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Early palliative care versus usual haematological care in multiple myeloma: retrospective cohort study

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► Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/spcare-2023-004524).

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Received 27 July 2023
Accepted 1 August 2023

To cite: Giusti D, Colaci E, Pioli V, *et al*. *BMJ Supportive & Palliative Care* Epub ahead of print: [please include Day Month Year]. doi:10.1136/spcare-2023-004524

ABSTRACT

Objectives Although early palliative care (EPC) is beneficial in acute myeloid leukaemia, little is known about EPC value in multiple myeloma (MM). We compared quality indicators for palliative and end-of-life (EOL) care in patients with MM receiving EPC with those of patients who received usual haematological care (UHC).

Methods This observational, retrospective study was based on 290 consecutive patients with MM. The following indicators were abstracted: providing psychological support, assessing/managing pain, discussing goals of care, promoting advance care plan, accessing home care services; no anti-MM treatment within 14 and 30 days and hospice length of stay >7 days before death; no cardiopulmonary resuscitation, no intubation, <2 hospitalisations and emergency department visits within 30 days before death. Comparisons were performed using unadjusted and confounder-adjusted regression models.

Results 55 patients received EPC and 231 UHC. Compared with UHC patients, EPC patients had a significantly higher number of quality indicators of care (mean 2.62±1.25 vs 1.12±0.95; p<0.0001)); a significant reduction of pain intensity over time (p<0.01) and a trend towards reduced aggressiveness at EOL, with the same survival (5.3 vs 5.46 years; p=0.74)).

Conclusions Our data support the value of integrating EPC into MM routine practice and lay the groundwork for future prospective comparative studies.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Early palliative care (EPC) is beneficial for patients with acute myeloid leukaemia or undergoing stem cell transplant but there are scanty information about its effect in patients with other haematological malignancies (HM).

WHAT THIS STUDY ADDS

⇒ Patients with multiple myeloma (MM) receiving EPC, when compared with those undergoing usual haematological care, have better pain control, with longer use of strong opioids; higher rates of symptom management; more frequent goals of care discussions; earlier access to home care services and a trend towards higher quality of end-of-life care.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This study supports the value of integrating EPC into MM routine practice and may also lay the groundwork for future prospective comparative studies either in this setting or in patients with other HM.

INTRODUCTION

Early palliative care (EPC) in patients with advanced solid cancers has shown several benefits, including increased survival.[1]

Recent studies have demonstrated that provision of EPC is useful also for patients undergoing stem cell transplantation and with acute myeloid leukaemia and recommended it as the new standard of care in this latter setting.[2–5] This success has raised

the need to identify other patients with haematological malignancies (HM) who may benefit from EPC.[6] Patients with multiple myeloma (MM) represent a prime example of a population that could potentially benefit from this approach, as MM is incurable and affected patients typically experience high and unmet symptom needs.[7 8]

On these grounds, we examined the presence of quality indicators for palliative and end-of-life (EOL) care in a cohort of consecutive patients with MM receiving outpatient EPC and compared them with those of a cohort of patients receiving usual haematological care (UHC).

PATIENTS AND METHODS

Study design and outcome

This is a retrospective cohort study of patients with MM who received EPC or UHC. We compared primary outcomes of quality indicators of PC and EOL care in patients who received EPC versus UHC. We also secondarily compared the number of treatments and overall survival (OS) between the EPC and UHC groups.

Population and interventions

From January 2011 to December 2020, all consecutive MM patients who had their treatment initiated at the study institution were considered eligible for this study. The demographic and clinical data extracted from hospital chart were reported in online supplemental material.

EPC was defined as integration of palliative care within 8 weeks from cancer diagnosis, as previously reported.[1 4] After starting in that time frame from the diagnosis of MM, the EPC visits were delivered as previously described[4] and reported in details in online supplemental material.

Usual haematological care

The frequency of UHC visits depended on the patient's specific MM treatment plan. Patients undergoing UHC received standard haematological care with the supportive care measures instituted by the haematological team. The haematologists who provided UHC had not any training in palliative care.

Quality indicators for palliative and EOL care

We conducted electronically structured and comprehensive reviews of electronic hospital chart to determine the presence of quality indicators for palliative and EOL care for EPC and for UHC patients as previously reported[4] and described in details in online supplemental material.

Statistical analysis

The statistical analysis is described in details in online supplemental material.

We used the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) cohort checklist when writing our report.[9]

RESULTS

Overall 290 consecutive patients with MM were enrolled. Four were excluded because they had started treatment at other institutions before transitioning their care to the study institution. Of the remaining 286 patients, 55 received EPC and 231 received UHC (online supplemental figure S1). Median time of follow-up was 41 (range 1–117) months for EPC and 38 (range 1–118) for UHC patients. Clinical characteristics of the patients are detailed in online supplemental table S1.

Quality indicators of palliative care

Table 1 shows that EPC patients received a significantly higher number of quality indicators of PC compared with UHC patients, (mean 2.62±1.25 vs 1.12±0.95 (adjusted MR 2.18 (95% CI 1.75 to 2.73; p<0.001)) (online supplemental figure S1A,B).

In the EPC group, the median times from the first documented goals of care (GOC) discussion and ACP promotion to death were 162 days (range 3–1368) and 76 days (range 3–924), compared with 29 days (range 2–1595) for GOC in UHC patients, (p<0.001and no calculable). The difference between patients of the two cohorts accessing home care services was not statistically significant (table 1).

In EPC patients but not in UHC patients, reduction in pain intensity improved significantly over time across the time points considered [mean Numeric Rating Scale (NRS) values 1.86±2.78 at T0, 1.03±2.24 at week 1 (p=0.01); 0.41±1.57 at week 4 (p=0.001)] (online supplemental table S2A).

Consistent with this, 40 (72.7%) out of 55 EPC patients received treatment with strong opioids

Table 1 Quality indicators for palliative care in patients with multiple myeloma receiving EPC or UHC

Indicators	EPC N=55 (%)	UHC N=231 (%)	Measure	Adjusted (95%CI)	P value
Psychological Support	64.4	28.6	OR	4.64 (2.41 to 8.43)	<0.0001
Assessing and managing pain	100	68.4	OR	nc	nc
Discussion of GOC	74.6	4.3	HR	21.44 (9.75 to 47.16)	<0.0001
Promotion of ACP	13.6	0.0	HR	nc	nc
Home care service utilisation	30.5	22.5	HR	1.1 (0.84 to 2.71)	0.1638

The analysis was adjusted for the following variables in the regression models: age (years), sex (male, female), stage (I, II, III), MMFS = Multiple Myeloma Frailty Score (fit, unfit, frail), intensity of first-line therapy (transplant, no transplant).
ACP, advanced care planning; EPC, early palliative care patients; GOC, goals of care; n, number; nc, no calculable; UHC, usual haematological care.

compared with 129 (55.8%) UHC patients (adjusted OR 1.88 (95% CI 0.93 to 3.82; p=0.07)).

Mean duration of treatment with strong opioids was significantly longer in EPC than in UHC patients (p<0.001)) (online supplemental table S2B).

Quality indicators of EOL care

Of the entire study cohort, 115 patients died (22 in the EPC group, 93 in the UHC group) and formed the group in which we assessed quality of EOL care.

The analysis of the indicators of aggressiveness at EOL showed that, compared with UHC patients, EPC patients were less likely to receive aggressiveness at the EOL. However, these differences were not statistically significant (online supplemental table S3).

Number of treatment lines and OS

We calculated the number of treatment lines received by patients of the two cohort and whether differences in such a number could have influenced the survival. Compared with UHC patients, the EPC group received a lower mean number of treatment lines (1.53±0.77 vs 1.90±1.21, MR of 0.76 (95% CI 0.60 to 0.97; p=0.03)) and less frequently three and four or more lines of treatment (adjusted OR 0.33 (95% CI 0.13 to 0.86; p=0.02) and 0.11 (95% CI 0.01 to 0.89; p=0.03, respectively) (online supplemental table S1 and figure S3A).

Median OS was 5.30 years for EPC group and 5.46 years for UHC group (adjusted HR 0.92; 95% CI 0.56 to 1.51; p=0.7429) (online supplemental figure S3B).

DISCUSSION

In this retrospective cohort study comparing patients with MM receiving EPC versus usual care, those receiving EPC had better pain control, with longer use of strong opioids; higher rates of symptom management; more frequent GOC discussions, earlier in the disease trajectory and a trend towards higher quality of EOL care.

Pain is the most frequent symptom and the most common cause of first PC consultation in patients with MM.[7 10] A recent study reported that a PC intervention within 1 year from diagnosis may significantly contribute to its reduction.[11] Our study provides novel insights by showing that in EPC patients, pain intensity was reduced already after 1 week, and throughout the follow-up, which was not the case for patients having received UHC. This finding underscores the relevance of integrating PC as early as possible in the disease trajectory of patients with MM.

Further primary clinical concerns of MM patients are represented by decreased emotional, physical and social functioning, coping with side effects and information needs.[7 12] In our study, EPC patients were offered more frequently psychological support and obtained more information about the likely trajectory of the disease than UHC patients. These results, which are in line with previous observations in other cancer populations, indicate that EPC may provide a better coverage of MM patients' needs and support its implementation also in MM routine practice settings.[2–4]

Guidelines in solid tumours and recent reviews in HM recommend engaging patients in conversations weighing explicitly the benefits and risks of continuing with disease-directed therapies and evaluating symptom-directed care.[6 13] Our findings indicate that EPC patients were more frequently involved in discussions of prognosis and GOC and in the promotion of ACP than UHC patients.

Our study did not show a significant decrease of aggressiveness of care at the EOL, although EPC patients showed reduced ratios in 7 out of 7 indicators. However, it should be noted that less than 5% of EPC MM patients received anti-MM treatment in the last 14 days of life, when receipt of disease-directed therapies by less than 10% of patients with cancer in that timespan has been described as a condition associated with less aggressiveness of care.[14] Moreover, the percentage of our EPC patients receiving anti-MM treatment in the last month of life is less than the 34% reported in a previous study of MM patients undergoing late palliative care, and suggests, again, that an earlier PC intervention may be associated with further reduction of aggressiveness at EOL.[14]

The trend for a reduced aggressiveness at EOL is further supported by the observation that significantly fewer EPC than UHC patients received three or more lines of treatment. Of note, prioritising symptom-directed care instead of disease-directed therapies did not negatively affect survival, as the OS of our EPC patients was similar to those of patients receiving UHC and similar to that reported in the literature.[8]

Our study has several limitations. The first one is the retrospective nature of the data. Also, incomplete data reporting may have underestimated the quality-of-care measures. Finally, being a single-centre study, results may have limited generalisability to other centres where trained supportive and palliative care teams may not be available. These limitations notwithstanding, our study represents one of the most comprehensive reports on patients with MM treated in a real-world setting and having received EPC.

In conclusion, our results suggest that EPC is feasible in patients with MM and results in better quality of care, including better management of pain, more psychological support, more frequent GOC and ACP discussions and a trend to reduced aggressiveness at the EOL, without negatively impacting survival. Our findings may also lay the groundwork for future prospective comparative studies in patients with MM.

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Contributors DG and LP have full access to all of the data used in the study and take the responsibility for the integrity of the data and the accuracy of the data analysis. DG, EC, VP, FBa, MMa, GL, MMo, FF, RM, FBe, AC, PB, AM, AG, IB, RD'A and LP have contributed to the acquisition, analysis and interpretation of data. LC, ES, GL, FG, EBo, SB, CAP, FE, OO, CZ, EBr, ML and EBa have commented on manuscript draft, final version and approved the submitted manuscript. FBa and RD'A performed statistical analysis.

Funding This research was partly supported by the Fondazione GIMEMA Franco Mandelli onlus and PNRR CN3 Terapia Genica-Spoke 2 (ML).

Competing interests FF: advisory boards for Jannsen and Novartis and travel grants from Jazz Pharmaceuticals outside the submitted work. RM: honoraria from AbbVie, Roche, Janssen, and Shire, outside the submitted work. FE: consultancy for Abbvie, Amgen, Janssen, Orsenix, Takeda, and grants from Amgen (to his Institution), outside the submitted work. EB: grants from Helsinn Healthcare, outside of the submitted work. ML: advisory board Abbvie, Novartis, Gilead science, Jazz Pharmaceuticals, Sanofi, MSD, Daiichi-Sankyo, Travel grant Gilead science.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and was approved by local Ethics Committee, protocol no. CE 833/2018. Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; internally peer reviewed.

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SUPPLEMENTAL MATERIAL

PATIENTS and METHODS

Population and Interventions

Demographic and clinical data

The following demographic and clinical data were extracted: age, sex, MM stage according to the International Staging System (ISS), geriatric vulnerability according to the Multiple Myeloma Frailty Score (MMFS)[1] for patients older than 65 years, type of first line treatment, and number of lines of therapy.

EPC intervention

Consistent with existing literature and with our previous experiences either in solid cancer or AML patients, the EPC visits comprised all palliative care-specific tasks such as assessment and management of symptoms, providing support in decision making and future planning, facilitation of coping, providing physical and emotional support as well as cultivation of the prognostic awareness [2–4]. The palliative care team also provided liaison with specific home-care services and regular phone calls to patients who could not attend scheduled visits. In line with previously reported studies, the frequency of EPC encounters was weekly for the first two months, and then monthly for every two months, according to the phase of treatment, until death[4]. More frequent follow-up EPC consultations were scheduled according to the patients' needs/wishes. The scheduled duration of the first EPC visit was approximately one hour, and follow-up appointments were around 30 minutes[2,4]. For the same reasons, we considered patients who received three or more visits in the EPC clinic to have undergone a full EPC intervention[2,4].

Quality Indicators for Palliative and EOL Care

Quality Indicators for Palliative Care

Consistent with existing literature and with our previous experience in AML patients, the following indicators of quality for PC were considered: providing psychological support, assessing and managing pain, discussing goals of care (GOC), promoting an advance care plan (ACP), and accessing home-care services[5]. *Psychological support* was defined as any of the following: (1) a psychiatric or neurogeriatric consultation; (2) a psychological interview; or (3) a prescription for psychotropic drugs by a specialist[6]. Pain assessment was determined as the number of times the pain intensity, measured using the Numerical Rating Scale (NRS), where evaluated and reported during the visits either EPC or UHC. Pain control was measured as decline of pain intensity at week 1 (time 1) and at week 4 (time 2) from baseline assessment.

The number of patients receiving strong opioids treatment and the duration of opioid therapy, were also recorded.

GOC discussions were considered to be present when the following elements were recorded in the hospital chart: goals and values, prognosis, treatment choices, life-sustaining treatment preferences, and discussion of either hospice or comfort care[5]. The promotion of ACP was abstracted from the chart when all the following elements were documented: (1) presence of a written advance directive; (2) documentation of a GOC discussion; and (3) identification of a surrogate decision maker[5].

Quality indicators for EOL care

In the subset of the cohort that died during the study period, we assessed four EOL care quality indicators deemed acceptable by more than 75% of 349 hematologic oncologists: no anti-MM treatment within 14 days before death; no cardiopulmonary resuscitation (CPR) and no intubation within 30 days before death; hospice length of stay >7days before death[7]. In addition, we assessed three indicators that were reported in the early work endorsing and developing these measures for patients with solid tumours and in our previous work showing the efficacy of EPC in improving EOL care in patients with AML[8]: no anti-MM treatment within 30 days before death; fewer than two hospitalizations and fewer than 2 emergency department accesses within 30 days before death[8,9].

Anti-MM Treatments

For the purpose of this analysis, the anti-MM treatments considered were all classes of drugs used in the treatment of patients with MM, including proteasome inhibitors, immunomodulatory drugs, standard chemotherapeutic agents, monoclonal antibodies, histone deacetylase inhibitors[10,11].

Statistical Analysis

Descriptive characteristics were reported as the mean ± standard deviation (SD) or as the median and range for numerical variables and as the absolute and percentage frequencies for categorical variables. Comparisons between the two groups (EPC and UHC patients) were performed using unadjusted and confounder-adjusted regression models. Variables that we adjusted for in our regression models included: age (years), sex (male, female), stage (I, II, III), MMFS (fit, unfit, frail), intensity of first line therapy (transplant, no transplant).

Linear models were used for continuous outcomes, logistic models for binary outcomes, Poisson models for count outcomes and Cox models for time-to-event outcomes. Results of regression models were reported as the mean difference (MD), odds ratio (OR), mean ratio (MR) and hazard ratio (HR), respectively. Uncertainty in results was expressed by using 95%

confidence intervals (CI). NRS score values at week1 and 4 were compared to the baseline scores using a Wilcoxon signed-rank test for paired data. For time-to-event outcomes, Kaplan-Meier curves were used to graphically display the incidence of events over time and to calculate median survival times. Statistical analyses were carried out by using R 3.6.3 software (The R Foundation for Statistical Computing, Wien). The significance level was set at $p < 0.05$.

Supplementary Tables

Table S1. Patients' Clinical Characteristics.

	Patients	EPC	UHC
	286	55	231
Age [median (range)]	66.5 (33-93)	67 (33-89)	66 (40-93)
Sex (N/%)			
Male	161 (56)	29 (53)	132 (57)
Female	125 (43)	26 (47)	99 (43)
MM ISS (N/%)			
1	83 (29)	22 (40)	61 (26,4)
2	63 (22)	12 (22)	51 (22,1)
3	67 (23.4)	21 (38)	46 (19,9)
n.a.	73 (25.6)	0 (0)	73 (31,6)
MMFS* (N/Pts >65y/%)			
Fit	47/157 (30)	13/37 (35.2)	34/120 (28,3)
Unfit	54/157 (34.3)	12/37 (32.4)	42/120 (35)
Frail	56/157 (35.7)	12/37 (32.4)	44/120 (36,7)
First Line Treatment (N/%)			
AutoSCT	113 (41.3)	17 (32.2)	96 (43.3)
Alkilating agents + Proteasome inhibitors	98 (34.2)	25 (45.4)	73 (30.3)
Proteasome inhibitors + steroids	14 (4.8)	2 (3.6)	12 (5.2)
Immunomodulatory drugs±Proteasome inhibitors	42 (14.6)	9 (16.3)	33 (14.2)
Alkylating agents	18 (6.2)	1 (1.8)	17 (7.3)
BSC	1 (0.3)	1 (1.8)	0 (0)
N° of AutoSCT (N/%)			
1	67 (23,4)	10 (18,6)	57 (24,7)
2	46 (15,9)	7 (11,9)	39 (16,9)
N° of Treatment Lines (N/%)			
1^-2	228 (79.7)	49 (89.1)	179 (77.5)

3-4	45 (15.8)	6 (10.9)	39 (16.9)
>4	13 (4.5)	0 (0)	13 (5.6)

EPC = Early Palliative Care; UHC = Usual Hematologic Care; M = male; F = female; MM = Multiple Myeloma; ISS = International Staging System; MMFS*[1] = Multiple Myeloma Frailty Score; *only for patients older than 65; ^ = only one extremely frail patient did not receive any treatment.

Table S2A,B. Duration of Treatment with Opiates and Pain Management.

A.	Pain Management over time (mean NRS±SD)				
	T0	W1	p	W4	p
EPC	1.86±2.78	1.03±2.24	0.0184	0.41±1.57	**0.001**
UHC	0.93±2.20	0.71±1.69	0.0678	0.73±1.75	0.0608
B.	Duration of Treatment with Opiates (mean days±SD)		p		
EPC	1061.33±946.45		**0.00007**		
UHC	556±604.02				

SD = standard deviation; EPC = early palliative care patients; UHC = usual hematologic care; NRS = Numerical Rating Scale; T0 = first evaluation; W1 = week 1; W4 = week 4.

Table S3. Quality measures of end-of-life care among Multiple Myeloma decedents who received EPC or UHC.

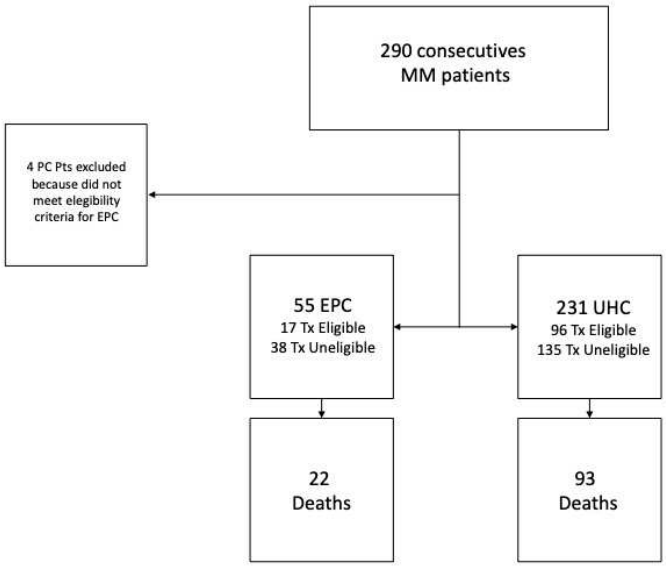
Indicators	EPC N=22 (%)	UHC N=93 (%)	Measure	Adjusted (95%CI)	p
No Anti-Myeloma Treatment					
Within 14 days of death	95.5	76.3	OR	8.33 (0.89-100)	0.06
Within 30 days of death	72.7	58.1	OR	2(0.60-6.66)	0.25
No Intubation					
within 30 days of death	100	96.7	OR	nc	nc
No CPR					
within 30 days of death	100	98.9	OR	nc	nc
Access to ED					
≥2 within 30 days of death	0	2.2	OR	nc	nc
Hospitalisation					
≥2 within 30 days of death	9.1	12.9	OR	1.63 (0.24-11.12)	0.61
Hospice					
length of stay >7days before death	13.6	9.7	OR	0.94 (0.20-4.553)	0.94

EPC = early palliative care patients; UHC = usual hematologic care; n = number; OR = odds ratio; ICU = intensive care unit; CPR = cardio-pulmonary resuscitation; nc= no calculable;

ED = emergency department. The analysis was adjusted for the following variables in the regression models: age (years), sex (male, female), stage (I, II, III), MMFS (fit, unfit, frail), intensity of first line therapy (transplant, no transplant).

Supplementary Figures

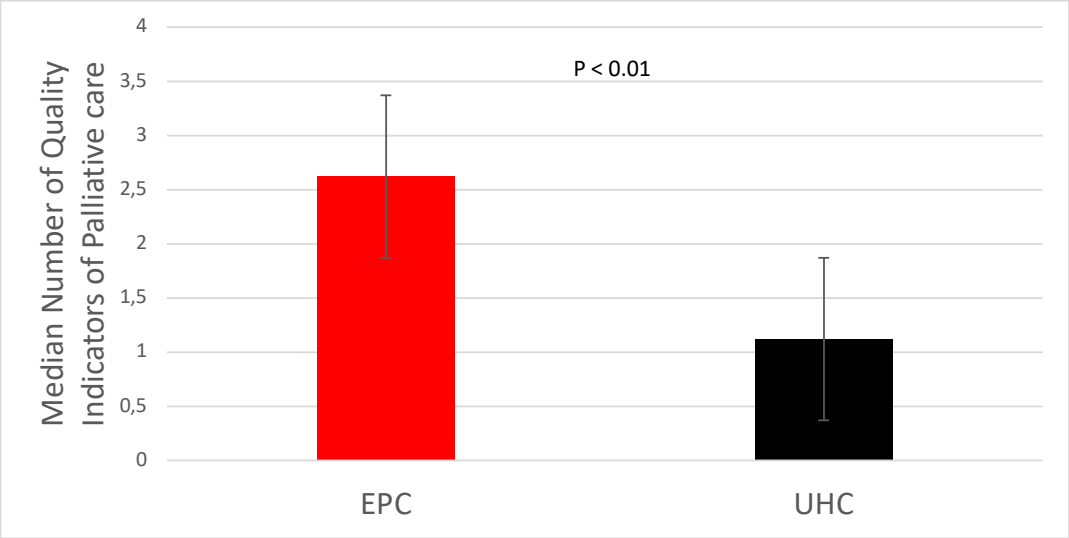
Figure S1. Study Flow Chart.



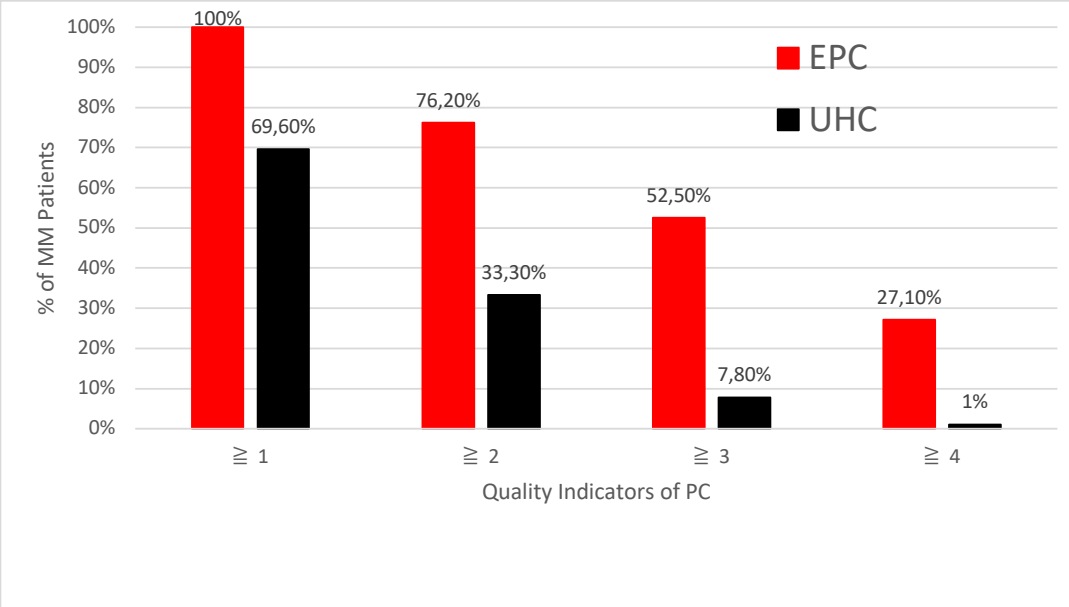
MM = multiple myeloma; PC = Palliative Care; EPC = early Palliative Care; Tx = Transplant; UHC = usual Hematological Care.

Figure S2A, B. Median number (A) and Frequency (B) of Quality Indicators of Palliative Care in MM patients.

A.

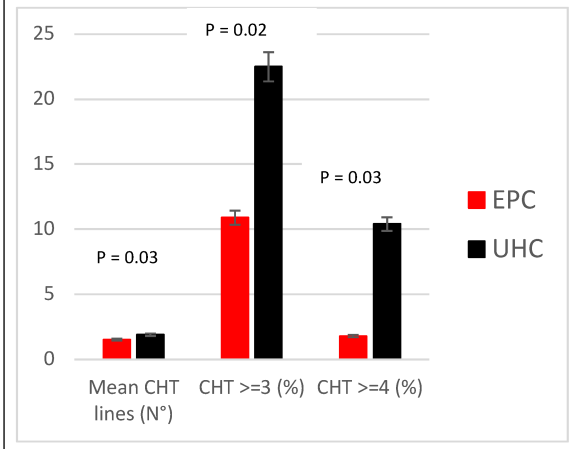


B.



MM = multiple myeloma; PC = palliative care; red columns = early palliative care; black columns = usual hematologic care; EPC = early palliative care patients; UHC = usual hematologic care.

Figure S3 A, B. Number of lines of therapy in Patients with Multiple Myeloma (C) and Overall Survival (B).



Red columns = early palliative care; black columns = usual hematologic care; EPC = early palliative care patients; UHC = usual hematologic care; CHT = anti-Myeloma treatments; red line = early palliative care patients; black line = usual hematologic care. The p values were adjusted for the following variables in the regression models: age (years), sex (male, female), stage (I, II, III), MMFS (fit, unfit, frail), intensity of first line therapy (transplant, no transplant).

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