Background: Evidence showed that early palliative care could have many benefits in clinical outcomes for patients living with advanced medical illnesses. In fact, most of these studies have not involved patients with advanced haematologic cancer (HC), which are known to be associated with significant physical and psychological symptoms. In Hong Kong, an Early Integrated Palliative Care (EIPC) collaboration involving both Haematology unit of Queen Mary Hospital (QMH) and the Palliative Medical Unit of Grantham Hospital (GH) has been started since early 2018 as a better way to improve the service gap. The HC patients failed 2 or more lines of cancer treatment are identified during the joint round and haematology clinic. Some of these patients will be referred to our PC services. Our joint PC clinic has multidisciplinary input from palliative care physicians, hematologists, and clinical psychologists. The clinic program is well coordinated and structured. The HC patients are initially seen by the parent team for disease treatment and then by GH PC team for symptom control and psychosocial care.

Methods: This was a retrospective study with a review of the clinical charts and electronic healthcare records of all patients who attended the Hematology PC clinic from June 2018 to September 2020. For the inclusion criteria, patients were found eligible if they had prospectively completed Edmonton Symptom Assessment Scale (ESAS) assessments for at least the initial and follow-up visits within a range of ≥7 days and ≤60 days of the first visit.

Results: Thirty-eight patients ultimately agreed to the referral. The mean age was 70.5 (12.5) years old. Twenty-five patients (66%) had myelodysplastic syndrome (MDS); 10 (26%) had acute myeloid leukemia (AML). Around 50–60% of patients reported significant symptoms of fatigue, anxiety, drowsiness, and anorexia; 42% of patients had significantly depressed moods while 37% had pain. There were significant symptom improvements for pain, depression, and anxiety after follow-up visits.

Conclusions: The study showed that our EIPC program resulted in a significant reduction in some of the important symptom item scores, including pain, anorexia, anxiety, and depression, after the follow-up visits.

Keywords: Early palliative care (early PC); haematology palliative care; symptom burden

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Introduction

Early interventions in cancer care are highly encouraged as the role of palliative care (PC) in solid malignancy has been redefined. Nowadays, PC intervention for patients becomes the standard care for patients with advanced malignancies. The benefits of PC, including improvement in quality of life, reduction of symptom burden, and psychological distress, have been shown in some of the previous studies (1).

However, there was an underutilization of PC services among patients with haematologic cancer (HC) (2). A large study revealed that patients with HC were more likely to have disease treatment (e.g., target therapy), repeated admissions, and remained to stay in an acute hospital most of the time, especially at the end of life (EOL) (3). Recent systematic reviews also showed that patients with HC, for example, myelodysplastic syndrome (MDS), were less likely to receive PC services at any time point (4-6).

It is also noted that these HC patients are more likely to die within a short period of time after receiving PC (7,8). Literature showed that patients with HC suffered from significant symptoms that were similar to patients with advanced solid malignancies (9,10). Several studies had shown that leukaemia patients have major physical and psychological problems (11,12). Likewise, those bearing bone marrow transplant patients are found to have poor QOL (13). Given the available published evidence—medico-psycho-social needs appeared early on in the illness of HC, it is evident that this group of patients are an under-represented population in PC.

Barriers that impose a limitation to expand PC into HC patients include the strong relationship between patient and haematology team, presence of multiple novel treatments, lack of an indication from curative to palliative treatment, and misconceptions regarding palliative care—often times being mistaken for EOL care (14-16). These factors often result in delayed referral to the PC team only when patients are approaching EOL. Although recent studies have suggested some potential triggers for HC patients to PC service (17,18), larger studies are required to show its impact on clinical outcomes. Notably, it is not uncommon for patients with relapsed or refractory HC to be treated with unnecessary treatments compared to solid cancer patients for their EOL care (19-22).

Most international guidelines recommend that PC service must be delivered concurrently with the active treatment of those advanced oncology patients in the early disease course (23,24). In fact, the benefits of early PC services included better symptom management and the reduction of unnecessary healthcare costs, which were already shown in several randomized controlled trials (25,26). Some studies showed improvement in patients’ quality of care and mood as early as 12 weeks after intervention (27,28). However, the data about early PC integration for HC patients remains limited. Hereby, we share our care model and the ways we manage the symptoms for advanced HC patients in an early integrated PC approach.

Description of model

In Hong Kong, an Early Integrated Palliative Care (EIPC) collaboration involving both Haematology Unit of Queen Mary Hospital (QMH) and the Palliative Medical Unit of Grantham Hospital (GH) has been started since early 2018 as a better way to improve the service for this group of patients (28). The haematology patients who have failed 2 or more lines of cancer therapy are identified during the joint round and haematology outpatient clinic. Some of these patients will be referred to our PC services like outpatient, home care, or day care services.

A Haematology Comprehensive Care Clinic (Hema-CCC) has been established, which provides palliative outpatient service in QMH since early 2018. It is a joint clinic with input from a palliative care physician, haematologist, nurse, and clinical psychologist. The clinic name “comprehensive care” is used instead of “palliative care” because it seems more acceptable to the advanced HC patients during their transition to PC service.

In general, it was agreed that patients with advanced HC who failed 2 or more lines of disease treatment could be referred to PC team because these are truly refractory patients (Figure 1). Some HC patients could be referred earlier if they failed first-line treatment in the presence of poor prognostic indicators (e.g., frail elderly, poor functional status, significant complications due to disease treatment). Since the clinic works parallel to MDS Clinic, thus it is expected most patients will be referred from this clinic.

Patients deemed suitable for comprehensive palliative and haematology input would be referred to Hema-CCC by haematologists. Attendance at this clinic allows for multidimensional assessment, continued medical treatment of their haematologic disease, symptom management, support of patients and their families, and further follow-up. The PC team consists of physicians and nurses who work closely with the HC patients and their caregivers. When
necessary, patients can be referred to a clinical psychologist, social worker, physiotherapist, and pain clinic. Hema-CCC is a joint clinic, which adopts the EIPC model and caters to all the ambulatory patients in the outpatient setting. The Hema-CCC provides on-site palliative care consultation and can allow patients to have earlier advance care planning (ACP) discussions while the hematologist is mainly responsible for the disease treatment in the clinic sessions.

In prioritizing patient access to Hema-CCC, referred patients are initially screened by phone via an experienced PC nurse. During this screening phone consultation, the patient’s symptom burden, psychosocial aspects, and caregiver support at home are assessed beforehand. Priority appointments will be given to those with high palliative care needs (e.g., ESAS score ≥7 or ESAS ≥4 with impact on daily activities) regarding the symptom or emotional aspects. The Hema-CCC is situated inside the QMH outpatient clinic in order to improve accessibility.

During the first attendance at the Hema-CCC, the haematology patients are initially seen by the parent team for cancer therapy and then followed by the PC team for symptom control and management of psychological, social, and spiritual issues in the same session. If the patients are deemed ready, ACP will be discussed with them in the subsequent sessions. Counseling and emotional support will be given to the family caregivers by the on-site PC nurse (Figure 2). As a routine, a comprehensive multidimensional assessment is provided to all HC patients in the first session performed by the PC team. It consists of symptom and mood aspects, functional performance, family dynamics, social support, religious background, and any presence of spiritual distress. The time of subsequent clinic visit appointment is based on the patient’s needs, wishes and prognosis. In-between the visits, our PC nurse contacts the patient regularly for general condition, symptom and mood response, drug compliance as well as practical support. The scheduled duration of each new and follow-up consultation is 60 and 30 minutes, respectively.

The transition from haematologist to palliative medicine specialist-led consultations will be gradual over the course of several sessions. Those still on active disease treatment and those with frequent need for blood transfusion are identified as potentially requiring more haematologist input. In addition, patients’ and families’ expectations will also be considered to individualize each consultation.

There are inter-professional team discussions with different allied health disciplines, including medical social workers and clinical psychologists, in case conference. They offer input for the care plan, and some of these patients will be referred back to the regional palliative care team afterwards (Figure 1). We present the following article in accordance with the STROBE reporting checklist (available at http://dx.doi.org/10.21037/apm-21-276).
Methods

This was a retrospective study with a review of the clinical charts and electronic healthcare records of all patients who attended the Hema-CCC from June 2018 to September 2020. For the inclusion criteria, patients were found eligible if they had Edmonton Symptom Assessment Scale (ESAS) assessments (29) prospectively for at least the initial and follow-up visits within a range of ≥7 days and ≤60 days of the first visit. The improvement in symptom response could be extremely variable depending on the evaluation time in the same patients. If the evaluation time is too early, patients who might ultimately respond could be misclassified into the nonresponse group. A reduction of 1 is viewed as a clinically significant improvement in that symptom response (30). As well, if the evaluation time is too late, HC progression may alter the efficacy of outpatient palliative care. Therefore, we set the evaluation time as one to eight weeks from the initial consult.

ESAS assessment (29) (including pain, fatigue, depressed mood, anxiety, somnolence, anorexia, decreased sense of well-being, and insomnia) is routinely used to check the patient symptom burden in terms of physical and psychological domains at regular interval. The intensity of symptom item is measured using an 11-point Numerical Rating Scale (0= no symptom; 10= the worst possible symptom). The significant symptom is defined as the ESAS score ≥4. Any other self-reported symptoms are also included in the symptom checklist for ongoing assessment.

An example of providing on-site PC assessment and interventions was an elderly MDS lady who presented with significant cancer pain, anorexia, and depressed mood while still on azacitidine for her disease treatment on the initial visit. The PC physician prescribed tramadol for her pain, megestrol acetate for anorexia, and used fluoxetine (as an antidepressant) together with psychosocial and spiritual care provided by our PC nurse and clinical psychologist. The symptom scores of her pain, anorexia, and depressed mood were improved subsequently at the 2nd and 4th visits [7 to 4 to 2; 6 to 2 to 0 and 8 to 3 to 2 (out of 10) respectively]. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). Ethical approval for this study was issued by the Institutional Review Board of the University of Hong Kong and Hospital Authority Hong Kong West Cluster (HKWC) (No: UW 18-282) and individual consent for this retrospective analysis was waived.

Statistical analysis

The categorical variables were shown as percentages with 95% confidence interval in order to estimate the difference from the baseline (initial Hema-CCC consultation) through these consultation visits. Continuous variables were presented as means with standard deviations, SD, or as medians with interquartile range (IQR). Pearson’s test and Fisher’s exact test were used to analyzing the categorical variables. Student’s t-test or Mann-Whitney, or Wilcoxon signed ranks tests depending on the distribution (normal or
non-normal) were performed to compare the continuous variables. P<0.05 were considered statistically significant while all reported P values were two-sided. The SPSS package (version 20 for Windows, SPSS, Inc., Chicago, IL, USA) was used for all the analyses.

**Results**

**Patient character**

In the period between June 2018 and September 2020, 41 advanced HC patients were eligible to be referred to Hema-CCC, and 38 patients ultimately agreed to the referral. The mean age was 70.5 [45–89] years old. The background and clinical features of all the advanced HC patients are shown in Table 1.

Regarding the diagnosis of HC, 25 patients (66%) had MDS; 10 (26%) had acute myeloid leukemia (AML), and 3 (8%) had other types hematological malignancies. Reasons for consultation were classified in the following categories: (I) symptoms control-32 patients (84 %); (II) shared-care visit: patients expected to develop significant symptoms or psychological and social issues that would warrant an early multidimensional assessment and follow-up although the HC patient had no specific problems at the time of referral-5 patients (13%), and (III) other reason-1 patient (3%).

**Changes in symptom score and the clinical response**

The number of patients with significant symptoms (ESAS ≥4) at the baseline was shown in Table 1. Around 50–60% of patients reported significant symptoms of fatigue, anxiety, drowsy, and anorexia, 42% of patients had significantly depressed moods, while 37% had pain. The median duration between the 1st visits at the Hema-CCC and the 1st follow-up, 2nd follow-up visit, 3rd follow-up visit, and 4th follow-up visits was as follows: 14 (IQR, 14–21) days, 28 (IQR, 25–35) days, 42 (IQR, 35–48) and 56 (IQR, 42–63) respectively.

The changes in symptom scores at each follow-visit were shown in Table 2. After 4th follow-up, the mean symptoms scores for pain, depression, anxiety, and appetite were significantly improved from 4.7 to 3.2 (P<0.017), 4.4 to 3.1 (P<0.023), 5.5 to 3.2 (P<0.003), and 5.2 to 3.7 (P<0.007) when compared with baseline respectively (Table 2). The clinical response rate % (95% confidence interval) of pain, depression, anxiety and appetite were 51.3% (34.5–67.7); 61.6% (43.6–75); 86.3% (56.2–79) and 75.3% (51.2–89.3) respectively after the 4th follow-up visit.

Most frequently prescribed medications included appetite stimulants, opioids, and antidepressants, and these were used in 30–50% of patients (Figure 3). On-
Table 2 Symptoms scores of advanced HC patients with significant symptoms (NRS ≥4) from baseline to 4th clinic visit

<table>
<thead>
<tr>
<th>ESAS item</th>
<th>At baseline, mean (SD)</th>
<th>At 1st FU, mean (SD)</th>
<th>At 2nd FU, mean (SD)</th>
<th>At 3rd FU, mean (SD)</th>
<th>At 4th FU, mean (SD)</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain</td>
<td>4.7 (1.8)</td>
<td>4.1 (2.3)</td>
<td>3.1 (2.5)</td>
<td>2.0 (1.7)</td>
<td>3.2 (2.1)</td>
<td>0.017*</td>
</tr>
<tr>
<td>Fatigue</td>
<td>5.3 (2.7)</td>
<td>5.4 (2.7)</td>
<td>5.7 (2.5)</td>
<td>5.6 (3.1)</td>
<td>5.8 (3.1)</td>
<td>0.241</td>
</tr>
<tr>
<td>Nausea</td>
<td>4.1 (1.1)</td>
<td>4.0 (1.7)</td>
<td>4.0 (1.3)</td>
<td>4.3 (3.1)</td>
<td>4.5 (3.3)</td>
<td>0.078</td>
</tr>
<tr>
<td>Depressed mood</td>
<td>4.4 (2.1)</td>
<td>4.1 (1.9)</td>
<td>3.2 (1.7)</td>
<td>2.9 (1.6)</td>
<td>3.1 (1.5)</td>
<td>0.023*</td>
</tr>
<tr>
<td>Anxious</td>
<td>5.5 (2.3)</td>
<td>4.3 (1.1)</td>
<td>2.2 (1.1)</td>
<td>2.1 (1.3)</td>
<td>3.2 (1.2)</td>
<td>0.003*</td>
</tr>
<tr>
<td>Drowsy</td>
<td>5.1 (2.1)</td>
<td>4.8 (1.8)</td>
<td>4.8 (1.8)</td>
<td>4.9 (1.4)</td>
<td>4.7 (1.8)</td>
<td>0.084</td>
</tr>
<tr>
<td>Appetite</td>
<td>5.2 (1.7)</td>
<td>4.9 (1.9)</td>
<td>3.8 (1.9)</td>
<td>3.7 (1.4)</td>
<td>3.7 (1.7)</td>
<td>0.007*</td>
</tr>
<tr>
<td>Wellbeing</td>
<td>5.8 (2.5)</td>
<td>5.9 (1.7)</td>
<td>5.5 (1.7)</td>
<td>5.2 (2.1)</td>
<td>5.5 (2.1)</td>
<td>0.127</td>
</tr>
<tr>
<td>Shortness of breath</td>
<td>2.6 (1.6)</td>
<td>2.7 (1.5)</td>
<td>2.5 (1.3)</td>
<td>2.4 (1.7)</td>
<td>2.7 (1.6)</td>
<td>0.825</td>
</tr>
<tr>
<td>Sleep</td>
<td>3.3 (1.2)</td>
<td>3.4 (1.3)</td>
<td>2.9 (1.1)</td>
<td>2.8 (1.3)</td>
<td>3.1 (1.3)</td>
<td>0.092</td>
</tr>
</tbody>
</table>

*Compare between baseline and 4th FU symptom mean score; *Statistically significant if P<0.05. ESAS, Edmonton Symptom Assessment Scale; FU, follow-up; HC, haematology cancer; SD, standard deviation.

Figure 3 Pharmacological interventions by PC team. PC, palliative care.

The site PC service utilization by this patient cohort was as follows: rapport building (100%), symptom advice (91%), illness understanding (72%), coping (38%), others (38%). Eighteen (37%) and 8 patients (21%) had received our home care and clinical psychologist support, respectively.

Of the initial 38-patient cohort, 5 (13%) died, and one defaulted further visit. Therefore, 32 patients (84%) were still able to attend the 4th follow-up.

Discussion

The importance of this study was to evaluate the process and clinical outcomes from the early integrated model for advanced HC patients. Although the haematology unit has started collaborations with our PC unit for several years, the establishment of the Hema-CCC was regarded (by both sides) as a step forward in this successful collaboration. As far as we know, there are only a few studies to show...
the outcomes of EIPC intervention for advanced cancer patients in Hong Kong. Our previous research has shown the beneficial effects of EIPC in patients who received bone marrow transplantation (31,32). Our study assessed the value and impact of EIPC conveyed at Hema-CCC. The results showed that some of the symptom burden could be improved quickly, with amelioration in patients’ perceived pain, mood, and appetite.

Today, the development of PC has expanded to a larger scope (33). Our new approach, in fact, is related to the appearance of novel therapies, including the new target and immunotherapy that could prolong the lifespan of oncology patients. As a result, patients with cancer have a longer life expectancy than before. Some regard advanced cancer as a chronic illness, although it cannot be totally cured (34). These patients are anticipated to have medico-psychosocial needs throughout their disease course. This is more common in advanced HC with the greater number of new disease treatments and unpredictable disease trajectories, emphasizing the key role of early PC in these patients.

In this study, patients with advanced HC were referred to the Hema-CCC with the majority just after 1st, and 2nd line treatment failed. And more than half of these HC patients reported significant symptoms, especially fatigue, anorexia, and mood problems. It is encouraging to note that some of these significant symptoms, including pain, depression, anxiety, mood, and anorexia, can be improved after a relatively short duration of PC service, which included pharmacological and non-pharmacological interventions. For instance, a number of these patients might worry about their symptom burden, disease course, or even caring issue in view of their old age. Most EIPC studies showed beneficial effects on quality of life and mood for solid cancer patients from the literature. However, there are mixed results for the impact on symptom burden (35). There is a significant improvement of some physical and psychological symptoms at the subsequent follow-up visits after PC interventions in our study. The improvement in the symptom burden in our study population might be explained by the presence of different reasons. These include early symptom assessment, coordinated and structured program, enhanced psychosocial care to patients and relatives from readily available on-site personnel (36,37). Indeed, the benefits of EIPC interventions were well described in the previous studies of those solid tumor patients (26,27). Our findings suggest that a standardized protocol with a structured design integrating both psychological and physiological outcomes was appropriate for this study sample. It is encouraging to note that a significant portion of patients can benefit from other services, including home care and clinical psychologist support.

Most of these patients could attend the scheduled appointment as there was a low default rate. As they were followed by the PC team closely for both physical and psychosocial care, we could develop good rapport gradually. All these will help to transit the HC patients from disease treatment to PC and finally to hospice use.

There are several limitations in this study. Firstly, it is a retrospective design, so some key statistics (e.g., number of patients and visits to the allied health professionals) cannot be measured. Secondly, the impact of concurrent disease treatment on patient symptom burden cannot be totally ruled out. Thirdly, only changes in physical and emotional symptoms are evaluated—other aspects of PC such as social and spiritual needs were not studied. Fourthly, not all eligible patients could be referred to the Hema-CCC because it is a pilot program with a limitation in manpower, and there is a pre-set quota, so these would account for the small number of patients recruited. Moreover, patient/family satisfaction has not been studied in this study. Nonetheless, the data reported did show the benefits of EIPC in this patient group. Further studies are required to delineate the efficacy of specific elements/components in this early integrated PC program and how to enhance the delivery of this program to patients and their caregivers. Indeed, EIPC is still an ever-expanding field, and so more studies are required to identify the specific area of PC in aiding patients and their relatives at different time points of their illness.

**Conclusions**

This study provides evidence and support that EIPC in patients with advanced HC is both feasible and beneficial. Our preliminary findings suggest that a collaborative approach between the PC and haematology team is crucial to achieving good outcomes for this group of patients. Further randomized controlled studies are warranted to prove its effectiveness.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at http://dx.doi.org/10.21037/apm-21-276

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). Ethical approval for this study was issued by the Institutional Review Board of the University of Hong Kong and Hospital Authority Hong Kong West Cluster (HKWC) (No.: UW 18-282) and individual consent for this retrospective analysis was waived.

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