**Psychological barriers to the use of opioid analgesics for treating pain in patients with advanced recurrent cancer (BAROC): protocol for a multicentre cohort study**

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**ABSTRACT**

**Introduction** Opioid analgesics are essential for treating cancer pain. However, patients are sometimes reluctant to use them because of concerns about addiction and dependence. Rapid pain relief following opioid administration may help overcome the psychological barriers to opioid analgesic use. This study aims to determine the relationship between psychological resistance to strong opioid analgesic use and pain amelioration speed in patients with advanced recurrent cancer.

**Methods and analysis** This ongoing, multicentre, observational study enrols patients aged 20 years or older with distant metastasis or advanced recurrent cancer receiving strong opioid analgesics for cancer pain for the first time. All participants, both inpatient and outpatient, were recruited from five Japanese hospitals. We are investigating the relationship between psychological barriers at the start of treatment and pain relief during the first week of treatment in these patients. The primary outcome is the Japanese version of the Barriers Questionnaire-II score at baseline. The secondary outcomes are the relationships between psychological barriers to strong opioid analgesic use and changes in pain over time. The participants are asked to fill out an electronic patient-reported outcome daily during the first week of treatment. The sample size was determined based on the number of patients in the year prior to study commencement who used strong opioid analgesics, met the eligibility criteria and could be expected to consent to participate in the study.

**Ethics and dissemination** The study protocol was approved by the ethics committee (approval ID B200600091) of Yokohama City University on 24 August 2020. The protocol has been reviewed by the institutional review boards at the four participating study sites. The results will be published in a peer-reviewed journal and will be presented at a relevant meeting.

**Trial registration number** UMIN000042443.

**Strengths and limitations of this study**

- This is the first multicentre observational study to evaluate psychological barriers to the use of strong opioids in Japan.
- Adverse events related to opioid analgesic use are assessed using the patient-reported outcomes version of the Common Terminology Criteria for Adverse Events (CTCAE) and CTCAE v.5.0-Japanese Clinical Oncology Group.
- A limitation of this study is its short observation period, which leads to an inability to confirm long-term variations in psychological barriers.

**INTRODUCTION**

In 2017, there were 24.5 million incident cancer cases worldwide, and 9.6 million people who died of cancer.\(^1\) The incidence of cancer increased by 33% from 2007 to 2017. In 2009, there were 775,601 patients with cancer in Japan.\(^2\) Cancer pain is the most concerning symptom of patients with cancer, with approximately 80% of patients with advanced cancer experiencing moderate to severe pain.\(^3\) Japanese studies have examined the percentage of patients with cancer requiring and undergoing treatment for pain relief.\(^4\) In a survey, 60% of patients with cancer had pain, with 20% having moderate to severe pain.\(^5\) Based on the prevalence of cancer in Japan, it is estimated that approximately 155,000 Japanese patients have moderate to severe pain and require opioid analgesics.

Patients with cancer often hesitate to manage their cancer pain using opioid analgesics. Their hesitation-related perceptions include concerns about addiction, gradual
loss of effectiveness, severe side effects, anxiety due to pain predicting disease progression and the idea that physicians are reluctant to talk about pain. The Barriers Questionnaire (BQ) quantitatively measures factors related to patients’ hesitation regarding opioid use. This scale was used to evaluate 270 patients with cancer, and it was found that 37%–85% of them were concerned about addiction and believed that good patients do not complain about pain and side effects. Additionally, older individuals, those from low-income households, and those with low levels of education had higher concerns related to medical narcotics. Furthermore, a relationship between the presence of barriers and pain intensity has also been reported. Moreover, patients’ mental anguish is positively correlated with pain, and opioid analgesics may be insufficient for pain management depending on the patients’ mental state.

A review investigating the barriers to cancer pain management related to healthcare professionals, patients, and systems revealed that patient-related barriers included cognitive and emotional barriers and treatment adherence. Cognitive barriers included underreporting of symptoms to doctors and painkiller-related misunderstandings. Large barriers were associated with race, sex, and poor medication adherence. In particular, a meta-analysis showed that Asians have greater barriers to cancer pain progression, tolerance, and lethality than Westerners. A survey conducted across 214 countries by the International Narcotics Control Board revealed that Japanese individuals consumed fewer medical narcotics per million people per day than those from other countries (1192 vs 3027, respectively). Barriers to narcotic use included lack of training and awareness among healthcare professionals, concern regarding dependency, limited financial resources, procurement issues, cultural behaviour, fear of diversion, and international trade control and regulation. Using a questionnaire, regulatory authorities of various countries found a high percentage of patients (56%) with concerns about dependency in East Asia, which includes Japan. This suggests that the higher the number of reported barriers, the lower the opioid analgesic use.

A Japanese questionnaire study found that 28% of patients with advanced and recurrent cancer believe that opioid analgesic use shortens their lifespan and causes addiction. A national survey of 5000 people revealed that 27%–38% of participants reported that opioids shorten lifespan, while 24%–33% reported that opioids cause addiction. This emphasises the need to thoroughly consider barriers when initiating treatment with opioids in Japanese patients. Despite barriers, acceptance of opioid use for pain relief is expected to improve through the practice of high-quality palliative care, pain relief following administration of narcotic medication, and improved confidence in drug safety. Consequently, we believe that pain relief immediately after drug administration is important for breaking these barriers and that patients who confidently use opioid analgesics will quickly achieve the optimal dose and experience immediate pain relief. Patients’ pain and mental state fluctuate daily and diurnally, and comparing preintervention and postintervention findings may lead to inaccurate results. A detailed assessment of the speed of pain relief requires repeated evaluation over time.

Several studies have shown a positive correlation between psychological barriers and pain level, possibly due to inadequate analgesic use. Furthermore, psychological barriers were lower when analgesics appropriate for the level of pain were used than when inadequate analgesics were used. However, the use of strong opioid analgesics has not been specifically studied. A study conducted at six medical centres in three countries that regulate the use of strong opioid analgesics examined psychological barriers in patients who had been using strong opioid analgesics for more than 72 hours and showed that patients who had been using strong opioid analgesics for a short period reported higher barrier scores than those who had been using them for a long time. Therefore, it is important for future cancer pain treatment to identify changes in psychological barriers during and after initiation of use of strong opioid analgesics. However, these are cross-sectional studies, and, to date, only a few studies have investigated the relationship between psychological resistance to strong opioid analgesic use on initiation and the speed of pain relief immediately after initiation in patients with advanced recurrent cancer. Therefore, we designed this study to address the need for sufficient verification of the relationship between psychological barriers and the speed of pain relief.

This study aimed to elucidate the relationship between psychological barriers to strong opioid analgesics use and the speed of pain relief in patients with advanced recurrent cancer. If it is found that cancer pain relief is difficult to achieve in patients hesitant to use strong opioid analgesics, this study may provide important information on how to assuage their reluctance and enable rapid pain improvement.

**METHODS AND ANALYSIS**

**Study design**

This is an ongoing, multicentre, longitudinal, observational study. We are investigating the relationship between psychological barriers at the start of treatment and pain relief during the first week of treatment in patients receiving strong opioids for cancer pain. We are also evaluating the relationship between psychological barriers and adverse events associated with the use of strong opioids.

**Patient and public involvement**

Patients were not invited to collaborate during the study design; therefore, this study protocol was developed without patient and public involvement. The enrolment was started in August 2020, and planned to close in October 2021.

Box 1  Eligibility criteria

Inclusion criteria
1. Patients diagnosed with remote metastasis or advanced recurrent cancer by a doctor.
2. First treatment with strong opioid analgesics for cancer pain.
3. Patients who are 20 years or older.
4. Highest intensity of pain in the last 24 hours of an NRS score of 4 or higher.
5. Patients providing written consent for participating in the study.

Exclusion criteria
1. Patients who have difficulty in providing ePRO data (eg, those who do not have a smartphone or cannot use a tablet).
2. Patients with cognitive impairments that would hinder PRO administration.
3. Patients with mental illnesses that would hinder PRO administration.
4. Patients whose main mechanism of pain is neuropathic.
5. Other factors that the attending physician deems inappropriate.

Patient Global Impression of Severity
Currently, the cut-off values for classifying the presence and magnitude of psychological barriers are unknown. We are using the Patient Global Impression of Severity (PGIS) to classify the participants’ JBQ-II scores. The PGIS has not been validated to classify psychological barriers. We are grading responses to the item ‘At present, how reluctant are you to use opioids for pain relief?’ using the following seven-point scale: (0) not at all; (1) not reluctant; (2) almost not reluctant; (3) neither; (4) slightly reluctant; (5) reluctant and (6) extremely reluctant.

Decision Regret Scale
Regret is a negative emotion experienced when one realises or imagines that one has made the wrong choice. It is a retrospective, unpleasant feeling and people tend to focus on ‘what is good’ rather than ‘what is bad’. It has been reported to be associated with negative emotions, such as disappointment, and involve some aspect of self-blame. We are evaluating regret using the DRS, which measures patient conflict regarding decision making during the treatment process. A Japanese version of the DRS has been developed and validated (Cronbach’s α=0.85). It consists of five items. The total score ranges from 0 to 100, with higher scores indicating greater regret.

PROs version of the CTCAE
The National Cancer Institute (NCI)-CTCAE is a standardised tool for assessing adverse events during cancer treatment. However, since grading is based on the clinician’s judgement, it may not be possible to accurately evaluate the patient’s condition, especially when subjective aspects are involved. Basch et al reported a discrepancy between clinicians’ and the patients’ assessments, indicating that clinicians underestimate CTCAE grades. Therefore, the NCI developed the PRO-CTCAE, which incorporates the concept of PRO into the CTCAE. Its Japanese version has been validated. In this study, we are evaluating the participants’ main symptoms, such as nausea/vomiting, constipation,
drowsiness, fatigue, and thirst. We are also evaluating an additional item to measure the psychological burden of using opioid analgesics.

**Brief Pain Inventory-Short form**

The effect of pain on daily life differs from pain intensity. It is related to the amount of pain that hinders activities such as walking, bathing, and sleeping. The BPI is a standardised scale that has been confirmed to be reliable and valid for assessing pain intensity and its effect on daily life. It is a 15-item questionnaire that evaluates pain. Each item is graded on an 11-point scale, with scores ranging from 0 to 10. The Japanese version of this scale has already been validated, and its reliability and usefulness have been established (Cronbach’s α=0.80). To decrease the burden on patients related to the number of questions to be answered, we are only using the ‘worst pain in the last 24 hours’ item of the BPI-SF, based on a report by Atkinson et al.32

**Personalized Pain Goal**

The Numerical Rating Scale (NRS) is generally used as an index of the average pain over 24 hours and the degree of pain-related disability in daily life (disturbance of life). It is an 11-point scale, with scores ranging from 0 (none) to 10 (the worst possible). A score of ≥4 indicates moderate pain/disability, while a score of ≥7 indicates severe pain/disability.33 From the perspective of personalized medicine for the treatment of cancer pain, it is important to involve the patient in treatment goal setting and provide

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**Table 1: Study timeline**

<table>
<thead>
<tr>
<th>Day</th>
<th>Visit 1</th>
<th>Time after initiating opioid therapy</th>
<th>Visit 2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0 (baseline)</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>PROs:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Psychosocial background</td>
<td>●</td>
<td></td>
<td></td>
</tr>
<tr>
<td>JBQ-II</td>
<td>●</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PGIS</td>
<td>●</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DRS</td>
<td>●</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PRO-CTCAE</td>
<td>●</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BPI-SF (strongest pain in the last 24 hours)</td>
<td>●</td>
<td>●</td>
<td>●</td>
</tr>
<tr>
<td>PPG</td>
<td>●</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Use of strong opioids before starting base medication with or without rescue medication (outpatients)</td>
<td>●</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Whether any dose of the base strong opioid was missed (outpatients)</td>
<td>●</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinician reported:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Demographics and medical history</td>
<td>●</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CTCAE v.5.0-JCOG</td>
<td>●</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Presence of increased opioid dosage</td>
<td>●</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Presence of opioid switching</td>
<td>●</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Use of strong opioids before starting base medication with or without rescue medication (inpatients)</td>
<td>●</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Whether any dose of the base strong opioid was missed (inpatients)</td>
<td>●</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*BPI-SF, Brief Pain Inventory-Short Form; CTCAE, Common Terminology Criteria for Adverse Events; DRS, Decision Regret Scale; JBQ-II, Japanese version of the Barriers Questionnaire II; JCOG, Japan Clinical Oncology Group; PGIS, Patient Global Impression of Severity; PPG, Personalized Pain Goal; PRO, Patient Reported Outcome.*
treatment with the aim of achieving those goals. The PPG has recently been used as an outcome measure to determine pain-relief goals in non-Japanese patients with cancer. In our study, patients are being asked to use the NRS to indicate their pain treatment goals. Pain treatment is considered to be successful (achievement of the PPG) if the patient’s NRS score for pain at the time of assessment is below the PPG.

Others
Since strong opioid use during the study period might affect the time to PPG achievement, the following items are being investigated: (1) whether any dose of the base strong opioid was missed, (2) presence of increased opioid dosage, (3) presence of opioid switching and (4) use of strong opioids before starting base medication with or without rescue medication.

Sample size
Since this is an observational study conducted to form a hypothesis rather than a confirmatory study conducted to test it, the sample size is focus on feasibility and is based on the number of patients receiving strong opioid analgesics at the main medical institution. At Yokohama City University Medical Centre, 378 patients started receiving strong opioid analgesics in 2019 (total oral and injection, excluding local use). Among them, 60% met the eligibility criteria, and 60% of them were assumed to be able to express consent, which leads us to estimate that 136 people could enrol into this study within 1 year. In addition, it is expected that 10–40 patients will be enrolled annually at Tokyo Medical University Hospital, National Cancer Centre Hospital East, Yokohama-Minami Kyosai Hospital and Kameda General Hospital. Based on these estimates, we set the sample size target at 200.

Data collection and timeline
We are using the electronic data capture (EDC) systems Viedoc 4 and ViedocMe (Viedoc Technologies, Sweden) and ePRO, to enrol the participants and collect their data. During enrolment, the investigators input their personal accounts and passwords into the system. Investigators at each site use the EDC system to input data into an electronic case report form. Patients are being administered the PROs using an ePRO on their device (smartphone, tablet or personal computer) at eight time points: at baseline and on days one to seven. The patients may register their phone number or email address in the EDC system and use the ePRO reminder function. The investigators are providing the patients with details about the trial. After obtaining patient consent, data regarding each patient’s psychosocial background; JBQ-II, PRO-CTCAE, and BPI-SF scores; and PPG are collected from their electronic device. Data regarding demographics, medical history, and CTCAE v.5.0-Japan Clinical Oncology Group (JCOG) score are collected, entered into the web-based EDC system at the study site, and linked to the baseline PRO data. After starting to receive opioids, each patient is asked to record their BPI-SF (worst pain in the last 24 hours) score daily for 7 days. On the last day, each patient is administered the JBQ-II, PGIS, DRS and PRO-CTCAE. Each patient’s CTCAE v.5.0-JCOG data is collected by an investigator at the time of their next visit (days 8–15). In addition, we are recording each patient’s use of strong opioid medication prior to starting base medication and whether any dose of the strong base opioid has been missed. The study timeline is presented in table 1.

Data monitoring
The data centre is located at the Department of Practical Pharmacy, Tokyo University of Pharmacy and Life Sciences, Tokyo, Japan. No personally identifiable information is being entered into the EDC system, and the participating sites are not communicating personal information to the data centre. Since this study involves data collection using an EDC system, the data is stored on the server during the study period. After the end of the study period, the data exported from the EDC system will be stored at the data centre until presentation or publication. Following this, the data will be stored at the research secretariat and data centre. Monitoring is being performed to ensure that the study is conducted according to the protocol and that the data is collected accurately. Central monitoring is being performed by the data centre based on the EDC data collected. The data centre has been submitting monthly monitoring reports to the researchers, is sharing information with the researchers at all the study sites, and is striving for improvement. There is no data monitoring committee, and auditing has not been planned for this study.

Harm
This is a non-intervention observational study with low invasiveness. We expect no serious harm to occur. However, the questionnaire contents may cause mental strain to the participants. Consent may be withdrawn even while filling the questionnaire, and the study is explained in detail to the participants prior to enrolment.

Statistical analysis
The primary outcome is the JBQ-II score at baseline. The secondary outcomes are the relationships between the total JBQ-II score and the time to PPG achievement, JBQ-II scores at baseline and at the second visit, changes in JBQ-II scores, and PPG achievement rate through Day 7. In addition, the proportion of adverse events will be calculated using the PRO-CTCAE and
investigating the relationship between psychological barriers and improvement in pain. It is important to use PROs, as pain improvement contributes to health-related quality of life.35–39 Psychological barriers may be influenced by opioid switching and analgesic use before the commencement of regular strong opioid analgesics.18 36 40 These data are also being collected using the EDC system.

The BAROC is the first multicentre study in Japan to evaluate the relationship between psychological barriers and cancer pain. The study sites include university hospitals, specialised cancer hospitals, and community hospitals, and it is expected that the enrolled patients will have diverse demographics. One of the characteristics of this study is that eligibility is not limited by performance status. This means that patients with a poor performance status may be eligible to participate in this study. Patients on strong opioid analgesics often have a poor performance status, and our data will reflect actual clinical practice.

Although the use of strong opioid analgesics can be beneficial in treating cancer pain, it can also cause adverse events. Nausea and drowsiness commonly occur during opioid induction. There is concern that these symptoms may lead to decreased adherence and, therefore, interruption of pain treatment. In addition, the occurrence of adverse events can cause anxiety, worry, and other psychological burdens, amplifying resistance to opioid analgesic use. In this study, data on adverse event occurrence is being collected not only from physicians but also from the patients themselves using the PRO-CTCAE. Because adverse events and psychological barriers are closely related, precision in adverse event assessment is required. Thus, it is important to use the PRO-CTCAE in addition to the CTCAE to consider the relationship between psychological barriers and adverse events and enable high-quality adverse event assessment.

Von Roenn et al used case scenarios to survey 897 physicians from the Eastern Cooperative Oncology Group about the prevalence of pain in patients with cancer and physicians’ perceptions of managing pain. Although the case scenarios described patients with moderate to severe pain, 51% of physicians reported that they would prescribe ‘weak’ opioids.41 However, for patients with cancer with moderate pain, low doses of morphine can result in a significantly greater reduction in pain intensity than weaker opioids with similarly good tolerability and early effects.42 Therefore, it is important to remove barriers to introducing strong opioids at an early stage and achieve rapid pain relief.

This study protocol has several limitations. First, this is an exploratory hypothesis-generating observational study. The number of participants was not determined using statistical methods and was based on the caseload of the participating institutions. Second, because this is an observational study, we are neither specifying the explanation to be provided to the patients before initiation of strong opioid analgesic use nor are we specifying the setting in which this explanation is to be provided; each
facility is following its protocol in this regard. Psychological barriers may fluctuate depending on the method of explanation and the environment at that time. There are situations in which treatment must be started despite significant barriers, as not using opioid analgesics even when the pain becomes severe can significantly reduce quality of life. This study was conducted in a population that has already started treatment. Therefore, the results from this study cannot be applied to populations in whom strong opioid analgesics have not yet been considered. Third, we exclude patients with cognitive impairment or mental illness and those who cannot operate a smartphone or tablet from this study. Therefore, we will not be able to enrol all patients receiving strong opioid analgesics. Most of the excluded participants are likely to be older adults. Finally, due to the COVID-19 pandemic, it may be difficult to recruit patients due to restrictions on hospital functions and patients’ reluctance to receive care. As a result, enrolment for this study may need to be delayed.

The psychological barriers to the use of opioid analgesics for treating pain in patients with advanced recurrent cancer (BAROC) study may provide important information that may help reduce psychological barriers to cancer pain relief in patients who are reluctant to use strong opioid analgesics. Clarifying the relationship between the achievement of pain relief goals and psychological barriers at the time of introduction of strong opioid analgesics will provide basic data for future interventional studies, encourage education of healthcare providers for reducing psychological barriers in advance to enable rapid pain amelioration and contribute to improving the quality of cancer pain treatment.

**Contributors** TTs contributed to the study conception and is the principal investigator. TTs, TF, TK, AKa and HHak participated in the design of the study. TF, TK and TY played a primary role in designing the data management approach. TK and TY played a primary role in designing statistical analysis. Data analysis and interpretation will be conducted by TTs, TF, TK and TY. TTs, RK, KM, AKs, TS, HM, TH, TM, HK, KK, TTs, HHat and YO have carried out recruitment and collected the data. All authors have read and approved the final manuscript and meet the criteria for authorship as established by the International Committee of Medical Journal Editors.

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