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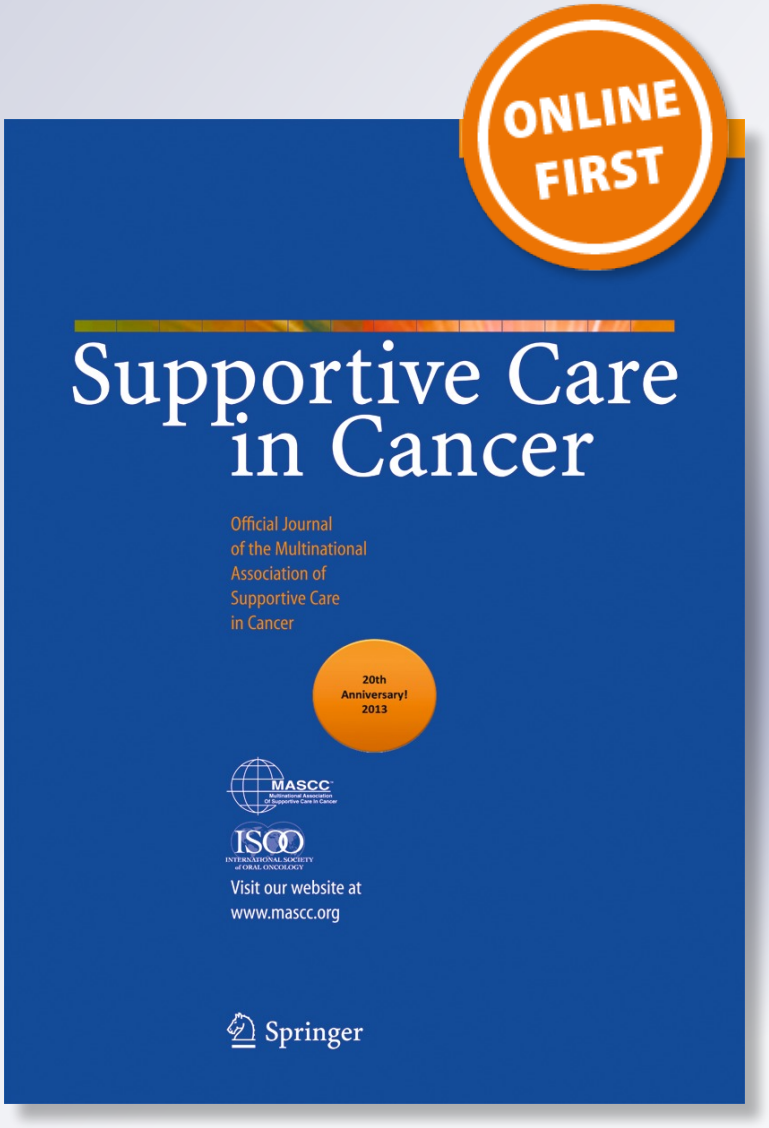

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ORIGINAL ARTICLE

Opioid use and effectiveness of its prescription at discharge in an acute pain relief and palliative care unit

Sebastiano Mercadante · Giovanna Prestia · Maurizio Ranieri · Antonello Giarratano · Alessandra Casuccio

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Abstract The aim of this study was to present how opioids are used in an acute pain relief and palliative care unit (APRPCU), where many patients with difficult pain conditions are admitted from GPs, home palliative care programs, oncology departments, other hospitals or emergency units, and other regional places. From a consecutive sample of cancer patients admitted to an APRPCU for a period of 6 months, patients who had been administered opioids were included in this survey. Basic information was collected as well as opioid therapy prescribed at admission and, subsequently, during admission and at time of discharge. Patients were discharged once stabilization of pain and symptoms were obtained and the treatment was considered to be optimized. One week after being discharged, patients or relatives were contacted by phone to gather information about the availability of opioids at dosages prescribed at time of discharge. One hundred eighty six of 231 patients were specifically admitted for uncontrolled pain, with a mean pain intensity of 6.8 (SD 2.5). The mean dose of oral morphine equivalents in patients receiving opioids before admission was 45 mg/day (range 10–500 mg). One hundred seventy five patients (75.7 %) were prescribed around the clock opioids at admission. About one third of patients changed treatment (opioid or route). Forty two of 175 (24 %), 27/58 (46.5 %), 10/22 (45.4 %), and 2/4 (50 %) patients were receiving more than 200 mg of oral morphine equivalents, as maximum dose of the first, second, third, and fourth opioid prescriptions, respectively. The pattern of opioids changed, with the highest doses administered with subsequent line options. The mean final dose of opioids, expressed as oral morphine equivalents, for all patients was 318 mg/day (SD 798), that is more than six times the doses of pre-admission opioid doses. One hundred eighty six patients (80.5 %) were prescribed a breakthrough cancer pain (BTcP) medication at admission. Sixty five patients changed their BTcP prescription, and further 27 patients changed again. Finally, eight patients were prescribed a fourth BTcP medication. Of 46 patients available for interview, the majority of them (n=39, 84 %) did not have problems with their GPs, who facilitated prescription and availability of opioids at the dosages prescribed at discharge. For patients with severe distress, APRPCUs may guarantee a high-level support to optimize pain and symptom intensities providing intensive approach and resolving highly distressing situations in a short time by optimizing the use of opioids.

Keywords Opioid use · Pain relief · Palliative care

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Introduction

Pain is one of the most prevalent, burdensome, and feared symptoms among cancer patients. Pain is experienced by at least 30 % of patients undergoing an oncological treatment for metastatic disease and by more than 70 % of advanced cancer patients. WHO guideline application has reported to achieve satisfactory pain relief in up to 90 % of patients with cancer pain, by using simple measures, even at home [1]. However, even when the basic principles for the use of

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analgesic drugs are adhered to, some patients experience insufficient pain relief, possibly because of the underuse of opioids. Mean doses of opioids vary widely between settings due to different population examined, generally at home, oncologic ward, hospice, or outpatient clinic. In a cross-sectional survey of 3,030 cancer patients among 143 palliative care centers in 21 European countries, only a minority of the patients who used opioids were receiving high doses [2]. Of those patients receiving morphine, approximately three quarters were treated with doses less than 150 mg/day. This observation may reflect that most patients are adequately treated at low or moderate doses of opioids or, more likely, that the doses are not appropriately increased in those patients who need the opioid treatment in the high-end dose range. Indeed, when higher doses of opioids are appropriately used for controlling pain, they have been found to be safe and effective when used by skilled people [3–5].

In a more recent large epidemiological study, patients who were already treated were considered poorly treated, according to a "generous" score such as the pain management index, which considers well treated all the patients on strong opioids, independently of the dose underestimating even poorer pain control [6]. Thus, even in specialized centers, opioid doses are underused or not optimally prescribed.

The acute pain relief and palliative care units (APRPCUs) have been differently described in the literature. These centers are characterized by the admission of a very selected cancer population presenting for pain and symptom management of severe intensity during all the trajectory of disease, also in patients who are still receiving active treatment of disease and not only at the end of life [7–10].

Another important question is what happens when patients optimally treated are discharged home. Despite achieving an adequate pain relief, patients discharged from hospital may have problems in obtaining the opioids prescribed because of GPs' concerns regarding the doses, as observed some years ago in a previous survey [11].

The aim of this study was to present how opioids are used in an APRPCU, where many patients with difficult pain conditions are admitted from GPs, home palliative care programs, oncology departments, other hospitals or emergency units, and other regional places. The secondary objective was to evaluate the effectiveness of this prescription when patients are discharged from the unit.

Patients and methods

The protocol study was approved by the ethical committee of the University of Palermo, and informed consent to use the data was obtained from patients or relatives. From a consecutive sample of cancer patients admitted to an APRPCU for a period of 6 months, patients who had been administered with opioids were included in this survey. Basic information was recorded, including tumor diagnosis, age, and gender. The activity of the APRPCU has been described elsewhere [9]. Other than providing medical treatment of pain and symptoms, time is spent for communication, education, and psychological care, particularly focusing on the individual needs. Special attention is paid to continuous education and practical training of the nurses during the rounds and in appropriate meetings in which the emerging cases are discussed. Patients are discharged at home once the most stable condition possible is reached, unless symptom control cannot be guaranteed for different reasons, including unfavorable clinical conditions, relatives unable to face the terminal phase at home, unavailability of home care, and so on.

Opioid therapy, including type of opioids, the maximum dose achieved with each opioid, and route of administration, prescribed at admission and, subsequently, during admission and at time of discharge was recorded. According to local policy, opioids were administered with the aim of achieving adequate pain relief (with an intensity of 4 or less on a numerical scale from 0 to 10), a limited number of breakthrough pain episodes (three episodes per day or less), and acceptable level of adverse effects (intensity of less than 2, in a scale from 0 to 3). Opioids, doses, and routes were used according to the clinical need to obtain the maximum benefit, individualizing the treatment. Opioid/route switching was performed by using initial conversion ratios previously described [12]. Patients were discharged once stabilization of pain and symptoms were obtained and the treatment was considered to be optimized.

Opioid escalation index (OEI), in milligrams or as percentage, was calculated from data recorded at admission and at discharge, according to the following formula: OEI % : $[(x - y)/y]/\text{days} \times 100$, where x is the last dose before death and y is the dose at −7, both expressed as equivalents of oral morphine; and OEImg is $(x–y)$/days [13]. For each prescription, the maximum dose of each opioid was recorded, as oral morphine equivalents. Oral morphine equivalents were calculated according to department policy [12], the conversion ratios used among opioids and routes of administration being the following: oral morphine 100=intravenous morphine 33=TTS buprenorphine 1.3=TTS Fentanyl 1=Intravenous fentanyl 1=oral methadone 20=intravenous methadone 16=oral oxycodone 70, transdermal buprenorphine 1.3.

One week after being discharged, patients or relatives were contacted by phone to gather information about the availability of opioids at dosages prescribed at time of discharge, particularly regarding the collaboration of GPs.

Statistical analysis

Data were collected and analyzed by the SPSS Software 14.0 version (SPSS, Inc.,Chicago, Ill, USA). Statistical

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analysis of quantitative data, including descriptive statistics, was performed for all the items. Frequency analysis was performed with chi-square test. The paired-sample Student's *t* test was used to compare the differences in opioid doses at the time intervals. The one-way analysis of variance was used to compare the different parametric variables. All *P* values were two-sided, and *P* values less than 0.05 were considered to indicate statistical significance.

Results

Two hundred thirty one patients were admitted to the APRPCU in the period taken into consideration. The mean age was 62.3 years (SD 11.8), and 117 patients were males. Almost all patients had an ECOG value of 2–3. The primary diagnoses were in a rank order: urogenital (n=45), lung (n=39), gastrointestinal (n=32), breast (n=30), pancreas (n=21), head–neck (n=18), liver (n=13), and others (n=33). The median time of admission was 7 days (range 3–15).

One hundred eighty six patients were specifically admitted for uncontrolled pain. Their mean pain intensity was 6.8 (SD 2.5), and they were receiving different regimens of analgesics, including non-opioid and opioid drugs, unsuccessfully. The mean dose of oral morphine equivalents in patients receiving opioids before admission was 45 mg/day (range 10–500 mg).

One hundred seventy five patients (75.7 %) were prescribed around the clock (ATC) opioids at admission. The maximum doses achieved of the first analgesic drugs achieved after dose titration are described in Table 1. Of these, ten patients were prescribed a combination of opioids or routes of administration, and seven of them were prescribed very high doses of opioids, as expressed in oral morphine equivalents. Three of them were treated with a combination of intrathecal opioids and local anesthetics, associated with systemic opioids (two patients on hydromorphone and one patient on oral morphine). Doses of intrathecal morphine achieved were relatively high (60 mg/day), and the global oral morphine equivalents were more than 6,000 mg/day.

The number of patients who changed treatment (opioid or route) and the maximum dose of each line of treatment, expressed as oral morphine equivalents, are presented in Table 1. Fifty eight, 22, and 4 patients were prescribed a second, a third, and a fourth opioid/route, respectively. The OEI% and OEImg were 3.9 (SD=13) and 2.1 (SD=19), respectively.

Forty two of 175 (24 %), 27/58 (46.5 %), 10/22 (45.4 %), and 2/4 (50 %) patients were receiving more than 200 mg of

Table 1 Number of patients who were prescribed opioids and route of opioid administration

	1° opioid		2° opioid		3° opioid		4° opioid		Discharge	
	Number	Dose mg/day	Number	Dose mg/day	Number	Dose mg/day	Number	Dose mg/day	Number	Dose mg/day
MO os	24	94 (111)	12	184 (108)	1	180			15	165 (150)
MO par (Iv-sc)	15	158 (100)	6	580 (511)	4	781 (890)	1	90	8	960 (1344)
ME os	11	377 (364)	8	662 (672)	6	226 (119)	1	225	23	441 (486)
ME iv	7	1,025 (1238)	6	230 (76)	1	375	1	125	3	185 (63)
HY os	26	360 (432)	10	443 (423)	7	333 (338)	1	240	37	618 (1358)
OX–paracetamol	5	26 (4)							2	38 (11)
OX os	16	48 (30)	2	60 (42)					12	96 (59)
OX–N os	16	48 (30)	1	20					12	44 (31)
CO–paracetamol	2	37 (10)							2	38 (11)
FEN TD	34	182 (194)	10	135 (106)	2	75 (63)			37	244 (644)
BUP TD	8	43 (25)	2	35 (7)	1	60			9	36 (16)
Tramadol	4	30 (0)							3	30 (0)
TAP	10	57 (38)	1	90					9	57 (41)
2 opioids or routes	10								9	
Total (mean)	175	205 (385)	58	318 (395)	22	467 (851)	4	170 (74)	175	318 (798)

Columns: 1° opioid=number of patients and maximum dose (SD) of the first opioid prescribed at admission; 2°opioid=number of patients who required a second opioid and maximum mean doses prescribed (SD); 3° opioid=number of patients who required a third opioid and maximum mean doses prescribed(SD); 4° opioid=number of patients required a fourth opioid and maximum mean doses prescribed (SD); Discharge=number of patients and final opioid prescribed at discharge, and mean doses

Drugs: *MO os* oral morphine, *MO par* parenteral morphine, *ME os* oral methadone, *ME iv* intravenous methadone, *HY os* oral hydromorphone, *OX–paracetamol* oxycodone and paracetamol (it is reported the dose of oxycodone), *OX os* slow-release oxycodone, *OX–N os* oxycodone–naloxone combination (it is reported the dose of oxycodone), *CO–paracetamol* codeine and paracetamol (it is reported the dose of codeine), *FEN TD* transdermal fentanyl, *BUP TD* transdermal buprenorphine, *TAP* tapentadol, 2 opioids or route=opioid combination (doses are not reported). Total doses are expressed as oral morphine equivalents

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oral morphine equivalents, as maximum dose of the first, second, third and forth opioid prescriptions, respectively. The pattern of opioids changed, with the highest doses administered with subsequent line options, especially for parenteral morphine, oral methadone, and hydromorphone. The mean final dose of opioids, expressed as oral morphine equivalents, for all patients was 318 mg/day (SD 798).

Older patients (>65 years) received lower doses of oral morphine equivalents (p=0.004) in comparison with adults at the first opioid prescription, but no difference were found in the subsequent lines. No gender differences were found. The mean pain intensity at time of discharge was 3 (SD 0.9).

One hundred eighty six patients (80.5 %) were prescribed a breakthrough cancer pain (BTcP) medication at admission. This means that some patients were initially prescribed an as needed medication without ATC medication, possibly due to an attempt of detoxification of patients presenting with opioid-induced toxicity. The number of patients who were prescribed BTcP medication and their doses in the first instance and then changed prescription is presented in Table 2. The majority of patients received parenteral opioids such as morphine and methadone, and transmucosal fentanyl with different delivery systems. Twenty six patients were prescribed non-opioids or opioids for moderate pain. Sixty five patients changed their BTcP prescription, and further 27 patients changed again. Finally, eight patients were prescribed a fourth BTcP medication.

Five patients died in the APRPCU during the admission. Three patients were discharged to other hospitals: two patients were transferred to hospice and one patient was transferred to an orthopedic ward. Data regarding emerging problems with prescription after discharge were available in 46 patients only.

Only 39 % of patients were available for interview. The majority of them (n=39, 84 %) did not have problems with their GPs, who facilitated prescription and availability of opioids at the dosages prescribed at discharge. Six patients encountered some problems with opioid prescription, and in one of these cases, it was due to the high doses of opioids prescribed at discharge.

Discussion

The findings of this study show that many patients may require complex treatments to obtain an adequate pain relief. As expected, most patients were admitted for pain control,

Table 2 Prescription of BTcP medication

	1° BTcP med		2° BTcP med		3° BTcP med		4° BTcP med		Discharge	
	Number	Mean dose (SD)	Number	Mean dose (SD)	Number	Mean dose (SD)	Number	Mean dose (SD)	Number	Mean dose (SD)
MO os mg	16	16 (49)	4	9 (5)	1	30	1	25	21	11 (19)
MO par (Iv-sc) mg	53	17 (30)	11	41 (68)	4	10 (6)	2	11(12)	31	33 (54)
ME os mg	1	5	1	5					1	5
ME iv mg	10	23 (19)	8	12 (15)	1	13	3	13(11)	4	19 (21)
SLF (μg)	18	394 (176)	11	304 (131)	5	680 (521)	1	600	23	365 (210)
FBT (μg)	26	622 (724)	15	626 (57)	9	911 (1,300)			44	613 (756)
OTFC (μg)	6	667 (854)	1	1,600	1	600			6	867 (918)
INFS (μg)	10	180 (129)	8	156 (111)	1	200	1	200	13	158 (91)
PCFE (μg)	9	255 (2,067)	3	300 (173)	3	300 (173)			9	233 (100)
Tramadol (mg)	11	39 (16)							11	39 (16)
OX–paracetamol	16	6 (2)			1	10			11	5 (1)
CO–paracetamol	5	376 (247)							5	376 (247)
Ketorolac	2	20 (14)			1	20			2	15 (21)
Paracetamol	3	550 (636)							3	550 (636)
INFS-PCFE			3	300–500 (173)					2	450 (212)
Total	186		65		27			8		186

Columns: 1° BTcP med=number of patients and maximum dose (SD) of the first BTcP medication prescribed at admission; 2° BTcP med=number of patients who required a second BTcP medication and maximum mean doses prescribed(SD); 3° BTcP med=number of patients who required a third BTcP medication and maximum mean doses prescribed(SD); 4° BTcP med=number of patients who required a fourth BTcP medication maximum mean doses prescribed (SD); Discharge=number of patients and final BTcP medication prescribed at discharge, and mean doses

Drugs: *MO os* oral morphine, *MO par* parenteral morphine, *ME os* oral methadone, *ME iv* intravenous methadone, *SLF* sublingual fentanyl, *FBT* fentanyl buccal tablet, *OTFC* oral transmucosal fentanyl citrate, *INFS* intranasal fentanyl, *PCFE* pectin nasal fentanyl, *OX–paracetamol* oxycodone–paracetamol (it is reported the dose of oxycodone), *CO–paracetamol* codeine–paracetamol (it is reported the dose of codeine)

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were undertreated, and were receiving inadequate analgesic treatment. This explains the large number of patients requiring intravenous morphine for a rapid titration, commonly used for patients who present with severe pain. More than 20 % patients received more than 200 mg/day of oral morphine equivalents, and three patients underwent an intrathecal therapy, with very high doses of spinal morphine and other systemic opioids. These opioid dosages were quite higher in respect to home care, oncological wards or hospice care patients recruited in largest studies [2, 6, 14], revealing a major complexity of pain syndromes. Doses of oral morphine equivalents at discharge were 8–10 times than the doses administered before admission. This is confirmed by the need to change opioids and/or routes in a consistent number of patients. One third of patients changed treatment and a minority of patients was administered a fourth line of treatment. Of interest, despite the opioid/route switching, which potentially should be translated in a decrease of equivalent oral morphine doses as often it occurs, opioid doses were increased in time at the second and the third switches.

According to local policy, patients were discharged only when the balance between analgesia and adverse effects was optimized [9]. This means that the final treatment was considered to be effective, when stabilization of symptoms is achieved. Of interest, the direction of patients after discharge was different, including home care assistance, oncology ward for a further evaluation to continue anticancer treatments, and only in a few cases hospice care in patients with an expected short survival, while a minimal amount of patients died in the unit, confirming previous data on the characteristics of patients admitted to the APRPCU [9]. It cannot be excluded that patients may further increase opioid dosage in the course of disease trajectory, as most patients were discharged with a relative long-survival expectancy.

Most of patients who received an opioid treatment were prescribed a BTcP medication, particularly at admission, when opioids doses were increased while providing an extra analgesia during titration. In fact, the first prescription was prevalently intravenous morphine, which is the favorite drug until stabilization is obtained. Prescription of BTcP medication changed, not necessarily because poor efficacy but to provide a rapid as easier delivery system for patients prepared to be discharged, according to the clinical need and patients' convenience. In most cases, the different formulations of transmucosal fentanyl and parenteral morphine were preferred, according to the temporal pattern of most episodes of BTcP. The pattern of BTcP medications was profoundly different from those recorded in hospice or oncological settings, where new products providing rapid analgesia were seldom prescribed [15–18]. Finally, doses prescribed were relatively high, like the doses of around the clock opioids, due to the local policy of administering doses proportional to opioid basal regimen [19]. This approach has been found as effective as safe for patients [20–22].

Despite the low number of patients available for a phone contact, data recorded were encouraging, as most patients could continue the treatment despite the large amount of opioids prescribed as around the clock and as a BTcP medication. In comparison to a previous survey, GPs were more compliant and less reluctant to prescribe opioids suggested at discharge, possibly because of the trust on the institution of provenience.

The appropriate use of opioids and continuous care seem to be worldwide determinant to achieve adequate pain control in most patients. The appropriate use of opioids may provide appreciable results, with more than 90 % of patients with mild pain for prolonged periods of time, even at home in an unselected population of cancer patients [23]. However, most patients continue to be undertreated by opioids, particularly in Italy [24]. In a home palliative setting, pain was fairly well controlled in the final week of life, with 20 % experiencing severe continuous pain [25]. Pain control in patients hospitalized in oncology centers was unsatisfactory and prescription inadequate in about 50 % of patients [26]. In another study, 82 % of patients had received inadequate treatment of cancer pain [27]. In a survey performed in a large number of Italian oncologic centers, despite receiving strong opioids, about 85 % of patients had their pain uncontrolled [28]. The recourse to strong opioids seems to be inadequate or delayed in a substantial percentage of patients, even when recruiting patients from the most traditional hospital with the longest history of assessment and treatment of cancer pain [29]. In a district of northern Italy, it has been estimated that only 38 % of opioid prescriptions were adequate and the opioid prescription inadequacy increased with the length of time from first prescription to patient death [30]. In a multicenter survey performed in a large number of palliative care units, hospice and home care, as well as oncological units, results suggest that the recourse to WHO third-level drugs still seems to be delayed in a substantial percentage of patients. This delay is probably related to several factors affecting practice in participating centers and suggests that the quality of cancer pain management in Italy deserves specific attention and interventions aimed at improving patients' outcomes [6]. In Italy, the use of opioids in the management of cancer pain has been for years at the lowest levels compared with other European countries, and this could potentially amplify the figures regarding the undertreatment of cancer pain observed all over the world [2, 24, 31]. Indeed, similar findings have been reported in most developed countries [32, 33].

It seems clear that it is necessary to resolve the most difficult cases in settings which can provide optimal analgesia because of a high-level experience and confidence with opioid treatment. The role of APRPC team is to assess

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and manage patients' and families' care needs during the course of the entire disease. There are several time-consuming tasks that make it increasingly difficult for a busy oncologist to address multiple palliative care needs for the pharmacological treatment of symptoms, education and counseling, and family support [7, 8]. This approach may be cost-effective and allows patients to be stabilized, even on higher doses of opioids, and then to be discharged to other settings to continue the treatment while providing advices and education [34]. Data from literature suggests that it is likely that such kind of patients may not be optimally treated in other potentially specialistic settings [6]. For example, patients with complex clinical situations, who were successfully switched in an APRPCU could maintain their symptom control successfully when discharged home, with only a minority of them loosing the clinical benefit for different reasons [35]. Several reports have described the components of innovative palliative care programs that include APRPCUs and the demographic and symptom profiles of patients admitted to such units, as well as cost-sparing end efficiency [36–42]. In contrast to traditional inpatient hospice, these units operate exactly like any other acute inpatient unit and are subjects to the same standard of clinical competence, administrative regulation, and financial responsibility. The focus of APRPCU is rapid symptom control with the length of stay shorter and the death rate lower than traditional hospices. The impact of early palliative care access is of paramount importance. Unfortunately, only a small proportion of comprehensive cancer centers have inpatient palliative care units [8]. The American Society of Clinical Oncology has steadily increased the visibility of palliative care and has developed education tools to improve oncologist skills in palliative care in the effort to integrate both processes simultaneously, rather than in different times and confining palliative care at the end of life [7]. Thus, APRPCUs should be developed as formal structures within each oncological department to provide a standardized and integrated approach.

This was an observational study, and data were not compared with those gathered from other settings. Such comparison studies are difficult to perform because "per definition" the type of population admitted in an acute unit, the modality of admission, resources, and experience are completely different and represent an obvious bias for studies of such a type. Pain and symptom intensities were not collected as it was not the focus of the study. Indirectly, however, it is possible to consider that pain and symptom control was optimal, because for local policy, patients are discharged only after an adequate symptom stabilization.

Finally, although it was not the focus of the present work, there are other relevant activities, including psychological, spiritual, communication issues, typical of any palliative care setting, which are of paramount importance to allow the best outcome of pain and symptom management.

In conclusion, for patients with severe distress, early referral to a palliative care team during the course of disease rather than at the end of life has been recommended [34, 43]. APRPCUs may guarantee a high-level support to optimize pain and symptom intensities providing intensive approach and resolving highly distressing situations in a short time by optimizing the use of opioids.

Conflict of interest There are no commercial associations that might create a conflict of interest in connection with submitted manuscripts for each author.

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