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CLINICAL REPORT

Effects of palliative intrathecal analgesia on patients with refractory cancer bone pain

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Abstract
This study examined the effects of intrathecal analgesia (ITA) using an extracorporeal pump with a subcutaneous port system in cancer patients with bone metastasis. Among the patients who died of cancer with bone metastasis at the palliative care unit of our institution, 11 who received ITA were selected. Changes in pain, opioid doses, the palliative prognostic index (PPI), and Eastern Cooperative Oncology Group Performance Scale after ITA were assessed. Pain, opioid doses, and PPI decreased after ITA (P = 0.002, 0.002, and 0.017). ITA for cancer patients with increased PPI due to refractory cancer bone pain decreased pain, opioid doses, and PPI.
(100 words).

Keywords Palliative care · Cancer pain · Bone Metastasis · Spinal injections

Introduction

Pain management and a reduced requirement for opioids may be effectively achieved in patients with unresectable pancreatic cancer by neurolytic splanchnic nerve block; however, it does not markedly improve quality of life (QOL) [1]. Therefore, the value of sympathetic neurolysis remains controversial [1–3]; if it decreases survival, this needs to be considered in general interventional treatments.

We performed a retrospective review to investigate the effects of intrathecal analgesia (ITA), an interventional treatment, in patients with refractory cancer bone pain.

Materials and Methods

Study design

We performed a retrospective analysis of cancer patients with bone metastasis who died in the palliative care unit of Saga-ken Medical Center Koseikan between April 2013 and February 2020. The study protocol was approved by the Institutional Research Ethics Board (No. 20-02-01-04).

Patients

Subjects were patients with bone metastasis who had received ITA. Bone metastasis was confirmed by radiologists using bone scintigraphy, computed tomography, or magnetic resonance imaging.

The following patient characteristics were examined: age, sex, body mass index (BMI), frailty [4], the primary lesion, stage at diagnosis, site of bone metastasis and pain, pain status, and the reasons for ITA. Patients without bone metastasis, those who died outside our palliative care unit,

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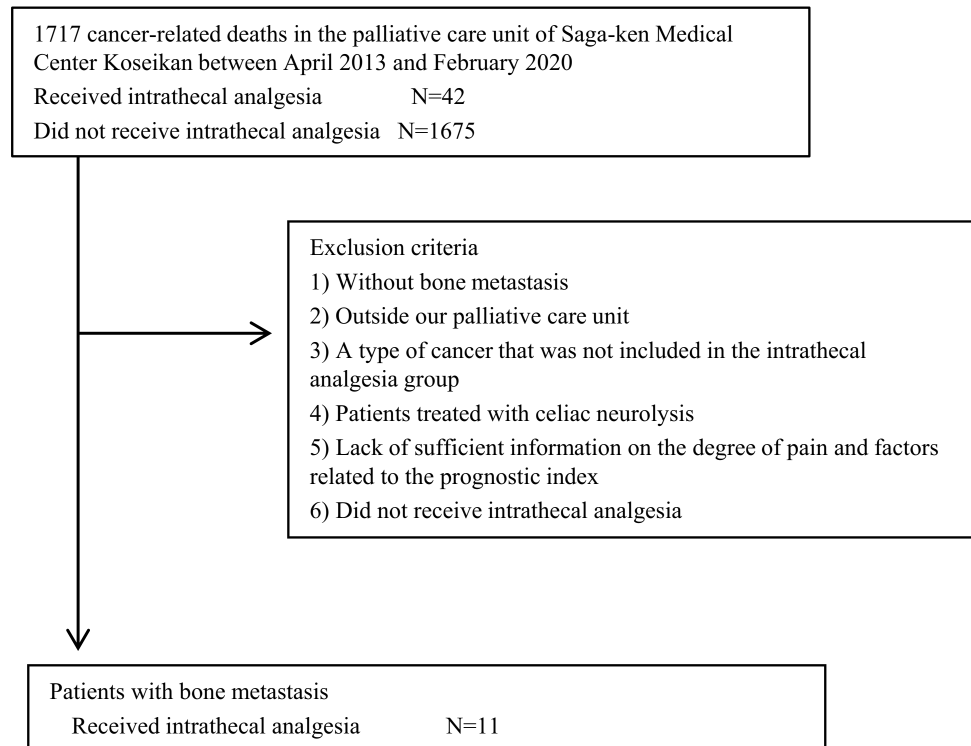
Fig. 1 Consort diagram



those treated with neurolysis, and those who lacked information on pain and factors related to prognostic indices in electronic chart records were excluded.

Among the items evaluated, physical activity levels were classified using the Eastern Cooperative Oncology Group Performance Scale (ECOG-PS and palliative performance scale (PPS) [5]. The results obtained were scored as the palliative prognostic index (PPI) in combination with oral intake and the presence of edema, dyspnea, and delirium [6].

ITA was performed within 7 days from the day (day 0) of evaluation of PPI. Changes in pain, the morphine milligram equivalent (MME) [7, 8], and PPI 4–16 days after the implementation of ITA were assessed as the after-ITA-day. The post-day 0 was defined as 50% from the day 0 to death. The pre-day 0 was set as within 21 days prior to the day 0. The degree of pain was evaluated using a numeric rating scale [9], with the absence of pain being rated as zero and intense pain as 10. Changes in pain, opioid doses, PPI, and ECOG-PS after ITA were assessed. Complications associated with ITA were examined.

Patient selection for ITA

The implementation of ITA was considered when pain persisted despite the administration of analgesics according to the WHO method [10], non-steroidal anti-inflammatory drugs, or acetaminophen, increases in the doses of potent opioids, opioid switching, or the introduction of adjuvant analgesics, causing refractory cancer pain (a poor response to standard opioid and/or co-analgesic therapy [11]), decreased oral intake or physical activity levels, opioid side effects, and ineligibility for radiotherapy. Patients with the following were excluded as candidates for ITA: hemorrhagic tendency, intracranial hypertension, metastasis at the puncture site, a previous history of surgical intervention at the puncture site, active infection, and no consent for ITA.

Intrathecal (IT) catheter placement

An IT catheter was placed according to a previously described protocol [12, 13] with some modifications. A polysulfone catheter was used (PORTA-A-CATH II POWER P.A.C. POLYSULFONE/TITANIUM, Smiths Medical, JP). Lumbar puncture was performed between T12 and L5, and the tip of the catheter was placed at the upper spinal level supplying the site of the most severe pain. A subcutaneous tunnel was created through the dorsal to lateral abdomen and the port was fixed on the subcutaneous facia in the lateral thoracic region.

Drug preparation

After the introduction of ITA, the administration of a mixture of morphine and bupivacaine was initiated [14, 15].

Table 1 Summary of 11 cases

Patient	Age	Sex	Stage at diagnosis	Frailty ±	BMI	Sites of bone metastasis 1: pelvis, 2: vertebrae, 3: appendicular, 4: thorax	Sites of pain 1.lower limb, 2.pelvis pain, 3.lower back, 4.upper back & chest	The link between sites of pain and bone metastasis 0: absence, 1: presence	Neuropathic pain	Reason for ITA 1: refractory cancer pain, 2: somnolence, 3: nausea, 4: constipation, 5: renal dysfunction, 6: delirium, 7: decline in oral intake, 8: decline in physical activity, 9: ineligible for radiotherapy
Colon: 1ʘ	54	F	III ≥	(+)	17.9	1	1	1	(+)	1, 2, 7, 8, 9
Colon: 2	66	M	IIIA	(+)	13.9	1	1	1	(+)	1, 2, 7, 8, 9
Colon: 3	75	M	IIIA	(+)	15.6	1	2, 3	1	(+)	1, 8
Cervix uteri:1	34	F	Ib1	(+)	20.8	1	1	1	(+)	1, 7, 8, 9
Cervix uteri:2	41	F	Ib2	(+)	22.3	1	1	1	(+)	1, 8, 9
Corpus uteri:1	73	F	IVB	(+)	18.6	1, 3	1, 2, 3	1	(+)	1, 3, 6, 7, 9
Ovarian:1	49	F	IC	(+)	16.4	1, 4	2	1	(+)	1, 2, 7, 9
Prostate:1	74	M	IV	(+)	18.8	1, 2, 3, 4	1, 3	1	(+)	1, 3, 5, 7, 8, 9
Renal:1	53	F	III ≥	(+)	21.6	2, 4	1	1	(+)	1
Stomach:1	39	F	IVB	(+)	18.3	2	4	1	(+)	1, 7, 8, 9
Lung:1	80	F	IA	(+)	21.3	1	1, 2, 3	1	(+)	1, 2, 8, 9
Median	54	M3(27.3%) :F8(72.7%)	NA	(+)	18.6	1:9(81.8%), 2:3(27.3%), 3:2(18.2%), 4:3(27.3%)	1:8(72.7%), 2:7(63.6%), 3:4(36.4%), 4:1(9.1%)	1	(+)	1: 11(100%), 2: 3(27.3%), 3: 2(18.2%), 4: 0(0%), 5: 1(9.1%), 6: 1(9.1%), 7: 7(63.6%), 8: 8(72.7%), 9: 9(81.8%)

Frailty, characterized by the presence of 3 or more of the following items: shrinking, weakness, poor endurance and energy, slowness, and a low physical activity level

BMI body mass index, *ITA* intrathecal analgesia, *NA* not applicable

ʘ Complication: Port site infection in the lateral thoracic region may have been caused by contamination from a stoma. On the 197th day after ITA, the patient developed fever. At the time, the worsening of pain in the lower limbs, headache, and somnolence. Neither nuchal stiffness nor symptoms in the upper respiratory or urinary tract were detected. A cerebrospinal fluid (CF) sample was not clear, and leukocytes were elevated; therefore, the patient was diagnosed with meningitis due to an IT catheter-related infection. Intravenously antibiotics ceftriaxone and vancomycin were administered. A culture test showed *Pseudomonas aeruginosa* (CF) and extended-spectrum beta-lactamase-producing *Klebsiella* (urine). Antibiotics were changed to meropenem. Fever subsequently resolved. Then, the IT catheter was exchanged, and the port site was changed to the right clavicle

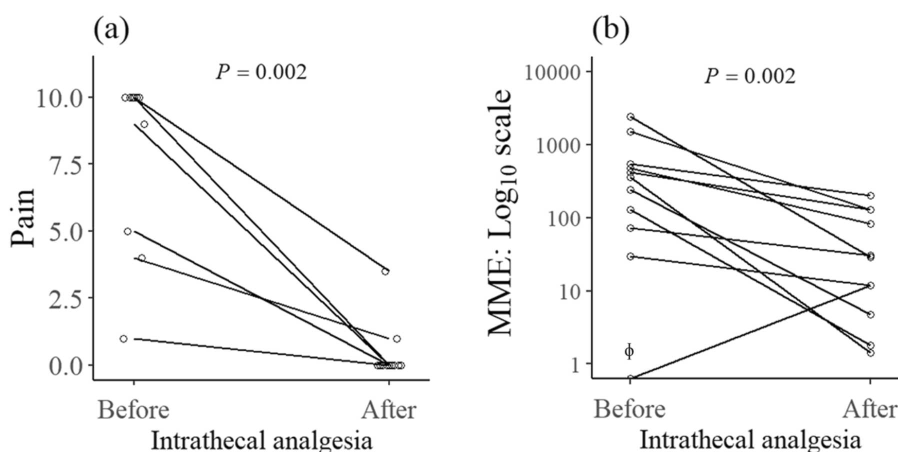


Fig. 2 (a) Changes in pain and (b) MME, morphine milligram equivalent. ϕ One case showed MME 0 on the day 0 because only methadone was administered without morphine conversion

The initial concentrations of each drug were at least 0.1 and 1 mg/mL, respectively. The concentrations and flow rates of each drug intrathecally were gradually adjusted. Drug administration was initiated using an extracorporeal pump (CADD-LEGACY® PCA MODEL6300, Smiths Medical, JP). The administration volume of the morphine-bupivacaine mixture was adjusted within ≤ 10 mL/24 h. The initial dose of morphine was adjusted with a target of 1/100 of the oral dose of morphine equivalent to the dose of the opioid before the implementation of ITA, and the dose of bupivacaine was adjusted to a level that did not cause motor nerve paralysis.

Statistical analysis

Nominal variables were expressed as a frequency (%) and continuous variables as a median (range). The results obtained after ITA were compared using the McNemar test or Wilcoxon signed-rank sum test. Statistical analyses were performed using R ver4.2.2 at the 5% level of significance.

Results

Baseline characteristics

Figure 1A shows a flowchart of the selection of patients. Among 1,717 patients who died of cancer during the study period in our institution, 42 received ITA. After the removal of patients based on exclusion criteria, 11 who received ITA were examined. Patient characteristics are shown in Table 1. Primary tumor origins were the colon in 3 cases (27.3%), cervix uteri in 2 (18.2%), and the corpus uteri, ovary, prostate, kidney, stomach, and lung in 1 each (9.1%). Median age was 54 (34–80) years and the male-to-female ratio was 3 (27.3%): 8 (72.7%). Stages at diagnosis were I in 4 cases (36.4%), II in 0, III in 4 (36.4%), and IV in 2 (18.2%). Median BMI was 18.6 (13.9–22.3) and all cases had frailty. Sites of bone metastasis were the pelvis in 9 cases (81.8%), vertebrae and the thorax in 3 each (27.3%), and appendicular in 2 (18.2%). Sites of pain were the lower limbs in 8 cases (72.7%), the pelvis in 7 (63.6%), the lower back in 4 (36.4%), and the upper back and chest in 1 (9.1%). Reasons for ITA were refractory cancer pain (100%), ineligibility for radiotherapy (81.8%), physical activity (72.7%), a decline in oral intake (63.6%), somnolence (36.4%), nausea (18.2%), renal dysfunction (9.1%), and delirium (9.1%). All cases of refractory pain were caused by bone metastasis, and neuropathic pain was due to nerve invasion or compression by cancer.

Effects of ITA

Figure 2 (**a**, **b**) and Table 2 show changes in pain and MME after the implementation of ITA. ITA attenuated pain and reduced MME ($P = 0.002$, 0.002) (Fig. 2a, b). PPI at each time point (pre, before, after, and post) of ITA are shown in Fig. 3a and Table 2. Median PPI was lower on the after-ITA-day than on the day 0 (before ITA) (Fig. 3a) ($P = 0.017$). No significant differences were noted in ECOG-PS, physical activity levels (palliative performance scale [PPS%], PPS [converted to PPI]), or oral intake after ITA. However, in many cases, PPS% and oral intake showed improvement (Fig. 3b and Table 2). There was one case of IT catheter infection after ITA (Table 1 annotations).

Table 2 Changes in Pain, Morphine, ECOG-PS, and PPI factors

	Pre-day 0	Day 0 (Before IT)	(After IT)	Post-day 0	*P*-value (Before vs After)
Pain	NA	10 (1–10)	0 (0–3.5)	NA	0.002
Morphine milligram equivalents	NA	360.0 (0–2400)*	28.8 (1.44–201.60)**	NA	0.002
Methadone 3/11 cases	NA	20 (20–30)[Ω]	0	NA	
Ketamine 2/11 cases	NA	21.6 (19.2–24)[Ψ]	0	NA	
PPI	2.25 (0–3.5)	3.5 (2.5–7.5)	2.5 (0–6.5)	2.5 (0–10.5)	0.017
ECOG-PS (0/1/2 /3/4)	0(0.0)/0(0.0)/3(33.3) /6(66.7)/0(0.0)	0(0.0)/0(0.0)/0(0) /10(90.9)/1(9.1)	0(0.0)/1(9.1)/1(9.1) /8(72.7)/1(9.1)	0(0.0)/1(9.1)/1(9.1) /5(45.5)/4(36.4)	0.5[†]
PPS%	55 (50–60)	50 (40–50)	50 (40–60)	50 (20–80)	0.125[††]
PPS convert to PPI	1.25 (0–2.5)	2.5 (0–2.5)	2.5 (0–2.5)	2.5 (0–4.0)	0.125[‡]
Edema (absent/present)	8(80.0)/2(20.0)[§]	9(81.8)/2(18.2)	9(81.8)/2(18.2)	8(72.7)/3(27.3)	NA
Dyspnea (absent/present)	10(100.0)/0(0.0)[§]	11(100.0)/0(0.0)	11(100.0)/0(0.0)	11(100.0)/0(0.0)	NA
Delirium (absent/present)	10(100.0)/0(0.0)[§]	10(90.9)/1(9.1)	10(90.9)/1(9.1)	10(90.9)/1(9.1)	NA
Oral intake (0/1/2.5)	6(60.0)/4(40.0)/0(0.0)[§]	4(36.4)/5(45.5)/2(18.2)	8(72.7)/3(27.3)/0(0.0)	7(63.6/3(27.3)/1(9.1)	0.117[‡‡]

PPI: Rated from 0 to 15, with higher scores indicating a worse performance status and poorer survival, combining PPS (converted to PPI): [> 60%: 0, 30–50%: 2.5, or 10–20%: 4.5], Edema: [−: 0 or + : 1], Dyspnea: [−: 0 or + : 3.5], Delirium: [−: 0 or + : 4.5], and Oral intake: [normal: 0, reduced to more than a mouthful: 1, or a mouthful: 2.5]

ECOG-PS: Rated from 0 to 4 (five-grade), with higher scores indicating a worse performance status and poorer survival

PPS: Rated from 100 to 10% (ten grades), with a lower score indicating a worse performance status

PPS (converted to PPI): Rated as 0, 2.5, and 4.5 (three grades), with higher scores indicating a worse performance status, PPS > 60% converted to PPI: 0, PPS 30–50% converted to PPI: 2.5, PPS 10–20% converted to PPI: 4.5

Edema: swelling due to fluid in the body, with the exclusion of unilateral lymph edema,

NA: not applicable

Column after IT: 4–16 days after the implementation of ITA, 8 (4–16)

Column post-day 0: 50% from the day 0 to death, 19 (7–132)

* Morphine row of column day 0: 10 cases in total, oral morphine milligram equivalent,

e.g. oral morphine, mg: oral oxycodone, mg: fentanyl citrate patch, mg = 60: 40: 2

** Morphine row of column after IT: 11 cases in total, intrathecal morphine milligram

[Ω] Methadone row of column day 0: 3 cases in total, without morphine conversion

[Ψ] Ketamine row of column day 0: 2 cases in total, without morphine conversion

[§] Edema, Dyspnea, Delirium and Oral intake row of column pre-day 0: 10 cases in total, one case had a missing value

[†] ECOG-PS row of column *P*-value: After IT status: (improvement/no change/deterioration) = (18/82/0%)

[††] PPS% row of column *P*-value: After IT status: (improvement/no change/deterioration) = (55/36/9%)

[‡] PPS (convert to PPI) row of column *P*-value: After IT status: (improvement/no change/deterioration) = (36/64/0%)

[‡‡] Oral intake row of column *P*-value: After IT status: (improvement/no change/deterioration) = (64/18/18%)

Discussion

We herein conducted a retrospective analysis of the effects of ITA with a subcutaneous port system in cancer patients with bone metastasis who died in the palliative care unit. Pain, opioid doses, and PPI significantly decreased after ITA.

Although neurolysis improved pain relief and delayed opioid dose escalations [16–18], its effects on QOL and survival remain controversial [1–3]. Among interventional treatments, we herein focused on ITA, which controls pain via different mechanisms from neurolysis.

PPI on the after-ITA-day improved from that on the day 0 (before ITA); however, we were unable to show a beneficial effect on the prognosis of patients because the control group in the preliminary study, in which the primary lesion, the diagnosis stage, and age were not matched, was insufficient.

More improvements were detected by PPS with ten grades than by ECOG-PS with five grades, and oral intake, which was not included in ECOG-PS, showed improvement. These factors may have contributed to the significant difference observed in PPI. Further studies on a larger number of subjects may reveal more significant differences.

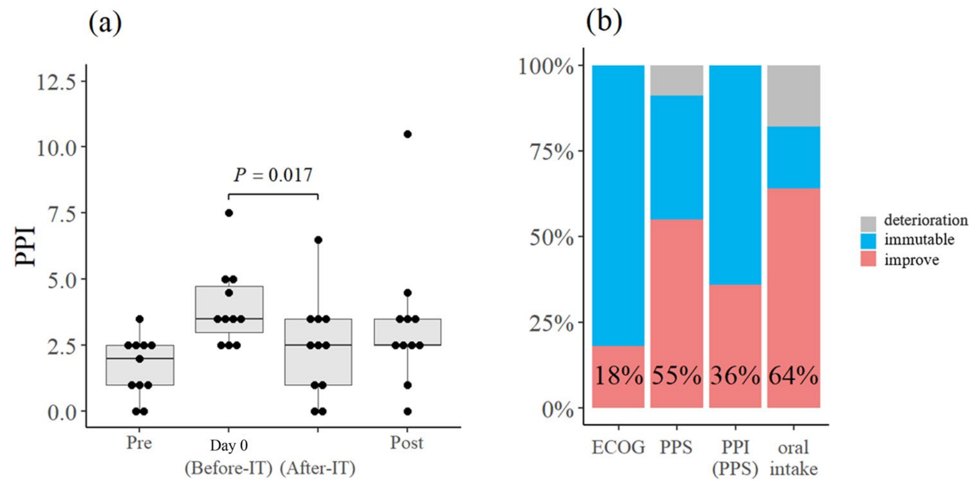


Fig. 3 **a** Changes in PPI and **b** ECOG-PS, PPS, PPI (PPS), and oral intake

As of December 2023 in Japan, ITA by subcutaneous reservoir implantation has not yet been approved, and the effects of the early implementation of ITA on the prognosis of patients remain controversial [19–21]. Therefore, based on the improvement observed in PPI, further evaluations of its indications are necessary.

Since ITA is an invasive method, careful considerations are required before its implementation, particularly contraindications for puncture, such as infection, bleeding/clotting abnormalities, intracranial hypertension, and bone metastasis at the puncture site.

The present study has a number of limitations that need to be addressed. This was a single-center retrospective study, patient selection was arbitrary, and the sample size was small.

In conclusion, the present results suggest that ITA reduced refractory cancer bone pain, opioid doses, and PPI.

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Author contributions Study concept and design: IH and ES; data collection: IH; manuscript preparation: IH; manuscript editing, review and approval: all authors.

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Data availability Raw data were generated at Saga-ken Medical Center Koseikan. Derived data supporting the findings of this study are available from the corresponding author IH on request.

Declarations

Conflict of interest The authors declare no conflicts of interest.

Ethical approval This study was received from the Saga-ken Medical Center Koseikan Institutional Research Ethics Board in Saga, Japan.

Prior presentation Part of this article was presented at the 25th Congress of the Japanese Society for Palliative Medicine (August 9–10, 2020, online, Japan).

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