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Single Case

A Cancer-Pain Analgesia as Prolonging Strategy of Surviving Time after Failure of Adjuvant Chemotherapy in Patient with Progressive Bone-Metastatic Hepatocellular Carcinoma

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Keywords
Hepatocellular carcinoma · Bone metastasis · Cancer-related pain · Intrathecal analgesia · Surviving time

Abstract
The hepatocellular carcinoma (HCC) with intrahepatic and bone metastasis shows poor survival of averagely 3 months. The bone metastasis and HCC itself might cause cancer-associated pain. An intrathecal (IT) analgesia might contribute to improve QOL and prolong surviving time (ST). A 71-year-old male presented with temperature and appetite loss continuing for 2 months. He looked pale and malaise. Computed tomography and tumor markers elevation confirmed diagnosis of HCC stage IV. To treat him, molecularly targeted therapy was started but abandoned because of side effects of life-threatening convulsions and loss of consciousness. Since this time, pain control strategy was planned as advance care plan. After dermal and oral opioids were administered, IT analgesia was introduced to conquer uncontrollable pelvic pain due to metastatic osteolytic lesions. Owing to IT analgesia against severe cancer-related pain, he had lived for 46 months. Comparing with reviews in which average ST is 3 months, this is the case with the longer ST in bone-metastatic HCC. From our experience, it must be emphasized that relieving cancer-related pain strategy for patients with progressive bone-metastatic HCC might contribute to prolong ST longer when adjuvant therapy has been failed.

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Introduction

The hepatocellular carcinoma (HCC) with intrahepatic and bone metastasis shows poor survival of averagely 3 months. To enhance quality of life (QOL) to enjoy life with longer surviving time (ST) is the strategy to struggle with advanced HCC. The bone metastasis and HCC itself might cause cancer-associated pain [1]. This cancer pain is reported ranging moderate to severe in 50% of all patients with HCC associated with bone metastasis, and this pain is persistent, regardless of analgesic agents such as opioids according to cancer pain guideline [2]. An intrathecal (IT) analgesia of opioids might contribute an enhancing QOL and prolong ST in advanced cancer patients. In the present report, we present a male case of HCC with intrahepatic and pelvic bone massive metastasis. His severe cancer pain was successfully managed with ITA. His ST was 46 months and seems extremely longer ST compared with the largest population-based investigation of average 3 months, although the relation between efficacious IT analgesia and extremely long ST in patients with HCC associated with intrahepatic and massive bone metastasis is still unclear.

Case Description

A 71-year-old male presented with temperature and appetite loss continuing for 2 months. He looked pale and malaise. He had drinking with tiny foods taken from his younger sister inhibited nearby. He had a past history of pressure fractures of thoraco-lumber vertebrae (T12-L2). His smoking and drinking habits were 10 cigarettes and 70 g alcohol daily for 50 years. The initial laboratory data were the follows: AST 146 U/L, ALT 62 U/L, T-bilirubin 0.8 mg/dL, albumin 2.0 g/dL, Na 130 mEq/L, K 3.3 mEq/L, Cl 95 mEq/L, and CBC showed WBC, RBC, and platelet levels of 4,480, 241 × 10^4, and 17.5 × 10^4/mm^3, respectively. He was diagnosed with compensatory cirrhosis (Child-Pugh Grade B). His abdominal and pelvic computed tomography (CT) showed irregularly rounded nodule in segment 8 (S8) with three daughter nodules (Fig. 1a–c), and left iliac bone irregular osteolytic change was also observed (Fig 3a). From these CT findings, additional tumor makers detected were alpha-fetoprotein and PIVKA-II of 406.7 ng/dL (reference: <10.0) and 2,741 mAU/mL (<39), respectively. Considering CT findings and tumor markers elevation, the diagnosis of HCC (stage IV A) was confirmed. To treat him, chemotherapy using molecularly targeted therapy (sorafenib, 800 mg/day) was commenced. At the time of completion of 8 cycles of molecularly targeted therapy (Fig 2, upper pink column), he developed severe side effects of life-threatening

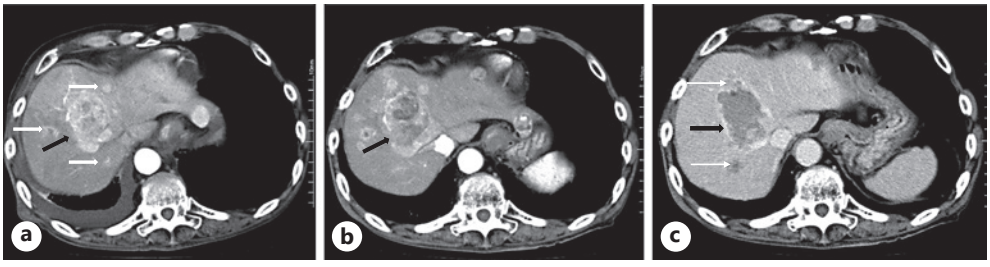

Fig. 1. The serial plain abdominal and pelvic CT images. **a** An arterial phase of abdominal enhanced (e-) CT shows HCC at S8 segment and three daughter nodules as intrahepatic metastases. Its diameters were 60 × 38 mm (at first visit). **b** An arterial phase of e-CT showed similar size of HCC. Its size was 55 × 37 mm (4 months after **a**). **c** A venous phase of e-CT showed similar sized daughter nodules (4 months after **a**). Black arrows: HCC, white arrows: daughter nodules.

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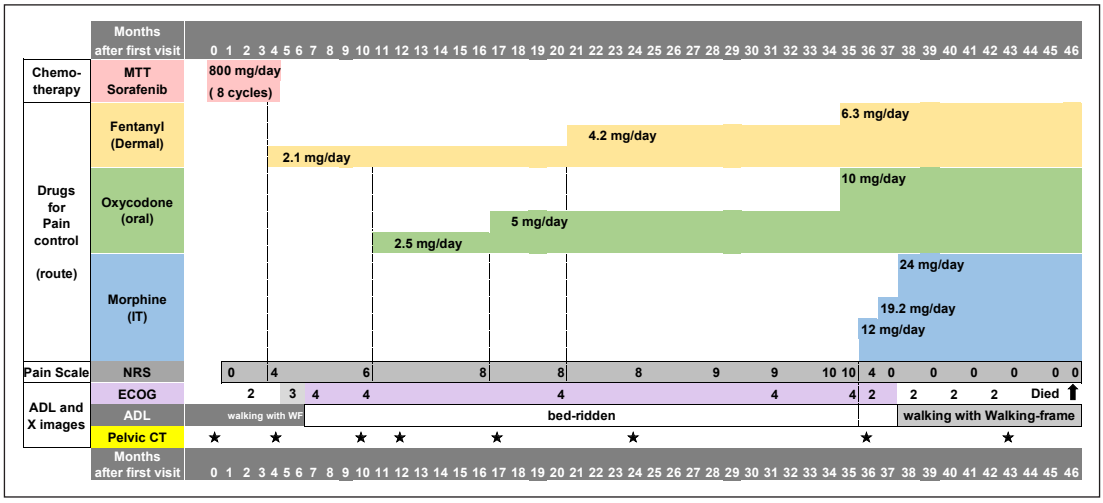

Fig. 2. The timeline of chemotherapeutic and analgesic agents and events, ADL, and pain scores. This figure consists of 8 columns. The domain of each column is as follows from top to bottom: 1st (pink); chemotherapy using sorafenib, 2nd (yellow) to 4th (blue); pain control agents (including 2nd for fentanyl, 3rd for oxycodone, and 4th for intrathecal analgesia using morphine), 5th (gray); pain score evaluated by NRS, 6th (purple); ECOG score, 7th (dark gray); ADL, and 8th (yellow); timing of taking pelvic CT images compatible with images in Fig. 3, respectively. ADL, activities of daily living; CT, computed tomography; ECOG, Eastern Cooperative Oncology Group performance status; IT, intrathecal analgesia; Mon, month; MTT, molecularly targeted therapy; NRS, numeric rating scale; WF, walking frame.

convulsions and loss of consciousness and further chemotherapeutic regimen was abandoned. As advance care plan, pain control strategy was planned. An IT analgesia was proposed, but he denied to accept. As second choice, fentanyl was started via dermal route and oral oxycodone were added 5 months later and continued (Fig 2Fig 2 and 3, middle yellow and blue columns) even after his discharge to home 11 months after the first visit to hospital. At 36 months, his pain felt at left lower back and leg had been growing uncontrollably. Serial pelvic CT images showed that metastatic osteolytic lesion at left iliac bone had been growing in size up to 151 × 131 mm in diameter with direct invasion into sacral spinal canal. These changes of bone metastases are shown serially from Figure 3b–h. At 37 months, he accepted IT analgesia once he had denied and injection port was implanted. Via this, morphine and bupivacaine were administered and his active life status had been improved, evaluated by Eastern Cooperative Oncology Group Performance Scale (ECOG-PS), from point 4 (defined completely disabled and cannot carry on any self-care, totally confined to bed or chair) to point 2 to be able to walk using walking frame with minimal cancer pain. Under relieving cancer-related pain by IT analgesia, he could have a calm end-of-life even when bone metastases had progressively growing and died at 46 months after diagnosis of rectal cancer.

Discussion

The metastasis to the bone from HCC occurs less frequently than other cancers [3]. The ST after diagnosis of HCC ranges from 6 to 20 months. However, the presence of bone metastasis reduces survival rate severely [3]. In the largest population-based study that investigated the prevalence of HCC in 1,567 cases, bone metastasis was positively associated with male sex, unmarried status, higher tumor (T) stage, lymph node (L) involvement, intrahepatic

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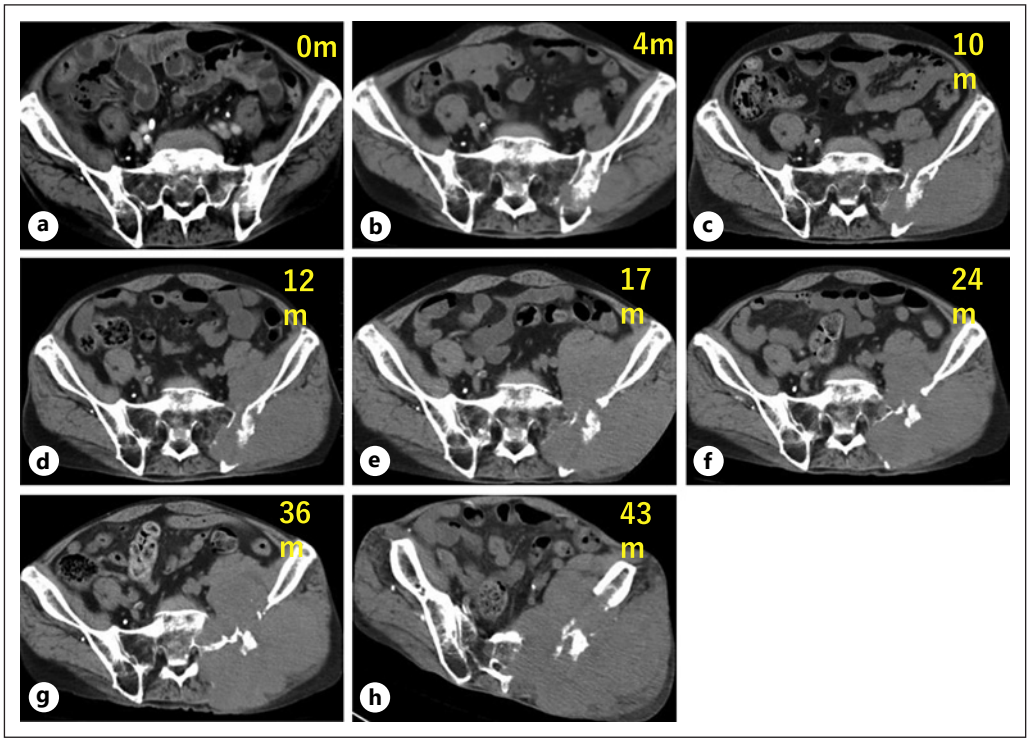

Fig. 3. a–h The serial pelvic CT images of progressive bone metastases. All images show serial pelvic CT images between his first visit and 43 months later. All CT images were taken at the same level of first sacral (S1) vertebra. These images were interpreted as the follows: (1) size of iliac metastatic lesion was growing, (2) left iliac bone was osteolytic changes with invaded metastatic carcinoma of HCC. Numerical numbers with alphabet "m" on right upper of each image shows months after the first visit taken images.

metastasis, and extrahepatic metastasis to lung or brain. Among these, male sex, higher T stage, and intrahepatic metastasis were seen in our case. Furthermore, this investigation proved that the median ST of patients with bone-metastatic HCC was 3 months (95% CI: 2.77–3.24 months) [1]. Another single-center study analyzed 1,143 patients with HCC and 69 of all (6%) had bone metastases. They concluded that an average ST in patients with bone metastases was 79 days and that four predictors of prognosis exist: age >60 years, poor Karnofsky Performance Status (vs. good and moderate), serum total bilirubin >3.0 mg/dL, and multifocality of HCC (vs. single tumor) [4]. In the other analysis, patients who have failed downstaging of metastatic HCC can achieve better prognosis than those without neoadjuvant therapy (median overall survival: 10.3 months vs. 4.0 months) [5]. Different from these STs analyzed in literatures, ST of our case was 46 months. To our best knowledge, this might be the longest ST in a patient with bone-metastatic HCC. This ST might be considered as a natural history of these conditional HCC when the neoadjuvant chemotherapeutic regimen has failed because of severe side effects as our case had.

Although it seems to be not easy to explain the reason of his longer ST, an effective cancer-related pain control using IT might be one possibility to contribute. In general, cancer-related pain due to bone region has invaded into the bone periosteum, marrow, and matrix where sensation nerve fibers such as A-delta and C are highly innervated [6]. IT analgesic opioids reach directly first to the spinal fivers rather than systemic circulation. An application of IT analgesia for delivering opioids has several advantages: (1) efficacy of pain reduction, (2) side effect reduction, and (3) cost-effectiveness [2]. This IT analgesic relief of cancer pain could

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contribute to improve QOL and prolong his ST. To confirm this hypothesis, a large accumulation of similar cases must be required to analyze.

In the clinical settings, however, an effective IT analgesic strategy against severe cancer-related pain relief seems to prolong ST in patients with bone-metastatic HCC in whom neoadjuvant therapy have been failed like this case. In addition, the targeted first-line therapy using lenvatinib [7, 8] or the others as immune checkpoint inhibitors including atezolizumab plus bevacizumab [9] are of worth to consider. However, we were not allowed by the government to apply these at the time when this case was treated. Radiotherapy must also be considered as an alternative to relieve bone metastasis cancer pain. However, we could not choose this option because of two reasons: one was patient's wish that not to get treatment outside of this island and another was our hospital's limitation of unavailability of radiotherapy equipment.

Conclusion

A 71-year-old male diagnosed with HCC fooled by pelvic metastases survived for 46 months was reported. Comparing with reviewed results of patients with advanced bone-metastatic HCC whose average ST was 3 months, this is the case with longer ST in bone-metastatic HCC. From our experience, it might be emphasized that relieving cancer-related pain strategy for patients with progressive bone-metastatic HCC might contribute to prolong ST when adjuvant therapy has failed.

Statement of Ethics

The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This report was approved by the Ethics Committee of Tokunoshima Tokushukai General Hospital, approval number is 22-01. Written informed consent was obtained from the patient's next of kin for publication of the details of their medical case and any accompanying images because the patient is deceased.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Funding Sources

The authors did not receive any sponsorship or funding and do not have any conflicts interest related to the case.

Authors Contributions

Yuji Inada and Teruyoshi Amagai have written the manuscript. Yuji Inada has taken written informed consent from the next of kin. Yuji Inada and Teruyoshi Amagai have created figures. Seiji Hattori, Yasuhiko Fujita, and Teruyoshi Amagai have supervised the written manuscript.

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Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

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