Randomized Clinical Trial of an Implantable Drug Delivery System Compared With Comprehensive Medical Management for Refractory Cancer Pain: Impact on Pain, Drug-Related Toxicity, and Survival

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Purpose: **Implantable intrathecal drug delivery systems (IDDSs) have been used to manage refractory cancer pain, but there are no randomized clinical trial (RCT) data comparing them with comprehensive medical management (CMM).**

Patients and Methods: **We enrolled 202 patients on an RCT of CMM versus IDDS plus CMM. Entry criteria included unrelieved pain (visual analog scale [VAS] pain scores ≥ 5 on a 0 to 10 scale). Clinical success was defined as ≥ 20% reduction in VAS scores, or equal scores with ≥ 20% reduction in toxicity. The main outcome measure was pain control combined with change of toxicity, as measured by the National Cancer Institute Common Toxicity Criteria, 4 weeks after randomization.**

Results: **Sixty of 71 IDDS patients (84.5%) achieved clinical success compared with 51 of 72 CMM patients (70.8%, *P* = .05). IDDS patients more often achieved ≥ 20% reduction in both pain VAS and toxicity (57.7% [41 of 71] *v* 37.5% [27 of 72], *P* = .02). The mean CMM VAS score fell from 7.81 to 4.76 (39% reduction); for the IDDS group, the scores fell from 7.57 to 3.67 (52% reduction, *P* = .055). The mean CMM toxicity scores fell from 6.36 to 5.27 (17% reduction); for the IDDS group, the toxicity scores fell from 7.22 to 3.59 (50% reduction, *P* = .004). The IDDS group had significant reductions in fatigue and depressed level of consciousness (*P* < .05). IDDS patients had improved survival, with 53.9% alive at 6 months compared with 37.2% of the CMM group (*P* = .06).**

Conclusion: **IDDSs improved clinical success in pain control, reduced pain, significantly relieved common drug toxicities, and improved survival in patients with refractory cancer pain.**

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PAIN OCCURS IN 67% of patients with metastatic cancer and is the most prevalent symptom of patients presenting to palliative care programs.[1,2] Approximately 5% to 15% of cancer patients have refractory pain and require advanced techniques such as adjunct medications, nerve blocks, or intraspinal implantable drug delivery systems (IDDSs).[3-5] Systemic drugs relieve pain but often have serious side effects including sedation, clouded thinking, constipation, or fatigue.[6] These symptoms are often severe enough to prevent adequate therapy, and fear of them constitutes one of the most important causes of inadequate opioid prescription by physicians, and inadequate use by patients.[5,7]

IDDSs deliver small doses of morphine directly to the spinal fluid, achieving pain relief with much smaller doses than with oral or parenteral routes. The IDDS consists of a small, battery-powered, programmable pump that is implanted under the skin of the abdomen and connected to a small catheter tunneled to the site of spinal entry. Although IDDSs have been in general use in patients with chronic refractory cancer pain since 1991, all the available data are from small, open-label, cohort studies.[8-11] There have been no randomized clinical trials (RCTs) of any methods to relieve such refractory pain. We performed this RCT to evaluate the effectiveness of IDDSs plus comprehensive medical management (CMM) compared with CMM alone in the management of refractory cancer pain.

PATIENTS AND METHODS

This prospective, multicenter, randomized study was designed to enroll 200 patients with advanced cancer and refractory pain, 100 to each arm. All participating investigation sites had pain management centers with a structured approach to pain management, where the IDDS is routinely used for cancer pain (Appendix).

From the Medical College of Virginia Campus of Virginia Commonwealth University, Richmond, VA; Johns Hopkins University Medical Center, Baltimore, MD; Center for Pain Relief, Charleston, WV; Valley Pain Treatment Center, Scottsdale, AZ; The Center for Clinical Research, Winston-Salem, NC; University of Minnesota, Minneapolis, MN; Marshfield Clinic, Marshfield, WI; Hospital de Zone, Morges, Switzerland; and Hospital de la Santa Creu I Sant Pau, Barcelona, Spain.

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Patients were randomly assigned to CMM or intrathecal pain therapy (IDDS) delivered by a programmable infusion system (SynchroMed Infusion System, Medtronic, Inc, Minneapolis, MN). Patients were stratified by center in permuted small blocks of either two or four patients, so no more than four consecutive assignments onto one arm at each site were possible. This intended to compensate for local variations in diagnosis and therapy and minimize the potential for investigators to anticipate the next treatment assignment. Randomization was central, by telephone.

Data were recorded at baseline; at 2, 4, 6, 8, 10, and 12 weeks; and then monthly through 6 months. The data collected at the scheduled visits were identical for both study groups, and were recorded at routine visits. All patients who survived had a full 4 weeks of treatment, regardless of treatment by the IDDS or CMM, with medication adjustments as routinely performed according to the Agency for Health Care Policy and Research (AHCPR) guidelines. The primary evaluation of clinical effectiveness was performed 4 weeks after randomization by comparing the two study groups with respect to both reduction in pain measured by the visual analog scale (VAS) (pain today on a 0 to 10 continuous scale ranging from no pain to the worst pain imaginable), and the composite drug toxicity score, the sum of 15 individual drug toxicity scores (0 to 4) selected before the trial. These were measured by the Common Toxicity Criteria (CTC) used by the National Cancer Institute (NCI) for all cooperative group clinical trials for the measurement of drug-related side effects, available at the NCI Web site (http://ctep.info.nih.gov/CTC3/default.htm). Toxicity scores were measured at each follow-up visit by patient responses to questions from a clinician familiar with changes in the patient's opioid dose.

Comprehensive medical management of pain and toxicity in both study arms was performed according to the guidelines described in Management of Cancer Pain: A Quick Reference Guide for Clinicians.[12] Those assigned to the CMM group received all pain therapy except spinally administered drugs, cordotomy, or other similar neurosurgical interventions. Those who received the IDDS started with morphine but could receive other analgesics if morphine proved to be inadequate for pain relief, using algorithms outlined by Staats.[4] Cross-over was allowed for clinical failure (VAS pain score persistently greater than 5 despite maximum tolerated drug dosages) after consultation with one of the lead investigators (T.J.S. or P.S.S.) to ensure consistent determination that pain was not being adequately controlled and that reasonable modalities had been tried. Other treatments such as radiation for palliation, chemotherapy for palliation, bisphosphonates, and so on, were allowed.

Patient Eligibility

All patients had a documented average pain VAS $\geq$ 5 at two measurements within a week of randomization, on a scale from 0 (no pain) to 10 (worst pain imaginable), despite 200 mg/d of oral morphine or the equivalent. Patients on lower doses were eligible if opioid side effects refractory to conservative treatment and severe enough to prevent upward titration were present. All patients had advanced cancer confirmed with histology/cytology, pain expected to continue throughout life, age $\geq$ 18 years, an expected life span $\geq$ 3 months, and were suitable for the IDDS (no mechanical barriers, obstruction of CSF flow, or active infection). The institutional review board at all centers approved the study, and informed consent was obtained for all patients.

Study End Points

Clinical success was defined in the protocol as at least a 20% reduction in the VAS pain scores from baseline to 4 weeks regardless of toxicity, or equal pain scores with at least a 20% reduction in toxicity. The investigators defined a 20% difference in pain scores as the smallest improvement patients were likely to view as clinically significant. Assuming a baseline average VAS of 7.5 as seen in other trials of IDDSs,[8-11] a 20% improvement in VAS would correspond to a mean change of 1.5. A 20% improvement in pain drug toxicity was similarly defined as clinically significant. The sample size of 200 was calculated to allow at least a 90% chance of detecting a difference in mean VAS change of 1.5 between the two study arms. Power estimates for toxicity were not possible because of the lack of published information on which to base statistical assumptions.

Secondary outcomes included the following: (1) differences in individual drug toxicities measured using the NCI CTC; (2) quality of life in patients and caregivers (Brief Pain Inventory, SF-12 Health Survey, and Caregiver Quality of Life); and (3) differences in health care resource use determined in accordance with established methods.[13] Mortality was followed to identify any detrimental effect of therapy on survival but was not a stated end point of the trial. Doses of opioid pain medications were summarized as the oral morphine equivalent dose.[12]

The time point 4 weeks after randomization was chosen because rapid improvement in symptoms was deemed a necessity for terminally ill patients. VAS and CTC scores were recorded at routine physician visits every 4 weeks on both study arms. The visit schedule was identical on each arm. The pumps did not need to be refilled more often than could be done on routine visits.

The trial used the definition of serious event as established by the International Conference on Harmonization, the standard guideline for good clinical practices. This definition includes events that resulted in or prolonged hospitalization, required invasive intervention, resulted in discontinuation of therapy, or were life threatening.

Trial of Intrathecal Morphine and Subsequent Implantation

A successful screening trial of intrathecal morphine was required before IDDS implant in patients not likely to benefit. The trial was performed within 24 to 48 hours of randomization whenever possible, and within 7 days in nearly all cases. Trial method (epidural injection, epidural infusion, intrathecal injection, or intrathecal infusion) and criteria for successful trial were at the discretion of the investigator, but all used standard methods.[11] Pumps were implanted as soon as practical after the trial of intraspinal morphine.

Statistical Analysis

All eligible patients with required data at baseline were included in the analyses. Results were reported as randomized regardless of the treatment actually received. Two-tailed tests were used unless specified. VAS scores and drug toxicities were analyzed using the nonparametric Mann-Whitney-Wilcoxon test. Values of $P < .05$ were established as significant before the trial started, with no adjustment for multiple hypothesis testing. All statistical analyses were performed using SAS (Version 8.2, SAS Institute, Inc, Cary, NC).

As-treated analyses of pain and toxicity were conducted to better understand the differences seen with treatment. In the as-treated analysis, all patients on the IDDS arm had at least 7 days' experience with the implanted pump. Multiple linear regression models were used that included adjustments for candidate baseline factors to control for differences in these patient groups after reassignment to the as-treated groups. The final models included only the baseline score and the treatment actually received.

Table 1. Baseline Characteristics of the Patients*

Characteristic	CMM Group (n = 99)	IDDS Group (n = 101)
Age, years	57.8 ± 13.7	56.2 ± 13.2
Male sex, %	59.6	51.5
Type of pain, %		
Neuropathic	14.3	12.9
Nociceptive	25.5	25.7
Mixed	60.2	61.4
Type of cancer, %†		
Lung	25.5	19.8
Breast	9.2	8.9
Prostate	11.2	5.9
Colon	9.2	5.0
Pancreas	5.1	6.9
Months since diagnosis	18.6	17.7
Median 25th to 75th percentile	6.1-43.8	8-46.4
Physician-predicted life expectancy, months	6	6
Median 25th to 75th percentile	6-12	6-12
Baseline medication use, %		
Opioids alone	39.8	41.6
Nonopioid adjunctive alone	2.0	2.0
Both	58.2	56.4
Morphine oral equivalent dose, mg/d	280	260
Median 25th to 75th percentile	120-686	135-641
No. of adjunctive medications	1	1
Median 25th to 75th percentile	0-2	0-2
Baseline VAS	7.59 ± 1.97	7.44 ± 1.97
Baseline Composite Toxicity Score‡	6.65 ± 5.58	6.95 ± 4.91

*Plus-minus values are means ± SD. Differences among the groups were not significant ($P \geq 0.05$).

†These categories are the top five sites overall.

‡The added scores of all the toxicity scales measured that were related to the treatment. The maximum would be 4 × 15 scales, or 60; the minimum would be 0.

Survival was analyzed using the Kaplan-Meier life-table and the log-rank test. The survival difference was explored by searching for prognostic factors that might have been left imbalanced after randomization. Adjustment for baseline factors (age, sex, natural history of the cancer, site of cancer, and physician-predicted life expectancy) and changes in VAS pain and toxicity at 4 weeks were performed by Cox regression analyses.

The principal investigators had full access to all data with no limitations on either access or publication. Medtronic provided data management and statistical support services to the study investigators. The trial design and statistical plan were reviewed and approved by the Massey Cancer Center Clinical Trial Support Unit and review boards at other NCI-designated cancer centers.

RESULTS

A total of 202 patients were enrolled at 21 centers (16 in the United States, four in Europe, and one in Australia) from April 1, 1999, to August 3, 2001. One patient in the CMM group did not meet eligibility criteria and was excluded from analysis. One patient withdrew consent to participate in the trial after randomization to the IDDS group but before baseline data were collected. Data collected on the remaining 200 patients (99 CMM patients and 101 IDDS patients) were analyzed.

The demographic and clinical characteristics were well balanced in the two groups, as listed in Table 1. There was no difference in cancer sites between the two treatments arms ($P = .32$). Neuropathic pain and mixed neuropathic-nociceptive pain were most common. Drug use was well balanced, with most patients receiving over 200 mg oral morphine equivalents daily plus adjuvant medications such as antidepressants (32.7% of CMM patients; 24.0% of IDDS patients); anticonvulsants (25.5% of CMM patients; 31.0% of IDDS patients); nonsteroidal anti-inflammatory agents (26.5% of CMM patients; 33.0% of IDDS patients); and, less commonly, steroids, analgesics, and neuroleptics.

Figure 1 shows patient disposition.[14] Pumps were implanted as soon as practical after randomization and the trial of intraspinal morphine. Follow-up started at baseline. By 14 days, 50% of patients randomized to the IDDS group had intrathecal pumps implanted, and 51 (70%) of 73 IDDS patients had pumps implanted within the first 4 weeks.

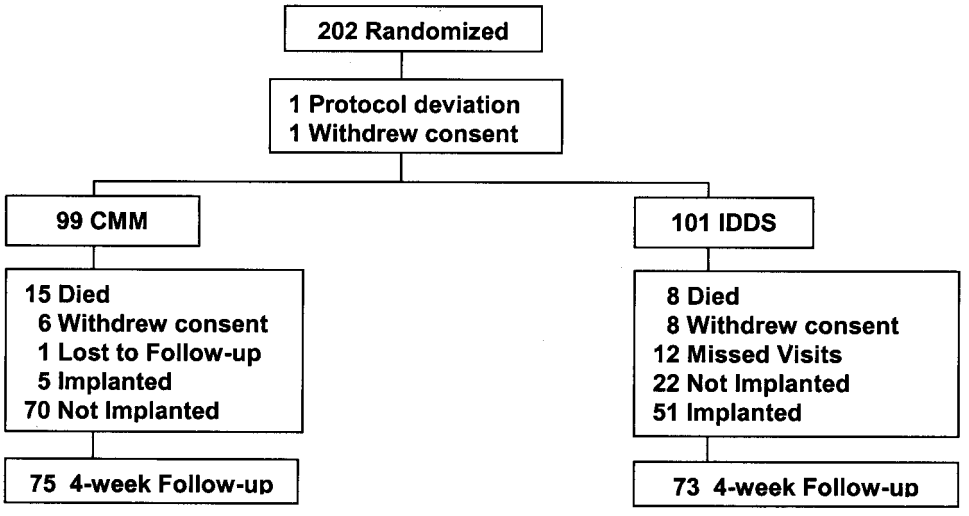

Fig 1. Analysis of patient disposition between randomization and the 4-week follow-up.

Patients were included in the analysis as IDDS patients if they had undergone implantation for at least 7 days before their 4-week follow-up. This was determined on the basis of the investigators' repeated statement that, within 7 days, patients would see a treatment effect.

All patients who survived had continuous treatment, regardless of IDDS or CMM, with medication adjustments as routinely made according to the AHCPR guidelines. About 20% of patients randomized to the IDDS had satisfactory relief of pain with CMM and never progressed to pump implant. In contrast, by 90 days after randomization, 32% of surviving CMM patients had crossed over to pump implant because pain was not controlled.

Of the 100 patients randomized to CMM, 70 of 75 alive were still on CMM before 4 weeks. Of the 102 patients randomized to the IDDS group, 51 of 73 available patients had pump implants. The number of patients who died or withdrew consent to proceed with CMM or the IDDS before 4 weeks was not statistically different (CMM, 21; IDDS, 17; $P = .26$). Five CMM patients had intractable pain that could not be managed by CMM alone and had a pump implanted before the 4-week visit. On the IDDS arm, 22 patients (21.5%) did not have a pump implanted within the 4 weeks after randomization because of either adequate pain relief, death, or other reasons.

Patients on both arms could have their medications changed in type and amount. During the first 4 weeks on trial, all IDDS patients had opioids in the pump: 48 of 51 with morphine, and three of 51 with hydromorphone (Dilaudid, Knoll, Mt Olive, NJ). In addition, 15 of 51 (29%) had a local anesthetic (bupivacaine) added. One patient had droperidol added, and two (4%) had clonidine added to the other drugs. In the United States, the only drug approved for use with SynchroMed is preservative-free morphine, but other drugs, especially local anesthetics, are commonly added.[4]

The median daily systemic morphine oral equivalent doses (MOEDs) were nearly equal at baseline, 272 mg for CMM patients and 250 mg for IDDS patients. By the 4-week evaluation, the median daily systemic MOEDs had increased to 290 mg for CMM patients and fallen to 50 mg for IDDS patients. By 4 weeks, the IDDS group also received an additional 600-mg MOED delivered intrathecally (2 mg/d actual median intrathecal dose).

The 194 serious adverse events reported were evenly distributed between the two study groups, with 95 (49%) occurring in the CMM group and 99 (51%) in the IDDS group, as listed in Table 2. Sixteen of these were associated with the implanted pump or related procedures, including one that was associated with an unsuccessful, preimplant screening test. Six were related to the pump pocket, five to the lumbar insertion site, and five to the catheter. Pump removal was required in one case because of infection. Surgical revision of the pump pocket was required in three cases, and one was resolved medically. In seven cases, surgical revisions of the catheter or the lumbar catheter insertion site were reported. Of IDDS patients, 14 (25.0%) of 56 had related complications. Two patients had two IDDS-related adverse events each.

The VAS and toxicity scores in the patients in both study groups improved from baseline to the 4-week time point, as listed in Table 3, and both exceeded the 20% pain relief goal. At 4 weeks, for CMM patients the mean VAS pain score fell from 7.81 to 4.76, a reduction of 3.05 (39.1%). For IDDS patients, the VAS pain score fell from 7.57 to

Table 2. IDDS-Related Serious Adverse Events

	CMM	IDDS	Total	Explantation	Pump Revision	Catheter Revision
No. of patients	98	101	199			
No. of patients w/SAE	69	62	131			
IDDS-related SAE	2	14	16	1	3	7
Pocket problems	2	4	6	1	3	
Infections	1	1	2	1		
Inflammation		1	1		1	
Pump flipping	1	1	2		1	
Pump migration		1	1		1	
Lumbar site		5	5			3
Wound dehiscence		2	2			2
Inflammation		1	1			1
Hematoma/seroma		2*	2			
Catheter problems		5	5			4
CSF leak		1	1			1
Kink		2	2			2
Nerve irritation		1	1			1
Occlusion*		1	1			

Abbreviation: SAE, serious adverse effect, as defined by the International Committee on Harmonization.

*Patient 1,003, hematoma resulted from unsuccessful attempt to introduce screening catheter past previously undiagnosed tumor growth, which blocked intrathecal space. Only one pump was explanted, or removed.

3.67, a difference of 3.90 (51.5%). The VAS change at 4 weeks was larger by 12.4% in the IDDS group, but the difference fell just short of statistical significance ($P = .055$).

The CMM group mean composite toxicity scores fell from 6.36 to 5.27, a reduction of 1.09 (17.1%); in the IDDS group, the mean composite toxicity scores fell from 7.22 to 3.59, a reduction of 3.63 (50.3%). The 33.2% larger reduction in the IDDS group was statistically significant ($P = .004$).

As listed in Table 4, the IDDS proved significantly superior to CMM in clinical success, a difference of nearly 14 of every 100 patients treated. IDDS patients more often achieved reduction in both pain and toxicity, and far less often no reduction in either pain or toxicity. At 4 weeks, 43 of 71 (60.6%) IDDS patients had a VAS less than 4, compared with 30 of 72 (41.7%) CMM patients.

All of the measured toxicities that could be attributed to opioids and other drugs used in pain therapy were reduced more in the IDDS group than in the CMM group, as shown in Fig 2. Significantly larger reductions ($P < .05$) in the IDDS group were noted for fatigue and depressed level of consciousness.

As shown in Fig 3, the as-treated reduction in mean VAS pain score in all those who received the IDDS, regardless of randomized assignment, was estimated by the regression model to be 1.4 points greater in patients receiving a pump implant than in those not receiving a pump ($P = .007$). Within the group randomized to the IDDS, those who actually received an IDDS experienced a reduction in mean pain VAS score 1.97 points larger than those who did not receive a pump ($P = .01$).

As shown in Fig 4, the as-treated reduction by the IDDS in mean composite toxicity score, regardless of randomized assignment, was estimated from the regression model to be 2.5 points greater than for CMM ($P < .001$). Within the group randomized to the IDDS, those who received the IDDS experienced a reduction in mean composite toxicity score 2.82 points larger than those who did not receive a pump ($P < .01$).

Figure 5 shows the Kaplan-Meier survival curves for the two groups according to randomization-assigned treatment. In the IDDS group, the estimated cumulative survival was 53.9% at 6 months compared with 37.2% for the CMM group ($P = .06$, log-rank test).

The survival difference was analyzed to identify factors that might have remained imbalanced after randomization. The two groups were similar in all baseline characteristics such as age, sex, natural history of the cancer, site of cancer, and physician-predicted life expectancy. Adjustment for these and other baseline factors in Cox regression analyses resulted in only small and insignificant changes to the size of the estimated hazard ratio for group assignment (results not shown). A survival analysis of time to censoring showed no differences between the two groups, suggesting completeness of reporting was comparable (results not shown).

To examine the plausibility of survival differences being a treatment effect, Cox regression analyses were performed that included age, sex, and changes in VAS pain and

Table 3. Reduction in Pain and Drug Toxicity from Baseline to 4 Weeks*

	CMM Group			IDDS Group			
Variable	No. of Patients	Baseline	Reduction at 4 Weeks	No. of Patients	Baseline	Reduction at 4 Weeks	*P*
VAS pain score†	72	7.81 ± 1.63	3.05 ± 3.16	71	7.57 ± 1.79	3.90 ± 3.42	.055
Common Toxicity Criteria‡	75	6.36 ± 5.65	1.09 ± 5.57	73	7.22 ± 5.00	3.63 ± 5.43	.004

*Plus-minus values are means ± SD.

†Three patients in the CMM group and two in the IDDS group were unable to complete the VAS score at the 4-week visit.

‡The added scores of all the toxicity scales measured that were related to the treatment. The maximum would be 4 × 15 scales, or 60; the minimum would be 0.

Table 4. Clinical Success and Failure of the Two Arms

Criteria	IDDS		CMM		*P*
	No.*	%	No.*	%	
VAS pain reduced by ≥ 20% regardless of increased toxicity, or equal VAS with ≥ 20% reduction in toxicity	60/71	84.5	51/72	70.8	.05
Both pain and toxicity reduced by ≥ 20%	41/71	57.7	27/72	37.5	.02
Neither pain nor toxicity reduced by ≥ 20%	8/71	11.3	17/72	23.6	.05

*No. of patients/total no. of patients.

toxicity at 4 weeks as covariates. These analyses excluded deaths before 4 weeks, and did not include a covariate for group assignment. Reduction in composite drug toxicity score was associated with improved survival (estimated hazard ratio, 0.95 per 1-point drop in composite toxicity score; $P = .05$). Because the IDDS group experienced a larger average reduction in toxicity score, the data suggest that the improved mortality in the IDDS group may be partially explained by effects of the intrathecal pain therapy.

DISCUSSION

The results of this multicenter, randomized trial demonstrate that patients with refractory cancer pain are more effectively treated with IDDSs than with comprehensive medical management alone. The IDDS patients had better pain relief, with significantly fewer drug side effects and with improved survival. Clinical success, measured by pain and drug toxicity together, was significantly improved on

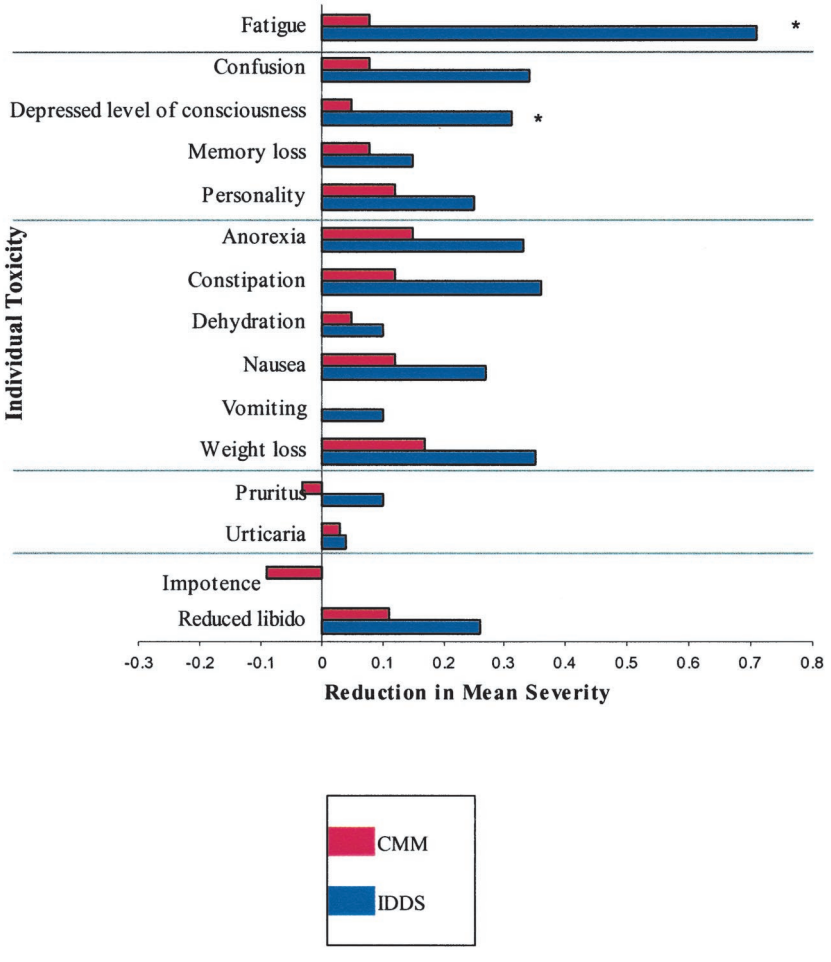

Fig 2. Reduction in individual toxicities from baseline to 4-week follow-up. *$P < .05$.

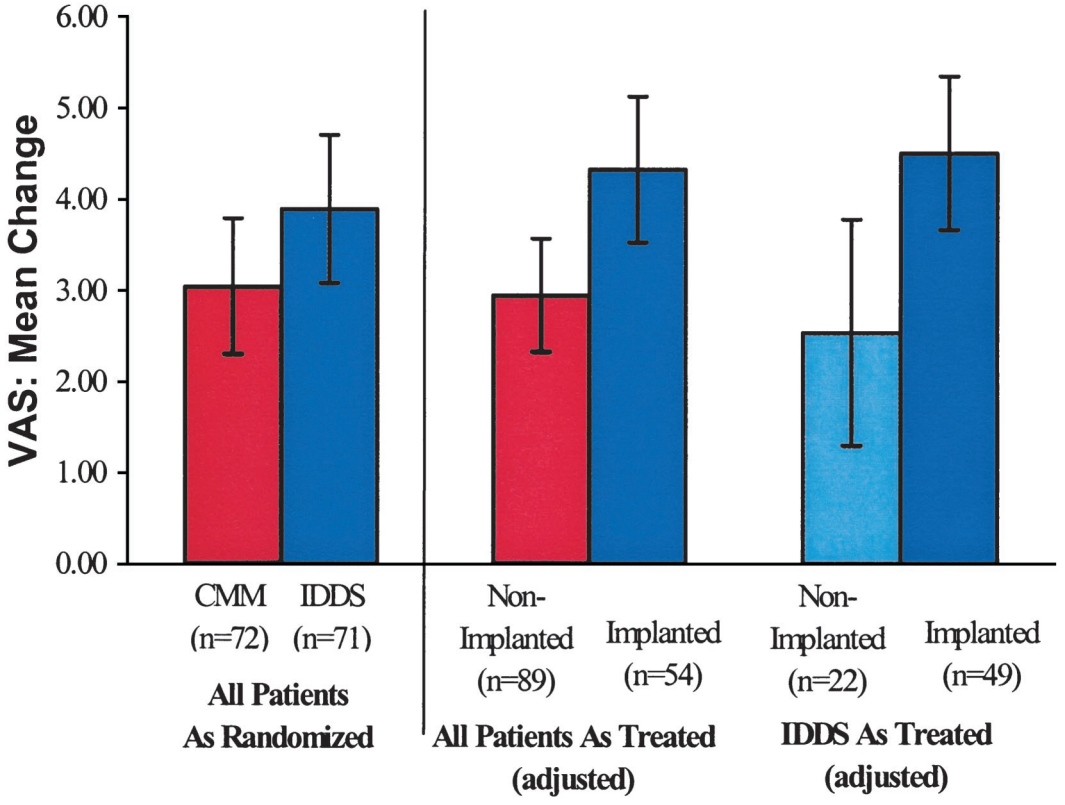

Fig 3. Reduction in VAS pain score from baseline to 4 weeks (as randomized and as treated). In the analysis of all patients as treated, the difference between nonimplanted and implanted is significant ($P = .007$). Error bars are ± 2 SE.

the IDDS arm ($P = .02$), with more patients achieving a ≥ 20% reduction in both pain and toxicity.

The present study also suggests that many of the most refractory cancer pain patients can achieve better pain relief. For 60% of patients in the IDDS group and 42% in the CMM group, pain scores at 4 weeks fell below 4 of 10, the point at which patients can assume more normal role function.[15] This improvement may be caused in part by referral to pain specialists and by use of the AHCPR Cancer Pain Relief Guidelines.[16] The 52% pain relief by the IDDS and 39% pain relief by CMM was 3 or 4 points on an 11-point scale, and the IDDS exceeded the recently proposed benchmarks of 50%[17] and 33%[18,19] pain relief. The anticipated 20% difference in improvement of pain alone between the two randomization groups was not achieved, and the observed difference fell short of statistical significance, because of the unexpected effectiveness of CMM. In the as-treated regression model, the patients who received the IDDS had significantly better pain relief ($P = .007$), but this result should be considered tentative.

Drug toxicity and fear of drug toxicity are two of the leading causes of failure of cancer pain therapy.[1,5,20] The results of this study suggest that by changing the route of administration, toxicities were reduced by 50% overall, 33% more than with systemic drugs ($P = .004$.) The increased analgesic effectiveness of small doses of opioid administered intrathecally, accompanied by reduced systemic exposure, resulted in a reduction in the frequency and severity of opioid side effects. Two of the most common side effects that prevent enjoyment of life—fatigue and depressed level of consciousness—were significantly reduced ($P < .05$) in the IDDS group compared with the CMM group.

The difference in 6-month survival between the study groups emerged during monitoring of study outcomes for patient safety. Because this was not a study end point, results should be interpreted cautiously. No analysis suggests that the survival difference is an artifact, but analysis will continue when follow-up is complete. A possible connection between pain control with reduced side effects and improved survival makes intuitive sense. Patients who feel better may be more active, have less chance of thromboembolism, achieve better nutrition, pursue and tolerate active treatment, and have more "will to live."[21]

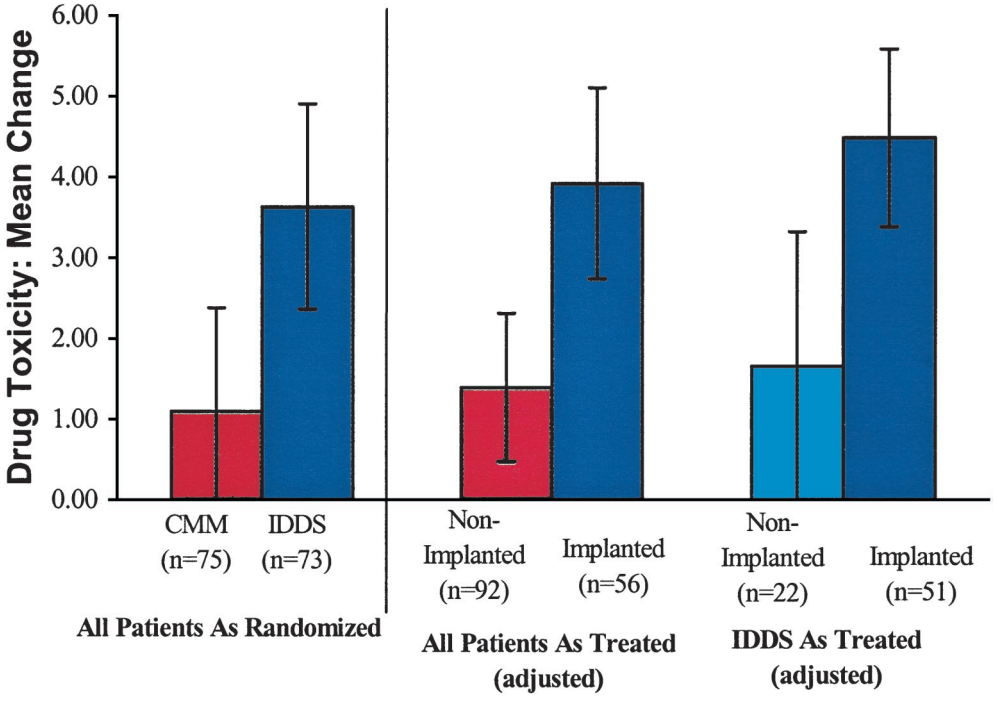

Fig 4. Reduction in toxicity from baseline to 4 weeks (as randomized and as treated). In the analysis of all patients as treated, the difference between nonimplanted and implanted is significant ($P = .008$). Error bars are ± 2 SE.

Other interventions to prevent complications from cancer, such as low-molecular-weight heparin[22] or recombinant erythropoietin,[23] appear to have a smaller but similar effect on survival and are being tested in large RCTs. It is possible that pain by itself, or complications from treatment of pain, could shorten life.[24] In the only other similar large RCT, intraoperative alcohol celiac plexus block versus normal saline placebo was associated with improved survival of nearly 3 months in unresectable pancreatic cancer patients who had pain.[25,26] Clearly, additional research is warranted.

Complications associated with the IDDS were not a clinical burden, probably reflecting the experience of the centers and personnel.[27,28] Only one pump required removal.

This trial has potential shortcomings. Alternative trial designs such as an intraspinal trial then implantation in all patients, then randomization to placebo or drug for 1 month were not feasible. First, an intraspinal trial and implantation in all patients, half of whom may not use it, was judged too invasive in vulnerable, terminally ill patients. Second, these patients have a short time to live, and placebo titration for a month would be difficult to justify. Although trial entry required ≥ 3 months to live, the 5.3-fold overoptimistic survival prognoses of doctors[29] made it imperative that pain relief be achieved as quickly as possible. Third, it would be impossible to truly blind patients and physicians, as the patient would have already experienced pain relief during the screening trial of intrathecal therapy; titration of placebo would be easy to detect. Fourth, if the patient had pain relief with intrathecal morphine screening, it would be ethically troubling to withhold the IDDS because it is an approved treatment. Finally, randomization after CMM had failed was not possible, as there would be no realistic options except the IDDS. Such methodology problems are the same for other therapies that appear to work in single-arm unblinded trials, such as opioid rotation, that have not been tested in large RCTs.

Although the Hawthorne effect, regression to the mean, and placebo effect might explain some of the change in pain scores, they seem unlikely to explain pain relief that persisted for 4 weeks, the markedly reduced toxicity, and better survival of the magnitude observed. Individual patient pain management was not possible from a central office, but patients were managed according to the AHCPR Cancer Pain Management Guidelines, and all cross-overs were approved. There was some variation in pain management practice (for both CMM and IDDS patients) from center to center that could not be controlled, but balanced randomization at each center would be expected to minimize impact on clinical trial results. Finally, these patients had refractory pain, and were not representative of the majority of patients in whom cancer pain should be relieved and side effects easily managed using less aggressive analgesic strategies.[6]

The cost-effectiveness of this intervention has not yet been formally studied in cancer patients (but is planned) because of the added cost of the pumps, the high daily

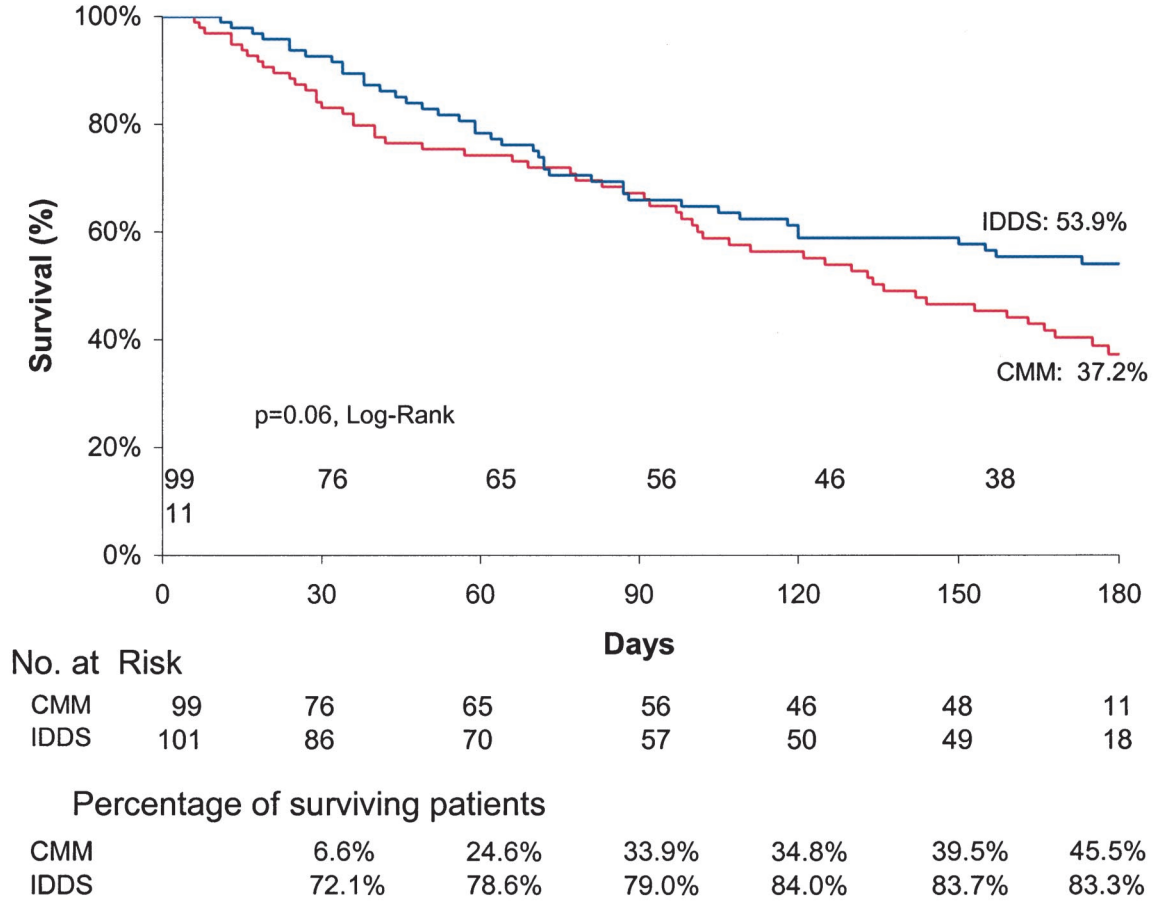

Fig 5. Kaplan-Meier survival curve of the IDDS and CMM groups, as randomized. Survival was higher in the IDDS group ($P = .06$, log-rank test).

cost of nonpump medicines, and the potential to prevent hospitalizations for pain management.[30] Future directions for research should include at least the following: comparing this method of pain relief with other methods that have been proven in RCTs; understanding the reasons for increased survival if this is confirmed with longer follow-up and other studies; clarifying when the IDDS should be used in the disease process (ie, when pain is still mild but predictably will get worse); studying the addition of other drugs to morphine in the IDDS; and developing smaller programmable pumps with patient-controlled analgesia capability to manage breakthrough pain.

In summary, in this trial, the IDDS plus CMM compared with CMM alone had better clinical success, with improved pain scores, significantly reduced drug toxicity scores, and improved survival. The results with respect to survival are preliminary and will require further study.

APPENDIX

The appendix listing the study investigators is available online at www.jco.org.

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