IS EARLY PALLIATIVE CARE INTERVENTION POSSIBLE IN PATIENTS WITH HAEMATOLOGICAL MALIGNANCIES?

¿ES POSIBLE LA INTERVENCIÓN PRECOZ DE CUIDADOS PALIATIVOS EN PACIENTES CON NEOPLASIAS HEMATOLÓGICAS?

Josep Porta-Sales[1], Maria Guerrero-Torrelles[2],
Deborah Moreno-Alonso[3], Silvia Llorens-Torrome[1],
Mercedes Galiano-Barajas[4], Josep Sarra-Escarré[5],
Victoria Clapés-Puig[6], Jordi Trelis-Navarro[1],
Anna Sureda-Balarí[6], Alberto Fernández de Sevilla-Ribosa[6]

1. Palliative Care Service, Catalan Institute of Oncology (ICO), Bellvitge Biomedical Research Institute (IDIBELL), L'Hospitalet de Llobregat-Barcelona
2. Facultat de Medicina i Ciències de la Salut. Universitat Internacional de Catalunya, Barcelona.
3. Palliative Care Service, Catalan Institute of Oncology (ICO), Girona.
4. Palliative Care Service, Catalan Institute of Oncology (ICO), L'Hospitalet L.-Barcelona.
5. Haematology Service, Catalan Institute of Oncology (ICO). Tarragona. Spain
6. Haematology Service, Catalan Institute of Oncology (ICO). L'Hospitalet L.-Barcelona.

Summary

Palliative care early intervention in solid tumours has been proved beneficial in terms of physical and emotional control, but also increasing quality of life and saving costs. No information is currently available about the potential benefit of palliative care early intervention in haematological malignancies. The present study aims to assess the symptom control benefit of an integrative early intervention palliative care outpatient clinic (MM-PAL) in patients diagnosed with Multiple Myeloma after its first running year. We retrospectively reviewed the clinical record of new patients who visited at the MM-PAL from February to December 2013. Pain, anorexia, constipation, insomnia, nausea and vomiting, dyspnoea, anxiety and sadness, were assessed in the first clinical encounter and for three follow-up visits. Symptoms were assessed using a Numerical Visual Scale (NVS) (0= No symptom present; 10= The worst possible intensity). Physical (anorexia, constipation, insomnia, nausea and vomiting, dyspnoea), and emotional (anxiety and sadness) symptom burden were calculated summing-up their scores. Worst and average pains were evaluated, and the pain's interference with general activity, sleep and mood. Sixty-seven patients diagnosed with plasma cell tumours (median time after diagnose 355 days) were first visited. After three visits (median follow-up time 60 days) the proportion of patients reporting moderate-severe pain (NVS ≥5), Worst pain (57% vs. 18%; P<0.0001) and Average pain (24% vs. 2%; P<0.0001) reduced significantly. The proportion of patients reporting no pain interference increased: general activity (52% vs. 82%; P=0.0001), sleep (73% vs. 91%; P=0.01) and mood (52% vs. 87.5%; P=0.0001). Both Physical and Emotional burden also improved. The proportion of patients with depression improved (13% vs. 5%; P=0.001). After the follow-up period 86.6% patients were alive and continue attending the MM-PAL. We can conclude that an early palliative care intervention is feasible in haematology, achieving good control of pain pain and other symptoms and attachment with the MM-PAL follow-up.

Keywords: *palliative care, palliative medicine, hematology, multiple myeloma, pain, neoplasms.*

Resumen

La Intervención Precoz de Cuidados Paliativos (IPCP) en tumores sólidos mejora el control de síntomas tanto físicos como emocionales, la calidad de vida y disminuye el gasto sanitario. Se desconoce el posible beneficio de la IPCP en tumores hematológicos. El objetivo del presente estudio es evaluar el beneficio en el control sintomático, tras la puesta en marcha de una consulta externa de IPCP (MM-PAL) en pacientes con mieloma múltiple. Se revisaron las historias clínicas de los pacientes visitados por primera vez en MM-PAL, desde febrero a diciembre de 2013. Durante la primera visita y las siguientes 3 visitas se evaluaron: dolor, anorexia, estreñimiento, insomnio, náuseas y vómitos, disnea, ansiedad y tristeza evaluándose con una Escala Numérica Visual (ENV) (0=Síntoma no presente; 10= La intensidad más alta posible). Se calculó la carga de los síntomas físicos (anorexia, estreñimiento, insomnio, náuseas y vómitos, disnea) y de los emocionales (ansiedad y tristeza) sumando sus puntuaciones. Se evaluaron el «Peor Dolor» y el «Dolor Promedio», y su interferencia en la actividad general, el sueño y el estado de ánimo. Se visitaron 67 pacientes y tras 3 visitas de seguimiento (mediana de seguimiento 60 días) la proporción de pacientes con dolor moderado-severo (ENV≥5) se redujo para el «Peor Dolor» (57% *vs.* 18%; $P<0.0001$) y el «Dolor Promedio» (24% *vs.* 2%; $P<0.0001$). El porcentaje de pacientes sin interferencia por el dolor mejoró: actividad general (52% *vs.* 82%; $P=0.0001$), sueño (73% *vs.* 91%; $P=0.01$), estado de ánimo (52% *vs.* 87,5%; $P=0.0001$). La carga sintomática física y emocional, y la proporción de pacientes deprimidos (13% *vs.* 5%; $P=0.001$) mejoraron. Finalizado el seguimiento 86,6% de los pacientes seguían vivos y eran visitados en MM-PAL. Concluimos que una IPCP es factible en hematología, obteniéndose un buen control del dolor y de los otros síntomas, así como la adherencia al MM-PAL.

Palabras clave: *cuidados paliativos, medicina paliativa, hematología clínica, mieloma múltiple, dolor, cáncer.*

Introduction

Palliative care aims to offer the best possible quality of life for patients with advanced diseases and their families, through a multidisciplinary and multidimensional approach. The World Health Organisation's definition of palliative care states that palliative care should be delivered early in the course of the disease and not only in the last stages of the diseases (World Health Organization, 2015). Even the WHO postulate an early palliative intervention , its facticity and benefit has not been demonstrate since the works of Temel *et al.* (Temel *et al.*, 2007; Temel *et al.*, 2010) showing the benefit of the palliative early intervention in advanced lung cancer patients. Currently, there is a rising interest in evaluating the potential benefits in terms of physical, emotional and financial of delivering early palliative care in other sorts of solid tumours (Groh, Vyhnalek, Feddersen, Fuhrer & Borasio, 2013; Otsuka *et al.*, 2013).

With respect haematological malignancies it has been warned the late and suboptimal intervention of the palliative care teams (Hui *et al.*, 2015; V. J. Manitta, Philip & Cole-Sinclair, 2010) arguing that in most cases is difficult to define or identify the last stages of haematological malignancies, so most patients could experience a rapid physical deterioration, and an unpredictable course that can change the therapeutic approach to healing in a situation of end of life in a short time (Corbett, Johnstone, Trauer & Spruyt, 2013; V. Manitta *et al.*, 2010; Odejide, Salas Coronado, Watts, Wright & Abel, 2014; Tazi, Nafil & Mahmal, 2011).

Multiple myeloma (MM) represents 1% of all cancers and 10% of all haematological malignancies (Rajkumar, 2011), but it has distinctive clinical features, as being an incurable disease from the diagnosis despite the increased survival rates obtained with new drugs. In the other hand, although MM patients can experience long low-symptomatic periods, the symptom burden used to be high, chiefly due to pain from diverse origins. Pain prevalence in MM patients is 80% with an incidence of 100% (Niscola *et al.*, 2007; Snowden *et al.*, 2011). Consequently, the MM clinical features make this haematological malignancy an archetypal disease to explore the benefits of an early palliative care intervention.

In our institution the patients' care is based on a multidisciplinary patient-centred model (Mate-Mendez *et al.*, 2013), therefore it was considered convenient for the haematology and palliative care services setting up an integrative MM PALliative outpatient clinic (MM-PAL), based in a next-door office, flexible agenda, proactive phone nurse assessment, advise and support, alongside a fluent communication among health professional involved. Additionally, evidence of the high prevalence of pain in MM patients in our area (Porta-Sales *et al*., 2015) supported the MM-PAL. The aim of this paper is to describe the experience of first year of an integrative early intervention palliative care outpatient clinic with clinical haematology in the symptom control of multiple myeloma patients at the Catalan Institute of Oncology-L'Hospitalet branch.

Patients and methods

We retrospectively review the clinical charts of patients visited at the MM-PAL from its set up in February 2013 until December 2013.We included patients diagnosed of MM or plasmocytoma that experienced any kind of symptoms related with the disease, antitumor treatment or other co-morbidities affecting the patients' wellbeing. Patients were addressed to the MM-PAL according to the haematologist's criteria for multidimensional assessment, treatment, patient and family support and follow-up. Patients were scheduled for MM-PAL visit priority following a screening phone call carried out by an experienced palliative care nurse who assesses physical and emotional burden, family worries and actual support, and potential transfer to the hospital difficulties, following the protocol of our service (Porta-Sales *et al*., 2005).

At the first clinical encounter a comprehensive multidimensional assessment was undertaken (Garzón-Rodríguez *et al*., 2010) including physical and emotional assessment, performance status, family structure and its emotional and practical support availability, and spiritual issues. After the MM-PAL first encounter, follow-up visits were scheduled according to the patients' needs and wishes, and where appropriate scheduled palliative nurse phone follow-up was scheduled, mainly for symptom reassessment, emotional and family support and medication supervision.

Routine symptom check-list assessment used at the MM-PAL was an adaptation of the Edmonton Symptom Assessment Scale (ESAS) (Bruera, Kuehn, Miller, Selmser & Macmillan, 1991; Carvajal, Hribernik, Duarte, Sanz-Rubiales & Centeno, 2013) including: pain, anorexia, constipation, insomnia, nausea and vomiting, dyspnoea, anxiety and sadness. If patients complain of other symptoms they were added to the symptom check-list for regular assessment. With respect pain intensity, it was assessed using an adapted version of the Brief Pain Inventory- Spanish version (Badia *et al*., 2003), assessing the «Pain right-now», and in the last 24 hours «Worst pain», «Best pain» and «Average pain». Pain intensity was scored using a Numerical Visual Scale (NVS) of 11 points (0= No pain; 10= The worst possible pain). It was also assessed, accordingly the patients' opinions, the pain interference (yes/no) of three aspects: general activity, sleep and mood. Other symptoms rather than pain were also assessed using the 11 points NVS. Pain prognosis was assessed using the Edmonton Classification System-Cancer Pain (ECS-CP) (Nekolaichuk, Fainsinger & Lawlor, 2005). The existence of a depressive episode was evaluated using the Endicott criteria (Endicott, 1984). Performance status was assessed using the Palliative Performance Score (Anderson, Downing, Hill, Caroso & Lerch, 1996) and the physical dependency using the Barthel index (Cid-Ruzafa & Damián-Moreno, 1997). The same data assessed at the first MM-PAL encounter were also recorded for the following visits in order to evaluate their course and adjust the patients' treatment strategy accordingly.

In summary, palliative care intervention in the MM-PAL is made up of a detailed multidimensional assessment (physical, emotional, functional, social and spiritual), resulting in a comprehensive care planning which included: pharmacological and non-pharmacological measures, and care coordination with other departments (e.g. radiation oncology, social work or psycoonchology). Communication with the haematologist in charge of the patient was extremely fluent, with no need for scheduling meetings. MM-PAL first encounter was scheduled for one hour, and the follow-up visits for 30 minutes. All patients can easily contact with the institution using a specific call-centre. If required, phone follow-up was scheduled and done by a experienced palliative care clinical nurse.

In order to evaluate changes through the 3 follow-up visits after first MM-PAL encounter, and for the purpose of this study the physical symptom burden and the emotional symptom burden was calculated (Bruera *et al*., 1991) The physical symptom burden is the sum of the scores of anorexia, asthenia, insomnia, constipation, nausea/vomiting and dyspnoea (range: 0-60), and the emotional symptom burden is the sum of the scores of sadness and anxiety (range: 0-20).

The study was approved by the local Ethics Committee.

Statistical analyses:

Categorical variables are shown as percentages with 95% CIs. Continuous variables are presented as means and standard deviations (SD) or as medians and interquartile range. Categorical data were compared using Pearson's χ^2 and Fisher's exact test. Continuous variables were compared using the Student's *t*-test or Mann-Whitney or Wilcoxon Signed Ranks tests depending on the distribution (normal or non-normal). A value of $p<0.05$ was considered statistically significant. All analyses were performed with the SPSS package (v. 20 for Windows).

Results

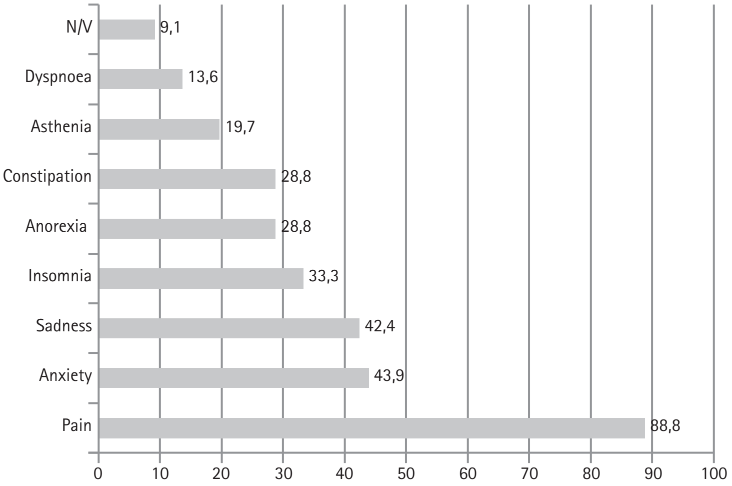
From February 2013 to December 2013, 67 new patients were visited; their main characteristics are shown in **Table 1**. The majority of patients (63 patients -94%) were diagnosed with MM and the remaining were diagnosed with solitary plasmocytoma. Main reasons for consultation were: pain in 37 (55%) patients, shared follow-up in 28 (42%), and others causes in 2 (3%). Symptom frequency at first encounter is shown in **Figure 1**. With respect to pain, 56 patients (88.8%) reported pain, of those 49 (87.5%) had one or more of the poor pain prognostic factors in the ECS-CP (data not shown).With respect the main pain site it was mainly located by the patient in the spine and limbs, with 1/8 of the patients complaining of polytopic pain. Forty six percent of the patients reported interference in their general activity and mood, and 27% in sleep. Nine patients (13%) referring mood disturbance suffered a depressive episode, accordingly the Endicott criteria.

Table 1. Demographic characteristics at the first visit of the patients cared at the integrative Multiple Myeloma Palliative outpatient clinic

Item	
Gender: women/men (n [%])	33 [49.3] / 34 [50.7]
Age (mean; SD [range])	68.6 y-old; SD11y-old [39-88]
PPS (Median [IQR])	80% [Q1: 70%; Q3: 90%]
Barthel Index (Median [IQR])	100 [Q1: 90; Q3: 100]
Time from diagnoses to consultation (Median [IQR])	355 days [Q1: 76; Q3: 1027]
MM stage: ISS (n [%])*	
I	29 [44]
II	17 [26]
III	20 [30]
MM antitumor treatment status at 1st clinical encounter (n [%])	
Yes	55 [82]
No	12 [18]

SD: Standard Deviation
PPS: Palliative Performance Status
IQR: Inter quartile range Q1-Q3
*Missing = 1patient

Figure 1. Symptom frequency (%) at first visit at the integrative Multiple Myeloma Palliative outpatient clinic



N/V: Nausea & Vomiting

The median time between the first clinical encounter at the MM-PAL and the first, second and third follow-up visits were: 14 days (IQ1:7; IQ3:14), 21 days (IQ1:21; IQ3:28), and 60 days (IQ1:45; IQ3:63), respectively. It was a significant improvement ($P<0.0001$) in median Worst and Average pain during the follow-up time. (**Figure 2**) The proportion of patients with moderate-severe ($NVS \geq 5$) Worst pain at first encounter were 57% and at the 3rd follow-up visit 18% ($P<0.0001$) and, moderate-severe Average pain were 24% and 2% ($P<0.0001$) at first encounter and 3rd follow-up visit, respectively. (**Figure 3**) The proportion of patients reporting no pain interference from the first encounter vs. 3rd follow-up visit increased; general activity (52% vs. 82%; $P=0.0001$), insomnia (73% vs. 91%; $P=0.01$) and mood (52% vs. 87.5%; $P=0.0001$). In parallel, the proportion of patients treated with strong opioids increased significantly during the follow-up period, from 43.3% at the first encounter to 79.1% at the 3rd follow-up visit ($P<0.0001$).

Figure 2. Evolution of the median scores of the Worst and Average pain through the follow-up time

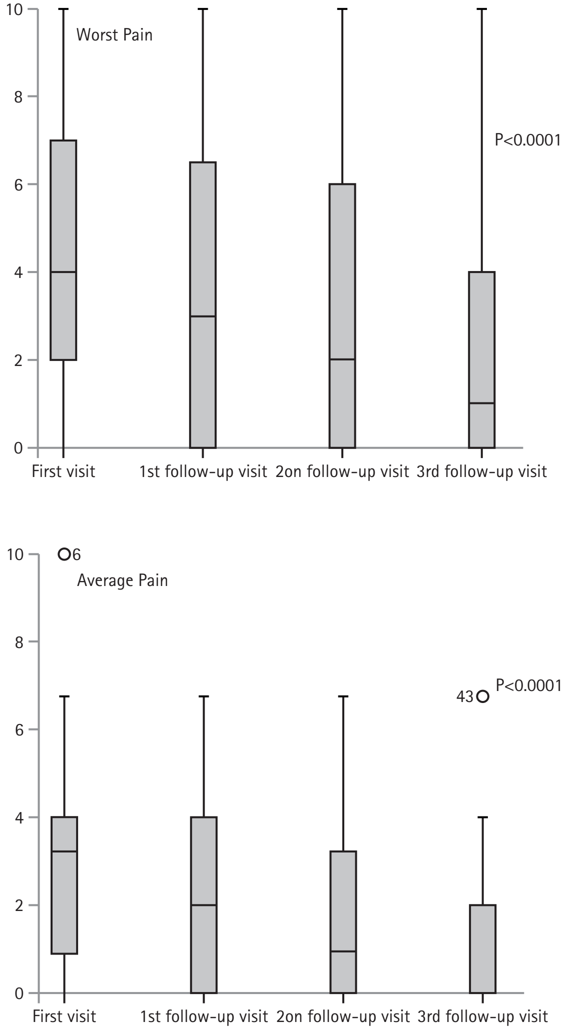
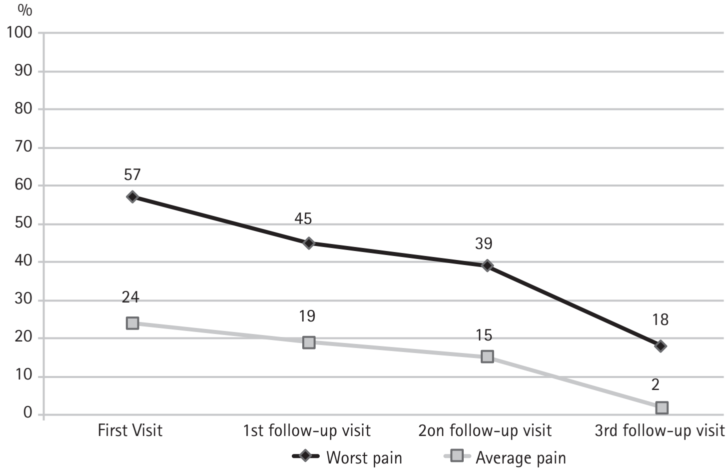
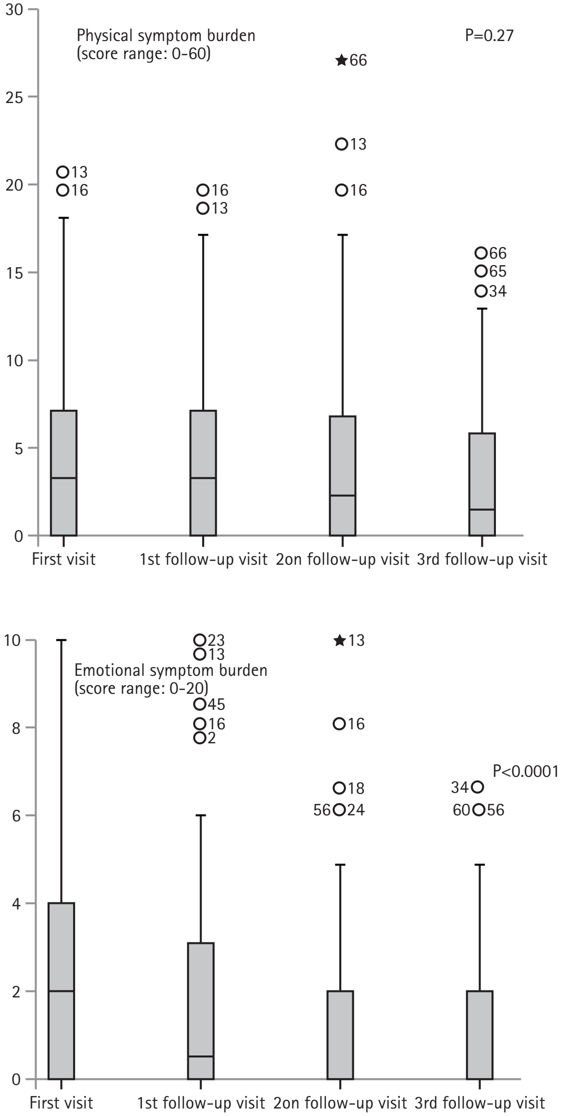


Figure 3. Evolution through follow-up of the proportion of patients with moderate-severe (NVS ≥ 5) Worst and Average pain



With regard physical symptoms other than pain, and emotional symptoms, the mean values at the first visit were mild: asthenia 0.77 (SD 1.91), anorexia 1.15 (SD 1.95), constipation 1.09 (SD 2.15), Insomnia 1.32 (SD 2.23), nausea/vomiting 0.14 (SD 0.46), dyspnoea 0.27 (SD 0.85), anxiety 1.14 (SD 1.64), and sadness 1.2 (SD 1.6). Even though, the median symptom burden was low, both median of physical symptom burden (excluding pain), and median of the emotional symptom burden decreased significantly alongside the follow-up. (**Figure 4**) The proportion of patients with a depressive episode also decreased significantly from the first encounter (13%) to the 3rd follow-up visit (5%) (P=0.001).

Figure 4. Evolution of the median scores of the physical and emotional burden scores during the follow-up time



During the follow-up period 5 patients (7.5%) died, 1 patient was transferred home for follow-up by the home palliative care team, and 3 patients were unavailable follow-up despite the efforts made to get in touch with them; therefore 58 patients (86.6%) were alive and continue attending the MM-PAL.

Discussion

To our knowledge, this is the first report publishing clinical results of an early palliative care intervention in patients with a haematological malignancy as the MM.

At the beginning the Hospice Movement/Palliative Care, in the early 70's, it was mainly associated with the care of the dying, and patients were admitted into hospices when «all curative and palliative measures» had been ruled out (Clark, 1999). More recently, clinicians have moved away from restricting palliative care to incurable disease. This new viewpoint is supported by the fact that the current improvements in antitumor treatments, including less toxic chemotherapy, more efficient radiotherapy and less aggressive surgery, alongside new tumour biological control methods. Consequently, patients are living longer with cancer than in the past, and especially older people who have other significant co-morbidities, so the exact definition of 'cure' is becoming less relevant (Sepulveda, Marlin, Yoshida & Ullrich, 2002).

Nowadays, palliative care intervention has been widely recognised for many oncology societies as a key quality aspect in the care of cancer patients (ASCO-ESMO consensus statement on quality cancer care.2006; [Declaración institucional para el desarollo de la atención multidisciplinar en cáncer en españa].2010; European Partnership Action Against Cancer consensus group *et al.*, 2014).

Temel et al (Temel *et al.*, 2007) published a phase II trial concluding that an early palliative care in the ambulatory setting in patients with newly diagnosed advanced non–small-cell lung cancer (NSCLC) is feasible without any harm to the patients. In a latter phase III trial (Temel *et al.*, 2010) enrolling newly diagnosed advanced NSCLC whom were randomly assigned to receive either early palliative care integrated with standard oncology care or standard oncology care alone; after 12 weeks follow-up it was demonstrated that early palliative care led to significant improvements in both quality of life and mood. Patients receiving early palliative care had less aggressive care at the end of life but longer survival. Afterwards, published revisions (Otsuka *et al*., 2013; Smith *et al*., 2012) provide evidence of the early involvement of palliative care benefits in cancer care, in terms of patient and family satisfaction, quality of life scores, less emergency department visits and reduction in economic expenditures. These findings have been supported by recent studies (Groh *et al*., 2013; Tangeman, Rudra, Kerr & Grant, 2014; Zimmermann *et al*., 2014).

The evidence of benefits in early palliative care interventions in solid tumours, encouraged a more prompt collaboration between palliative care and haematology (Epstein, Goldberg & Meier, 2012), because it is still subobtimal. There is recent evidence that referrals to palliative care in case of haematological tumours are delayed in comparison with solid tumours (Hui *et al*., 2014). This could be attributed to different causes; on the one hand, the special clinical course characteristics of haematological malignancies that can change the therapeutic approach to healing to a situation of end of life in a short time (Manitta *et al*., 2010). On the other hand, the limited haematologist's training in palliative care, the unrealistic expectation of antitumor treatments, the inadequacy of home care services and the close and sometimes paternalistic relationship between the patients and families or caregivers are factors that also can influence early consultation to the palliative care team (Corbett *et al*., 2013; Manitta *et al*., 2010; Odejide *et al*., 2014; Tazi *et al*., 2011).

In our study, patients with MM were referred to the MM-PAL after a median time from diagnosis of 355 days, which can be considered a short time in the context of a disease with a current median survival of 7 years (Morgan *et al*., 2009) and nearly half of them for shared intervention and not only for pain control as the principal explicit request. This allows us to consider an early diagnosed cohort of MM patients. It is notable that after pain, emotional symptoms (sadness and anxiety) were the two most prevalent symptoms. In a study (Jordan *et al*., 2014) enrolling 154 MM patients with a mean time after diagnosis of 3.7 years, the more prevalent symptoms were fatigue (59 %), bone pain (51 %), sleepiness (36 %), hypoesthesia or paresthesia (33 %), and muscle cramps (31 %), and 51% were considered moderate-severely symptomatic. In contrast, in our study the symptom, with the exception of pain, intensity at the first clinical encounter could be considered mild which could be a reflection of the early patient referral. Boland *et al*. (2013), in a prospective cross-sectional cohort study reported that 50% of MM patients reported pain; the same authors (Boland *et al*., 2014), using the Sheffield Profile Assessment Referal for Care (SPARC) as comprehensive assessment tool, evaluate the needs of 32 patients diagnosed with MM who were with stable disease after the first treatment post autologous stem cell transplantation (ASCT). They found that 50% of patients referred to tiredness, 33% insomnia and somnolence, 44% pain, 33% were worried about treatment's side effects, 31% had their sexual life affected by the illness, and 40% was worried about their families. In summary, even though the symptom prevalence can change accordingly with the moment and the stage of the MM, different studies show the need to face the great varaiety of needs of these patients and their families, the treatment individualization of the symptom burden and introducing the advanced care planning (Boland *et al*., 2013; Manitta, Zordan, Cole-Sinclair, Nandurkar & Philip, 2011; Niscola, Tendas, Scaramucci & Giovannini, 2014; Odejide *et al*., 2014).

Physical and emotional symptom improvement in our study could be the result of many concurrent reasons: early symptom assessment and its treatment, support from nursing phone follow-up, better treatment decision-making and antitumor treatment. Areas and reasons for palliative care benefit are well described in the literature with evidence in pain and symptom control, anxiety, reduced hospital admissions, and expenditure (Gomez-Batiste *et al*., 2010; Higginson & Evans, 2010). Furthermore, studies are needed to better identify aspects that most benefit patients and their families at the different stages of the course of MM. Our findings show that is feasible a palliative care intervention in MM patients, with the 86.6% of the patients followed at the MM-PAL after a median time of 60 days, and together with significant improvement of emotional and physical symptoms.

Limitations worth noting. First, data collection reliability could be considered affected by being a retrospective study and the variable time of collection. We consider that this problem is minimized due to the fact that only two researchers were involved in data assessment and collection (JPS, MGT). Secondly, the results only reflect changes in pain and other physical and emotional symptoms, so other relevant aspects in palliative care as social and spiritual issues has not been reported giving only a partial picture of the palliative care intervention; even though, we deem that the information given offers a valid information that reflects the benefit obtained by patients.

Conclusions

This study adds a new perspective that is possible an early palliative care intervention in patients with haematological malignancies, despite the papers describing the difficulties in the interaction between palliative care and haematology.

Disclosures

Part of this study was presented as oral communication in the 10th Spanish Congress of the Palliative Care Society (SECPAL), held in Madrid, 8-10 November 2014.

Acknowledgements

We thank all the haematology and palliative care services personnel without whom most of this work could not have been done. We also thank Dr. Cristina Monforte and Prof. Albert Balaguer from the *WeCare* Chair: end of life care, Universitat Internacional de Catalunya. (Barcelona) for its support, and our gratitude for the English editorial support to Rebecca D. Latter.

Conflicts of interest: None

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Josep Porta-Sales. MD. PhD
Palliative Care Service of the Institut Català d'Oncologia
Avda. Gran Via de l'Hospitalet, 199-203
08907 L'Hospitalet de Llobregat
Barcelona. Spain
jporta@iconcologia.net