
Trials that included only patients with haematologic malignancies							
Inpatient	El-Jawahri 2021[18]	High risk AML receiving intensive chemotherapy	PC physician, APN or physician assistant	Within 72 h of receiving chemotherapy	Standard care with referral upon request	QOL, depression, anxiety, PTSD. EOLc preference discussions, less chemotherapy near EOL	Symptom burden, hospice use and length of stay, hospitalization the last week of life
	El-Jawahri 2016, El-Jawahri 2017[17,80]	HM receiving allogenic or autologous stem cell transplantation	PC physician or APN	Within 72 h of admission for transplantation	Standard care with referral upon request	- At week 2: QOL, depression, anxiety, symptom burden, caregiver depression - At month 3: QOL, depression - At month 6: depression, PTSD	- At week 2: fatigue, caregiver QOL and anxiety - At month 3: anxiety, fatigue, symptom burden - At month 6: QOL, anxiety
Inpatient, outpatient and telephone	Rodin 2020 (phase II)[19]	Newly diagnosed or recently relapsed AML/ ALL within one month of admission	- Specialized PC physician and nurse and -Therapist trained in EASE-Psy plus psychiatrist/ psychologist at request	-Triggered by ESAS-AL symptoms ≥4 or upon request –12 EASE-psy sessions over 8 weeks	Standard care with referral upon request	- Pain intensity and pain interference at 12 weeks with daily activities - Traumatic stress symptoms at weeks 4 and 12	Symptom severity, symptom related distress, depressive symptoms, QOL, satisfaction with care
Outpatient	Loggers 2016[81]	HM planned for allogenic or autologous stem cell transplantation	APN or RN trained in PC	During the 2-week evaluation period immediately before HCT	N/A Acceptability of EPC	- 69% provided consent to participate in EPC consult. Comfort with EPC was high (82%)	No control arm
Trials that included patients with solid tumours and haematologic malignancies							
ED	Grudzen 2016 (phase II)[82]	Advanced solid tumour; relapsed stage III/IV lymphoma or myeloma, non-transplant or chemotherapy candidate (5.1%)	Palliative care physician, nurse practitioner, social worker and chaplain	Same or following day of ED admission	Standard ED care	QOL	- Survival, ICU admission, hospice discharge
Mixed in person (outpatient) and telephone	Bakitas 2015[101]	Advanced solid or HM (5%), within 1 to 2 months of diagnosis, prognosis 6 to 24 months	PC board certified physician (in person), and an APN (telephone)	Estimated survival 6–24 months	Delayed PC intervention after 3 months	Survival	QOL, health care utilization, chemotherapy in the last 14 days, home death

Abbreviations: QOL, quality of life; EOLc, end-of-life care; PTSD, posttraumatic stress disorder; PC, palliative care; ED, emergency department; ICU, intensive care unit; EPC, early palliative care; APN, advance practice nurse; RN, registered nurse; N/A, not applicable; AML/ALL, acute myeloid leukaemia and acute lymphocytic leukaemia; HM, haematologic malignancy.

and depression for patients receiving the intervention.[80] It is noteworthy that the PC intervention in this study included mostly rapport building, symptom management and assistance with coping while illness understanding, decision-making and advance care planning received significantly less focus.

In Canada, a phase II trial of a combined psychosocial and PC intervention (EASE – Emotion And Symptom Engagement) delivered mainly in the inpatient setting in patients with newly diagnosed or relapsed acute leukaemia demonstrated feasibility of this model as well as improved pain control and decreased traumatic stress symptoms.[19] The positive impact of early specialized PC for patients with acute myeloid leukaemia was affirmed by a randomized controlled trial demonstrating better quality of life and reduced levels of anxiety, depression and PTSD in high-risk acute myeloid leukaemia patients randomized to early inpatient PC compared to usual care.[18]

Further new intervention studies are underway, including a multi-centre randomized phase III trial of EASE for patients with newly-diagnosed acute leukaemia and several other trials of early PC in patients with leukaemia, multiple myeloma, lymphoma, myelodysplastic syndrome and mixed haematologic malignancies (Table 3) (clinicaltrials.gov). These include a trial of funding to receive palliative blood transfusions while enrolled on hospice for patients with HMs at the EOL[83] and a trial of outpatient PC for patients with multiple myeloma.[84]

MODELS FOR PC IN HAEMATOLOGY

PC is provided by interdisciplinary teams, which allows delivery of multidimensional care addressing the complex supportive care needs of people facing life threatening diseases.[20,21] However, there is no single model of PC that is appropriate for all settings. Instead, the model of PC provision will depend on national health policies, access to training and education of specialized PC providers, availability of resources, societal and health professional attitudes towards PC, and the setting where PC is delivered. As well, models of care will depend on the disease trajectory, such that models developed for patients with solid tumours may not be appropriate for patients with HMs. Broadly, models of early PC delivery be categorized according to who delivers PC (i.e., primary, secondary and tertiary PC, discussed above); where PC is delivered; and how it is determined who receives PC (i.e., the referral process).

Who delivers care: primary, secondary and tertiary PC

Family physicians, haemato-oncologists and palliative care physicians all have important roles in providing primary, secondary and tertiary care, respectively. The domains of palliative care and roles of each level of provider in delivering this care are outlined in Table 4, with the recognition that the boundaries between providers' roles are ill-defined and are based on patient need as well as provider skill. As most HM patients are treated in cancer centres, most PC for HM patients is secondary, delivered by haemato-oncology teams. Haemato-oncologists should therefore have better PC training; specifically, HM residents should complete at least a one-month rotation in PC, including information on symptom management, communication skills, cultural competence, multidisciplinary care, and ensuring timely referrals to PC specialists.[6] Haemato-oncology team meetings with a palliative focus have been shown to foster a culture change allowing for more goal-concordant care and should be implemented by haemato-oncology teams.[85] Tertiary (specialized) PC provided by PC consultants should be available to provide specialized PC for more complex situations such as refractory symptoms, severe psychosocial distress, or family conflict. The referral process to tertiary PC will be discussed below.

Where care is delivered: outpatient, inpatient, home and virtual models

As mentioned above, most models of early PC with proven benefit for patients with advanced solid tumours involve routine involvement of specialized PC delivered in the outpatient setting, either through freestanding PC clinics or in an embedded within the oncology clinic (Table 1). The principle for these clinics is that the PC team provides support with symptom control, coping with illness, decision-making and future planning, in a model that emphasizes care that is flexible, attentive, patient-led and family-centred.[86] This outpatient model works well for patients with solid tumours, who have an illness course that is relatively predictable, and for whom referral ideally occurs at the diagnosis of advanced illness. This model may be of benefit for patients with indolent HMs or for relatively fit patients with bone marrow failure. For these groups of patients, longer term outpatient involvement of PC may improve symptom control, provide psychosocial support, and assist with advance care planning. However, to date, there have been no randomized controlled trials of such an outpatient model for HMs.

For patients with aggressive HMs, inpatient treatment of their disease is necessary, and a model of concurrent early involvement of PC in the inpatient setting is appropriate. As mentioned above, there have been several trials that have demonstrated the feasibility and benefit of involving inpatient PC teams upon admission for treatment of acute leukaemia or stem cell transplantation, with benefits demonstrated long after discharge.[17,18,80] Providing further ad hoc telephone PC or psychosocial support after discharge may also help to ease the often-challenging transition from hospital to home.[31]

TABLE 3 Ongoing early palliative care clinical trials in patients with haematologic malignancies[b]

[Principal Investigator]; status; phase; setting	Country; year registered	Patients; Cancer diagnosis	Comparison group	Intervention		Outcomes[a]
				Clinician providing PC	Timing of early PC	
[El-Jawahri] Active, not recruiting N/A inpatient	NCT02975869 USA 2016	>60 years old: -High risk AML	Standard leukaemia care	Collaborative PC and leukaemia specialist	Newly diagnosed, relapsed, primary refractory	**QOL**, psychological distress, symptom burden, PTSD, EOL discussion preference, chemotherapy within 30 days of death, admission within 7 days of death, hospice utilization
[El Chaer] Recruiting Phase II; Inpatient and outpatient	NCT04482894 USA 2020	≥18 years old: -AML, ALL, MDS, CMML	Standard care with referral upon request	PC specialist	Newly diagnosed, relapsed, primary refractory	**Place of death**, survival, duration, admissions duration/type/ frequency, ER visits, hospice service use, transfusions, QOL, code status change, GOC discussions
[Samala] Recruiting Phase II Outpatient	NCT04248244 USA 2020	≥18 years old: -MM	No comparison group	Specialized physician, APN, care coordinators	Within 8 weeks of diagnosis	**QOL, anxiety, depression, health care utilization**
[Tanzi][102] Unknown Phase II Outpatient	NCT03743480 Italy 2020	≥18 years old: -Incurable haematological tumour and last line of therapy	Standard care with referral upon request	Integrated PC team	Soon after decision of last active treatment	**Adherence to palliative care program**, QOL, anxiety, depression, PPS.
[Rodin & Zimmermann] Recruiting Inpatient & outpatient & telephone	NCT04224974 Canada 2020	≥18 years old: Newly diagnosed AML and ALL	Standard care with referral upon request	-Supportive psychotherapy: trained therapist -Symptom triggered referral: PC specialists	Within 2 weeks of admission for treatment of acute leukaemia	**Traumatic stress symptoms, physical symptom severity**, QOL, ASD, depression, satisfaction with care, pain, survival, quality adjusted life years
[Booker] Not yet recruiting N/A Virtually (phone or zoom)	NCT05190653 Canada 2022	≥18 years old: -Haematologic malignancy -Family caregiver	Standard care with referral upon request	PC nurse practitioner or physician	Scheduled for SCT	**QOL**, symptom burden, patient and caregiver prognostic understanding, caregiver QOL
[Scarfò][103] Recruiting Open label Virtually (App)	NCT04370457 Italy 2020	≥ years old: -CLL/SLL or MDS -Users of internet connected device	Standard care with PC if needed	MyPal ePRO: PROs at baseline, monthly times 6, and at 12 months	Scheduled to receive any line of therapy for CLL/SLL or MDS	**QOL**
[Guastella] Recruiting Phase III Not specified	NCT03800095 France 2019	≥70 years old: -AML, MDS, diffuse large B cell lymphoma	Standard care with referral upon request	Palliative and supportive care team	At diagnosis in AML, MDS; after 3rd line therapy in lymphoma	**QOL**, symptoms, survival, satisfaction with care, cost effectiveness

TABLE 3 Continued

[Principal Investigator]; status; phase; setting	Country; year registered	Patients; Cancer diagnosis	Comparison group	Intervention: Clinician providing PC	Intervention: Timing of early PC	Outcomes[a]
[Bénite] Completed Phase II Not specified	NCT02631811 France 2021	≥18 years old: -First relapse on AML or ALL, transplant ineligible	Standard care with referral upon request	Multidisciplinary palliative care team	Within 8 weeks of diagnosis	**QOL**, symptom intensity, depression, anxiety, quality of EOL, survival

Abbreviations: QOL, quality of life; PPS, palliative performance scale; EOL, end of life; GOC, goals of care; PTSD, post-traumatic stress disorder; ER, emergency room; PC, palliative care; FACT, functional assessment of cancer questionnaire; N/A, not applicable; ESAS, Edmonton System assessment system; GDS, Geriatric Depression Scale; AML, acute myeloid leukaemia; ALL, acute lymphocytic leukaemia; MQOL-E, McGill Quality of Life Questionnaire; MDS, myelodysplastic syndrome; MM, multiple myeloma; SCT, stem cell transplantation; CLL/SLL, chronic lymphocytic leukaemia and small lymphocytic leukaemia; ASD, acute stress disorder; e-PRO, electronic patient reported outcomes; APN, advance practice nurse.

[a]Primary outcomes appear in bold.

[b]All trials listed are registered in clinicaltrials.gov.

Home-based PC is usually provided later in the course of advanced disease, when it becomes difficult for patients to travel to and from the hospital, and when the focus is exclusively on EOL care. The further expansion of home-based PC earlier into the disease trajectory, particularly in patients with bone marrow failure, would be much enabled by the capacity to provide transfusions of blood products in the home setting. This has been implemented in some countries with negligible risk.[41,42,87] However, in most countries home blood transfusions are impossible due to regulatory and financial constraints, presenting a substantial barrier for early PC in the home setting for HM patients.[88]

A novel mode for PC delivery is telemedicine, in which PC is delivered via telephone or video conference to the patient.[89] Telemedicine in PC has become increasingly common during the COVID-19 pandemic, due to the requirement for social distancing and reluctance of many patients to come to the hospital.[90,91] This model of care is particularly promising for patients who are receiving care in outpatient or home settings, to avoid the necessity for travel on the part of the patient or clinician and provide more efficient care. Randomized controlled trials of virtual PC are needed to determine its effectiveness compared to in-person models.

How specialized PC referral is determined: clinician-initiated and automated systems for aggressive HMs

Referral to specialized PC can either be based on judgement of the referring clinician or automated in some way. Referral initiated on clinical judgement by oncologists or haemato-oncologists is currently the most popular method and remains synonymous with usual care, both in practice and for clinical trials.[20,92] Oncologists are increasingly making early referrals to PC services at their centres for patients with solid tumours, thanks to the solid evidence favouring multidisciplinary care and the policies and advocacy supporting this approach.[93] On the other hand, haemato-oncologists face several barriers to effectively integrating PC into their practice under this model, as described above.[64,92] Therefore, despite the high symptom burden and needs, clinician-initiated referral results in most patients diagnosed with HMs being referred very late or never to PC.[26,48]

Interventions in most existing randomized controlled trials both in solid tumours and for HMs have consisted of routine referral for all patients shortly after the diagnosis of advanced disease (in solid tumours),[72] or shortly after admission for autologous or allogeneic haematopoietic stem cell transplantation or for acute leukaemia treatment.[17–19] Automatic referral to PC upon admission to hospital for treatment led to improved outcomes in two randomized controlled trials: one in HMs requiring stem cell transplantation and the other in acute leukaemia (Table 2).[17,18,80] Compared to usual care, patients receiving automatically

TABLE 4 Domains and providers of palliative care for patients with haematological malignancies

Domain	Primary PC – Primary care providers	Secondary PC – Haemato-oncology care teams	Tertiary PC – Specialty PC teams
Domain 1: Structure and processes of care	• Understanding the value of PC • Familiarity with the core principles of PC	• Basic PC assessment in HM • Address common sources of suffering in HM	• In-depth PC assessment and consultation • PC education for other providers
Domain 2: Physical aspects of care	• Assessment of symptom burden, functional status, and quality of life • Developing a palliative treatment plan consistent with patient and family needs and preferences	• Identify and treat common symptoms associated with HM (nausea and vomiting, cancer pain, fatigue, anorexia and cachexia, constipation, dyspnea, delirium etc.) • Starting opioid treatment, titration, rotation and managing side effects.	• Consult for complex and intractable symptoms • Advanced pain and symptom management (i.e methadone, lidocaine, interventions etc.)
Domain 3: Psychological and psychiatric aspects of care	• Screen, assess and manage for psychological concerns	• Understanding of psychological issues facing patients with HM (anxiety, depression, etc.) • Addressing grief and loss of patients and families	• Expertise in management of refractory symptoms • Care coordination for patients with extreme mental distress, cognitive and/or communication disorders
Domain 4: Social aspects of care	• Perform and integrate social assessments • Identify patient strengths, availability of caregiving and support, access to food housing and transportation etc.	• Assessment in the context of HM needs (prolonged admissions, prognostic uncertainty etc.) • Plan care management and delivery • Identify and address caregiver burnout	• Address complex family dynamics and intense social needs
Domain 5: Spiritual, religious, and existential aspects of care	• Spiritual screening and assessment of spiritual distress	• Utilize resources available within HM setting, patient and family, community, and care setting	• Address complex spiritual needs • Spiritual care specialist care
Domain 6: Cultural aspects of care	• Knowledge of how culture influences patient and family decision making and their approach to illness, dying and bereavement.	• Expertise in taking into account and navigating cultural aspects in the context of severe haematological illness	• PC specialists and cultural representatives aid in navigating cultural nuances
Domain 7: Care of the patient nearing the EOL	• Timely hospice referrals • Skills in conversations with patients and families about dying • Skills in managing EOL symptoms	• Timely hospice referrals in the setting of HM and prognostic uncertainty • Skills in difficult conversations about prognosis in the setting of HM and prognostic uncertainty • Skills in managing EOL symptoms in HM	• Managing difficult EOL conversations • Managing difficult EOL symptoms including judicious use of palliative sedation
Domain 8: Ethical and legal aspects of care	• Understanding basic ethical principles applicable at the EOL • Basic advance care planning	• Advance care planning for patients with HM • Managing common scenarios causing ethical and legal conflicts	• Specialist PC, ethicists and ethics committees provide high quality care aligned with patient goals

Note: Adapted from Clinical Practice Guidelines for Quality Palliative Care, 4th edition 2018, National Coalition for Hospice and Palliative Care.[22]
Abbreviations: PC, palliative care; HM, haematological malignancies, EOL, End of life.

specialized PC experienced better quality of life and reduced psychological symptoms, including depression, anxiety, and post-traumatic stress disorder. Therefore, automatic referral upon admission for the group of HMs that includes aggressive life-threatening diseases with a high risk of harm (alongside a realistic possibility for long-term cure) would be ideal in settings with sufficient PC resources.

An alternate model to automatic referral entails referral to specialized PC according to specific triggers (e.g., moderate symptoms, severe psychological distress). As yet, there is no conclusive evidence for this model in solid tumours or HMs. However, a phase II trial of an intervention entitled Symptom screening with Targeted Early PC (STEP) demonstrated the feasibility of such a model in patients with solid malignancies.[94] Here, patients attending outpatient oncology clinics were screened at each visit for symptoms using the Edmonton Symptom Assessment System; patients with moderate physical (e.g., pain, dyspnea, nausea) or psychological (e.g., depression, anxiety) symptoms, or with severe constitutional symptoms (e.g., fatigue, appetite), received a phone call from a PC nurse who discussed their symptoms and offered a formal PC appointment.

Lastly, the EASE intervention described above involved both automated and triggered components.[19] In this

intervention, patients with newly diagnosed or relapsed acute leukaemia who were randomized to the EASE intervention received an automated referral to a psychosocial clinician who provided a tailored psychotherapy delivered over 8 weeks, and weekly physical symptom screening over 8 weeks, with a triggered referral to an inpatient PC team if symptoms were scored above a certain threshold. The intervention was found to be feasible, with promising results for several patient-reported outcomes: significant treatment-group differences favouring EASE were observed in traumatic stress symptoms at 4 and 12 weeks, and in pain intensity and interference at 12 weeks.

Possible models for patients with bone marrow failure and indolent HMs

To date, all RCTs have included patient with aggressive disease: either patients with acute leukaemia or those undergoing stem cell transplantation. The trajectory as well as the aggressive, high-risk, high-gain nature of these diseases are mirrored in the models of triggered inpatient PC that have been proven to be of benefit. For other disease trajectories, different models may be needed. In indolent relapsing–remitting diseases, there are often challenges of illness understanding and advance care planning due to prognostic uncertainty, and symptoms such as pain and fatigue may also be prominent. For this patient population, the early outpatient integration of specialized PC, with its expertise in symptom management as well as complex decision making may be most beneficial. This could occur using preapproved triggers of symptom severity and may also result from improved referrals due to increased awareness of PC among haemato-oncologists. As well, bone marrow failure diseases may demand a rethinking and adaptation of home-based PC and hospice care. The low risk of home transfusion may be vastly outweighed by cultural, bureaucratic, and financial barriers that need to be removed in order to allow for proper care at home. For many of these patients, home care may not be feasible as the need for complex inpatient interventions may be needed to achieve goals of care. In these cases, hospice or PC units may need to adapt to the patients' complex needs.

CONCLUSIONS AND FUTURE DIRECTIONS

As evidence of the benefits of PC in HM continues to evolve, our understanding of the unique needs of this population continues to grow. Existing models of early tertiary PC for HM are based on specialist PC intervention triggered by admission for inpatient treatment for aggressive HMs, and have demonstrated benefit in randomized controlled trials.[17–19] Future trials of outpatient PC for patients with multiple myeloma and of enabling blood transfusions in hospice settings are underway and will pave the way to enabling better integration of PC for HMs with indolent disease and with bone marrow failure.

In addition to further research on models of tertiary PC, secondary PC services by haemato-oncologists need to be improved, both through better training for haemato-oncologists in PC and by expansion of HM research into the PC needs of this population. A PC rotation incorporated into residency training for haemato-oncological oncologists would provide insight into the possible benefits of integrating PC earlier in the disease trajectory and provide basic education in symptom management, communication skills and advance care planning. Importantly, progress in the integration of PC for patients with HM will necessitate a mutual understanding and collaboration between haemato-oncologists and PC providers across all levels of care.

As the understanding of the biology of HM and targeted treatments continue to progress, HM patients will continue to face challenges in maintaining quality of life and in making treatment decisions in the context of prognostic uncertainty. With its interdisciplinary and holistic approach, PC has much to offer these patients. Increased understanding of PC by haemato-oncologists as well as improved models for integration of tertiary PC will open the door to improved quality of care for this underserved population.

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CONFLICT OF INTEREST

The authors report no conflict of interests.

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None.

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