

Randomized Trial of Low-Dose Morphine Versus Weak Opioids in Moderate Cancer Pain

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Published online ahead of print at www.jco.org on December 7, 2015.

Written on behalf of the Early Strong Opioid Treatment Study Investigators. Investigators are listed in the Data Supplement.

Supported by Azienda Ospedaliero Universitaria Policlinico (I. Trenti) and by USL (M. Annichiarico), Modena and by Direzione Generale Sanità e Politiche Sociali, Regione Emilia-Romagna (K. Petropulacos). This work is part of Programma di Ricerca Regione Emilia Romagna-Università, Ricerca per il Governo Clinico, 2010–2012 (3b211-19 to M.L.).

Terms in [blue](#) are defined in the glossary, found at the end of this article and online at www.jco.org.

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Authors' disclosures of potential conflicts of interest are found in the article online at www.jco.org. Author contributions are found at the end of this article.

Clinical trial information: EUDRACT2010-024298-37.

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0732-183X/16/3405w-436w/\$20.00

DOI: 10.1200/JCO.2015.61.0733

A B S T R A C T

Purpose

The WHO guidelines on cancer pain management recommend a sequential three-step analgesic ladder. However, conclusive data are lacking as to whether moderate pain should be treated with either step II weak opioids or low-dose step III strong opioids.

Patients and Methods

In a multicenter, 28-day, open-label randomized controlled study, adults with moderate cancer pain were assigned to receive either a weak opioid or low-dose morphine. The primary outcome was the number of responder patients, defined as patients with a 20% reduction in pain intensity on the numerical rating scale.

Results

A total of 240 patients with cancer (118 in the low-dose morphine and 122 in the weak-opioid group) were included in the study. The primary outcome occurred in 88.2% of the low-dose morphine and in 57.7% of the weak-opioid group (odds risk, 6.18; 95% CI, 3.12 to 12.24; $P < .001$). The percentage of responder patients was higher in the low-dose morphine group, as early as at 1 week. Clinically meaningful ($\geq 30\%$) and highly meaningful ($\geq 50\%$) pain reduction from baseline was significantly higher in the low-dose morphine group ($P < .001$). A change in the assigned treatment occurred more frequently in the weak-opioid group, because of inadequate analgesia. The general condition of patients, which was based on the Edmonton Symptom Assessment System overall symptom score, was better in the morphine group. Adverse effects were similar in both groups.

Conclusion

In patients with cancer and moderate pain, low-dose morphine reduced pain intensity significantly compared with weak opioids, with a similarly good tolerability and an earlier effect.

J Clin Oncol 34:436-442. © 2015 by American Society of Clinical Oncology

INTRODUCTION

The WHO guidelines on cancer pain management—or [palliative care](#)—are based on a sequential, three-step, analgesic ladder according to pain intensity: nonopioids (paracetamol or nonsteroidal anti-inflammatory drugs) to mild pain in step I; weak opioids (eg, codeine or tramadol) to mild-moderate pain in step II; and strong opioids to moderate-severe pain in step III.¹⁻³ Despite the widespread use of this ladder, unrelieved pain continues to be a substantial concern in patients with either solid or hematologic malignancies,⁴⁻⁸ and a common reason is represented by the inadequacy of analgesic therapy, which may be influenced by multiple

factors, including a nonspecific setting for cancer pain and opiophobia.^{4,9,10} Some authors have questioned the sequential WHO analgesic ladder, and in particular, the usefulness of step II opioids.^{9-11,12} Current international guidelines recognize that low doses of a step III opioid (eg, morphine or oxycodone) may be used instead of codeine or tramadol for patients with mild-moderate pain,¹³⁻¹⁶ although such recommendations are weak, because they have been made on the basis of three trials with methodologic flaws, low statistical power, and selection bias.¹⁷⁻¹⁹

Our study, called the Early Strong Opioid Treatment in Cancer Pain: Morphine Versus Weak Opioids was a randomized controlled multicenter study designed to evaluate the efficacy and tolerability of low doses of morphine in comparison

with standard doses of weak opioids in the treatment of moderate cancer pain in opioid-naïve patients.

PATIENTS AND METHODS

A multicenter, 28-day, open-label, randomized controlled trial was performed at 17 Italian oncology centers. The 1:1 random allocation, stratified by age (< 75 years ν ≥ 75 years) and participating center, was centralized using a computer-generated procedure.

The study protocol was approved by the ethics committee of each participating center and was registered on the National Clinical Trial Register and with the European Clinical Trials.

Study Population

Patients with cancer who are opioid naïve, with moderate pain intensity (4-6 on the standard Numerical Rating Scale [NRS], range 0-10)²⁰ were included in the study after screening for eligibility criteria: age > 18 years; Karnofsky performance status of 60% or more; absence of cognitive impairment or psychiatric illness; and estimated survival of at least 3 months. Pain was related to cancer and to anticancer therapy, and other additional causes of pain could be recorded. The Edmonton Symptom Assessment System (ESAS) was used to assess nine symptoms commonly experienced by patients with cancer during the previous 24 hours: pain, tiredness, nausea, depression, anxiety, drowsiness, appetite, feelings of well-being, and shortness of breath. The severity of each symptom was rated on a numerical scale of 0 to 10 (0, no symptoms; 10, worst possible severity). The sum of individual symptom scores, from 0 to 10, corresponds to the ESAS overall symptom score, ranging from 0 to 90.²¹⁻²³ The ESAS, validated in the Italian language,²⁴ was administered to the patients. Opioid-naïve patients were patients receiving neither opioid analgesics nor chronic opioid analgesics around the clock, at study inclusion. Exclusion criteria were as follows: contraindication to opioid use; chronic renal failure (glomerular filtration rate < 30 mL/min); severe hepatic or respiratory failure; malabsorption syndrome; uncontrolled diarrhea, nausea, vomiting because of cancer therapies; subileus or intestinal obstruction; radiotherapy or radiometabolic therapy; current use of investigational drugs; or inability to take oral medications.

Study Treatments and Procedures

Patients were randomly assigned to receive either low-dose oral morphine (M) or a weak opioid (WO) from randomization until day 28. The WO group could receive oral formulations of tramadol alone or in combinations with paracetamol, or codeine in fixed combination with paracetamol, the only one oral formulation of codeine available in Italy, at the time of the study, according to the routine clinical practice of each center, by adhering to a procedure of WO prescription, described in the study protocol (Data Supplement). This group, regardless of the drug used, was considered as a whole when compared with the M group. The minimum effective dose of WO was scheduled for a progressive increase, if necessary up to the maximum recommended dose: 240 mg/die, or 180 in fixed combination with paracetamol, for codeine; and 400 mg/die, or 300 mg/die if patients were older than 75 years, for tramadol. The maximal daily dose of paracetamol was set at 4000 mg/day. The switch from one to another WO was allowed.

Patients assigned to the M group underwent a 3-day titration phase with normal-release oral morphine up to 30 mg daily,²⁵ and, thereafter, continued treatment with slow-release morphine (Data Supplement). Both the switch to a strong opioid in the WO group and the switch to another strong opioid in the M group were allowed only when the therapeutic dose was reached by titration and were considered as an end-point event, at the end of study observation. Patients were monitored weekly, on days 7, 14, 21, and 28 after randomization. The baseline and weekly control visits included the following evaluations: pain intensity by NRS, cancer symptoms with ESAS, Karnofsky performance status, continuation or switch of assigned analgesic treatment, change of dosage, and adverse

effects associated with treatment. The frequency of adverse effects was assessed prospectively at every follow-up visit. This included asking the patients about the presence of vomiting, constipation, dry mouth, itch, dizziness, somnolence, cognitive impairment, pseudohallucinations, myoclonic jerks, and other expected opioid-related toxicities.

Outcomes

A patient experiencing a reduction of pain intensity of 20% or more from baseline was defined as a responder patient,²⁶ and the number of responder patients at 28 days or at the end of observation, whichever came first, was assumed as the primary end point. The proportion of pain reduction was calculated by the following formula: (pain intensity at final time – pain intensity at initial time)/(pain intensity at initial time) \times 100. Secondary outcomes included improvement in physical symptoms and overall well-being as assessed with ESAS²¹⁻²³; number of patients with a clinically meaningful ($\geq 30\%$) and highly meaningful ($\geq 50\%$) reduction of pain intensity from baseline²⁷; mean increase of opioid dosage calculated as opioid escalation index percentage according to the formula (OMD – OSD)/OSD/days \times 100, where OSD is the opioid starting dose and OMD the opioid maximal dose.²⁶ Type and incidence of adverse effects, and therapy discontinuation because of adverse effects, were evaluated at each ambulatory visit.

Statistical Analysis

Assuming as clinically significant a 30% increase in response rate in the M group from an expected 45% in the WO arm, and a power of 80% at a significant level of a two-sided P value of .05, a sample size of 426 patients (213 per arm) was calculated. After considering an increasingly slower accrual of patients, possibly corresponding to the publication of recommendations recognizing M as a possible treatment for step II,¹⁵ the steering committee decided to perform an interim analysis when 240 patients were enrolled (Data Supplement). Therefore, this analysis has been conducted by intention to treat on the population included in the interim and followed up according to the protocol.

Categorical variables are presented as frequencies and proportions and continuous variables as medians and interquartile ranges (IQRs). Differences in clinical characteristics were analyzed with the χ^2 test or Fisher's exact test and the Mann-Whitney U test for categorical and continuous variables, respectively. Binary outcomes were reported as proportions and were compared using the χ^2 test, whereas continuous outcomes were reported as medians (IQRs) and compared with the Mann-Whitney U test. A multivariate logistic regression model was performed to estimate the treatment effect adjusting for the effects of other covariates known to be of prognostic importance, such as pain intensity at baseline, age, sex, Karnofsky performance status, adjuvant analgesic therapy, rescue therapy, tumor type, and anticancer treatment. Results were expressed as odds ratios with 95% CI. A linear mixed model was used to evaluate the time course of the pain intensity score by study arm. Statistical analysis was done using SAS software, version 9.3 (SAS Institute, Cary, NC).

RESULTS

Study Population

A total of 240 opioid-naïve patients with cancer with moderate pain (NRS, 4 to 6) were enrolled onto the study from 17 centers (median, 9; IQR, 3 to 14). Of 240 patients, 118 patients (49.2%) were assigned to low-dose oral morphine (M) and 122 (50.8%) were assigned to weak opioids (WO).

In this latter group, 103 patients (84.4%) received a fixed combination of codeine (99 patients) or tramadol (four patients) with paracetamol; for 19 patients (15.6%), tramadol alone was the choice. The median initial dosages in the WO group were 150 mg

Table 1. Characteristics of Patients at Baseline

Characteristics	Weak Opioids (N = 122)	Morphine (N = 118)
Male sex	68 (55.7)	56 (47.5)
Age, years		
Median	68	68
Interquartile range	59-74	58-74
Cancer		
Solid	108 (88.5)	100 (84.8)
Hematologic	14 (11.5)	18 (15.3)
Current antitumor treatment	61 (50.0)	71 (60.2)
Karnofsky performance status, %		
60	9 (7.4)	5 (4.2)
70	48 (39.3)	42 (35.6)
80	28 (23.0)	35 (29.7)
90	23 (18.9)	18 (15.3)
100	14 (11.5)	18 (15.3)
ESAS overall symptom score		
Median	21	19
Interquartile range	14-33	12-29
Pain intensity (NRS)		
Median	5	5
Interquartile range	4-6	5-6
Cause of pain*		
Cancer	117 (95.9)	104 (88.1)
Treatment	8 (6.6)	15 (12.7)
Other†	2 (1.6)	6 (5.1)
Type of pain*		
Visceral	69 (56.6)	59 (50.0)
Somatic	62 (50.8)	61 (51.7)
Neuropathic	5 (4.1)	15 (12.7)
Pain characteristics		
Incidental pain	38 (31.2)	43 (36.4)
Not incidental	84 (68.9)	75 (63.5)
Previous analgesic therapy	100 (82.0)	98 (83.1)
At fixed times	19 (19.0)	21 (21.4)
As needed	81 (81.0)	77 (78.6)
Rescue therapy (prescription)	105 (86.1)	106 (89.8)
Adjuvant therapy	79 (64.8)	78 (66.1)
Duration of pain, days		
Median	30	30
Interquartile range	14-60	15-60

NOTE. Data are presented as No. (%) unless indicated otherwise. Abbreviations: ESAS, Edmonton Symptom Assessment System; NRS, Numerical Rating Scale.

*Multiple selection possible.

†Associated conditions recorded as other causes of pain in addition to cancer and treatment.

(IQR, 150 to 300) for tramadol alone; 1590 mg (IQR, 1590 to 1590), and 950 mg (IQR, 594 to 1081) for the combination codeine + paracetamol and tramadol + paracetamol, respectively. The median dose of M, after titration, was 30 mg (IQR, 30 to 30).

The baseline characteristics were well balanced between the two randomized groups, as listed in Table 1, in which the strict comparability of symptom severity, assessed with ESAS, is also evident, with a median (IQR) overall symptom score of 21 (14 to 33) in the WO and 19^{12,22} in the M arm (Data Supplement).

Outcomes

Of the original randomized cohort of 240 patients, 13 patients (eight in the M and five in the WO group) could not be included in the analysis because they dropped out of the study for various reasons before the first measure of the primary end point (Fig 1).

The primary end point of pain reduction of 20% or more from baseline was achieved in 88.2% of patients (97 of 110) in the M group and in 54.7% of patients (64 of 117) in the WO group (odds ratio, 6.18; 95% CI, 3.12 to 12.24; $P < .001$). Full adjustment for baseline covariates did not modify this result (Table 2).

As shown in Fig 2, the advantage of M over WO was already evident at the first control at 1 week of observation (80.9% v 43.6%; $P < .001$) and remained constant at each follow-up (Fig 2A). At the end of the observation period, a satisfactory pain control was registered in both groups, although with a statistically and clinically significant advantage for M (median NRS score, 1; IQR, 0 to 2) compared with WO (median NRS score, 2; IQR, 0 to 4; $P = .02$; Fig 2B). Moreover, the results of the linear mixed-model analysis to evaluate the time course of pain intensity score in each group showed that over time there was a greater reduction in pain intensity in the group treated with morphine (interaction $P = .001$; Fig 2B).

The findings related to the other measures of outcome are strictly consistent with the main results. A clinically meaningful ($\geq 30\%$) and highly meaningful ($\geq 50\%$) pain reduction was found more frequently in patients treated with M than in those treated with WO, with proportions and statistical significance mirroring the broader estimate obtained for the primary end point (Table 2).

The general condition of patients, which was based on the ESAS overall symptom score, was better in the morphine group (median score, 10; IQR, 6 to 15) than in the weak-opioid group (median score, 19; IQR, 10 to 17; $P < .001$; Table 3).

The patterns of switching between treatments and of dosage adjustments are also informative on the management sides of pain control. Forty-one patients (35.0%) in the WO group switched to a strong opioid and 17 (15.5%) in the M group switched to another strong opioid ($P = .001$); over the study period, 60.9% (67 of 110) of the M group and 40.2% (47 of 117) of the WO group modified neither the dosage nor the drug assigned ($P = .002$). On the other side, 28.2% (33 of 117) of the WO patients and 13.6% (15 of 110) of the M patients required a dosage increase ($P = .007$). The opioid escalation index (OEI% \pm standard deviation) was lower in the M than in the WO group (4.76 ± 6.44 v 8.76 ± 6.81 ; $P = .002$).

Adverse Events

Both drug treatments were well tolerated. Only five patients in each group discontinued their assigned treatment because of adverse effects or poor tolerability (three and two patients per group, respectively). No differences in the intensity and frequency of opioid-related symptoms were observed between the two groups (Data Supplement).

DISCUSSION

In this multicenter, 28-day, open-label, randomized trial, low-dose morphine significantly reduced pain intensity, as compared with weak opioids in patients with cancer and moderate pain, as early as 7 days after treatment. Constipation, dizziness, and other opioid-related adverse effects were not over-represented, in terms of either intensity or frequency, in the low-dose morphine group. The late

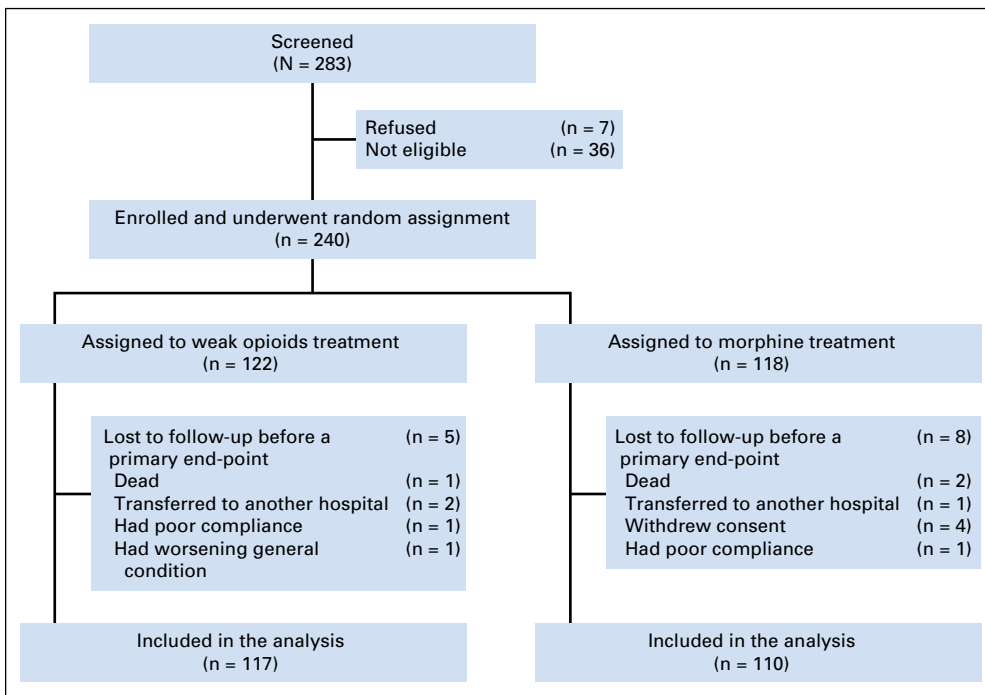


Fig 1. Study enrollment, randomization, and follow-up. All of the participants who were randomly assigned were included in the analysis with the exception of the 13 participants who discontinued follow-up before the primary end point.

and lower effect of treatment with weak opioids led to a more frequent switch to step III strong opioids.

In an early retrospective study by Ventafridda and colleagues,¹¹ the effectiveness of step II of the WHO method had a time limit of 30 to 40 days and, for most patients, the shift to step III was made mainly because of inadequate analgesia rather than adverse events. In current daily clinical practice, step II is often bypassed in favor of strong opioids, although the strategy is not supported by strong scientific evidence, because it was investigated by only two randomized controlled studies enrolling only 92 and 54 terminally ill patients, respectively,^{17,18} and one prospective study.¹⁹ In the study by Marinangeli and colleagues,¹⁷ a significantly better pain relief was achieved in patients with mild-moderate pain treated with strong opioids, compared with those treated with step II opioids, with only nausea more frequent in the former group, whereas no differences in other opioid-related symptoms were observed. In a study by Maltoni and colleagues,¹⁸ patients receiving step III opioids had a significant

advantage in terms of a reduction in the number of days with the worst pain, but more frequently showed grade 3 and 4 anorexia and constipation. In a prospective study by Mercadante and colleagues¹⁹ that enrolled only 110 patients with moderate-severe pain, treatment with low-dose morphine (starting dose of 15 mg/day and in patients ≥ 70 years 10 mg/day) was effective and well tolerated. However, these three studies reported inconclusive results because of the low number and representativeness of the patient sample and the low statistical power, leading to a weak recommendation for either a step II opioid or low doses of a step III opioid, as an alternative, in international guidelines.¹⁴⁻¹⁶ To the best of our knowledge, our study has provided the first formal proof that, although step II opioids are effective when used for limited time intervals, low-dose morphine can be usefully anticipated and can substitute for weak opioids in patients with cancer and moderate pain, more than half of whom are receiving active antitumor therapy (Table 1), because of greater efficacy and a comparable toxicity profile.

Table 2. Outcomes

Outcome	Weak Opioids (N = 117), No. (%)	Morphine (N = 110), No. (%)	Odds Ratio (95% CI)	P	Adjusted Odds Ratio* (95% CI)	P
Primary outcome						
Responders†	64 (54.7)	97 (88.2)	6.18 (3.12 to 12.24)	< .001	6.89 (3.33 to 14.25)	< .001
Secondary outcomes						
Patients with a meaningful pain reduction‡	55 (47.0)	91 (82.7)	5.40 (2.92 to 9.97)	< .001	5.74 (3.03 to 10.90)	< .001
Patients with highly meaningful pain reduction §	49 (41.9)	83 (75.5)	4.27 (2.42 to 7.53)	< .001	4.58 (2.52 to 8.33)	< .001

*Adjusted by pain intensity at baseline, age, gender, Karnofsky performance score, adjuvant therapy, rescue therapy, cancer type and anticancer treatment.

†Patients with pain intensity reduction at least 20% from baseline.

‡Patients with $\geq 30\%$ pain intensity reduction from baseline.

§Patients with $\geq 50\%$ pain intensity reduction from baseline.

The observed advantages in the clinical outcome coincide with the doubling of the estimates formulated in the original protocol and translate into a statistical significance ($P < .001$) of the difference, in the primary end point, already in a population which is a half of the one planned, in the original statistical design. The clinical reliability and significance are confirmed by the coincidence of similarly statistically significant findings in the secondary end points (Table 2), and the ESAS results (Table 3). The minimal clinical difference for improvement and deterioration of each of the nine ESAS symptoms is one point or more.²⁸ When the magnitude of symptom changes was assessed by ESAS in the two groups, treatment with low-dose morphine was associated with a significant improvement in either physical or emotional symptoms, providing a further argument in favor of its use in opioid-naïve patients with cancer with moderate pain.

Support of the findings could be seen in the consistency between crude estimates and the results obtained in the fully adjusted multivariate analysis, which could, on the contrary, be rather sensible to the instability associated with the small numbers of the population.

Despite confidence in the outcome of the study, we are aware of aspects of the trial, which could be considered structural, more than formal, weaknesses, namely, the lower and too long accrual of patients, assessed in an exploratory interim analysis which became (because of the surprising available evidence) a, somehow, mandatory stopping rule; the absence of pharmacologic quantification of rescue prescriptions; the open-label design. Relevant to this, opiophobia caused by the reluctance of patients and/or their families to accept strong opioids is a well-described cause of undertreatment of pain and may result in a low compliance with the recommended doses.⁴ A double-blind study was not possible

because the WO group potentially could have received three different drugs/oral formulations, according to potentially different clinical practice in each of the 17 centers. The open-label design also had the advantage of allowing physicians to titrate the morphine to the optimal dose on a personalized basis and also to rotate to the alternative opioid rapidly in case of uncontrolled pain and/or adverse effects. The choice to perform a nonprofit study was an obvious limitation for a double-blind design. It is, however, reasonable to see those weaknesses also against either the overall background given in the introduction, or the mandatory pragmatism of this trial, which was promoted by a fully independent group of clinicians, with no external financial support. Unfortunately, the best type of strong opioid has not been established and the morphine equivalent daily doses were not available; therefore, more research is needed to compare the most commonly used μ -opioid agonists such as morphine, hydromorphone, fentanyl, and methadone as first-line opioids, in terms of both pain intensity and adverse effects. It is also recommended that future studies prospectively determine the morphine equivalent daily dose.

In conclusion, our study demonstrated that compared with step II opioids, low-dose morphine provided an earlier and a more adequate level of analgesia for moderate cancer pain, with a fairly good tolerability profile and a positive impact on overall well-being. In most countries, strong opioids are highly regulated, and oncologists, family physicians, and internists may prefer to prescribe weak opioids because of lower regulatory requirements, including special prescriptions forms.²⁹⁻³¹ However, our data show that this intermediate step may be less effective and more expensive. The current WHO recommendation has the three-step pain ladder as the basis for treatment of cancer pain. New guidelines, including that by the EAPC, describe a two-step

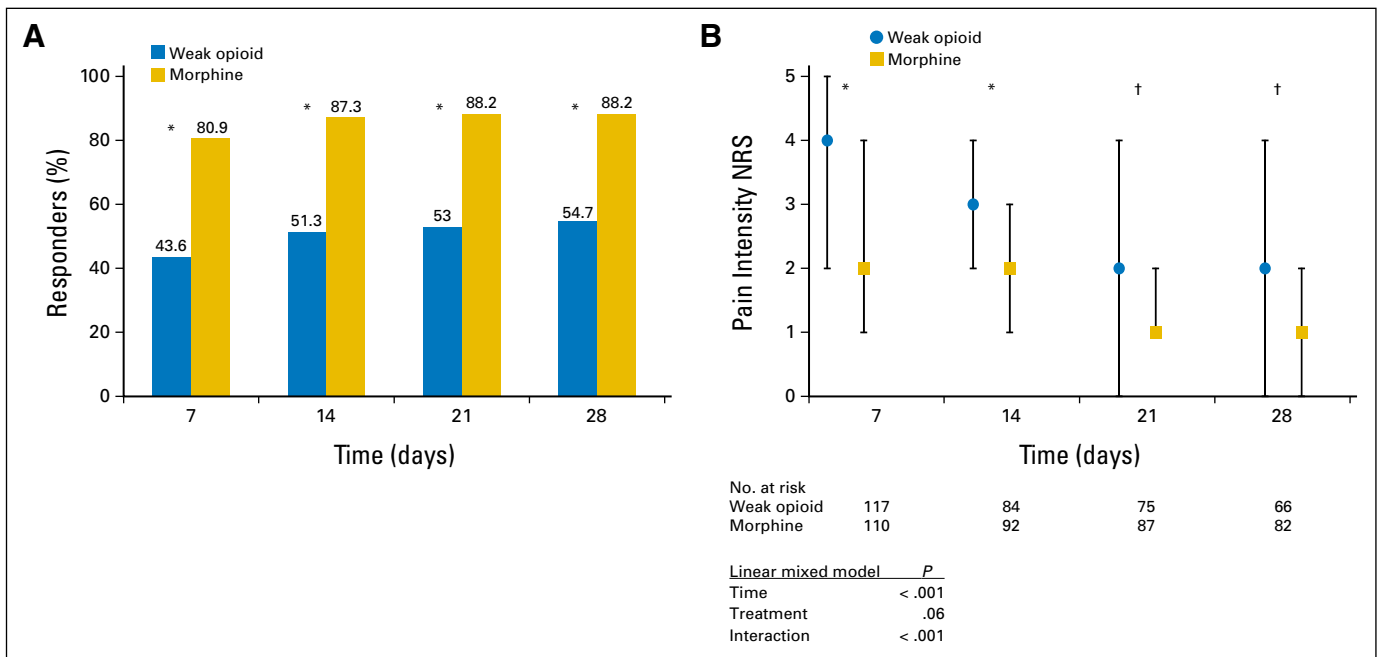


Fig 2. Responder patients and pain intensity (numerical rating scale [NRS]) at different follow-up times by treatment group. (A) Percentage of responder patients (who achieved $\geq 20\%$ pain reduction from baseline) at each follow-up. The P value is for the between-group comparison performed using the χ^2 test. (B) Pain intensity evaluated using the NRS at each follow-up. Data are shown as median and interquartile range. A linear mixed model for repeated measurements was done on pain intensity score. * $P < .001$, † $P = .02$ by Mann-Whitney U test.

Table 3. ESAS at End of Study

ESAS Item	Weak Opioids	Morphine	P
Pain	4 (1-6)	1 (0-3)	< .001
Tiredness	3 (2-6)	2 (1-3)	< .001
Nausea	1 (0-3)	1 (0-1)	.03
Depression	2 (1-4)	1 (0-2)	< .001
Anxiety	2 (0-4)	1 (0-2)	< .001
Drowsiness	3 (1-4)	1 (0-2)	< .001
Appetite	2 (1-5)	1 (0-2)	< .001
Well-being	3 (1-5)	1 (0-2)	< .001
Shortness of breath	0 (0-1)	0 (0-0)	.01
ESAS overall symptom score	19 (10-17)	10 (6-15)	< .001

NOTE. Data are presented as median (interquartile range). Abbreviations: ESAS, Edmonton Symptom Assessment System.

approach as an alternative.¹⁵ To abolish the second step will simplify treatments and perhaps give patients with cancer better pain control. Whether the findings of this study, which are in favor of starting directly with a step three opioid, may contribute to changing the WHO guidelines must be confirmed by other phase IIIb/phase IV studies.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at www.jco.org.

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Final approval of manuscript: All authors

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GLOSSARY TERMS

palliative care: care designed to address symptoms and maximize quality of life, regardless of patient prognosis

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Randomized Trial of Low-Dose Morphine Versus Weak Opioids in Moderate Cancer Pain

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No relationship to disclose

Marilena Romero

No relationship to disclose

Carla Ida Ripamonti

Consulting or Advisory Role: TEVA Pharmaceuticals Industries, Amgen, Norgine, Otsuka

Fabrizio Artioli

No relationship to disclose

Daniela Sichetti

No relationship to disclose

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No relationship to disclose

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No relationship to disclose

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No relationship to disclose

Barbara Melotti

No relationship to disclose

Pier Franco Conte

No relationship to disclose

Fausto Roila

Travel, Accommodations, Expenses: Astellas Pharma, MSD, Novartis, Roche, Bristol-Myers Squibb, Merck, Janssen, Exelixis, Eli Lilly, BiParSciences/Sanofi, Boehringer Ingelheim, Pfizer, GlaxoSmithKline

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No relationship to disclose

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No relationship to disclose

Acknowledgment

This work is dedicated by Elena Bandieri and Fabrizio Artioli to the memory of their mentor Carlo Carapezzi, and by Elena Bandieri and Mario Luppi to Alessandro Liberati, for his inspiration to independent clinical research.

Appendix

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