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Effects of an Intrathecal Drug Delivery System Connected to a Subcutaneous Port on Pain, Mood and Quality of Life in End Stage Cancer Patients: An Observational Study

Mariateresa Giglio, MD[1], Angela Preziosa, MD[1], Roberta Mele, MD[1], Nicola Brienza[2], Salvatore Grasso[3], and Filomena Puntillo[1,2]

Abstract

Background: In cancer patients with limited life expectancy, an implant of an intrathecal (IT) drug delivery system connected to a subcutaneous port (IDDS-SP) has been proposed as a successful strategy, but conflicting results are reported on quality of life (QoL). The aim of this prospective observational study is to report the effects on pain, mood and QoL of an IT combination therapy delivered by an IDDS-SP in malignant refractory pain.

Methods: Adult patients in which IT therapy was recommended were recruited. An IT therapy with morphine and levo-bupivacaine was started: VASPI score, depression and anxiety (evaluated by the Edmonton Symptom Assessment System -ESAS-), the Pittsburgh Sleep Quality Index (PSQI), the 5-level EuroQol 5D version (EQ-5D-5L) and the requirements of breakthrough cancer pain (BTcP) medications were registered, with adverse events rate and the satisfaction of patients scored as Patient Global Impression of Change (PGIC).

Results: Fifty patients, (16 F/34 M) were enrolled (age 69 ± 12). All had advanced cancer with metastasis. The median daily VASPI score was 75, the median depression score was 6, and the median anxiety score was 4, median PSQI was 16. At 28 days, a significant reduction in VASPI score was registered as well as in depression and anxiety item. Also, PSQI decreased significantly. The EQ-5D-5 L showed a significant improvement in all components at 14 and 28 days. Patient Global Impression of Change scores showed high level of satisfaction. A low incidence of adverse events and a reduction in BTCP episodes were also registered.

Conclusion: Intrathecal combination therapy delivered by an IDDS-SP could ensure adequate control of cancer related symptoms, such as pain, depression, anxiety and sleep disturbances. These effects, with low rate of AEs and reduced BTcP episodes, could explain the improvement in QoL and the overall high levels of patients' satisfaction.

Keywords

cancer pain, morphine, intrathecal therapy, quality of life, depression, anxiety, sleep

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[1]Anaesthesia, Intensive Care and Pain Unit, Policlinico Hospital, Bari, Italy
[2]Department of Interdisciplinary Medicine, University of Bari "Aldo Moro", Bari, Italy
[3]Department of Emergency and Organ Transplantation, University of Bari "Aldo Moro", Bari, Italy

Corresponding Author:
Filomena Puntillo, Department of Interdisciplinary Medicine, University of Bari "Aldo Moro". Anaesthesia, Intensive Care and Pain Unit, Piazza G. Cesare 11, 70124 Bari, Italy.
Email: filomena.puntillo@uniba.it

Background

Cancer-related pain treatment has improved over the last decades. Systemic opioids, as suggested by the World Health Organization analgesic ladder, can successfully reduce pain in the majority of cancer patients.[1] Unfortunately, 10-15% of them still suffer from severe and refractory pain, especially in the advanced phases of disease and require additional pain management modalities,[2,3] like interventional pain techniques.[4] Intrathecal (IT) drug delivery offers proven benefits for the treatment of patients with chronic intractable pain, since it may improve analgesia with smaller doses and possibly achieve a reduction in systemic or cerebral side effects compared to oral or systemic supplied medication alone.[4-9] Several trials[6,7,9] reports that spinal administration of drugs combination is a safe and effective method of pain management in patients with severe cancer pain and can greatly reduce the need of systemic opioids. Moreover, new evidence[7] suggest that spinal pain management should be considered for cancer patients with severe pain, even during the early phase of the illness trajectory, to provide adequate pain relief and better quality of life (QoL) for a longer period. A recent meta-analysis[10] confirms the statistically significant and sustained decrease in cancer pain with IT drug delivery, compared with baseline.

In cancer patients with a life expectancy of less than 3 months, a minimally invasive implant of an IT drug delivery system connected to a subcutaneous port (IDDS-SP) has been reported as a successful strategy[8,11] but conflicting results are reported on the effects of this device on QoL and patients' activities of daily living (ADL).[12,13]

The suffering of the whole person is the most important feature of cancer-related pain.[14] In these patients, pain shows the same symptom pattern as depression.[15] A strong association between pain severity and distress symptoms such as anxiety and depression in cancer patients has been described.[16] Moreover, the prevalence of insomnia in cancer patients is almost 50%.[17] Cancer patients with insomnia had significantly higher rates of pain, nausea, dyspnea, and anxiety. Multivariate logistic regression analysis showed that patients with moderate to severe pain and anxiety had 2-3 times higher rates of insomnia.[18]

The aim of this study is to report the effects on pain, mood and QoL of IT combination therapy delivered by an IDDS-SP in malignant pain refractory to high doses of oral opioids.

Materials and Methods

This prospective observational study was conducted according to the ethical principles of the current amended version of the Helsinki Declaration and IASP's guidelines for pain research in humans. Approval from the local Ethical Committee was obtained (cod EXIT01, approved on the 13th of October2021, approval number 7036) and each patient gave signed informed written consent. This monocentric study took place in the Pain Center of Policlinico Hospital, Bari. The reporting of this study conforms to STROBE guidelines.[19] All patient details were de-identified.

Eligible consecutive patients were at least 18-years-of-age with severe cancer refractory pain with life expectancy lower than 3 months in which IT therapy was recommended because of inefficacy or intolerance to strong systemic opioid treatment. Inefficacy was defined as mean daily VASPI score (0-100 mm, with 0 mm representing no pain and 100 mm representing the worst pain imaginable) at rest $\geq$ 70 mm although strong systemic opioid treatment (more than 200 mg/day of oral morphine equivalents). Intolerance was defined as the occurrence of severe adverse events-AEs (even with dosage less than 200 mg/day of oral morphine equivalents) which prevents a further increase in the opioid dosage to obtain pain relief. More than 1 opioid rotation had to be done before defining pain refractoriness. Moreover, in all patients with a neuropathic component of pain, a combined therapy of anticonvulsants, antidepressants or corticosteroids was prescribed[20] before enrolling them. All patients were treated with the best available therapy (opioid rotation, adjuvant drugs, chemo-hormono- immuno-target- or radiotherapy) to evaluate if less aggressive approaches adequately control pain and QoL. The presence of psychological distress or the presence of aberrant behaviors were further identified as predisposing factors to difficult pain control before enrolment. Patients were excluded if they had signs of sepsis or inadequately treated infection or brain metastases. Life expectancy was evaluated by a multiprofessional team (ie, oncologists, pain therapists and palliative physicians) as this may help refine the prognostic estimate.[21] For all patients an early palliative program was activated, involving oncologists, pain therapists and palliative physicians.

At the first visit, medical history, concomitant medications, VASPI score, numbers of breakthrough cancer pain (BTcP) episodes, and the Karnofsky Performance Status Score (KPSS) were recorded for each patient. Moreover, we registered levels of depression and anxiety with the Edmonton Symptom Assessment System (ESAS),[22] the QoL with the 5-level EuroQol 5D version (EQ-5D-5L)[23] and sleep disturbance with the Pittsburgh Sleep Quality Index (PSQI).[24] After enrolling, the implant of an IDDS-SP (Celsite® Port, BBraun) was planned. The procedure was performed under fluoroscopy in order to verify the correct position of the catheter tip according to pain syndrome. The day of the implant, the patients were asked to stop their previous opioid therapy and to assume a short-acting oral morphine dose (30 mg) as rescue medication even more times a day if their background pain was poorly controlled. Patients that were already assuming rapid onset opioids for breakthrough pain were also asked to continue, as needed.

An IT combination therapy with morphine and levobupivacaine was chosen to obtain synergistic effect on pain relief. The initial IT dose of morphine was calculated for each patient based on the equivalent daily dose of morphine; an oral/IT ratio of 300/1 was used. Levobupivacaine was chosen since it has less neurotoxic and cardiotoxic effect, as compared to bupivacaine, and it is more potent and produces a longer effect in comparison to ropivacaine.[25] The initial dose of levobupivacaine was 3 mg/die, as recently reported.[26] No maximum dose limit was defined for morphine. For levobupivacaine the maximum dose was fixed to 10 mg/day according to what was recently suggested for bupivacaine.[27] The refill procedures were aseptically performed by experienced nurses of the pain clinic.

Primary outcomes were the reduction of VASPI score, the reduction of depression, anxiety, and sleep disturbance, the improvement of QoL and the reduction of BTcP medications. Secondary outcomes were evaluation of AEs rate and the satisfaction of patients scored as Patient Global Impression of Change (PGIC).

Efficacy and Safety Measurements

VASPI score, ESAS, EQ-5D-5 L were evaluated at pre-implant and post-implant at 14 days (T14) and at 28 days (T28), together with systemic medications used to control BTCP and basal pain. Post implant PGIC and AEs were also registered. Finally, PSQI was calculated at pre-implant and at T28. PGIC is a 7-points scale depicting patient's rating of overall improvement. Patients rated their change as "very much improved = 3," "much improved = 2," "minimally improved = 1," "no change = 0," "minimally worse = −1," "much worse = −2," or "very much worse = −3. All AEs were coded with the Coding Symbols for Thesaurus of Adverse Reaction Terms, Fifth Edition, Dictionary. For each AE, the investigator determined the severity, the relationship to every study drug, and if the AE was serious or nonserious. Serious AEs are those that were fatal, immediately life threatening, or significantly disabling.

Statistical Analysis: median and mean VASPI score, ESAS, PSQI and satisfaction of patients were calculated at T14 and T28 postimplant; at same times the mean changes were compared to zero using a Wilcoxon signed-ranks test or Student's t-test when assumptions of normality were met. The null hypothesis, which states that the mean change is not different from zero, was tested in each case. All tests were two-tailed with a α level < .05 considered statistically significant. The tests were performed with the program, SPSS, version 12.0 for Windows.

Results

During the study period, 55 consecutive patients were considered potentially eligible. Of these, 5 were excluded (3 for inadequately treated infection, 2 for brain metastases). In total, 50 patients, 16 females and 34 males were enrolled. Their mean age was 69 ± 12. All had advanced cancer with metastasis, 85% of patients had bone metastases, all already treated with radiotherapy and other bone targeted therapies. The median daily VASPI score at rest was 75 (range 70-90) the incident VASPI score was 100 mm. The median KPSS was 50 (range 40-80). In 90% of patients the pain recognized a mixed component, both neuropathic and nociceptive. The IDDS-SP was used to control pain for a median of 1 month (range 1-5 months).

Table 1 depicts demographic data of the patients and the distribution of the different types of carcinomas.

Before enrollment, all patients were treated with high doses of morphine equivalents (mean dose 360 ± 60 mg) but all of them had a poorly controlled pain and/or experienced adverse events related to high doses of opioids. Moreover, in all patients more than 1 opioid rotation was performed before considering an invasive approach, and all patients with a neuropathic pain component undergone a combined therapy

Table 1. Demographic Data of Included Patients.

Demographic Data of Included Patients	n = 50
Age (mean ± DS)	69 ± 12
F/M	16/34
Pancreatic Cr	9
Urotelial Cr	6
Mammalian Cr	4
Gastrointestinal Cr	11
Lung Cr	17
Hepatic Cr	1
Melanoma	1
Limphoma	1

F. female, M: male, Cr carcinoma.

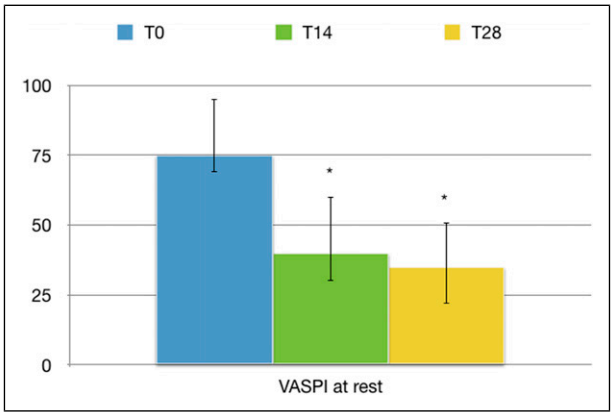

Figure 1. The reduction of VASPI score (median) over time * indicates $P < .05$. (T0 = day of IT catheter placement, T14 = 14 days T28 = 28 days).

of corticosteroids, anticonvulsants, or antidepressants, as clinically indicated. In 8 patients the presence of aberrant behaviors was identified as predisposing factors to difficult pain control. The median depression score in ESAS was 6 (range 4-8), and the median anxiety score was 4 (range 2-7), median PSQI was 16 (range 10-22). The EQ-5D-5L was −.0089 (median value, range .5160 to −.1604) with the worse values in pain and anxiety/depression items. The initial IT mean daily doses were .96±0.3 mg for morphine and 3 mg for levobupivacaine.

At T14 and T28, a significant reduction in VASPI score was registered (median 40 mm, range 30-60, $P < .05$ and 35 mm, range 20-50, $P < .05$, respectively, Figure 1). At T28 the mean daily doses were 1.4 ± .8 mg for morphine and 3.8 ± 1.8 mg for levobupivacaine. Supplementary figure 1 provided a detailed description of the daily doses of morphine and levobupivacaine used at each time point.

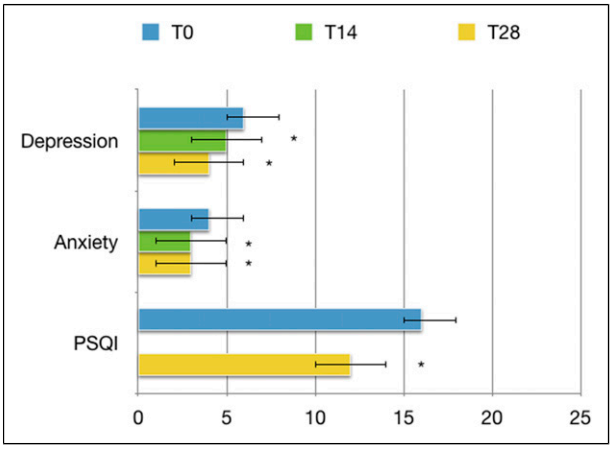

Figure 2. The reduction of Depression and anxiety score (evaluated by the Edmonton Symptom Assessment System -ESAS-) and of the Pittsburgh Sleep Quality Index (PSQI) (median) over time. * indicates $P < .05$ at both T14 and T28 (T0 = day of IT catheter placement, T14 = 14 days T28 = 28 days).

The depression item of the ESAS decreased significantly at T14 (median 5, range 3-7, $P < .05$, Figure 2) at T28 (median 4, range 3-6, $P < .05$) as well as the anxiety item of ESAS at T14 (median 3, range 2-6, $P < .05$) and at T28 (median 3, range 2-6, $P < .05$, Figure 2). At T28 also PSQI decreased significantly (median value 12, range 8-18, $P < .05$, Figure 2). In the PSQI, almost all patients (85%) rated their quality of sleep as very much improved and reported their sleep efficiency (that was calculated as number of hours slept/number of hours spent in bed x 100) ranging from 75 to 84%, confirming a better self-perceived resting time. The EQ-5D-5L showed a significant improvement in all components (pain, anxiety/depression, self-care, mobility, and ADL) of QoL at T14 (median .5282, range −.0076 to .07472) and the same values were registered at T28 (median .5418, range −.0724 to .7472, $P > .05$, respectively, Figure 3). Patient Global Impression of Change scores showed high level of satisfaction at T14 as well at T28 (see Figure 4) which was strongly correlated with VASPI reduction (Figure 5).

All patients stopped their previous systemic opioid therapy. 70% of patients reported a sporadic intake of 30 mg of short acting oral morphine in the first 14 days after implant, 30% of patients continued to intake only acetaminophen as needed. Eight patients reported they sporadically took transmucosal fentanyl to control BTcP out of 42 patients pre-implant (see Table 2). Forty-four patients survived to 28 days, 32 patients survived at 2 months and 8 patients at 3 months.

During the entire follow up, 2 patients (4%) experienced confusion, 4 (8%) reported difficulty to void in the first 24 hours, 3 (6%) nausea and 2 (4%) vomiting. Nor infection neither complication related to the IDDS-SP refill were registered.

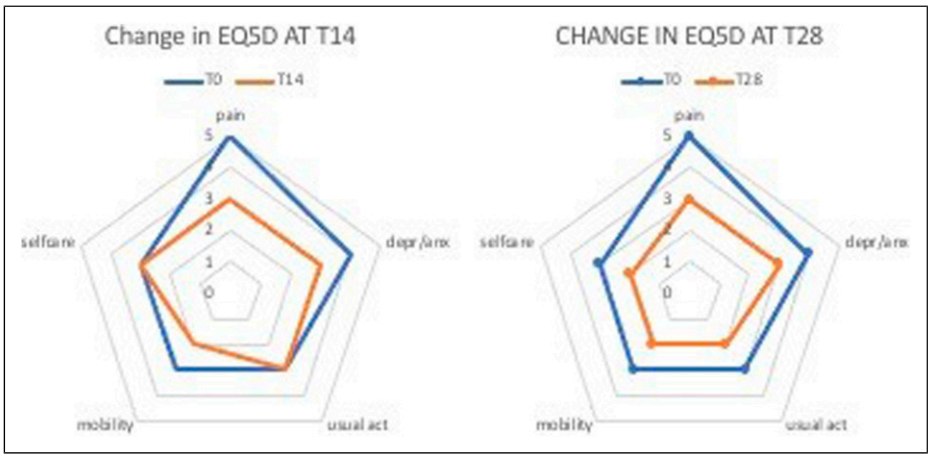

Figure 3. The change of 5-level EuroQol 5D version (EQ-5D-5L) in the overall score as well as in every component (ie change in usual activities, mobility, pain, self-care, anxiety/depression) at T14 (14 days after implant) and at T28 (28 days after implant).

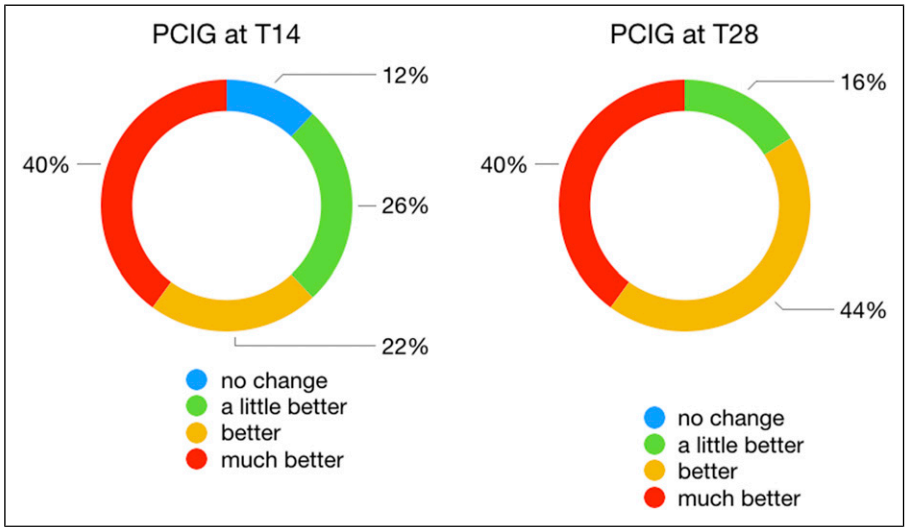

Figure 4. The PGIC (Patient Global Impression of Change) at 14 days post implant (T14) and at 28 days post implant (T28). PGIC is a 7-points scale depicting patient's rating of overall improvement. Patients rated their change as "very much improved (3)," "much improved (2)," "minimally improved (1)," "no change (0)," "minimally worse (−1)," "much worse (−2)," or "very much worse (−3).

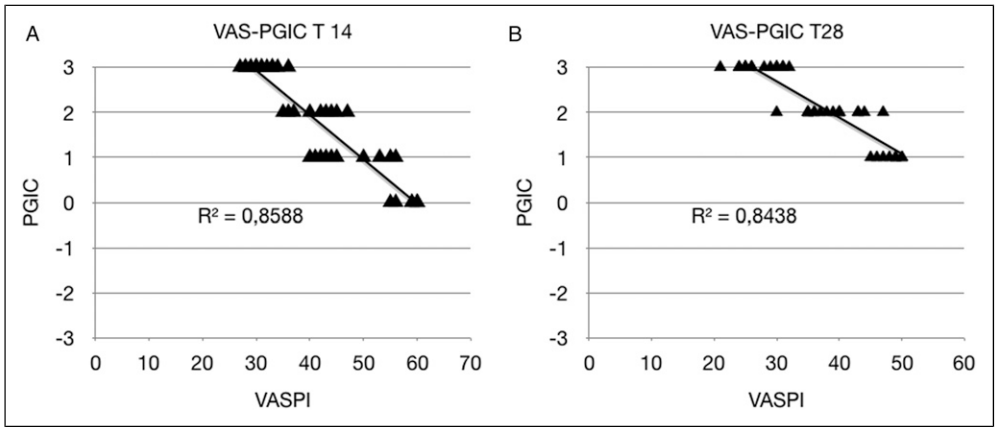

Figure 5. Correlation of VAS score at rest and PGIC (Patient Global Impression of Change) at 14 days post implant (T14) and at 28 days post implant (T28).

Table 2. Morphine Equivalents Intake for Basal Pain Day and Morphine Equivalents for Breakthrough Pain Expressed in Mean and Median Value at the Beginning (T0) and at the End (T28) of the Study Period.

	T0				T28			
	N	Mean	N	Median	N	Mean	N Median	Median
Morphine equivalents(mg/day)	50	360	50	360	18	30	18	30
Breakthrough dose, mcg/d	42	666	42	600	8	520	8	400

Discussion

The current study suggests that an IT therapy with IDDS-SP may be successful strategy in patients with malignant pain refractory to high doses of systemic opioids. It allows stable control of pain, as demonstrated by the significant reduction of VASPI score, a reduction of systemic opioids requirements for BTcP and also a better control of depression and anxiety as well as a significant improvement in sleep quality. Moreover, even if more invasive than systemic therapy, the IDDS-SP led

to a significant improvement in QoL and high levels of satisfaction.

Cancer pain is strongly associated with psychological symptoms, such as mood disturbance, depression, emotional distress, depressive feelings, fear, anxiety, and worry has been reported.[15] Psychological distress is believed to have a direct effect on sympathetic nervous system activation, release of endogenous opioids, and level of muscle tension. Inflammation is 1 the common denominator to both pain and depression, starting the activation of several pathways that can trigger the transition from sickness to depression and from acute to chronic pain.[28] Moreover, in advanced cancer patients a suboptimal pain control may be associated with intractable depression.[29] Experimental animal evidence suggest that pain signal conducted through the amygdala pathway can trigger negative emotions, such as anxiety, depression, and aversion.[30] In clinical practice, almost 54% of cancer patients reported depression and 39% reported anxiety.[31] Insomnia and poor sleep quality are common problems in patients with cancer, which are largely overlooked in routine clinical practice. They interfere with the coping ability, symptoms, and treatment outcomes.[15] Recent evidence suggests a clear association between sleep disturbances and cancer symptoms so that symptoms control is essential to maintain patients' sleep quality.[15] Moreover, positive correlation of anxiety and depression scores with sleep disturbances was recently found.[29] Therefore, to address the problem of adequate cancer pain management, clinicians must not only investigate and treat pain intensity but should also assess and monitor symptoms associated with pain, such as depression, anxiety and sleep disturbance, since all these factors could interplay and potentiate each other.

Our results seem to confirm this hypothesis, showing that adequate pain control in cancer refractory patients can also allow a better control of other cancer-related symptoms such as depression, anxiety and sleep disturbance. Moreover, the combination of local anesthetics with morphine, lowering the doses of both drugs, allows a low incidence of AEs and a better pain control with a reduced need of BTcP medications. Other authors have reported that a combination of morphine and levobupivacaine for highly refractory cancer-related pain significantly decreases mean pain intensity and systemic opioid consumption, with mild AEs.[32,33] Our paper confirms these findings, suggesting that cancer pain control could be managed with low doses of IT drugs, exploiting their synergistic effect.

Recent evidence supported the use of totally implantable IDDS in order to control cancer pain in patients with limited life expectancy[10,34] with a reduced risk of infection, while external devices carry more risks of infections, disconnection and reduced mobility, even if they have the advantage of easy operation and cost savings.[12] Conflicting results[12,13] are emerging on the effects of IDDS-SP on QoL and patients' ADL, since some authors reported that the significant benefits of adequate pain relief translated into improvements in patient life quality with significantly better QoL scores,[13] while others noted a reduction in the ability to participate more fully in daily activities,[12] due to the impaired mobility related to the external system. In the present trial, almost 50% of patients referred an improvement of mobility self-care and ADL, even with an external device. Although doubts and fears about wearing an external device and the consequent reduced mobility, the significant improvements on pain and on other cancer related symptoms, together with the increasing quality of sleep and the reduced incidence of AEs, the reduced need of rescue medication to control BTcP, could all explain our results. These beneficial effects in turn explain the very high levels of patient satisfaction. Surprisingly, also patients with presence of psychological distress or aberrant behaviors reported high levels of pain control and satisfaction with an external device. Accordingly, a recent paper[35] showed that IT therapy was perceived as most valuable by family carers of advanced cancer patients, since it improved QoL for their relatives, by reducing pain and the intolerable side effects of systemic analgesia, enabling individuals 'to be themselves' through their final illness and dying phase.

In the present trial, no infection related to the IDDS-SP was observed. It was a bit surprising result, since others[7] described an infection rate of 5%. However, other papers[6,26] reported very low infection rate related to an external device. Maybe this result could be explained by the low survival time and therefore a low period of use of an external IT delivery system, maybe also by a very careful use by both patients and caregivers, that were very well trained about the system. Moreover, only experienced nurses are allowed to refill the system, and the procedure was conducted by 2 of them in a completely aseptic way.

The present observational study has some limitations related to the study design and the very difficult-to-treat category of patients enrolled. The non-randomized nature of the study does not permit to reach firm conclusion. In addition, a sample size calculation was not undertaken, limiting the strength of our conclusions. The short life expectancy due to cancer progression limited the time of observation. Moreover, evaluating the life expectancy for these patients is often very challenging, even if IDDS could allow an adequate pain control with increased survival.[36]

The choice of an external device is often a big issue for these patients, due to concerns related to the risk of infection rate, disconnection, and reduced mobility, while internal pumps are equally effective with a lower rate of complications and better accepted by patients.[10,34] However, this strategy suggests rapid and efficacious cancer-related symptoms control and calls for more studies enrolling a larger population of oncological patients with cancer related refractory pain even in early stages.

We cannot exclude that the activation of an palliative care program for the patients enrolled could have improved their QoL overall, including better pain perception and cancer related symptom control such anxiety and depression, promoting physical and mental health, and better use of health-care resources.[37] On the other side, a correct pain follow up for these patients along their disease evolution is crucial to identify the correct strategy (ie interventional vs medical 1) to improve

QoL. Therefore, the involvement of pain physicians trained and experienced in cancer pain management is still the cornerstone of an adequate management of this complex category.

Finally, a rigorous cost analysis was not planned, so no definite conclusion can be made whether IDDS-SP was a cost-effective strategy in this difficult to treat population. However, recent evidence suggest that the most important driver of cost-effectiveness was level of pain reduction and that although cost savings could be modest per patient, these were considerable when accounting for the number of potential intervention beneficiaries.[38]

Therefore, more studies are needed, enrolling a larger population of oncological patients with cancer related refractory pain, even in early stages, to assess the real efficacy of an invasive approach both in term of pain control, patients satisfaction, cost and feasibility.

Conclusions

Our study suggests that IT combination therapy of morphine and levobupivacaine delivered by an IDDS-SP, despite being an invasive treatment, may be considered for cancer patients with severe pain. It may assure adequate pain relief and reduce other cancer related symptoms, such as depression, anxiety and sleep disturbance. These positive effects, together with the low rate of AEs and the reduced requirements of rescue medications, could explain the improvement in QoL and the overall high levels of patients' satisfaction registered.

Appendix

Abbreviations

QoL	Quality of life
IT	Intrathecal
IDDS-SP	Intrathecal drug delivery system connected to a subcutaneous port
ADL	Activities of daily living
IASP	International association for the study of pain
VASPI	Visual analogic scale of pain intensity
AEs	Adverse events
BTCP	Breakthrough cancer pain
KPSS	Karnofsky Performance Status Score
ESAS	Edmonton Symptom Assessment System
PSQI	Pittsburgh Sleep Quality Index
PGIC	Patient Global Impression of Change
EQ-5D-5 L	5-level EuroQol 5D version
T14	14 days post implant
T28	28 days post implant

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Authors' Contributions

FP, MG, AP, RM were involved in patients enrollment, intrathecal device placement data collection. FP, NB, LD, MG gave a major contribution in writing the manuscript. GV revised it. All authors read and approved the final manuscript.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Ethics Approval and Consent to Participate

This prospective observational study was conducted according to the ethical principles of the current amended version of the Helsinki Declaration and IASP's guidelines for pain research in humans. Approval from the local Ethical Committee was obtained (cod IDDS-SP001).

Consent for Publication

Each patient gave signed informed consent.

Availability of Data and Materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

ORCID iDs

Mariateresa Giglio https://orcid.org/0000-0002-4901-0045
Filomena Puntillo https://orcid.org/0000-0001-7274-6467

Supplemental Material

Supplemental material for this article is available online.

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