The Relief of Nociceptive Pain Induced by Panitumumab Could be Sustainable during Chemotherapy

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Abstract: Anti-epidermal growth factor receptor (EGFR) antibodies and tyrosine kinase inhibitors, which are molecular-targeted drugs used in cancer treatment, are suspected to have analgesic effects on cancer-related pain. The relieving effect of EGFR inhibitors on neuropathic pain has been described to persist for approximately 20 days in patients with colorectal cancer. Since the administration of panitumumab, ananti-EGFR antibody, is repeated every 14 days, its relieving effect on cancer-related pain should be maintained until the next administration. To test this hypothesis, we investigated the chronological changes in symptoms before and two and 14 days after administration. A retrospective study using electrical patient charts demonstrated that the analgesic effects of panitumumab sustained in 8 out of ten patients with colorectal cancer (80%) until the start of next cycle of chemotherapy. The relief of nociceptive pain can be maintained in most of the patients during chemotherapy by repeated use of this agent, once pain relief has been achieved.

Keywords: Panitumumab, cancer-related pain, pain relief, nociceptive pain, visceral pain, somatic pain, neuropathic pain, colorectal cancer.

INTRODUCTION

Panitumumab (Pmab), a molecular targeting drug directed against epidermal growth factor receptor (EGFR), is administered every two weeks in combination with cytotoxic chemotherapeutic agents for the treatment of KRAS wild-type (WTKRAS) colorectal cancer [1]. The addition of Pmab to conventional chemotherapy significantly improved progression free survival in patients with WT KRAS tumors. Recently, EGFR has received attention for it's the rapeutic potential against pain [2, 3]. There have been several reports that EGFR inhibition provides rapid relief of cancer-related neuropathic pain [4-6]. A significant reduction in the intensity of cancer-related pain has been observed irrespective of the antitumor effects in cancer patients treated with EGFR inhibitors [7, 8]. In contrast, oxaliplat in-induced peripheral neuropathy was not alleviated by the administration of this agent [9]. Pain begins with the detection of noxious stimuli by nociceptors [10]. Preclinical studies have implicated that EGFR signaling pathways, such as MAPK andPI3K/AKT, are associated with neuropathic pain [2, 11, 12]. Some reports have suggested that EGFR antagonism can restore the effectiveness of morphine against pain [13] and block the development of morphine tolerance [13, 14].

Neuropathic pain was reduced by Pmab administration in patients with colon cancer [15], and the analgesic effects of EGFR inhibition continued for 17-21 days after administration [5]. On the other hand, there are few clinical reports regarding the relief of nociceptive pain induced by EGFR inhibition [4], partly because more therapeutic options for nociceptive pain were available including NSAIDs and opioids, compared to neuropathic pain. We previously reported that nociceptive pain [visceral pain (VP) and somatic pain (SP)] is rapidly relieved after Pmab administration in patients with colorectal cancer [8, 9]. In the present study, we further examined whether the relief of nociceptive pain would continue until the next Pmab

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administration, because Pmab-containing chemotherapy is usually repeated every 14days.

METHODS

We recruited 79 patients with colorectal cancer who received Pmab plus FOLFOX, FOLFIRI, or levofolinate followed by 5-FUinfusion for 48h between 2012 and 2022 in Nagoya Memorial Hospital. A retrospective survey was conducted using electronic patient charts to determine the chronological changes in symptoms on days 0 (just before Pmab administration), 2 (two days after Pmab administration), and 14(14 days after Pmab administration).In cases where applicable descriptions in the medical charts were available for multiple cycles of chemotherapy for the same patient, the first description was adopted.

When cancer-related pain [VP, SP, or neuropathic pain (NP)] was rapidly relieved by Pmab administration on day 2, we tracked the description of this symptom [16] until Day 14. In our hospital, outpatients receiving continuous administration of 5-FU visit the hospital on day 2 to remove the needle, and they usually receive the subsequent cycle of Pmab-containing chemotherapyon day 14. This study was approved by the Ethics Committee of the Nagoya Memorial Hospital (#2024-005).

RESULTS

Prior to chemotherapy, 22 individuals experienced cancer-related pain among the 79 colorectal cancer patients recruited on Pmab-containing regimens. Patients with prescribed analgesic dose changes within 3 days of starting chemotherapy or without a pain status report from physicianson Day 14 were excluded from the present analysis. As a result, ten patients finally met the criteria nine patients complained of nociceptive pain, and one had NP before chemotherapy. On Day 2, cancer-related pain was relieved in all patients (VP 6, SP 3, and NP 1). By Day 14, pain relief persisted in 5 out of 6 VP patients (83%), all 3 SP patients (100%), and none of the NP patients (Figure **1**). Patient characteristics are listed in Table 1.Before the initiation of Pmab-containing chemotherapy, four patients required analgesics for pain relief, and on day 14,two patients discontinue danalgesic use and the other two continued taking them even after Pmab administration. Cancer-related

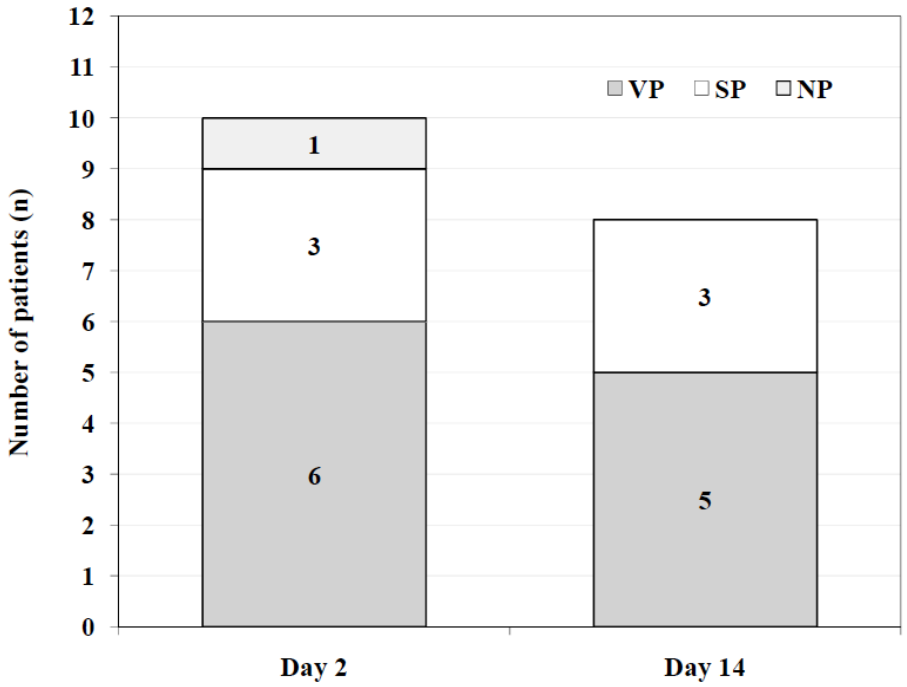

Figure 1: Pain relief induced by panitumumab on Day 2 and 14.

On Day 2 cancer-related pain was relieved in ten patients [nociceptive pain in 9 (VP 6, SP 3) and NP 1]. On Day 14 relief of cancer pain persisted for VP 5 and SP 3.

VP: visceral pain,SP: somatic pain, NP: neuropathic pain.

Day 2: two days after the administration of panitumumab.

Day 14: 14 days after the administration of panitumumab.

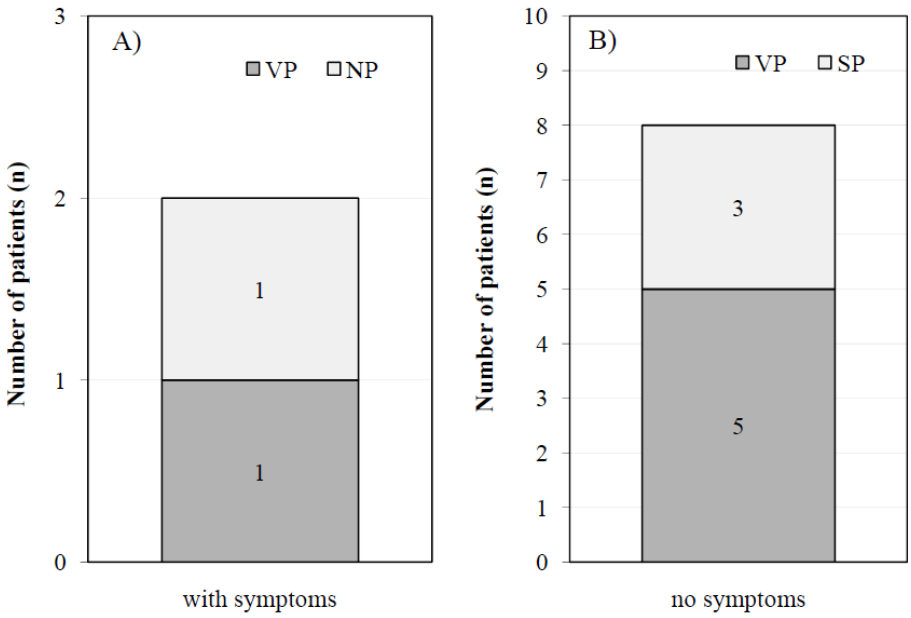

Figure 2: Presence or absence of cancer-related pain on day 14 after panitumumab administration.

A. Cancer-related pain flared up in two patientswith colorectal cancer during the period of chemotherapy withdrawal (VP 1 and NP 1).

B. Pain relief was sustained in eight patients by the next cycle of panitumumab-containing regimen (VP 5 and SP 3).

VP: visceral pain, SP: somatic pain, NP: neuropathic pain.

pain flared up in two patients during the withdrawal period of chemotherapy (VP 1 and NP 1), whereas pain relief was sustained in eight patients by the next cycle of the panitumumab-containing regimen (VP 5 and SP 3) (Figure **2**). The number of patients who were prescribed acetaminophen decreased from three to one by the administration of Pmab. Among the three patients administered celecoxib on day 0, two continued taking this drugon day 14. One patient was administered tramadol on day 4 after Pmab administration. Oxycodone, a strong opioid, was eventually added to celecoxib for pain relief for two patients before the next cycle of chemo therapy (Table **1**).

DISCUSSION

The use of Pmab improved cancer-related pain on day 2 in10 patients and sustained pain relief was achieved until the next scheduled cycle in eight patients. These eight patients complained of nociceptive pain before chemotherapy. In other 2 patients (VP 1 and NP 1), pain relief was attained with Pmab administration for only a few days. Since the analgesic effects of anti-EGFR antibodies have been reported to be independent of antitumor effects [7, 8], the association between the duration of pain relief and tumor progression was not investigated in the present study. Therefore, we cannot define the precise reason why the pain flared up within a few days in these two patients, even though pain relief was rapidly achieved by Pmab administration.

Martin LJ, *et al*. clearly demonstrated that EGFR inhibition produced robust analgesic effects in the mouse model of inflammatory pain and chronic constriction injury as well as in the model of neuropathic pain [2]. They also found that injection of epiregulin (EREG), the natural lig and for EGFR, increased nociception in a dose-dependent manner. Preclinical studies revealed that EREG contributed to the establishment of chronic pain and gene polymorphism of EREG was associated with the pain severity, which may serve as a response biomarker for EREG-EGFR-based pharmacotherapy of chronic pain [3]. While the signaling mechanism of EREG on pain have yet to be discovered, the application of EREG onto the spinal dorsal nerve roots of rats increased spontaneous activity of neurons. It is also described that EREG is associated with activation of the immune system and inflammation and this molecule may contribute to pain through a systemic process [17]. Accordingly, the targeting either EGFR or EREGh as analgesic properties for both neuropathic and nociceptive pain. Although the relieving effect of Pmab on neuropathic pain has been observed in clinical

Table 1: Characteristics of Patients with Pain Examined in this Study

Characteristics	(n=10)	
Age (year)	68.2 ± 6.0	
Pmab (mg)	317.3 ± 83.1	
Height (cm)	162.0 ± 7.4	
Weight (kg)	55.0 ± 10.9	
BMI (kg/m²)	20.8 ± 2.8	
WBC (×10²/μL)	65.7 ± 27.6	
Hb (g/dL)	11.0 ± 1.5	
Plt (×10^4/μL)	25.2 ± 14.1	
AST (U/L)	41.2 ± 31.6	
ALT (U/L)	29.4 ± 23.6	
BUN (mg/dL)	16.8 ± 7.6	
Cr (mg/dL)	0.8 ± 0.3	
eGFR (mL/min/1.73m²)	73.6 ± 23.9	
ALB (g/dL)	3.2 ± 0.6	
Ratio of patients receiving analgesics (+/-):	6/4	
Pain characteristics (VP/SP/NP):	6/3/1	
Gender (M/F):	6/4	
Metastasis (+/-):	9/1	
Regimen: FOLFOX/FOLFIRI/LV-Fu	3/7/0	
Analgesic	**Before (n)**	**After 14 days (n)**
Acetaminophen	3	1
Celecoxib	3	2
Oxycodone	0	2
Tramadol	0	1

VP: Visceral pain; SP: Somatic pain; NP: Neuropathic pain.

settings [5-7, 15], the clinical efficacy of this agent on nociceptive pain remains unknown. The present study supports our previous findings that Pmab exerts analgesic effects on nociceptive pain in patients with cancer [8].

In our study, nociceptive pain was rapidly relieved by Pmab administration, similar to neuropathic pain, and the duration of pain relief was similar for neuropathic and nociceptive pain [15]. Considering the hypothesis that the analgesic mechanism of Pmab is associated with a direct effect on receptors that are important for pain processing [2], it might be reasonable that a similarity was observed in the rapid relief and duration of pain improvement between the two types of pain.

This study has several limitations. First, the present findings were obtained from a single institute and the sample size was very small. Second, in the present study, the presence of pain was evaluated through interviews and description of three attending physicians (RF, ST, and KI) without quantitatively measuring the pain intensity. Without any description by physicians on the medical charts, cancer-related pain can be overlooked. Accordingly, the credibility of the results was dependent on the individual physicians. Third, this was a retrospective observational study and not a randomized placebo-controlled trial. The placebo effect cannot be ruled out for the rapid relief of cancer-related pain and duration of pain improvement because there is no comparable drug. Fourth, confounding factors such as the state of metastatic lesions and history of treatment cannot be neglected when interpreting the obtained data. Finally, we did not have basic data on the molecular mechanism underlying the Pmab-induced analgesic effects against nociceptive pain.

In conclusion, we suspect that the relief of nociceptive pain in patients with WTKRA Scolorectal cancer could be sustainable during chemotherapy with a Pmab-containing regimen at conventional intervals. The dual activities of EGFR inhibition on nociceptive and neuropathic pain would be confirmed with more

clinical data showing the beneficial effects of Pmab on nociceptive pain. Once targeting either EGFR or EREG has been established to reduce the severity of both type of pain in clinical settings, selective inhibition of EREG should be a promising strategy. Because EGFR inhibitors are associated with adverse side effects including skin rash, perionychia, and folliculitis, directly targeting EREG may constitute an improved therapeutic option for the management of cancer-related pain.

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COMPETING INTERESTS

The authors declare that they have no competing interests.

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Not applicable.

AUTHOR CONTRIBUTIONS

SY and KI drafted the manuscript. RF, YS, ST, and KI provided medical care. SY, SH, SN, and SK reviewed patients' medical records. SY and MK performed computational analyses. All the authors have read and approved the final manuscript.

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