Integration of Oncology and Palliation Benefits Patients with Advanced Cancer and Unmet Needs: A Prospective Observational Study

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Research Article

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Abstract

Background: Patients with advanced cancer and bone metastases may have unmet palliative care needs that go unnoticed during clinical oncological practice. This observational study describes palliative care needs and interventions identified because of participation in a clinical study.

Methods: Patients with advanced cancer and painful bone metastases included in the Palliative Radiotherapy and Inflammation Study (PRAIS) aiming to predict the response of radiotherapy (RT) were eligible. All patients met with the palliative care (PC) study team prior to start of RT, after they had completed patient reported outcome measures (PROMs). Symptoms prompting interventions by the study team were documented in the patient charts and reviewed.

Results: One hundred-and thirty-three patients were reviewed; 63% males, mean age 65 and mean Karnofsky score (KPS) 73. Interventions were initiated in 50% (n=67) of the patients. Most common were changed opioid management (69%), treatment of constipation (43%) and nausea (24%) and nutritional advices (21%). Patients receiving interventions had lower mean KPS (70 vs 77 p <0.001), shorter survival time after study inclusion (median 28 vs. 57.5 weeks p = 0.005) and were more often opioid naïve (12% vs 39% p <.001) compared with the non-intervention group.

Conclusions: Adverse symptoms are often not identified in routine oncological consultations prior to RT for cancer pain. Special attention should be directed to frail patients. These findings call for an early and systematic integration of palliative care in patients with advanced cancer.

Trial registration: ClinicalTrials.gov NCT02107664

Introduction

Improved diagnostic procedures and improvements of the tumor-directed treatments, especially systemic therapies, has led to prolonged survival and a higher prevalence of patients with metastatic disease (1). The complex health status of many of these patients requires interventions from the palliative care team to improve or maintain their functioning and quality of life (QoL). Palliative care represents an interdisciplinary medical specialty with focus on preventing and relieving suffering and obtaining best possible QoL for patients who are facing a serious and/or life-threatening illness (2). Several randomized controlled trials have demonstrated that provision of palliative care early in the course of the disease leads to improved QoL for patients with cancer and may have a positive effect on survival (3–8). These findings have led to explicit recommendations of early integration of palliative care into mainstream cancer care (9, 10). Palliative care should therefore be provided alongside with the anticancer treatments and not be limited to end-of-life care. Despite this, there is a sparsity of data demonstrating if, and to what degree, integrated oncology and palliative care is provided to the relevant patient groups outside clinical trials (11).

Bone metastases are common among patients with solid cancers, but the occurrence varies across primary cancer diagnoses. Bone metastases occur in 65–80% of patients with advanced prostate or breast cancer, 40–50% patients with lung cancer, and in <10% of those with gastrointestinal cancer (12, 13). Pain, one of the most frequent and feared symptoms in cancer, is often caused or aggravated by bone metastases (14, 15). Radiotherapy (RT) provides effective pain relief with complete relief in one-third of the patients (16). Pain relief may occur rapidly, with 40% of responders showing benefit within 10 days, both with single or multiple fractionated treatment in uncomplicated bone metastases (17).

The Palliative Radiotherapy And Inflammation Study (PRAIS) was initiated in 2013 as an observational academic study of patients commencing palliative RT for cancer induced bone pain. The overall aim of PRAIS was to predict the response of RT to painful bone metastases in patients with advanced cancer (18) in order to improve the selection of patients who are most likely to benefit from RT. The patients were included before start of RT and completed several Patient Reported Outcome Measures (PROMs) for assessment of pain and other symptoms, level of functioning, psychological distress and QoL. During the first study consultations at Oslo University Hospital (OUH), the study team observed that several included patients reported symptoms in addition to pain like constipation and nausea all of which indicated need for palliative care interventions. These observations were taken as an indication of unmet palliative care needs in the patient population that had not been covered during previous clinical consultations. To explore the hypothesis of unmet needs, the electronic hospital records of all patients included in PRAIS at OUH were retrospectively reviewed. The objectives were to describe a) the number and types of palliative care interventions that were initiated by the study team in the first study consultation, and b) the characteristics of patients who received these interventions versus those who did not.

Methods

Patients

Totally 574 patients from seven centers in Europe were enrolled in the PRAIS study (ClinicalTrials.gov registration NCT02107664) (19). Between January 2015 and December 2017, a sample of 179 patients was included at OUH. Inclusion criteria were an established cancer diagnosis, referral to palliative RT for verified (CT/MRI) painful bone metastases, age ≥18 and ability to comply with trial procedures. Exclusion criteria were on-going RT, RT administered within the previous four weeks or pathological fracture in long bones. Further details regarding criteria for participation have been presented elsewhere (18).

Patients, who are referred to OUH for palliative RT, be it from within or outside the hospital, meet for a routine appointment at the oncology outpatient clinic prior to start of CT dose planning and RT. This scheduled appointment with the oncologist consists of a standard clinical examination, supplemented with blood tests, additional imaging and other examinations if necessary. Based on this, the indications for RT are confirmed. As per routine, the oncologist then plans the RT in detail (total dose and fractionation), informs patients (and their informal caregivers) about the treatment and follow-up plans

and refers them to RT. To identify potentially eligible patients for the PRAIS study, the OUH study team screened the lists of new patients registered for RT for bone metastases awaiting CT dose planning and start of RT. This resulted in a sample of 179 patients that were included in the PRAIS study population at OUH. The present study on unmet needs was confined to outpatients able to commute for RT resulting in a sample of 134 patients i.e. 75% of the included population.

Study procedures

In the main PRAIS protocol patients were approached by a study nurse who identified patients when they met for CT dose planning. At the Oslo site the PRAIS study team consisted of a physician and nurse experienced in palliative cancer care. The team approached the identified patients when they met for CT dose planning. Patients were evaluated for participation in PRAIS by asking the following two questions, “Do the bone metastases cause you pain?” and “Have you undergone RT the last 4 weeks?” Patients answering “yes” to the first question and “no” to the next were regarded as eligible and received detailed oral information about the PRAIS study. They also received the written study information including the consent form and a set of PROMs questionnaires. They were informed that if they decided to participate, the first study consultation would take place one hour before the first RT fraction, and they were instructed to bring the signed consent form and complete the study questionnaires. The time gap between CT dose planning and start of RT varied from 0 to 7 days.

The questionnaire packet consisted of the following forms; EORTC QLQ-C15 PAL for health-related quality of life (20), two questions from the Brief Pain Inventory (BPI) (21) on worst and average pain the last 24 hours, supplemented by two questions about pain at the planned irradiated site at rest and movement, respectively (11-point numeric rating scale) (22), the Leeds Assessment of Neuropathic Symptoms and Signs (LANSS) (23), the Patient-Generated Subjective Global Assessment (PG-SGA) of nutritional status (24) and the Patient Health Questionnaire regarding depression (PHQ-9) (25).

The study team was responsible for the consultation prior to RT. The primary focus was to obtain the necessary information to complete the case report forms (CRFs). As PRAIS was an observational study, no interventions other than RT were planned according to the PRAIS protocol, and the patient responses on the questionnaires (baseline, weeks 3, 8, 16, 24 and 52) were intended for study purposes only. However, as the patient-centred focus is prioritized in palliative care, the team performed a brief review of the questionnaires at baseline. When high symptom burden defined as scores ≥4 on the 0 -10 numerical rating scales, or substantial needs related to e.g. physical function, self-care or home care services were detected, it was discussed with the patients. If necessary, appropriate interventions or referrals to other health care specialists were initiated and documented in the electronic patient records.

Data Collection

Demographic and clinical data for the present study were extracted from the CRFs. The following variables were selected: age, gender, living situation, length of education, primary diagnosis, and date thereof (month, year), metastases to other sites than bone and Karnofsky performance status scale (KPS) (26). Primary cancer diagnoses were grouped as; breast, urological, lung, gastro-intestinal (GI) and

unknown. Urological cancer included prostate, bladder and kidney, lung cancer included mesothelioma and thymoma, and GI cancer included all cancers in the GI tract.

In 2018, when inclusion of patients for the PRAIS study was completed, a systematic retrospective review of the baseline consultations and the related interventions that were documented in the patients' electronic records was done. For this purpose, the study team developed a data extraction tool to ensure consistency in the data extraction. Experienced clinicians (three oncologists, two nurses) developed the tool in an iterative process, based on clinical judgement and experience. Main areas were medication issues, i.e. prescription of drugs and correction of doses, non-pharmacological interventions and referrals to other health care professionals or services.

Statistics

Statistical analyses were performed using the software SPSS version 25 (IBM Corp. Armonk, NY). Data are presented with descriptive statistics; categorical variables as frequency with percentages and continuous variables as mean with standard deviation (SD). To compare the characteristics of the patients who got palliative care interventions with those who did not, Pearson Chi-Square tests were used on categorical variables, and two-tailed t-tests on continuous variables. The significance level was set at 5%. Survival time was calculated from date of study inclusion. Date of death was extracted from the electronic patient records, with last update October 2020.

Ethical considerations

The Regional Committee for Medical and Health Research Ethics, Central Norway approved the PRAIS study and the amendment for this sub-study (2013/1126/REK Middle Norway). All patients gave their written informed consent before inclusion. The study was carried out in accordance with ICH GCP and the World Medical Association Declaration of Helsinki (1964).

Results

Of the 134 eligible outpatients, one withdrew the consent to participation after the baseline consultation with the study team, leaving a study sample of 133. Patient characteristics are listed in Table 1. The sample consisted of 63% males, mean age was 65 years (SD 9.6), and mean KPS score 73 (SD 9.1). The most common cancer diagnoses were GI (31%), urological (31%) and lung (19%). Seventy-five percent of the patients had metastases to other sites in addition to the bone metastases, and 57% of these had two or more non-bone metastases. At the last update of death (September 2020), 117 patients (88%) had died. Median survival time after study inclusion was 32.0 (1-248) weeks, and 27 (23.3%) had died within three months from inclusion in the PRAIS study.

Table 1
Patient characteristics and comparison between patients receiving and those not receiving clinical interventions.

		Total N = 133	Interventions n = 67	No interventions n = 66	*p-value*
Age	Mean years (SD)	65 (9.6)	65.0 (10.3)	64.8 (9.0)	*0.92*
KPS[a]	Mean score (SD)	73.2 (9.1)	69.7 (7.8)	76.7 (9.0)	*<0.001*
		n (%)	n (%)	n (%)	
Gender	*Male*	84 (63.2)	39 (58.2)	45 (68.2)	*0.28*
	Female	49 (36.8)	28 (41.8)	21 (31.8)	
Living conditions	*Alone*	30 (22.6)	18 (26.9)	12 (18.2)	*0.41*
	Spouse/partner	72 (54.1)	37 (55.2)	35 (53.0)	
	Spouse/partner and children	24 (18.0)	9 (13.4)	15 (22.7)	
	Children[b]	7 (5.3)	3 (4.5)	4 (6.1)	
Educational status	*≤ 12 years*	71 (53.4)	35 (52.2)	36 (54.5)	*0.86*
	> 12 years	62 (46.6)	32 (47.8)	30 (45.5)	
Type of cancer	*Breast*	20 (15.0)	10 (14.9)	10 (15.2)	*0.26*
	Urological	41 (30.8)	15 (22.4)	26 (39.4)	
	Lung[c]	25 (18.8)	14 (20.9)	11 (16.7)	
	Gastro-intestinal	41 (30.8)	25 (37.3)	16 (24.2)	
	Unknown origin	6 (4.5)	3 (4.5)	3 (4.5)	

[a] Karnofsky Performance Status, [b] Children >18 years included, [c] Including mesothelioma (n=2) and thymoma (n=1),[d] Percentage exceeds 100, due to multiple metastases

		Total N = 133	Interventions n = 67	No interventions n = 66	*p-value*
Location of other metastases[d]	*Liver*	52 (39.1)	30 (44.8)	22 (33.3)	*0.21*
	CNS	5 (3.8)	4 (6.0)	1 (1.5)	*0.37*
	Lung	45 (33.8)	28 (41.8)	17 (25.8)	*0.07*
	Other	73 (54.9)	38 (56.7)	35 (53.0)	*0.72*
Opioid naïve		34 (25.6)	8 (11.9)	26 (39.4)	*<0.001*

[a] Karnofsky Performance Status, [b] Children >18 years included, [c] Including mesothelioma (n=2) and thymoma (n=1),[d] Percentage exceeds 100, due to multiple metastases

Palliative care interventions were initiated in 50% (n=67) of the patients at the discretion of the PRAIS study team at the baseline study consultation. The highest proportion of interventions was performed in patients with GI cancers (37%). Patients who received palliative care interventions had a significantly lower mean KPS (70 vs 77 p <0.001) and shorter survival time after study inclusion (median 28 vs. 57.5 weeks p = 0.005) compared with those who did not receive any interventions. Additionally, 34 (26%) patients were opioid naïve at inclusion, 12% among those who received palliative care interventions and 39% among those not receiving any interventions (p <.001). Number and types of clinical interventions initiated by the study team are listed in Table 2. Of the 99 (74%) patients who already received opioids at inclusion, 20 needed dose adjustments and 12 needed advice on how to manage their previously prescribed opioids. A total of 46 patients received interventions related to opioid management (start up new, switch, adjustment and advices on self-management, especially extra doses when needed). Opioid management was the only intervention for 16 patients of which 13 needed adjustment of dosing and three were opioid naïve.

Table 2
Numbers and types of clinical interventions initiated by the PRAIS study team.

Interventions	n	(%)
No. of patients receiving opioid management	46	
Started naïve	3	(6.5)
Switch	11	(23.9)
Adjustment of dose	20	(43.5)
Advice on self-management	12	(26.1)
No. of patients receiving prescriptions other than opioids[a]	43	
No. of prescriptions other than opioids	64	
Non-opioid analgesics	10	(15.6)
Laxantia	29	(45.3)
Antiemetics	16	(25.0)
Other[b]	9	(14.1)
No. of patients referred to other health care services[a]	23	
Total no. of referrals to other health care services	30	
Specialized palliative care at local hospitals	13	(43.3)
Outpatient departments, OUH[c]	5	(16.7)
Community health care services	4	(13.3)
Other health care professionals, OUH[d]	5	(16.7)
Hospitalization at OUH	3	(10.0)
[a] Several patients received more than one prescription/referral		
[b]Gastric ulcer prophylaxis (n=3), antimycotica (n=2), corticosteroids (n=1), benzodiazepines (n=1), discontinuation of medication (n=2), blood transfusion (n=1)		
[c] Radiology (n=2), oncology (n=3)		
[d] Dietitian (n=3), physiotherapist(n=1), priest (n=1)		

Most patients receiving palliative interventions received multiple interventions (51 of 67). A high number of prescriptions for other medications than opioids were issued (n=43), with laxantia and antiemetic medication being the most common. The consultations also revealed that many patients reported relatively high numbers of symptoms, particularly constipation (n=29) and nausea (n=16), while general

advice on how to handle symptoms, e.g. nutrition, oral care, fatigue, sleep disturbances, and whom to contact if the symptoms worsened, were necessary in 13 cases. As shown in Table 2, 23 patients were referred to other health care services. Two patients were referred to radiological examinations due to suspected new bone metastases and deep vein thrombosis, and three to the oncological outpatient clinic for multiple interventions, e.g. correction of hypercalcemia, blood transfusions and problems with a venous access port. For six patients, referrals to multiple services were necessary, and three patients were hospitalized due to sever symptoms.

Discussion

The patients included in the PRAIS study at OUH, who all had painful bone metastases, reported several clinically significant symptoms and complex problems which were undetected during the oncological consultation leading to referral to RT. At the baseline consultation the study team initiated interventions, often multiple, for half of the patients. About two thirds of the initiated interventions were connected to opioid management due to inadequate effects and/or information about the administration of previously prescribed analgesics. Prescriptions for treatment of common symptoms such as constipation and nausea, were also issued. Patients who received palliative care interventions, were characterised by significantly lower mean KPS, more use of opioids at inclusion and shorter survival time after inclusion compared with those not receiving any interventions. These findings indicate that palliative care needs were not sufficiently attended to in the outpatient routine oncological clinic.

It is well known that patients with advanced cancer typically experience multiple symptoms (27, 28). All the included patients received oncological and/or palliative care at their local hospitals or in the primary health care. Thus, it could be expected that symptoms and other palliative needs had been identified and treated by their responsible physicians or care teams. The finding that this was not always so is in line with other studies (7, 29) showing that several common symptoms in patients with advanced cancer such as pain, constipation, nausea, depression and poor sleep, may go undetected by health care providers and therefore remain inadequately controlled. A recent study reported that 30% of patients treated with palliative RT for pain did not receive any palliative care the last six months before RT (29). These findings underline the importance of integrating palliative care into mainstream oncology care as it is recommended by both ASCO and ESMO (9, 10) based upon the positive effects from a series of randomize studies (3–8). One may question whether that is the case at the patient level in this cohort since a minor assessment in this study detected a series of unmet needs.

Several factors may have contributed to our findings. One reason may be that health care providers underestimate symptom intensity (30), possibly because systematic symptom assessment is not an integral part of daily clinical routines and practice and therefore not performed (11). When routines for assessment are lacking it is demonstrated that up to 50% of patients' symptoms and functional impairments may go undetected by clinicians (31). In pain management such underestimation is found to be an important barrier to adequate treatment (32), despite pain being one of the most studied symptoms in cancer and still experienced by more than half of cancer patients in general (15). Other

potential reasons for our findings may be that their symptom burden had increased from referral for palliative RT until coming to OUH, or a long-time span between the consultations at the oncological clinic and the one with the PRAIS study team. However, this was only the case for a few patients since the time from referral to the appointment at the oncology outpatient clinic and start of RT was scheduled to be one week or less according to the study protocol.

The significant proportion of the symptoms identified by the PRAIS study team that probably should have been detected and taken care of at an earlier stage, underlines the premise of the decade-long debate of integration of oncology and palliative care to improve patient treatment and care (11). The fact that half of the patients reported unmet palliative care needs indicate that they did not receive necessary palliative care services and lack of integration of palliative care into mainstream cancer care opposed to existing guidelines (9, 10). We strongly believe that better routines for self-report of symptoms by patients that are recognized and managed by health care professionals in a patient-centred manner, are crucial for initiation of care before patients' symptoms severely worsen (29). In the present study the unmet palliative care needs were disclosed by rapid reviews of the patients´ self-reports of symptoms. It has repeatedly been shown in several studies that routine use of PROMs improves symptom control, perceived QoL, patient and caregiver satisfaction, and communication between clinicians and patients (7, 8, 33, 34) and discloses previously unnoticed problems (35). Still barriers towards PROMs persist and relate to technology limitations, uncertainty about ease and benefits of use, and competing demands within established clinical workflows (36).

In most clinical studies data collected by PROMs are used as explanatory variables, secondary outcomes or, less often, as the primary study outcome. Thus, patient responses on PROMs are not evaluated during the study, by fear of influencing study results. This is not that relevant in an observational study such as PRAIS especially as the definition of RT effect was a combined measure of pain intensity and opioid dose i.e., if a substantial opioid dose was initiated the patient would be considered RT non-responder even if he or her experiencing stable or reduced pain. The fact that the study team consisting of a physician and a specialist nurse looked at the forms and implemented interventions as needed, underlines the benefit of study participation. From a clinical point of view, the better the symptom management and health status in patients with advanced cancer, the more likely it is that they can comply with treatment over time. In relation to this, we would like to point to the common misconception that patients with advanced cancer are too fragile and unwilling to participate in clinical studies and complete questionnaires (37). Gysels et al (38) have documented that palliative care patients have several good reasons for participating in research such as gratitude and concerns about care, having someone to talk to and need for information. Additionally, they did not perceive participation as time-consuming. Research participation may actually have a therapeutic benefit (39, 40) which also is supported by the present study.

Strengths of this study are the long experience in palliative care by the study team, and the fact that necessary interventions were implemented immediately, documented in the patient records and communicated to follow-up teams. Still some limitations apply. First, the patient population was heterogeneous in terms of disease stage, primary diagnosis and frailty, which is shown by the range in

KPS and survival time from inclusion. Second, the self-report forms were subject to a quick review by the study team, with emphasis primarily being on scores of 4 and above (0-10 scale). However, it may well be that a symptom score of less than 4 also was perceived to be of importance to the individual patient. Additionally, persons from the study team participated in the development of the data extraction tool after they had consultations with the patients. Thus, it cannot be ruled out that they were aware of their own documentation in the patient records and that this have influenced what data to extract while other information may have been overlooked. Given the nature of this study and the fact that this report comes from one of the seven centres in the PRAIS study, results might not be representative of patient population in the study as a whole.

Conclusion

Half of 133 patients referred to RT because of painful bone metastases, needed multiple palliative care interventions although they already had received oncological consultations before inclusion in the PRAIS study. Interventions were related to inadequate analgesic management and treatment of common symptoms such as pain, constipation and nausea. Patients who needed palliative care interventions had lower mean KPS and shorter survival time compared with those not in need of such interventions. Importantly, the value of an integration of oncology and palliative care and systematic use of PROMs as a part of patient centred care is emphasized once again. Another take home message is that patients with advanced disease may benefit from study participation, even in observational, descriptive studies like this.

Declarations

Ethical approval and consent to participate

The study was in accordance with national law, institutional ethical standards, and the 1964 Helsinki Declaration and its later amendments. The Regional Committee for Medical and Health Research Ethics, Central Norway approved the PRAIS study and the amendment for this sub-study (2013/1126/REK Middle Norway).

All patients gave their written informed consent before inclusion.

Consent for publication

Not applicable.

Availability of data and materials

The dataset generated and analyzed during the current study is not publicly available because of the terms of the data collection approval, but parts of the data can be made available from the corresponding author upon reasonable request.

Competing interests

The authors declare that they have no conflict of interest.

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Authors contributions

AB analysed and interpreted the data and wrote the manuscript. EB was involved in the planning of the study, recruited patients, carried out the chart reviews, analysed data and contributed in the writing process. HS was involved in the planning of the study, recruited patients, carried out the chart reviews and contributed in the writing process. JHL was involved in the planning of the study and contributed in the writing process. MJH was involved in the planning of the study, analysed and interpreted the data and was a major contributor in the writing process. PK was involved in the planning of the study and contributed in the writing process. RH contributed in the writing process. SK was involved in the planning of the study and contributed in the writing process. NAa was involved in the planning of the study, analysed and interpreted the data and was a major contributor in the writing process. All authors reviewed and approved the final manuscript.

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