Improving quality of care for cancer pain: an Italian five-year project

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ABSTRACT

BACKGROUND: cancer pain is still undertreated as for inappropriate use of opioids, as for reason related to other factors. To increase knowledge of cancer pain, the "Mario Negri" Institute promote a series of initiatives to improve the quality of care and patients' outcomes.

METHODS: a series of activities were launched including literature review, clinical studies and training schemes.

RESULTS: literature reviews shown a prevalence of undertreatment ranged from 8% to 82% and a raw prevalence of BTcP (Breakthrough Cancer Pain) of 51%. In the outcome research study mean worst pain at baseline was 6.8, and 38.3% received a strong opioids. Prevalence of BTcP was 40.3%, and 33.9% of the patients were not receiving rescue therapy at the study inclusion. About analgesic effectiveness of oral and transdermal opioids (TD), treatments with TD were associated with a lower probability to switch (OR=0.83) and to drop out from the study (OR=0.68).

CONCLUSIONS: the initiative, still ongoing, has allowed a) the creation of a unit for the study and evaluation of cancer pain, b) the production of clinical evidence about the epidemiology, quality and effects of cancer pain management in Italy, c) the design and promotion of a Randomized Controlled Trial to evaluate the effectiveness of four major opioids.

Key words: Cancer pain; Epidemiology; Outcome research study

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INTRODUCTION

Despite significant progress in knowledge of the mechanisms underlying the development and progression of cancer and the increasing availability of new drugs, long-term survival for the most common solid tumors is still disappointing. Most patients with advanced or metastatic cancer suffer pain [1] and, despite several guidelines for cancer pain management [2-6], undertreatment is widely documented, reaching 82% of patients in some settings [7]. Undertreatment is usually attributed to inappropriate use of opioids for several reasons related to the health care provider, patient, family, institution and society [8], where fear of

the opioids' effects may be the most important factor from the patient's point of view [9, 10].

In Italy, opioid consumption rates are still among the lowest in Europe [11, 12], even though their prescription was promoted by specific laws in 2010. According to recent reports, the per capita cost of strong opioids is 1.17 Euros, and 0.78 Euros for weak opioids. Non-opioid drugs are still the "most prescribed" analgesics, with a per capita cost 11.7 times that of weak opioids and 7.8 times the strong opioids [11].

To improve cancer pain management in Italy, between 2003 and 2004, the "Mario Negri" Institute, a non-for-profit foundation in Milan, set up a multi-disciplinary board of experts consisting of representatives from industry, scientific societies and patients' associations to discuss the quality of pain treatment in Italy and possible improvements. Experts identified the need for activities aimed at improving the quality and quantity of evidence available, using research, training and communication [13, 14]. According to these recommendations, over the next five years the following steps were taken: 1) systematic reviews of the literature in order to obtain the information required to set the subsequent stages of research and training; 2) organization of meetings and training sessions involving future participants in clinical studies; 3) design and conduct of a prospective outcome research study to collect empirical information on the epidemiology, quality and impact of cancer pain management.

Here we report the results of this initiative, still ongoing, that has allowed the creation of: a) an established network of Italian hospitals; b) a unit dedicated to the study and evaluation of cancer pain; c) the production of clinical evidence about the epidemiology, quality and effects of cancer pain management in Italy.

The outcome research study ran through 2006 and 2007, involving more than 100 Italian hospitals and including 1 801 patients with cancer pain. The objectives of the study were: a) to describe a large cohort of cancer patients in terms of types of pain, patterns of care and patient-reported outcomes; b) to assess the quality of analgesic treatments in terms of the relation between patients' reported pain intensity and the potency of the prescribed analgesic drug; c) to compare the effects of various analgesic options, using appropriate statistical methods, such as the propensity score.

RESULTS

The primary and secondary research has been summarized in several scientific papers, some published and others forthcoming. Table 1 lists the publications with a short description of the most important features.

Literature reviews

Before conducting a prospective study, the literature was reviewed with three specific objectives: a) to identify the best method for evaluating the presence and frequency of undertreatment, b) to estimate the prevalence and impact of some phenomena related to cancer pain, such as breakthrough cancer pain (BTcP), and c) to evaluate the effectiveness of some analgesics that, although frequently used in practice, had scant evidence of their risk-benefit profiles, such as transdermal buprenorphine.

Review on undertreatment

As regards undertreatment, we identified and reviewed 44 studies that met the eligibility criteria, and 26 used the same instrument to identify and quantify undertreatment, the Pain Management Index (PMI) developed by Cleeland in 1994 [15]. The PMI compares the most potent analgesic prescribed with each patient's reported level of worst pain.

To construct the index, we determined which of four levels of therapy was the most potent one used: 0, no analgesic drug; 1, a non-opioid drug (e.g., a non-steroidal anti-inflammatory drug); 2, a weak opioid (e.g., codeine or tramadol); and 3, a strong opioid (e.g., morphine, fentanyl, buprenorphine, oxycodone, etc.). We then measured pain intensity on an 0 to 10 Numerical Rating Scale (NRS) grouping the scores as follows: 1 to 3, mild; 4 to 7, moderate; 8 to 10, severe. To apply a pain score for PMI we classify level of pain intensity as: 0 for no pain, 1 for mild pain, 2 for moderate pain, and 3 for severe pain. The PMI, computed by subtracting the pain level from the analgesic level, ranges from -3 (a patient with severe pain receiving no analgesic drugs) to +3 (a patient receiving morphine or similar drugs and reporting no pain). Negative scores were considered undertreated pain, and scores of 0 or higher as an indicator

of acceptable treatment. According to their score, patients were classified as "overtreated" (score +1 or more), "normotreated" (score 0) or "undertreated" (score <0).

TABLE 1

PUBLICATIONS LIST

REF	YEAR	AUTHORS	TITLE	JOURNAL	SUMMARY
2	2006	Apolone at al.	Pain in cancer. An outcome research project to evaluate the epidemiology, the quality and the effects of pain treatment in cancer patients.	Health and Quality of Life Outcomes	Protocol of the outcome research study
1	2006	Apolone et al.	A multidisciplinary project to improve the quality of cancer pain management in Italy. Background, methods and preliminary results.	Journal of Ambulatory Care Management	Description of the Project and preliminary results of the first initiatives
4	2008	Apolone et al.	Factors influencing the decision to take or reject opioids for cancer pain: are we on target?	Annals of Oncology	Report about the poor patients awareness on diagnosis and prognosis in the Outcome Research Study
3	2008	Deandrea et al.	Prevalence of undertreatment in cancer pain. A review of published literature.	Annals of Oncology	Review of 26 studies using the Pain Management Index to evaluate pain treatment
5	2009	Apolone et al.	Pattern and quality of care of cancer pain management. Results from the cancer pain outcome research study group.	British Journal of Cancer	Main results from the Outcome Research Study including 1 801 patients with a focus on appropriateness of prescriptions for cancer pain
6	2009	Apolone et al.	Effects of Transdermal Buprenorphine on Patients-reported Outcomes in Cancer Patients. Results from the Cancer Pain Outcome Research (CPOR) Study Group.	Clinical Journal of Pain	Evaluation of 432 patients assuming buprenorphine in the outcome study
7	2009	Deandrea et al.	Managing severe cancer pain: the role of transdermal buprenorphine: a systematic review.	Journal of Therapeutics and Clinical Risk Management	A systematic review on about 5 000 patients to assess the effectiveness and safety of transdermal buprenorphine
8	2011	Greco et al.	Epidemiology and Pattern of Care of Breakthrough Cancer Pain in a Longitudinal Sample of Cancer Patients: Results From the CPOR-SG.	Clinical Journal of Pain	Evaluation of breakthrough cancer pain prevalence in patients enrolled in the outcome research study
9	2012	Apolone et al.	Evaluation of the comparative analgesic effectiveness of transdermal and oral opioids in cancer patients: a propensity score analysis.	European Journal of Pain	Results of a propensity score analysis on 366 patients receiving transdermal or oral opioids.
10	2012	Corli et al.	An exploratory analysis on the effectiveness of four strong opioids in patients with cancer pain.	Pain Medicine	Results of a multivariate analyses carried out to explore the differences in prescriptions and in outcomes in 258 patients receiving 4 alternative strong (morphine, oxycodone, fentanyl, and buprenorphine)
11	2012	Corli et al.	How to evaluate the effect of pain treatments in cancer patients: results from a longitudinal outcomes and endpoints Italian cohort study.	European Journal of Pain	Assessment of the comparative performance of several outcomes and endpoints to describe the effect of analgesics in 1 461 patients monitored for 28 days

In the 26 studies, the proportion of patients with negative PMI ranged from 8% to 82% with an average weighted estimate of 43%. Multivariate analysis showed that the main factors associated with a higher probability of inadequate treatment were: the publication of the study prior to 2001, originating from a European or Asian country, a low economic level of the country of origin of the article (per capita income <$ 40 000 per year), and the setting of care, with the worst reported levels of appropriateness in studies from departments other than oncology. This data indicated that about 1 in 2 patients with cancer is not adequately treated for pain [16].

Review on effectiveness of transdermal buprenorphine

The systematic review of the effectiveness of transdermal buprenorphine for cancer pain took into account 19 studies and 12 were analyzed in detail (six RCTs and six observational), for a total of 5 000 patients [17]. Given the poor quality of reports and the variety of methods and outcomes, statistical pooling was not feasible as the type of data was not appropriate for combining the results statistically. Nevertheless a narrative appraisal of each study enabled us to identify and comment some characteristics of the drug under evaluation and summarize its risk-benefit profile.

Three clinical trials including only 453 cancer patients documented its analgesic efficacy, in terms of the responders' status. Post-marketing and outcome research studies gave satisfactory results in terms of effectiveness. Safety and tolerability, often reported together for cancer and non-cancer patients, were in line with what was expected, given the opioid nature of the drug, and the reported incidence from observational studies, when evaluable, was low, mostly in terms of serious events. The evidence for comparative efficacy and safety is indeed scanty, as most of the efficacy data are from placebo trials.

Review on prevalence and impact of Breakthrough Cancer Pain

For the review of the prevalence and impact of BTcP, 15 eligible clinical trials were retrieved and analyzed from 1990 to 2010. Despite the heterogeneity of definitions and the variability in terms of case-mix and design, it was possible, in the context of the wide between-studies heterogeneity, to estimate that more than one in two patients with cancer pain also experienced BTcP with some differences reflecting clinical and organizational variables. The raw prevalence of BTcP was 51.0% (33% to 95%). The overall pooled prevalence was 56.3%, with wide heterogeneity. The prevalence rates were lowest in studies where the baseline worst pain was moderate (37.6%), in studies conducted in outpatient clinics (39.9%), and in studies published in 2010 (40.5%). The prevalence was highest in studies conducted in hospices (90.7%) and those conducted during the first half of the 1990s (74.6%). The prevalence was higher in studies done in palliative settings, in samples where the patients were younger, more frequently female, or did not have metastatic cancer. When year and setting were both entered in a meta-regression, only the type of setting held statistical significance.

The Outcome Research Study

In this multicenter, open-label, prospective, non-randomized study [18] each center could enroll up to 25 patients and inclusion criteria were: advanced or metastatic cancer, chronic pain of any intensity despite pain treatment in place or planned, age at least 18 years, life expectancy at least one month, ability to read, understand and provide informed consent. After enrolment/inclusion, the following screening assessments were carried out and recorded weekly for the first month, with a final visit at week 12 (at the end of the study): (a) medical history including cancer history, (b) physical examination, (c) record of medications and recent therapies, including analgesics, (d) pain and symptom assessment, (f) patients' and physicians' satisfaction with pain treatment and (g) patient's self-reported quality of life. Patients' and physicians' reports were collected using standardized forms at scheduled visits. Self-administered questionnaires were completed when the patient attended regular visits at the center or during admission or at home, depending on the setting of care. Investigators recorded information about patients and

disease, pain medications and type and number of rescue doses in a case report form.

Pain characteristics (intensity, relief and so on) were the primary outcome measures. Other patient-reported outcomes were collected too, such as satisfaction with care, quality of life and symptoms. Pain was measured using five items from the Italian version of the Brief Pain Inventory [19] assessing intensity of worst, actual, least and average pain and pain relief with an 11-point numerical rating scale.

From February 2006 to March 2007 110 centers recruited 1801 valid cases that constituted the baseline cross-sectional sample; there were 1 461 patients with complete data at 28 days and they form the longitudinal sample.

Epidemiology of cancer pain, quality of information and treatment

Patients recruited were more frequently male, and had severe pain (mean worst pain at baseline 6.8). Half had bone metastasis, episodes of BTcP and were still receiving active anticancer treatment. The most frequent primary tumor sites were lung, breast and colon-rectum. Sixty-one percent of patients were treated with strong opioids. Rescue therapy was given in 43.6% of cases. Table 2 summarizes the results.

The prevalence of undertreatment, evaluated with the PMI, in the overall sample was 25.3%, with variability depending on the characteristics of each patient, the type of recruiting center and the level of assistance provided. After multivariate analysis the type of recruiting center and the presence or absence of adjuvant therapy were significantly related to undertreatment. Physicians reported that only 30.3% of the patients knew their prognosis.

These results confirm the high prevalence of undertreatment in Italy and the low propensity of physicians to prescribe opioids, regardless of the setting of care [20-22].

Transdermal buprenorphine in cancer patients

Out of the 1 801 patients, 432 (24%) received transdermal buprenorphine (TDS) during the 28 days of the study [23]. Comparing patients according to the type of analgesic drugs received, on average patients receiving buprenorphine were somewhat older, with a lower prevalence of bone metastasis and BTcP, and less frequently on anticancer chemotherapy. In the sample receiving the drug under evaluation, all outcomes showed a significant improvement of pain control over the 28 days: 34% of patients experienced an improvement of at least 2 points in the worst pain intensity, a difference considered important from the clinical point of view [24]. A few patients (19%) reported a decrease in satisfaction, or worsened in terms of pain relief. During the study, physicians raised the dose to control pain by an average of 16-17%. Results were in line with those of patients receiving other World Health Organization-level III opioids.

Despite the limitations of its design, this study highlighted the potential of this drug and the need for new comparative studies.

Prevalence and impact of BTcP

Another important analysis on the same sample focused on the prevalence of BTcP [25]. In our 1 801 patients, the prevalence of BTcP was 40.3% and most patients (33.9%) were not receiving rescue therapy at the time of study inclusion. On average, patients with BTcP were younger, more frequently presented bone metastasis and neuropathic pain, and had more severe pain at baseline, with a linear trend related to the number of attacks per day. A multivariate logistic regression was then fitted to take account of the confounding effect of each variable. After adjustment, the type of recruiting center, was still moderately associated with BTcP: the Oncology wards were 30% less likely to recruit patients with BTcP than palliative care units, used here as a reference category as they had the higher prevalence of BTcP (OR=0.7, 95% CI: 0.5-0.9, P=0.025).

Another multivariate logistic regression analysis evaluated the relationship between selected variables at baseline and presence of BTcP in oncology centers after adjusting for confounding factors: patients with bone metastasis, aged less than 50 years, or having neuropathic pain had a substantially higher risk of being classified with BTcP (OR >1.5 and P<0.01).

These analyses show that, despite the high prevalence of BTcP and its importance in chronic cancer pain, its definition and treatment are still underestimated.

TABLE 2

CHARACTERISTICS OF PATIENTS AT BASELINE (N=1 801)

Characteristics	%	Mean, SD
Age		63.9, 12.1
Female	47.3	
Karnofsky PS, <50	11.5	
Primary tumor		
Lung	21.8	
Breast	15.9	
Colon-rectum	13.7	
Prostate	7.9	
Gynecological	6.1	
Pancreas	6.0	
Genito-urinary	6.1	
Stomach	5.5	
Head&Neck	4.5	
Liver	1.2	
Others	9.9	
Unknown	1.4	
Bone metastasis	46.8	
Previous surgery	58.0	
Previous chemotherapy	65.2	
Previous hormonotherapy	20.0	
Previous radiotherapy	40.3	
Others	5.4	
Ongoing chemotherapy	49.0	
Patient aware of prognosis (reported by physician)	30.3	
Type of recruiting center		
Oncology center	59.4	
Palliative care	17.0	
Pain center	15.1	
Hospice	7.7	
Others	0.8	
Pain intensity (0-10)		
Worst (previous week)		6.8, 2.2
Average (previous week)		4.5, 2.0
Current		3.4, 2.7
Least (previous week)		2.6, 2.0
Pain relief (0-100)		55.1, 26.4
Patients with breakthrough pain	48.4	
Patients with neuropathic pain	25.7	
Type of analgesic care		
Around the clock therapy		
None	5.9	
Only NSAID	8.8	
Only weak opioids	10.6	
NSAID with weak opioids	14.1	
One strong opioid	38.3	
NSAID/weak opioid+strong opioid	19.2	
More than one strong opioid	3.1	
Rescue therapy		
None	53.2	
Only NSAID	24.9	
Only weak opioids	3.8	
NSAID with weak opioids	2.9	
One strong opioid	11.8	
NSAID/weak opioid+strong opioid	3.2	
More than one strong opioid	0.2	
Adjuvant therapy		
Corticosteroids	40.1	
Anti-convulsivants	15.8	
Antidepressant	10.8	
Biphosphonates	18.5	

Comparative effectiveness of four strong opioids in patients with cancer pain

A further analysis evaluated the effectiveness of four strong opioids on the 1 801 patients enrolled [26]. Morphine, oxycodone, fentanyl and buprenorphine were administered during a three week follow-up period and their effectiveness was compared using several measures, classified as primary and secondary, such as pain intensity, pain intensity difference (PID), proportions of non-responders (NR) and full-responders (FR), percentages of switches, and dose escalation. Despite some baseline differences among groups, the mean intensity of Worst Pain (WP) and Average Pain (AP) was very similar in the four subpopulations. The PID from baseline to the final visit, showed moderate but not significant differences between drugs in both univariate and multivariate analysis. The Average Pain-FR rates were very similar between groups (68.2-71.4%), while Average Pain-NR ranged from 15.5% with buprenorphine to 22.5% with morphine. In terms of Worst Pain-FR, there were 62.9% with buprenorphine and 47.5% with morphine, while the least NR were in the morphine population (15.0%), and the most with fentanyl (27.3%). Multivariate analysis showed that patients given oral morphine more frequently had poorer performance than with other drugs, as responders or non-responders.

The main objective of this exploratory analysis was to see whether there is variability in choice and in outcome regarding opioids, independently from their pharmacological differences. A secondary objective was to investigate which endpoints were best to produce preliminary findings for a more formal comparison of the effectiveness of analgesics using statistical methods such as the propensity score, and to design a confirmative (RCT) to compare the effectiveness of the opioids that are commonly used in clinical practice to treat cancer pain.

Analgesic effectiveness of transdermal and oral opioids in patients with cancer pain

To compare the effectiveness of the two routes of opioid administration (oral vs. transdermal=TD) we applied the Propensity Score (PS) in a sub-group of patients enrolled in the outcome study, starting the WHO third-step therapy during the scheduled follow-up of 28 days [27]. We analyzed 366 eligible cases and a set of primary and secondary effectiveness and safety endpoints.

Patients receiving TD opioids differed from those receiving oral analgesics: TD patients were older, more frequently had colon-rectal cancers, with less bone metastasis, were more frequently cared in oncology wards, receiving less information about their prognosis and with a lower prevalence of neuropathic pain and a shorter duration of the underlying cancer.

All outcomes directly related to pain (worst and average pain intensity, pain relief) steadily improved over time in both groups, in terms of statistical significance ($p<0.05$) and clinical relevance. There were significant differences between TD and oral cases concerning the daily dose escalation and pain relief. TD were also associated with a lower probability of needing to switch (OR 0.83), to drop out from the study (OR 0.85) and to have an "opioid escalation index" greater than 5% (OR 0.68), even if p-values were always higher than 0.05. These was a significant different only in the prevalence of nausea/vomiting (25.1% for TD and 13.6% for oral, $p=0.0075$).

The conclusion of this analysis was that, according to the methods applied in this specific sample, TD was at least equivalent in effectiveness to the oral opioids but patients receiving TD had a higher probability of nausea and vomiting. Our data confirmed what is known from clinical research on the efficacy and safety of TD in cancer patients, although evidence on comparative efficacy and safety is indeed scant, as most of the efficacy data are from placebo trials with small samples or from retrospective studies. Despite warnings and limitations, in this sample the PS helped to understand the actual effectiveness of TD better when compared with oral analgesics and adds evidence about the value of this method on observational data.

Discussion and ongoing activities

In the light of these important results, we decided to design a new clinical trial. It is a RCT, with four treatments arms, open-label, phase IV, prospective, multicenter, with a follow-up of 28 days. The primary aim is to evaluate the effectiveness/performance of four

major opioids (oral morphine and oxycodone, transdermal fentanyl and buprenorphine) in patients with moderate to severe cancer pain. This is a superiority trial with oral morphine as active comparator and the other three opioids as test-treatment. Eighty centers have been involved, with the aim of recruiting 1 000 patients. The trial is now in progress [28].

The sample population comprises patients with advanced/progressive/metastatic cancer with average pain in the last 24 hours ≥4 (measured with a 0 to 10 NRS). These patients can already have received drugs of the WHO 1 and/or 2 (paracetamol, NSAIDs, codeine, tramadol) and at the time of enrollment/inclusion, need a step-3 strong opioid. Patients are randomized in a standardized manner to receive one of the four drugs as background "around-the-clock" (ATC) therapy.

Five follow-up visits are scheduled: after 72 hours and on days 7, 14, 21, 28. The at 72-h visit is additional, in view of the importance of evaluating the first clinical impact of the new step-3 treatment (analgesia and initial adverse effects) and the definitive daily dosages.

Pain is assessed with the Brief Pain Inventory Italian version, administered when the patient attends regular visits at the center or at home, depending on the setting of care. At the same time, quality of life, satisfaction measures and symptoms/side effects check-lists are administered. We will use a set of primary and secondary endpoints of analgesic efficacy and security to check the efficacy of the different opioids.

The proportion of NR is the primary efficacy endpoint. The percentage of FR the daily dose escalation, the need for dose adjustment and rescue analgesic drugs and the percentage of switches to another opioid because of lack of efficacy are the secondary efficacy endpoints. Safety and tolerability are also evaluated.

Groups of patients randomized to receive morphine (active treatment) are to be compared with those randomized to the other three drugs, considered experimental, so as to give three comparisons (morphine vs. fentanyl, morphine vs. buprenorphine and morphine vs. oxycodone). A further aim, the patient's genome-wide profile will be analyzed to check for any correlations with clinical outcomes.

The study was launched in March 2011 and to date 56 centers are active, with a total of 237 patients. Given the limited understanding of the efficacy of cancer pain treatment, data collected in this study will certainly help improve our knowledge of the effectiveness of opioids in cancer pain and on the best strategies (dose, switching) to be used by physicians to reduce it.

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