Original article

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Palliative sedation at home: A medical act practicable everywhere

Abstract

Background: Few studies regarding palliative sedation (PS) have been carried out in-home care (HC) setting. This study aimed to describe the prevalence of PS and its associated factors for end-of-life cancer patients sedated at home in a single institution for 12 months.

Patients and methods: A retrospective study was carried out by the Tuscany Tumour Association including adult patients with a diagnosis of onco-haematologic disease, who had undergone palliative sedation at home (HPS) or not (non-HPS), in one year. Sociodemographic variables (sex and age) and clinical variables (primary tumour location, active treatment (AT) or best supportive care at the time of palliative sedation, causes of sedation, duration of sedation) were gathered from the clinical histories of the cohort of patients died at home.

Results: From January to December 2018, 591 died at home mean age was 74 years ± 14 years, 311 (52%) patients were males, and 246 (42%) were still on AT. 110 (19%) received HPS. Dyspnoea (52%) and delirium (42%) were the main refractory symptoms leading to HPS. Univariate analysis showed a significant difference between HPS and non-HPS patients according to age and gender with younger (χ^2 = 2.8, p = 0.0043) male (χ^2 = 5.5, p = 0.019) patients more likely to undergo PS. Furthermore, adjusted odds ratios for each tumour showed that the risk of sedation was lower among patients with gastrointestinal cancer (OR adj = 0.59; 95% CI: 0.37–0.94), and higher for patients with melanoma (OR adj = 5.36; 95% CI: 1.35–21.24).

Conclusions: This study confirms the feasibility and the important role as a therapeutic tool played by HPS in advanced cancer patients. It underlines the importance to pay particular attention to those patients more likely to undergo HPS (i.e. younger, males and/or melanoma patients), limiting useless or detrimental end-of-life antineoplastic treatments.

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Key words: palliative sedation, home care, palliative care, end-of-life care, cancer

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Introduction

Palliative sedation (PS) was defined by the European Association for Palliative Care (EAPC) as "the controlled use of medicinal products intended to induce a state of decreased or absent awareness to relieve the suffering that is untreatable in an ethically acceptable way for patients, families, and health professionals" [1]. Despite a precise definition, uncertainties existed in the application of PS, including the feasibility of in-home care setting, the identification and definition of the refractory symptom, the drugs to be used and clinical monitoring during PS [2]. Before resorting to PS, even in the face of acute clinical situations where death is judged imminent, it remains of primary importance to verify the actual refractoriness of the symptom to the best possible treatment. For this purpose, it becomes of crucial importance to refer to a unique definition of refractoriness, as in the following definition: "The refractory symptom is a symptom that is not adequately controlled, despite efforts to identify a treatment that is tolerable, effective, practised by an expert and that does not compromise the state of consciousness" [3].

The clinical and ethical appropriateness of PS depends precisely on the refractory judgment of the symptom. In other words, PS can and must intervene only when any further therapeutic intervention cannot bring relief to the patient or succeeds in doing so but in a time that is no longer sustainable for the patient, or at the same time entails intolerable side effects [4]. PS has been used for years with an incidence ranging from 2–52%, depending on several factors such as ethnicity, religion, institutional policies/national legislation and on the appropriate and timely decision-making process, which should be based on real patient needs [5]. This variability is probably greater when considering the palliative sedation at home (HPS), as most of the studies regarding PS have been conducted in hospice (HS) and Palliative Care units [6].

HPS has a strong rationale as cancer patients spend most of their time at home, particularly in the last weeks of life [7] and home has been regarded as the favourite place to die by Italian patients [8]. Nonetheless, the literature about HPS remains poorer compared to HS and burdened by a lack of systematization regarding the drugs used, the procedure and the monitoring of sedation and potential adverse events of PS [9].

The drugs used for PS are many different according to literature experience, with a marked preference for benzodiazepines. These drugs require an induction that achieves the patient's lowering of consciousness to obtain relief from suffering and then continues with the administration in a tailored way to the needs and requirements of the patient. Moreover, hot topics regarding PS are the maintenance of hydration and the continuation of concomitant symptomatic therapies: on this, there is still no unanimous consensus and robustness of evidence [10]. In consideration of the paucity of literature regarding HPS, and the lack of systematic protocols in the homecare setting, this work intends to be a contribution to clinical practice with the aim to describe the prevalence, characteristics and feasibility of HPS for end-of-life cancer patients in a single institution during 12 months.

Patients and methods

A retrospective study of medical records was carried out from January to December 2018 by the Tuscany Tumour Association (ATT) which manages an oncological home care service, which operates with a multidisciplinary team (palliative care specialists, nurses, psycho-oncologists, nutritionists and physiotherapists) in the metropolitan area of Florence. The service is active 7 days a week; physicians and nurses also guarantee a 24-hour availability service. All patients over 18 years with a diagnosis of oncological or haematological malignancies were included. Each procedure of HPS was performed following international guidelines in patients with:

— The life expectancy of hours/days
— Severe symptoms refractory to standard treatments
— Informed consent of the patient or — if unable to express it — of the caregiver [11].

Team members must all agree that the aforementioned criteria were all met before proceeding with palliative sedation. The drug sequence approved and used by the ATT team for HPS was the following schedule:

Induction: delorazepam 2 mg i.v. bolus, eventually followed by a further 2 mg after 5 minutes up to adequate sedation of the patient

Maintenance: haloperidol 20 mg, chlorpromazine 300 mg and delorazepam 12 mg diluted in 1000 ml of sodium chloride 9% in a 24-hour infusion (i.e. 21 ml/h).

Doses of delorazepam and chlorpromazine were adapted based on the response, meaning as a good response to HPS continuous and deep sedation. The dose of opioids was not modified if the pain was well controlled. Midazolam was not used because it was not available in the home care setting at ATT. During the HPS, physicians and nurses monitor intensively

the depth of sedation twice a day using the Ramsay Sedation Scale (RSS) [12], and they were on-call in case of emergency. An expert psychologist supported relatives as needed during the HPS period. Being an observational retrospective study of deceased patients treated in clinical practice, and approval by institutional review boards was not required (Normative reference: Gazzetta Ufficiale Della Repubblica Italiana, Serie generale number 72, of March 26th, 2012).

Each case of death at home during the study period was collected; patients who received and who did not receive HPS were categorized accordingly. Socio-demographic variables (sex and age) and clinical variables [primary tumour location, Active Antineoplastic Treatment (AT) or Best Supportive Care (BSC) at the time of sedation, causes and duration of sedation] were gathered from patients' clinical records. Data were reported as mean and standard deviation (SD) or frequencies. The alpha level for all analyses was set to $p < 0.05$. Continuous data were tested initially for equality of variances using Levene's test, and the Shapiro normality test was used subsequently to test for normality. Based on these findings, statistical comparisons were performed using either Student's *t* test or the Mann-Whitney U-test. The Chi-Square (χ^2) test or Fisher's exact test was used to compare categorical data. A multivariate logistic model was used to estimate the risk of HPS according to gender, primary tumour location (yes/no), length of discharge (days), and type of treatment (AT/BSC) as independent variables. Breast cancer and gynaecological tumour were not adjusted for sex. Adjusted odds ratios (OR adj) were reported with 95% confidence intervals (CIs). All statistical analyses were performed using STATA software (Stata Corp. 2015. Stata Statistical Software: Release 14. College Station, TX: Stata Corp LP.

Results

From January to December 2018, 1241 cancer patients were followed at home by the PC team of the ATT and a total of 762 patients were deceased. The study population consisted of the 591 patients who died at home. The median age was 74 years ± 14 years. Two-hundred and forty-six (42%) patients were receiving AT, 110 (19%) received HPS, 311 (52%) were males. The most frequent primary tumours were gastrointestinal (38%), lung (21.3%) and breast (7%) (Fig. 1). The median duration of sedation (from initiation until death) in HPS patients was 23 hours (range: 1–120). The median duration of supportive care (from the taking charge until death) was 107 days

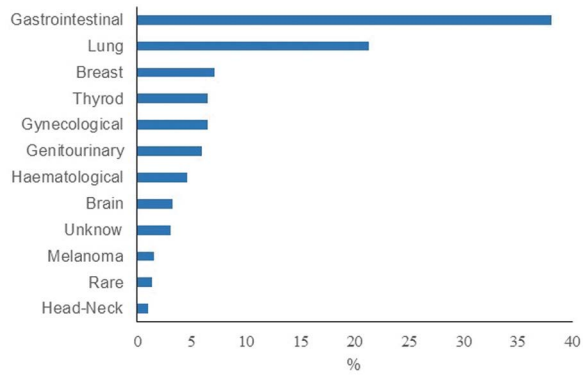

Figure 1. Distribution of the types of cancer among the study population

(range: 1–1108) for HPS patients and 119 days (range: 1–1885) for non-HPS patients, respectively.

Refractory symptoms more frequently reported as indication to sedation were: dyspnoea in 57 patients (51.8%), delirium in 46 patients (41.8%), vomiting in 3 patients (2.7%), seizure in 1 patient (0.9%), bleeding in 1 patient (0.9%) and pain in 2 patients (1.8%), respectively. As reported in Table 1, univariate analysis showed that age and gender were significantly related to the HPS procedure, with younger ($\chi^2 = 2.8$, $p = 0.0043$) male ($\chi^2 = 5.5$, $p = 0.019$) patients more likely to undergo PS. Furthermore, adjusted odds ratios for each tumour type showed that the probability of undergoing HPS was significantly lower among patients with gastrointestinal cancer (OR adj = 0.59; 95% CI: 0.37–0.94), and significantly higher for patients with melanoma (OR adj = 5.36; 95% CI: 1.35–21.24) (Fig. 2).

Discussion

Clinical research about PS is still scanty, even more considering the home care setting. As described by other authors [13], the typical patient of the present study population is a 75-years old man. Similarly, also the indications/symptoms leading to HPS initiation (dyspnoea 51.8% and delirium 41.9%) were aligned to what was previously reported [14] and in contrast with older data [15]. A modern approach and greater opioid availability likely make pain an infrequent indication for PS. Younger patients may present more complex clinical situations and be more aggressively treated in the last days of life [16, 17], therefore they are more likely to undergo HPS, as in the present study's experience.

The rate of patients who received HPS among those who died at home (19%), was higher compared to the literature (from 5% to 15%) [18]. Interestingly,

Table 1. HPS and non-HPS patients' features and univariate analysis according to gender, type of treatment at the moment of PS, primary tumour location and mean duration of palliative care (PC)

Variables	Sedation HPS (n=110) (%)		Non-HPS (n=481) (%)		Chi-Square/T-test	p-value
Gender						
Male	69	22%	242	78%	5.5352	**0.019**
Female	41	15%	239	85%		
Mean age (years) (SD)	74 (13.6)		77 (11.1)		2.8680	0.0043
Treatmen						
ATT	49	20%	197	80%	0.4746	0.491
BSC	61	18%	284	82%		
Type of Cancer						
Breast						
yes	7	17%	35	83%	0.1130	0.737
no	103	19%	446	81%		
Lung						
yes	27	21%	99	79%	0.8383	0.360
no	83	18%	382	82%		
Gastrointestinal						
yes	31	14%	194	86%	5.6063	**0.018**
no	79	22%	287	78%		
Gynaecological						
yes	10	26%	28	74%	1.5909	0.207
no	100	18%	453	82%		
Thyroid						
yes	6	16%	32	84%	0.2137	0.644
no	104	19%	449	81%		
Melanoma						
yes	5	56%	4	44%	8.2340	**0.004**
no	105	18%	477	82%		
Brain						
yes	4	21%	15	79%	0.0772	0.781
no	106	19%	466	81%		
Genitourinary						
yes	8	23%	27	77%	0.4425	0.506
no	102	18%	454	82%		
Haematological						
yes	4	15%	23	85%	0.2694	0.604
no	106	19%	458	81%		
Rare						
yes	3	38%	5	62%	1.9098	0.167
no	107	18%	476	82%		
Head and Neck						
yes	1	17%	5	83%	0.0152	0.902
no	109	19%	476	81%		
CUP						
yes	4	22%	14	78%	0.1597	0.689
no	106	19%	467	81%		
Mean duration of PC (days), (SD)	107 (167.2)		119 (193.7)		0.6725	0.5021

CUP — carcinoma of unknown primary

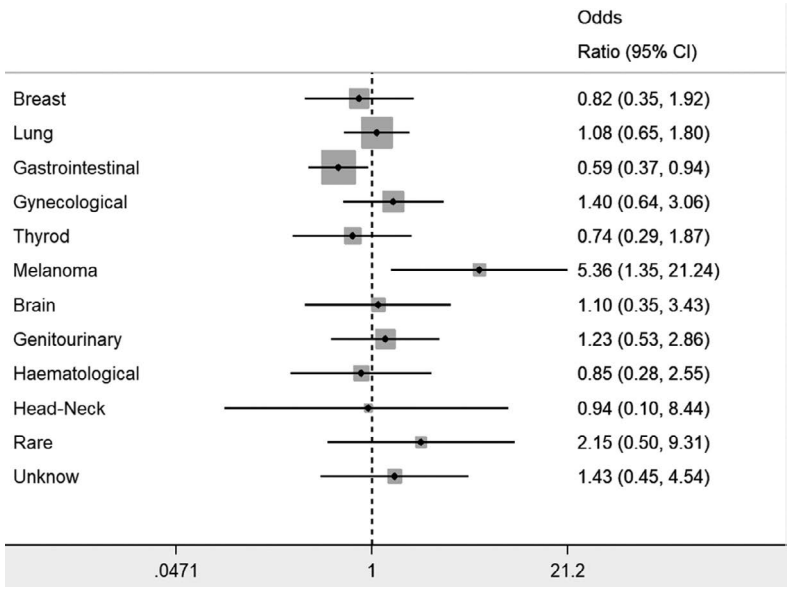

Figure 2. Risk of HPS according to multivariate logistic analysis for each type of cancer

42% of the overall patients were still under AT at the moment of death, 20% of whom received HPS. This result is slightly higher than those reported elsewhere (5–32%) [19] and might be related to the "prisoner's dilemma" of prescribing end-of-life chemotherapy [20]. While the goal of an AT with a palliative intent should be to improve or maintain quality of life, it has been revealed that end-of-life AT has limited benefits and is associated with worse quality of life and risk of toxicities [21].

The statistically significant higher probability of advanced melanoma patients undergoing HPS could be related to the tendency of these malignancies to develop brain metastases, and therefore neurologic symptoms such as delirium. However, considering the wide confidence intervals, this result must be carefully considered. Analogously, the opposite significant trend of advanced gastrointestinal cancer patients could be related to the lower tendency to metastasize to the brain. Moreover, advanced gastrointestinal cancer patients usually develop a high burden of symptoms/complications such as ascites and intestinal sub-occlusion, which often require hospitalization, impairing the probability of receiving HPS. The specific and standardized protocol of deep and continuous PS, with a daily fixed-dose of haloperidol, chlorpromazine and delorazepam, as suggested by both national [22] and European [23] guidelines, probably led to a median PS duration since the induction of 23 hours, slightly shorter compared to the 24–72 hours reported in the literature [24]. As previously described, Midazolam has not been used because "off label" in HPS setting in Italy [25].

Our study has several limitations. First, the retrospective nature of the analysis, with loss of some clinical and "decision-making" data; furthermore, the sample size, although conspicuous for being a single-institution study, limited the stratified analysis by cancer type; moreover, a more comprehensive assessment of the patient symptoms with validated tools such as the ESAS [26] or the PERSONS [27, 28] scores, could have supplied interesting data regarding additional factors influencing the choice of HPS.

This analysis underlines the importance to pay particular attention to those patients more likely to undergo HPS (i.e. younger, males and/or melanoma patients), limiting useless or detrimental end-of-life antineoplastic treatments. Prospective multicentre studies are certainly warranted to confirm the important role played by PS as a therapeutic tool in the home setting.

Declaration of conflict of interests

The authors declare that there is no conflict of interest.

Funding

None declared.

Availability of data and materials

The datasets used during the present study are available from the corresponding author upon reasonable request

Ethical statement

The procedures followed were by the precepts of Good Clinical Practice and the Declaration of Helsinki.

Authors' contributions

All authors contributed to the publication according to the ICMJE guidelines for the authorship. All authors read and approved the manuscript and agree to be accountable for all aspects of the research in ensuring that the accuracy or integrity of any part of the work is appropriately investigated and resolved.

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