Retrospective Evaluation of the Analgesic Effects of Molecular Target Agents Against Cancer Pain and Oxaliplatin-Induced Chronic Peripheral Neuropathy

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Abstract: Epidermal growth factor receptor (EGFR) has received significant attention for its therapeutic potential for pain relief. The relief of neuropathic pain after treatment with anti-EGFR antibodies or tyrosine kinase inhibitors has been previously described. However, few reports have investigated the association of cancer-related nociceptive pain or chronic chemical induced peripheral neuropathy with the analgesic effects of EGFR inhibition.

Therefore, we conducted a retrospective survey of 191 patients with colorectal cancer receiving chemotherapy plus molecular targeting drugs to examine the analgesic effects of anti-EGFR antibodies against either cancer pain or oxaliplatin-induced peripheral neuropathy. We identified a significant difference in the improvement rates of nociceptive pain between panitumumab- and bevacizumab-treated patients (100% vs. 9.1%; $p < 0.01$), but not oxaliplatin-induced peripheral neuropathy.

In conclusion, panitumumab may be effective at reducing cancer-related nociceptive pain.

Keywords: EGFR, Panitumumab, cancer pain, nociceptive pain, chronic chemical induced peripheral neuropathy.

INTRODUCTION

Pain begins with the detection of noxious stimuli by the nociceptors [1]. Recently, epidermal growth factor receptor (EGFR) has received attention for its therapeutic potential against pain [2]. There have been several reports that EGFR inhibition provides rapid relief of cancer pain [3, 4, 5]. Cancer patients administered EGFR inhibitors have reported a significant reduction in pain scores independent of anti-tumor effects [6, 7]. Preclinical studies have implicated that EGFR signaling pathways, such as MAPK and PI3K/AKT, are associated with neuropathic pain [2, 8, 9].

Panitumumab (Pmab), a molecular targeting drug directed against EGFR, is used in combination with cytotoxic chemotherapeutic agents for the treatment of KRAS wild-type colorectal cancer [10]. We previously encountered a case of colon cancer in which somatic pain was alleviated immediately after Pmab administration, despite tumor progression [7]. Among the anti-cancer agents used for the treatment of colorectal cancer, oxaliplatin is well known to cause chronic peripheral neuropathy as a side effect [11]; however, it remains unclear whether EGFR inhibition can affect the intensity of peripheral neuropathy induced by oxaliplatin.

Therefore, we conducted a retrospective survey of colorectal cancer patients receiving chemotherapy in combination with either Pmab or bevacizumab (Bmab) at Nagoya Memorial Hospital to examine the analgesic effects of molecular target drugs against cancer pain, as well as oxaliplatin-induced peripheral neuropathy.

METHODS

We recruited 191 patients with colorectal cancer who received either Pmab or Bmab plus FOLFOX, FOLFIRI, or levofolinate followed by 5-FU for 48 h between 2012 and 2020. We then selected patients who complained of cancer pain or oxaliplatin-induced peripheral neuropathy prior to the start of pharmacotherapy.

The change in symptoms was determined by the description in chart records before and 2 days after administration of either Pmab or Bmab, as our

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outpatients receiving continuous administration of 5-FU visited the hospital 2 days after administration to remove the needle. At this time, the quality and intensity of pain were assessed by attending physicians [12].

The statistical analysis software eZR ver 1.36 [13] was used for comparison between groups. Analysis of continuous variables was performed between three or more groups using one-way analysis of variance followed by Bonferroni's multiple comparison test and between two groups using Student's t-test. For the analysis of nominal variables, Bonferroni's multiple comparison test was performed following Fisher's accuracy test analysis for more than three groups. Statistical significance was set at $P < 0.05$.

This study was approved by the Ethics Committee of Nagoya Memorial Hospital (#2021-013).

RESULTS

Prior to the initiation of chemotherapy plus molecular target drugs, cancer pain was evident in 17 of the 68 patients administered Pmab-containing regimens (25.0%), and 21 of the 123 patients administered Bmab-containing regimens (16.8%) (Figure **1**). Oxaliplatin-induced peripheral neuropathy was present in 18 (26.5%) patients taking Pmab and in 70 (58.0%) patients taking Bmab. The incidence of oxaliplatin-induced peripheral neuropathy significantly increased in patients receiving Bmab-containing regimens. Patients whose prescribed doses of analgesics were modified within 3 days of the start of chemotherapy and those whose intensity of pain was not described in medical charts before and after treatment with the target drugs were excluded from the subsequent comparison.

After excluding patients who did not meet the criteria, cancer-related nociceptive pain was observed in 10 patients taking Pmab (6, visceral pain; 4, somatic pain) and 11 taking Bmab (6, visceral pain; 5, somatic pain), whereas cancer-related neuropathic pain was reported in 3 and 4 patients taking Pmab and Bmab, respectively. The characteristics of patients included in the comparative analysis are shown in Table **1**. Rapid relief of either visceral or somatic pain was demonstrated in all of 10 patients complaining of nociceptive pain before the start of Pmab-containing regimens. In contrast, there was only one case of improvement in nociceptive pain (visceral pain) among the 11 patients receiving Bmab-containing regimens (Figure **2**). There was a significant difference in the rates of improvement between Pmab- and Bmab-treated patients (100% versus 9.1%; $p < 0.01$). Conversly, oxaliplatin-induced peripheral neuropathy was alleviated in one of 13 patients taking Pmab (8.3%) and in 3 of 53 patients taking Bmab (5.7%), respectively. There were no significant differences in the improvement rates of oxaliplatin-induced peripheral neuropathy between the two groups. The improvement rate was significantly higher among the patients complaining of nociceptive pain before Pmab

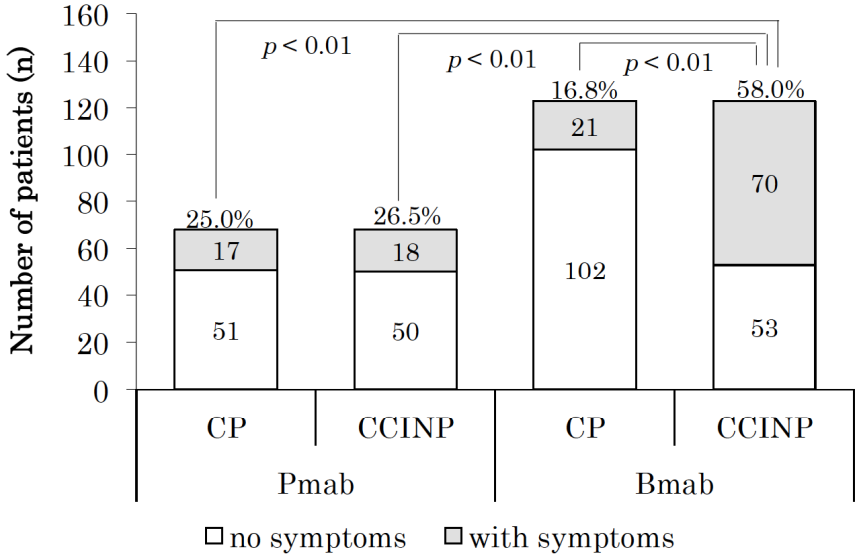

Figure 1: Frequency of CP and CCINP in the patients receiving Pmab and Bmab.

Statistical difference was determined using Bonferroni's multiple comparison test following Fisher's exact test.

Pmab: panitumumab, Bmab: bevacizumab, CP: cancer pain, CCINP: chronic chemical induced peripheral neuropathy.

Table 1: Characteristics of Analyzed Patients Complaining of Nociceptive Pain or Oxaliplatin-Induced Peripheral Neuropathy

Characteristics	Pmab		Bmab	
	NCP(n=10)	CCINP(n=13)	NCP(n=11)	CCINP(n=53)
Age (year)	69.2 ± 5.7	64.2 ± 8.7	68.6 ± 9.8	68.2 ± 9.8
Pmab (mg)	305.7 ± 83.7	327.2 ± 84.3		
Bmab (mg)			275.9 ± 68.8	272.9 ± 42.0
Height (cm)	159.5 ± 8.3	160.9 ± 10.6	160 ± 7.4	159.2 ± 7.6
Weight (kg)	51.0 ± 15.1	56.8 ± 11.7	56.1 ± 13.8	55.6 ± 8.9
BMI (kg/m^2)	19.7 ± 4.4	21.8 ± 2.9	21.7 ± 4.3	21.9 ± 2.9
WBC ($x10^2/\mu L$)	61.1 ± 22.2	45.8 ± 8.3[a]	70.4 ± 40.8	48.1 ± 17.3[b]
Hb (g/dL)	10.9 ± 1.4	12.4 ± 1.6	11.8 ± 2.0	11.7 ± 1.4
Plt ($x10^4/\mu L$)	23.6 ± 13.2	20.7 ± 8.0	20.4 ± 5.8	19.4 ± 5.8
AST (U/L)	39.5 ± 32.3	28.8 ± 5.7	37.5 ± 27.7	26.9 ± 11.8
ALT (U/L)	28.8 ± 24.0	24.0 ± 9.0	19.4 ± 7.4	20.7 ± 10.1
BUN (mg/dL)	17.2 ± 7.1	12.8 ± 3.1	13.4 ± 4.2	13.8 ± 3.3
Cr (mg/dL)	0.8 ± 0.3	0.7 ± 0.2	0.7 ± 0.2	0.8 ± 0.2
eGFR ($mL/min/1.73m^2$)	62.9 ± 24.2	67.8 ± 17.4	65.1 ± 19.7	61.9 ± 18.3
ALB (g /dL)	3.3 ± 0.6	3.5 ± 0.6	3.5 ± 0.6	3.6 ± 0.4
Acetaminophen (n)	3	1	4	1
Celecoxib (n)	3		6	7
Loxoprofen (n)			2	
Oxycodone (n)	1	1	4	1
Morphine (n)			1	1
Tramadol (n)	1		1	
Methadone (n)			1	1
Pregabalin (n)		1	2	3
Gosya-zinkigan (n)				4
Ratio of patients receiving analgesics	5/10	2/13[c]	9/11	14/53[d]
Gender (M/F)	5/5	9/4	9/2	31/21
Metastasis (+/-)	9/1	11/2	11/0	51/2
Regimen	2/8/0	6/4/3	2/8/1	27/21/5
FOLFOX/FOLFIRI/LV-FU				

[a]Pmab/CCINP vs. Bmab/NCP; $p = 0.036$.
[b]Bmab/NCP vs. Bmab/CCINP; $p = 0.013$.
Statistical difference was determined by Student's t-test or Bonferroni's multiple comparison test following one-way ANOVA.
[c]Pmab/CCINP vs. Bmab/NCP; $p = 0.0184$.
[d]Bmab/NCP vs. Bmab/CCINP; $p = 0.0058$.
Statistical difference was determined by Bonferroni's multiple comparison test following Fisher's exact test.
Pmab: panitumumab, Bmab: bevacizumab, NCP: nociceptive pain, CCINP: chronic chemical induced peripheral neuropathy.

administration, compared to the other three groups ($p < 0.01$): those complaining of oxaliplatin-induced peripheral neuropathy before Pmab administration, those complaining of nociceptive pain before Bmab administration, and those complaining of oxaliplatin-induced peripheral neuropathy before Bmab administration (Figure **2**).

Among the 68 patients on Pmab, improvements in cancer-related neuropathic pain was observed in one

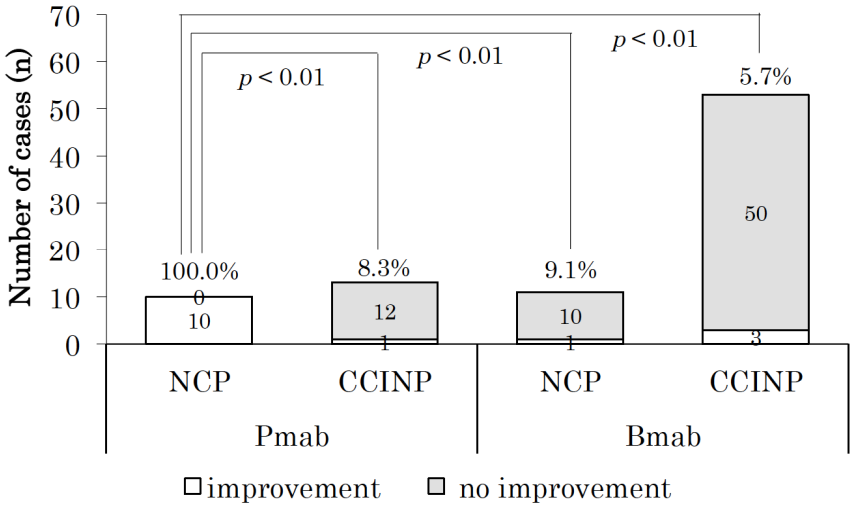

Figure 2: Comparison of improvement rate in NCP and CCINP before and after the administration of either Pmab or Bmab. Statistical difference was determined by Bonferroni's multiple comparison test following Fisher's exact test. Pmab: panitumumab, Bmab: bevacizumab, NCP: nociceptive pain, CCINP: chronic chemical induced peripheral neuropathy.

out of three patients. On the other hand, among the 123 patients on Bmab, improvements were not entirely observed in 4 patients complaining of neuropathic pain. However, it was not possible to compare the rate of improvement in neuropathic pain between the Pmab- and Bmab-treated patients, owing to the small number of cases.

DISCUSSION

The present results indicated that Pmab administration rapidly alleviated the severity of nociceptive pain in patients with colorectal cancer, whereas Bmab-containing regimens did not provide such analgesic activity. Although an analgesic effect of EGFR inhibition on neuropathic pain has been previously suggested [4, 5, 6], improvements in neuropathic pain following treatment with Pmab were not evident in this retrospective study because of the small sample size. The intensity of oxaliplatin-induced peripheral neuropathy decreased in less than 10% of the patients receiving either Pmab or Bmab. Accordingly, the reduction in nociceptive pain observed in this study was suspected to be exclusively dependent on the use of Pmab.

This study has several limitations. First, the sample size was small. Second, all the present findings were obtained from a single institute. Pain improvement rates were compared between patients with colorectal cancer receiving Pmab- and Bmab-containing regimens. It is reasonable to assume that the incidence of cancer-related pain or oxaliplatin-induced peripheral neuropathy should be affected by disease conditions. Although confounding factors, including the states of metastatic lesions, the usage of opioids, and previous chemotherapy, cannot be neglected when interpreting our findings, we did not analyze these factors. Third, this study had a retrospective observational design. Although the rapid relief of pain induced by Pmab suggests that the analgesic mechanism is associated with a direct effect on receptors important for pain processing, we have no basic data on the molecular mechanism of Pmab-induced analgesic responses against nociceptive pain. However, several preclinical studies have demonstrated that EGFR is abundantly found in sensory neurons of the dorsal root ganglion [14], and that EGFR antagonists induce analgesia. Our speculation might be supported by recent findings that epiregulin, an endogenous ligand for EFGR, is the primary activator of pain hypersensitivity [2, 15]. Lastly, the possibility of a placebo effect must be considered, as this study was not a randomized, placebo-controlled trial. However, relief of nociceptive pain was observed in all patients receiving Pmab-containing regimens (100%), which was in sharp contrast to the improvement rate (9.1%) among the patients receiving Bmab-containing regimens. It is unlikely that such a large difference in analgesic activity could be caused by the placebo effect.

In conclusion, the present study demonstrated that Pmab, an EGFR antibody, may trigger rapid relief of cancer-related nociceptive pain, but did not alleviate oxaliplatin-induced peripheral neuropathy.

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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 wrote the manuscript. SY, MK, SH, and YK reviewed the patients' medical records. SY and MK performed the computational analyses. All authors have read and approved the final manuscript.

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