Does an oral analgesic protocol improve pain control for patients with cancer? An intergroup study coordinated by the Eastern Cooperative Oncology Group

C. S. Cleeland1*, R. K. Portenoy2, M. Rue3, T. R. Mendoza1, E. Weller2, R. Payne1,4, J. Kirshner5, J. N. Atkins6, P. A. Johnson7 & A. Marcus8

1The University of Texas M. D. Anderson Cancer Center, Houston, Texas; 2Beth Israel Medical Center, New York, New York; 3Dana-Farber Cancer Institute, Boston, Massachusetts; 4Duke Institute on Care at the End of Life, Duke University Divinity School, Durham, North Carolina; 5Syracuse Hematology-Oncology CCOP, Syracuse, New York; 6Southeast Cancer Control Consortium Inc. CCOP, Goldsboro, North Carolina; 7Carle Clinic, Urbana, Illinois; 8AMC Research Center, Denver, Colorado, USA

Received 23 August 2004; revised 28 January 2005; accepted 1 February 2005

Abstract: The aim of this study was to determine whether dissemination of a clinical protocol for pain management would improve outcomes in community oncology practices.

Patients and methods: A pain management protocol was developed based on accepted guidelines. After baseline assessment, oncology practices were randomly assigned to ‘analgesic protocol’ (AP) sites, where oncologists implemented the guidelines in a group of lung or prostate cancer patients, or to ‘physician discretion’ (PD) sites, where customary treatment was continued. Patients treated on protocol and a comparison group of patients with pain due to breast cancer or myeloma were monitored for change in pain using the Brief Pain Inventory, and for change in other symptoms or mood.

Results: The protocol terminated early because of poor accrual. We compared groups using proportions of patients who had no or mild pain at follow-up. Although measures of protocol adherence did not suggest the occurrence of major practice change, the proportion of lung or prostate cancer patients with no or mild pain increased significantly from baseline for those treated at AP sites compared with those treated at PD sites. There was no significant difference between the breast and myeloma patients treated at AP sites versus those treated at PD sites.

Conclusion: A protocol for cancer pain management can improve pain control. Diffusion of these benefits to other patients was not confirmed. Given the small sample size, these findings require confirmation in a larger trial.

Key words: Brief Pain Inventory, cancer pain, management guidelines, randomized clinical trial

Introduction

Most patients with metastatic cancer develop pain. At least one-third of these patients have pain severe enough to interfere with function [1] and more than two-thirds require opioid therapy when the disease is advanced. Cancer pain is often suboptimally managed, primarily because of inadequate pain assessment or lack of aggressive treatment [1–3]. Undertreatment continues to be a problem [4–6] despite the availability of consensus-based guidelines [7–11]. Predictors of inadequate management include patient characteristics, physician practice and the type of treatment setting [1, 2].

Preliminary evidence indicates that improving assessment can improve pain management, and may improve the management of other symptoms as well. In a 1997 randomized clinical trial, Trowbridge et al. [12] found that standardized pain assessment alone improved cancer pain management and reduced patient-reported pain severity. Further improvement in symptom management might be achieved if standardized assessment were coupled with simple protocols or guidelines for symptom management. For example, Du Pen and colleagues [13] found that the institutional use of a simple protocol for cancer pain management reduced pain severity.

Studies undertaken by the Eastern Cooperative Oncology Group (ECOG) [1, 3] have suggested that the undertreatment of pain is prevalent among the institutions that participate in this network. We hypothesized that dissemination of a specific clinical protocol for the oral analgesic management of cancer pain through a trial sponsored by ECOG and the National...
Cancer Institute would increase adherence and lead to improved treatment practice and patient outcomes. We also speculated that patients who were followed in the same practice but were not specifically placed on the clinical protocol would nonetheless benefit from diffusion of knowledge. Finally, we hypothesized that improved treatment of pain would further result in improvement in other symptoms, in mood and in quality-of-life measures.

Patients and methods

Study design

This was an intergroup study. To reduce variability that might be associated with the type of treatment setting (cancer center versus community practice), we studied patients with pain who were being followed at 24 Community Clinical Oncology Programs (CCOPs) associated with National Cancer Institute-sponsored clinical trials groups (ECOG, University of Rochester Cancer Center, the Cancer and Leukemia Group B, and The University of Texas M. D. Anderson Cancer Center). Of these, 12 were designated minority CCOPs, meaning that most patients fit the federal definition of minority status. ECOG data suggests that these patients are at higher risk for undermedication [1]. To ensure the balancing of intervention versus control sites, we stratified the patients by CCOP minority/non-minority status.

The study was structured in two successive phases, both conducted among patients with pain at the CCOP sites: an initial, pretrial study that established baseline levels for pain severity and treatment efficacy; and a randomized controlled clinical trial that examined the effectiveness of the analgesic protocol. Eligibility requirements and outcome measures were the same for the pretrial study and the clinical trial.

Pretrial study. Prior to the clinical trial, we conducted a cross-sectional study in the CCOPs to determine the prevalence and severity of pain in the groups targeted for the clinical trial, and to examine the adequacy of pain management. Each of the 24 participating CCOPs enrolled 10 patients who met the eligibility requirements established for the clinical trial. We used the outcome measures designated for the clinical trial to obtain patient-reported data on symptom severity and interference (for pain in particular) and on treatments. We also assessed adequacy of pain treatment. Patients filled out assessment forms at the clinic on the day of their scheduled visit.

Clinical trial of the analgesic protocol. We used a randomized cluster design for the clinical trial. The CCOPs were randomized to either the intervention (use of the analgesic protocol, AP) arm or the control (pain treatment by physician discretion or ‘usual care’, PD) arm, and were stratified according to minority and non-minority status. Each institution identified a nurse or data manager who was responsible for all aspects of this study. At the AP (intervention) sites, all eligible, consenting patients with pain and either metastatic non-small-cell lung cancer (NSCLC) or prostate cancer were treated according to the analgesic protocol. A second group at the AP sites (those with pain from breast cancer or multiple myeloma) was monitored to test for diffusion of changes in analgesic practice. At the PD (control) sites, patients were treated for pain as usual. The Institutional Review Board at each study site approved the study, and informed consent was obtained for all patients.

Each CCOP randomized to the AP arm was sent a copy of ‘A clinical protocol for the pharmacologic management of cancer pain’. Each AP site identified a physician and nurse to receive special instructions in the purpose and use of the analgesic protocol through semi-annual meetings with an ECOG resource team. Physicians at each PD site were aware of the study and knew they were to treat as usual. During all phases of the study, the resource team was available to the physicians and nurses treating by protocol to answer questions.

To begin, each AP site enrolled two to four patients in a run-in phase of the study so that investigators at the intervention sites could familiarize themselves with the clinical protocol, the study procedure and the forms to be completed. Because of slow accrual to the clinical trial, these run-in patients were combined with the rest of the patients in the final analysis.

Eligible outpatients with metastatic or recurrent NSCLC, prostate cancer, breast cancer or multiple myeloma who were scheduled for physician appointments in the designated institutions on a predetermined date, were asked to participate in the study. Patients were recruited when they checked in for their scheduled appointment. The designated nurse or data manager at each institution was available to work with physicians during the clinic session to identify and recruit patients.

All patients were consecutively accrued in the pretrial study and the clinical trial. Patients enrolled in the pretrial study did not participate in the clinical trial. Patients were to be consecutively recruited for the clinical trial until each CCOP had its quota of NSCLC and prostate cancer patients, along with sufficient breast cancer and multiple myeloma patients; however, the study terminated before quotas were met because of poor accrual.

Patients completed the consent form and assessment questionnaires during their scheduled clinic visit T1 (day 1), before being seen by their physician. They were given take-home copies of the assessment questionnaires to complete at T2 (day 15) and T3 (day 29), and self-addressed envelopes in which to return the completed assessments. If requested by the patient, or if deemed beneficial for the patient by the research nurse or data manager, the research nurse contacted the patient by telephone to assist in the completion of the questionnaires. T2 was chosen as the primary outcome assessment point, because this allowed sufficient time for clinic staff to implement adjustments in oral analgesic medication but without a high probability of significant disease progression causing additional pain. Assessment at T3 allowed evaluation of any sustained changes in pain or treatment. At no time were scores on outcome measures, including numeric pain ratings, conveyed to the treating physicians.

After completion of the assessment forms at T1, the physicians at the AP sites began to treat their NSCLC and prostate cancer patients according to the analgesic treatment protocol. Enrolled NSCLC and prostate cancer patients at the PD sites were treated as usual. At T2 and T3, the nurse or data manager contacted each patient to ensure completion of the assessment forms over the telephone. The patient was asked to return the forms to the site in person or in the envelope provided. During these phone calls, the nurse or data manager made a note of the types and doses of pain medications and adjuvants the patient was taking.

After T3, the data manager reviewed the patients’ charts and completed an oral analgesic protocol adherence form for all patients registered at the AP sites. From this information it was possible to determine how closely the prescribed treatment adhered to the treatment suggested by the analgesic protocol.

Study participants

Patients in both the pretrial study and the clinical trial were outpatients who had pathologically confirmed metastatic NSCLC or prostate cancer, histologically confirmed metastatic breast cancer, or multiple myeloma. Patients with NSCLC had bone or chest pain due to disease. Patients had to have rated their worst pain as 4 or greater on the Brief Pain Inventory’s 0–10 pain worst scale, be at least 18 years old, and have an expected life span of at least 2 months. Patients could not be receiving palliative radiotherapy or have had surgery within the past 30 days.
Treatment protocol

The ECOG Pain Subcommittee established a group to develop the protocol for the clinical trial. The working group, chaired by Russell Portenoy, included medical oncologists, an anesthesiologist and a neurologist specializing in cancer pain management, a psychologist specializing in pain assessment, a nurse oncologist, and a nursing professor specializing in patient barriers to pain treatment. Several of these members had also served on pain guideline committees.

The working group developed an oral analgesic protocol encompassing common treatment recommendations from existing guidelines for cancer pain management [7, 8, 10]. The majority of protocol recommendations had been shown to be effective in randomized clinical trials. Additional steps were included because they appeared consistently in existing cancer pain management guidelines, or because of consensus among the working group. The protocol established decision rules for symptom assessment, analgesic choice (depending on pain type and severity), starting doses and titration, and use of adjuvant medications (tricyclics for burning pain, anticonvulsants for stabbing pain). The working group made specific recommendations for the management of expected opioid-related side-effects and for opioid rotation or dose reduction for side-effects management. In response to needs identified in prior ECOG studies [1, 3], the protocol specified type and frequency of pain assessment and reassessment. It directed that patients be given an educational pamphlet that encouraged patients to report their pain to their doctors and nurses, provided basic information about analgesic use, and covered common patient concerns about using opioid analgesics (addiction, side-effects, increased tolerance to analgesic effects). The protocol was also presented graphically as a flow chart summarizing the sequence of treatment and major decision points. As an example of the way the protocol was written, the specific instructions for a patient not responsive to initial opioid therapy are given in Table 1.

Outcome measures for pretrial study and the clinical trial

Patients enrolled in either the pretrial study or clinical trial were given three questionnaires: the Brief Pain Inventory (BPI), the Symptom Distress Scale (SDS) and a short form of the Profile of Mood States (POMS-SF).

The BPI [14] uses 0–10 scales to measure present pain and worst, least, and average pain over the previous 24 h, and to measure how much pain interferes with functions such as activity, walking, work, mood, relations with others and enjoyment of life. The BPI also asks patients to report how much pain relief they experienced (as a percentage).

The BPI provided the primary outcome measures; patients did not keep a pain diary. Because the study lacked the necessary statistical power to detect differences according to the original analysis plan (mean pain worst), we compared groups using proportions of patients who responded to treatment on this same end point. A responder was defined as a patient whose pain worst changed from moderate or severe (5 or greater on the BPI at T1) to none or mild (0–4) at T2 [15, 16]. This range was selected because previous studies have shown that patients who report pain of 5 or greater on this item experience significantly greater pain-related interference with function than those with mild or no pain [1, 17, 18]. We also used the percentage of patients with pain in the mild range to assess change at T2 for the breast and myeloma patients treated at the AP and PD sites.

The BPI also allowed calculation of a Pain Management Index (PMI) [1], which was used to assess the adequacy of pain management. The PMI reveals the extent to which pain (determined as the BPI pain worst scores) is managed using the drug categories recommended in widely accepted treatment guidelines [4].

Other secondary outcome measures were (1) reduction in non-pain symptoms, (2) changes in analgesic administration and (3) changes in mood state. To measure the impact of the intervention on other symptoms, patients completed the SDS [19], which measures nausea, fatigue, insomnia, appetite, difficulty breathing, pain (frequency and intensity) and outlook. Affective status was assessed using the POMS-SF [20], which was developed for cancer patients with pain. Prescription of analgesic and adjuvant pain-related medications was recorded at T2 and T3. Research nurses completed an analgesic protocol adherence form at T3 for those patients treated at AP sites to monitor whether or not protocol recommendations were followed.

Statistical analysis

Descriptive statistics were used to summarize patient characteristics and scores on all outcome measures. The main objective of the study was to determine whether there were significant differences between the AP and PD arms in terms of pain reduction. The study was originally powered to detect a 0.80 difference in the mean reductions in pain worst scores in the two arms with 80% power (two-sided alpha of 0.05). Assuming a standard deviation of 2.19, allowing for cluster randomization, and taking into account the possible occurrence of missing data, the required sample size was 308. Knowing a priori that the study was underpowered to detect differences between arms using mean pain worst scores, we decided to examine differences in proportions rather than differences in mean levels.

To examine for clinically meaningful reductions in pain, the level of BPI pain worst at T1, T2 and T3 was analyzed as a dichotomous variable, considering as responders patients who rated their level of pain between 0 and 4 (‘mild’) on the 0–10 scale. We performed McNemar tests within groups from T1 to T2 and from T1 to T3 to analyze the dichotomized responses. We then compared the proportion of patients in each of the AP and PD arms whose moderate or severe pain (5–10) had improved to no or mild pain (0–4) from T1 to T2 or from T1 to T3. These analyses were performed separately for the lung/prostate and breast/myeloma patients. Hypotheses tests involving the lung/prostate group evaluate the treatment effect, while those for the breast/myeloma group assess diffusion of knowledge.

Another outcome measure used was percentage change in the BPI pain worst ratings between the baseline assessment and a follow-up assessment at T2 (the primary outcome period) within treatment arms. We reported a percentage reduction in pain worst between T1 to T2 and T1 to T3 by treatment arm separately for lung/prostate and breast/myeloma patients.
To account for the inflation of Type I error in the within-arms comparisons, we applied Bonferroni’s correction and set the alpha level at 0.006 rather than the traditional 0.05.

To take into account the clustering of the design, patients’ characteristics at baseline for the run-in and study phases combined were compared using the Rao and Scott corrected Pearson statistic [21] for categorical variables and an adjusted Wald test for continuous variables [22].

For the analysis of the POMS-SF and SDS instruments, generalized linear mixed models (glimmix macro) [23] were used to test for differences between the AP and PD arms. Since standard practice may vary with institution, and institution was the unit of randomization, it is reasonable to assume that there could be some correlation in the data. To allow for this, we used SAS PROC MIXED to fit mixed-effects linear models with institution included as a random effect, and assigned treatment group as a fixed effect [23]. All P values were two-tailed.

**Results**

The pretrial baseline study was activated in April 1994 and the clinical trial of the protocol intervention was closed, due to slow accrual, in November 1999.

**Pretrial study**

Of the 225 pretrial-study patients, 47% had breast cancer, 26% had NSCLC, 25% had multiple myeloma and 2% had prostate cancer. Approximately 72% had experienced pain for more than the past 6 months. The level of pain at its worst in the previous 7 days was moderate for 53% of the patients and severe for 47%, with a mean (SD) of 7.2 (2.0) on a 0–10 scale. On average, study patients reported 66% relief provided by medication. Approximately 24% of the patients reported having received opioids conventionally used for severe pain (e.g. morphine), 32% received opioids conventionally used for moderate pain (e.g. codeine), 43% received non-opioid drugs, and 1% received no analgesic drugs. Sixty per cent of the patients had negative PMI scores, indicating poor adherence to recommended guidelines for the selection of drugs for cancer pain. There was considerable variability among CCOPs (15%–67%) in the percentage of patients with a negative PMI.

**The clinical trial**

Of 136 patients who enrolled in the intervention phase of the study, 129 were eligible. Figure 1 portrays the patient flow for the clinical trial. At the AP sites, 27 NSCLC or prostate cancer patients were treated with the analgesic protocol and 26 breast cancer or myeloma patients were followed. At the PD sites, 49 NSCLC or prostate patients and 27 breast cancer or myeloma patients were followed. Table 2 describes the characteristics of the patients and Table 3 describes certain baseline pain levels in each of the clinical trial conditions.

At T1, there were no significant differences in patient characteristics of NSCLC and prostate patients by treatment group, except for prior treatment with chemotherapy (26% in the AP arm and 69% in the PD arm, P=0.002). Twenty-one per cent of the NSCLC and prostate patients received opioids conventionally used for severe pain and 30% received opioids for moderate pain; non-opioid drugs were administered to

---

**Figure 1.** Patient flow through randomized trial.
42%, and 7% received no analgesic drugs. NSCLC and prostate patients at the AP sites received fewer opioid analgesic drugs than patients at the PD sites (33% versus 61%, respectively, \( P = 0.045 \)). Sixty-eight per cent of all patients had negative PMI scores at T1.

There were no significant differences in levels of pain or duration of pain by treatment group. There were no differences in the physicians’ judgments of the etiology of pain between the two groups of NCSLC/prostate patients or between the two groups of breast/myeloma patients, although the NSCLC/prostate patients had somewhat less bone pain and somewhat more pain due to neural involvement (see Table 3).

When the intent-to-treat analysis of the primary end point was performed on all patients as randomized (including six patients that were ineligible for the run-in and study phases), the results were similar to a completers’ analysis.

The proportion of responders to pain treatment, defined as a category shift from T1 to T2 in pain worst from moderate or severe (5–10) to mild or no pain (0–4), was 48% (11/23) among NSCLC and prostate cancer patients at the AP sites and 15% (3/20) among similar patients at the PD sites. These proportions (48% versus 15%) were statistically different (\( P = 0.008 \)), indicating that a significantly greater percentage of patients in the AP group experienced a significant reduction in pain. This test examining change from T1 to T2 corresponded to the primary outcome assessment point. At T3, the pain levels for 52% of the AP patients and 19% of the PD patients had lessened from moderate or severe at T1 to mild or none, which was also statistically significant (\( P = 0.045 \)). This test examining change from T1 to T3 corresponded to the secondary outcome assessment point, where our interest was in evaluating any sustained changes, thus representing a different conceptual hypothesis. Therefore, we did not control for Type I error rate and used a significance level of 0.05.

In the test of diffusion, the proportions of breast cancer and myeloma patients in the AP and PD arms who achieved mild or no pain during the study were not significantly different—29% (7/24) in the AP group versus 19% (5/26) in the PD group at T2, and 36% (9/25) versus 31% (8/26), respectively, at T3.

The mean of the primary end point pain worst for NSCLC and prostate cancer patients treated at the AP sites decreased

<table>
<thead>
<tr>
<th>Table 2. Patient characteristics, run-in and study phases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient characteristics</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>No. of patients</td>
</tr>
<tr>
<td>Age: Median, range</td>
</tr>
<tr>
<td>Sex</td>
</tr>
<tr>
<td>Male</td>
</tr>
<tr>
<td>Female</td>
</tr>
<tr>
<td>Race</td>
</tr>
<tr>
<td>White</td>
</tr>
<tr>
<td>Hispanic</td>
</tr>
<tr>
<td>Black</td>
</tr>
<tr>
<td>Unknown</td>
</tr>
<tr>
<td>Primary disease</td>
</tr>
<tr>
<td>Lung</td>
</tr>
<tr>
<td>Prostate</td>
</tr>
<tr>
<td>Breast</td>
</tr>
<tr>
<td>Myeloma</td>
</tr>
<tr>
<td>Performance status</td>
</tr>
<tr>
<td>0–1</td>
</tr>
<tr>
<td>2–3</td>
</tr>
<tr>
<td>Prior treatment</td>
</tr>
<tr>
<td>Chemo/immunotherapy</td>
</tr>
<tr>
<td>Hormonotherapy</td>
</tr>
<tr>
<td>Radiotherapy</td>
</tr>
<tr>
<td>Concurrent diseases</td>
</tr>
</tbody>
</table>

NSCLC, non-small-cell lung cancer.
from 6.6 at T1 to 4.8 at T2, a 27% reduction, and remained reduced by 27% at T3 (both $P<0.002$). Pain worst for NSCLC and prostate patients treated at PD institutions went from 7.3 at T1 to 6.8 at T2, a 7% non-significant reduction ($P<0.73$), and to 6.4 at T3, a 12% non-significant reduction ($P<0.02$). Note that to control Type I error rates in these within-arm comparisons, a significant result was associated with a $P$ value less than 0.006.

Using this critical alpha value, there were non-significant decreases in pain worst at T2 (11%) and at T3 (18%) for breast cancer and myeloma patients.

### Table 3. Baseline pain characteristics at T1 (day 1): run-in and study phases

<table>
<thead>
<tr>
<th>Patient characteristics</th>
<th>NSCLC and prostate patients</th>
<th>Breast cancer and myeloma patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Analgesic protocol</td>
<td>Physician discretion</td>
</tr>
<tr>
<td></td>
<td>$n$</td>
<td>%</td>
</tr>
<tr>
<td>No. of patients</td>
<td>27</td>
<td>49</td>
</tr>
<tr>
<td>Pain for more than the past 6 months</td>
<td>19</td>
<td>70.4</td>
</tr>
</tbody>
</table>

### Type of pain (physician interpretation)

- **Headache**: 0 (0.0) - 1 (2.0) - 1 (1.3)
- **Bone**: 20 (74.1) - 36 (73.5) - 56 (73.7)
- **Pleuritic**: 10 (37.0) - 16 (32.7) - 26 (34.2)
- **Visceral**: 5 (18.5) - 3 (6.1) - 8 (10.5)
- **Neural involvement**: 6 (22.2) - 7 (14.3) - 13 (17.1)
- **Postoperative**: 0 (0.0) - 1 (2.0) - 1 (1.3)

### Level of pain at its worst in the last week: mean (SD)

- **Moderate (4–7)**: 6.6 (2.1) - 7.3 (1.8) - 7.0 (1.9)
- **Severe (8–10)**: 6.4 (1.9) - 6.7 (1.8) - 6.6 (1.8)

### Level of pain; mean (SD)

- **At its least in the last week**: 3.1 (1.8) - 2.9 (2.5) - 3.0 (2.3)
- **On the average in the last week**: 4.4 (1.7) - 4.8 (2.2) - 4.7 (2.0)
- **Right now**: 3.5 (2.2) - 4.0 (2.7) - 3.8 (2.5)

### Pain interfered with (in the last week); mean (SD)

- **General activity**: 5.4 (3.3) - 6.6 (2.4) - 6.2 (2.8)
- **Mood**: 5.5 (2.8) - 5.5 (2.5) - 5.5 (2.6)
- **Walking ability**: 5.0 (3.6) - 5.4 (3.1) - 5.2 (3.3)
- **Normal work**: 5.7 (3.9) - 7.0 (2.6) - 6.5 (3.1)
- **Relations with other people**: 3.7 (3.1) - 4.3 (2.8) - 4.1 (2.9)
- **Sleep**: 4.6 (3.0) - 5.4 (3.2) - 5.1 (3.1)
- **Enjoyment of life**: 5.4 (3.3) - 6.1 (2.7) - 5.8 (2.9)

### Analgesics

- **None**: 5 (18.5) - 0 (0.0) - 5 (6.6)
- **Non-opioid**: 13 (48.2) - 19 (38.8) - 32 (42.1)
- **Weak opioid**: 5 (18.5) - 18 (36.7) - 23 (30.3)
- **Strong opioid**: 4 (14.8) - 12 (24.5) - 16 (21.1)

### Pain management index

<table>
<thead>
<tr>
<th>$\text{Pain management index}^a$</th>
<th>$\text{PMI} / C0_3$</th>
<th>$\text{PMI} / C0_2$</th>
<th>$\text{PMI} / C0_1$</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\text{PMI} / C0_3$</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>$\text{PMI} / C0_2$</td>
<td>2</td>
<td>9</td>
<td>9</td>
</tr>
<tr>
<td>$\text{PMI} / C0_1$</td>
<td>3</td>
<td>2</td>
<td>6</td>
</tr>
</tbody>
</table>

*Pain management index (PMI) of $\text{PMI} / C0_3$ corresponds to a patient with severe pain receiving no analgesic drugs; PMI of 3 corresponds to a patient receiving morphine or equivalent and reporting no pain.

NSCLC, non-small-cell lung cancer.
the breast and myeloma patients treated at AP institutions. Similar non-significant decreases were noted for the breast and myeloma patients seen at PD institutions at both T2 (10%, $P < 0.045$) and at T3 (16%, $P < 0.014$). Thus, there were no differences in the percentage reduction in pain worst for breast and myeloma patients between AP and PD institutions (Figure 2).

A comparison of results by sex and by race showed that, although the primary end point pain worst generally decreased from T1 to T2, the changes over time were not significantly different between the AP and PD treatment arms for males or females and for whites or other races.

Change in pain relief from baseline to T3 was significantly higher for AP than PD lung and prostate cancer patients (19.2% versus 1.6%, $P = 0.02$).

**Secondary outcomes**

The proportion of patients with a negative PMI was marginally reduced for all treatment groups, but there was no evidence that improvement in this practice measure was greater for those patients treated by protocol. There were no significant changes in the POMS-SF mean scores or in the six dimensions of mood scores (depression, vigor, confusion, tension, anger and fatigue) by treatment groups, and there were no substantial reductions in the SDS mean scores or symptom categories, except for the item intensity of pain for the AP treatment arm ($P = 0.005$). Because of the length of the trial, guidelines published during its course that call for aggressive pain management until the patient’s pain is in the mild range, might have influenced pain management practices. We tested for this possibility by examining the percentage of patients with a negative PMI at baseline, comparing those who entered during the first half of the study (February 1998 to November 1998) with those who entered during the last half (December 1998 to November 1999). We found no significant difference.

**Adherence to the protocol**

Adherence to the pain management protocol was monitored for the 27 NSCLC or prostate cancer patients in the AP treatment arm, using an oral analgesic protocol adherence form. Five patients left the study before T3 for the following reasons: one patient could not tolerate oral administration, two patients had pain crises and two patients died. At T3 or the end of the study, about 67% of the patients were continuing on pain medication per protocol, 11% of the patients had discontinued pain medication and 18% were continuing with additional pain treatment. One patient received pain medication that was not permitted by the protocol. Adherence to the protocol was also assessed using the PMI and a more detailed exploration of prescribing practice. As noted, there were no significant changes in the PMI. At study entry, most of the NSCLC and prostate cancer patients at AP institutions (63%) received an opioid/non-opioid combination as their primary analgesic. Approximately 41% of the patients did not have changes in dosage of pain medication and 22% had their dosages increased above the initial level.

**Discussion**

The cross-sectional prettrial study indicated that a majority (60%) of patients with moderate to severe cancer pain were not prescribed analgesics appropriate to their level of pain. Confirming previous studies [1, 2], there was considerable variation by treating site in the adequacy of pain management and the percentage of patients with moderate to severe pain.

The PMI, which measures the appropriate matching of analgesics with pain severity, is one way to assess adequacy of treatment. Although the PMI did not reveal substantial change in practice in this study, patients with NSCLC or prostate cancer and moderate or severe pain who were treated according to the oral analgesic protocol had a significantly greater reduction in pain than did patients at PD institutions. The proportion of patients with no or mild pain (responders) at both T2 and T3 was also significantly greater for the AP group. The percentage reduction in pain approximates levels that have been considered to be clinically significant by other criteria [24, 25]. There were no significant changes in other symptoms or mood.
The proportion of breast or myeloma patients with no or mild pain also showed some improvement (see Figure 3), but did so at both the AP and the PD sites. Although diffusion of practice change could therefore not be discerned, the small sample size (26 AP patients and 27 PD patients) was under-powered to detect this phenomenon. The original study design required 400–408 breast cancer and myeloma patients to detect hypothesized differences.

The striking change in pain at the AP sites, despite the small sample size, suggests that the dissemination of a clinical protocol may lead to quality improvement in cancer pain management. A recent study [16] also suggests that adherence to a pain management protocol can result in a majority of patients with advanced disease maintaining their pain intensity in the mild range over time. While there was little reduction in the proportion of patients with a negative PMI over the course of this study, the PMI does not reflect actual dose of analgesic prescribed, adequacy of side-effects management, or use of adjunctive medications, all components of the protocol. It also does not reflect patient adherence to medications or the effects of the protocol-mandated patient education.

The protocol used in this trial differed from earlier guidelines [9] by operationalizing treatment decisions (such as stipulating specific drug and dosage recommendations for given levels of pain, giving specific side-effects management instructions, and specifying particular adjuvant analgesics for neuropathic pain), but was quite similar to more recent cancer pain management guidelines, such as those of the National Comprehensive Cancer Network [11].

These newer guidelines direct that aggressive attempts at pain management should persist until the patient’s pain is in the mild range (BPI pain worst score of 4 or less). In this study, only about half (52%) of the NSCLC and prostate cancer patients treated by protocol, 18% of these patients at PD sites and about 30% of breast cancer and myeloma patients, achieved this level of pain control by T2. Even among those treated according to the protocol, this outcome is inadequate. The protocol and its implementation in this study should be viewed as a potential tool for generating needed improvement. Given the outcomes of this study, however, it should not, by itself, be considered sufficient to achieve desirable goals for symptom control.

This study has several limitations. First, patients were only assessed at 2 and 4 weeks, although pain would be expected to be a continuing problem for these patients with metastatic disease as long as they survived. Secondly, data collection for the pretrial study began in early 1995. Significant changes in the adequacy of pain management may have occurred in the intervening years, although we found no indication of pain management change over time when we compared baseline PMIs for patients entering the first half of the trial with those entering the last half. Thirdly, we did not use daily patient diaries as outcome measures. Diaries might have captured overall fluctuations in pain level and the analgesics taken by patients during the trial. Finally, the trial was designed for a much larger number of patients. The intended sample would have provided a better test of the potential diffusion effects of the protocol in the AP settings, and the possible effects of the protocol on secondary outcome measures. The findings require confirmation in such a larger trial.

Although the pretrial study accrued its intended sample relatively rapidly, it was very difficult to accrue patients to the clinical trial itself despite increases in per-patient credits provided by the NCI and repeated investigator meetings at the semi-annual ECOG gatherings. Interviews with the COOP investigators prior to termination of the study suggested several reasons: investigators felt that symptom management protocols were of substantially lower priority than standard curative protocols; that participation in symptom management protocols was less academically important than participation in curative protocols; and that their prior experience did not prepare them to perform symptom management protocols.

ECOG has responded to some of these concerns by forming a Pain and Symptom Management Committee and by providing additional research support for sites willing to give priority to symptom management protocols. The need for the investment of resources and research in the management of pain and other symptoms, and the opportunity for NCI-sponsored cooperative groups to contribute to this effort, were emphasized in recent reports of the Institute of Medicine’s National Cancer Advisory Board [26] and the National Institutes of Health State of the Science Conference Statement on Symptom Management in Cancer [27]. Involvement of the NCI-sponsored cooperative groups in systematic evaluation of treatment methods to reduce symptoms could provide enormous benefits to thousands of cancer patients whose pain is not being effectively alleviated.

Acknowledgements
This study was coordinated by the Eastern Cooperative Oncology Group (Robert L. Comis, M.D.) and supported in part by Public Health Service Grants CA23318, CA66636, CA21115, CA45809, CA45808, CA045389 and CA26582.
from the National Cancer Institute, National Institutes of Health and the Department of Health and Human Services. The study contents are solely the responsibility of the authors and do not necessarily represent the official views of the National Cancer Institute.

References
