

# A Case of Sigmoid Colon Cancer in which Somatic Pain was Rapidly Alleviated after Panitumumab Administration Despite Tumor Progression

Shu Yuasa<sup>1,3</sup>, Megumi Kabeya<sup>1,3</sup>, Ryuichi Furuta<sup>2</sup>, Satoshi Hibi<sup>1</sup>, Chiaki Koga<sup>3</sup>, Seiji Nagao<sup>3</sup> and Kenji Ina<sup>2,3,\*</sup>

<sup>1</sup>Department of Pharmacy; <sup>2</sup>Department of Medical Oncology; <sup>3</sup>Palliative care team, Nagoya Memorial Hospital, Nagoya, Japan

**Abstract:** We present a 72-year-old woman with sigmoid colon cancer in whom the somatic pain was alleviated rapidly after the administration of anti-epidermal growth factor antibodies. Our patient had received 4 cycles of FOLFIRI therapy (irinotecan, 5-fluorouracil, and leucovorin) in combination with panitumumab (Pmab) for the treatment of unresectable primary cancer accompanied with multiple liver metastases and peritonitis carcinomatosa. As grade 3 paronychia eventually occurred, chemotherapy was stopped. After recovery of the grade 3 paronychia, Pmab was re-introduced and administered every alternate cycle to reduce the extent of adverse events. The patient had complained of somatic pain in the lower right abdomen just before re-initiating Pmab administration. The pain intensity decreased immediately after the administration of Pmab. On the next day her pain had remarkably alleviated and she was free from pain for a week. This phenomenon was repeatedly observed. After the re-introduction of Pmab, tumor response was evaluated on computed tomography, which showed progressive disease. We demonstrated that Pmab was effective in the alleviation of somatic pain, although the size of the tumors gradually increased.

**Keywords:** Panitumumab, anti-EGFR antibody, somatic pain, colon cancer.

## INTRODUCTION

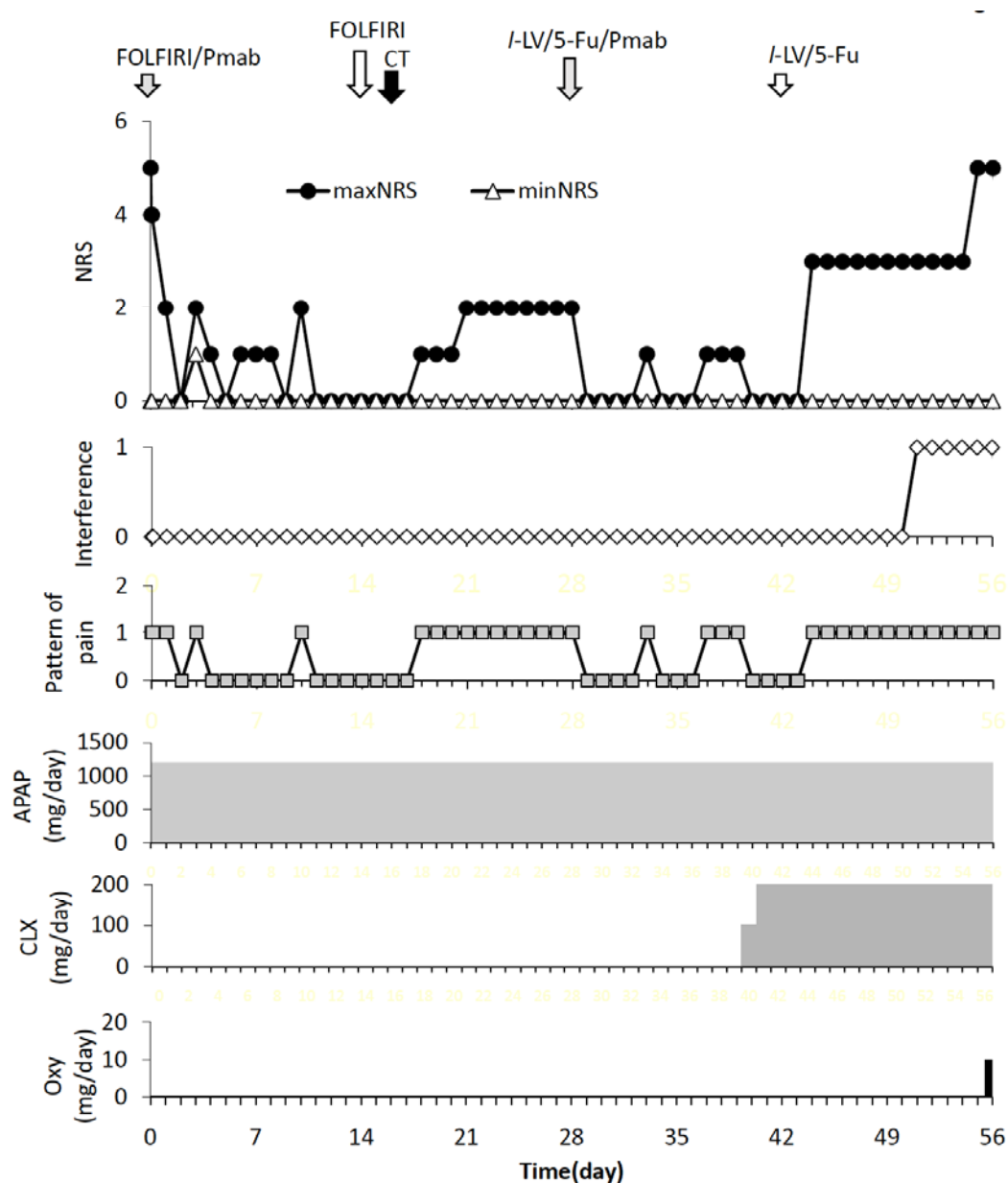
Panitumumab (Pmab), a molecular-targeted agent directed against the epidermal growth factor receptor (EGFR), is commonly used for the treatment of *KRAS* wild-type colorectal cancer [1, 2]. Anti-tumor effects are rapidly observed because of chemotherapy plus anti-EGFR antibodies, which sometimes causes the concomitant reduction in disease-associated pain [3]. The use of cetuximab was reported to be associated with a relief in neuropathic pain in patients with colon cancer [4]. We encountered a patient with colon cancer who received Pmab; alleviation of somatic pain appeared to be induced by the administration of Pmab, although the size of the tumors gradually increased. Therefore, to examine if Pmab has a pain-relief effect, we monitored a patient with sigmoid colon cancer who received Pmab-containing chemotherapy by using a numerical rating scale (NRS) for somatic pain.

## CASE REPORT

The patient was a 72-year-old woman who had wild-type *KRAS* status sigmoid colon cancer with multiple liver metastases and peritonitis carcinomatosa. She received palliative colostomy for a bowel obstruction and was subsequently treated with 14 courses of

FOLFOX (oxaliplatin, 5-fluorouracil, and leucovorin) plus bevacizumab and 18 courses of FOLFIRI (irinotecan, 5-fluorouracil, and leucovorin) plus bevacizumab. However, she eventually complained of lower right abdominal pain and started receiving 400 mg acetaminophen three times a day. Owing to disease progression, Pmab was administered instead of bevacizumab. During the Pmab administration her complaint of pain almost disappeared. After finishing 4 courses of FOLFIRI plus Pmab, grade 3 paronychia occurred and chemotherapy was stopped. Abdominal pain in the lower right quadrant recurred due to treatment interruption, which was mainly considered movement-related somatic pain. After recovery of the paronychia, Pmab was re-introduced and was administered every alternate cycle to reduce the extent of adverse events. After obtaining informed consent from the patient, we consecutively recorded the maximum and minimum NRS, pain pattern, and daily life difficulties caused by pain during the periods of Pmab administration (Figure 1). Her NRS scores were recorded on the day before and immediately, at 1 hour, and 2 hours after each administration of Pmab, and then once a day for the subsequent 4 weeks. Study procedures were approved by the in-hospital ethics committee and conducted according to the principles of the Declaration of Helsinki and Good Clinical Practice Guidelines. During the periods of monitoring, 2 courses of FOLFIRI and then 2 courses of 5-fluorouracil and leucovorin without irinotecan were administered every alternate week, whereas Pmab was infused twice every

\*Address correspondence to this author at the Department of Medical Oncology, Nagoya Memorial Hospital, 4-305 Hirabari, Tenpaku-ku, Nagoya 468-8520, Japan; Tel: +81-52-804-1111; Fax: +81-52-803-8830; E-mail: kina@hospy.or.jp

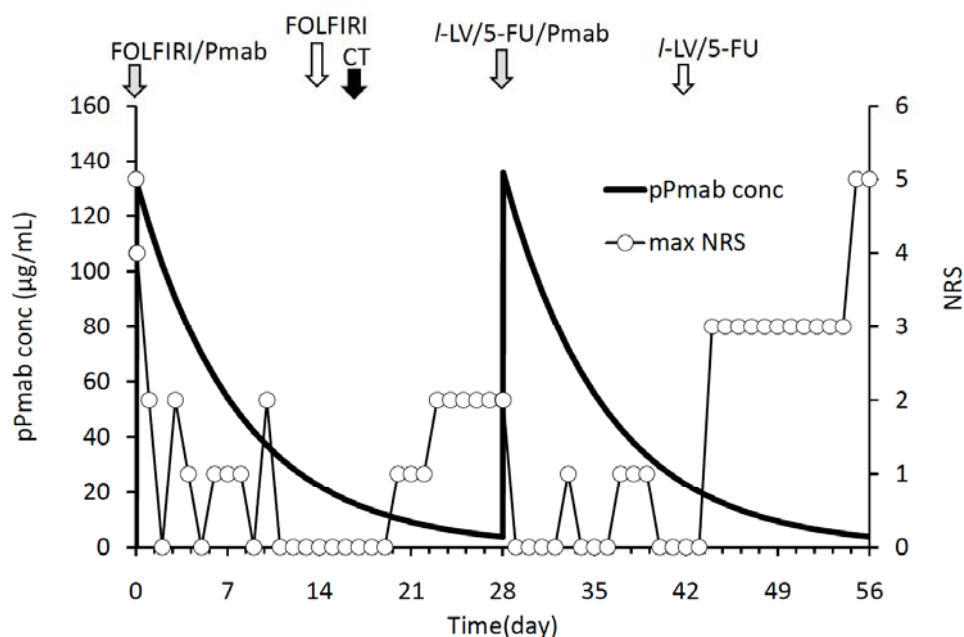


**Figure 1:** Changes in the maximum numerical rating scale (NRS) score, minimum NRS score, pain pattern, and daily activities interference caused by pain along with the administration of chemotherapeutic agents and analgesics.

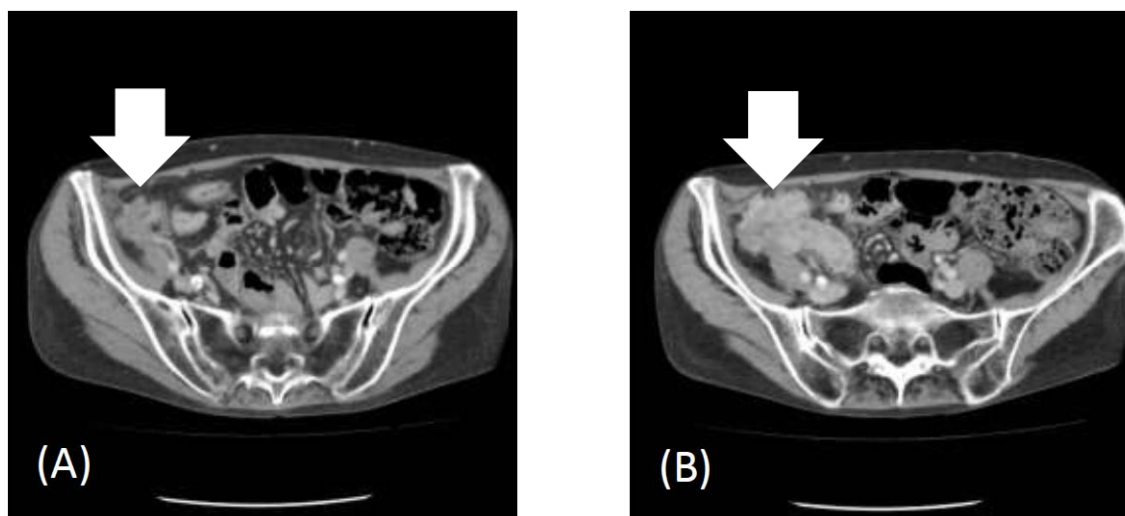
I-LV: leucovorin, interference: daily activities interference caused by pain, (0: no, 1: yes); pain pattern: 0, no pain, 1: intermittent pain, and 2: continuous pain; APAP: N-Acetyl-p-aminophenol (acetaminophen); CLX: celecoxib; Oxy: oxycodone.

4 weeks. The maximum NRS score was 5 on the day before re-initiating Pmab, it decreased immediately after the first Pmab administration, and it further decreased gradually up to day 17. Her pain completely disappeared on day 11 and complete pain relief was achieved for a week. Symptoms of abdominal pain recurred on day 18, 4 days after the second course of FOLFIRI therapy without Pmab. The second Pmab administration was done on day 29, but irinotecan infusion was skipped at the patient's request. Similar pain alleviation was observed again after the second administration of Pmab combined with 5-fluorouracil

and leucovorin. No interference in daily activities caused by pain was observed until day 56 since the start of NRS monitoring. The site and nature of her pain did not change. At the same time, the predictive serum concentration of Pmab calculated based on the data of Doi *et al.* [5] is shown in Figure 2. The profiles of pain relief correlated well with the pharmacokinetics of the estimated Pmab concentration. According to the RECIST criteria, the tumor response was evaluated by using computed tomography (CT), which showed progressive disease after Pmab infusion (Figure 3).



**Figure 2:** Profiles of the maximum numeric rating scale (NRS) score and predictive plasma concentrations of panitumumab (Pmab) (pPmab conc).



**Figure 3:** Computed tomography scans of the intra-abdominal tumor (A) before the administration of panitumumab-containing chemotherapy, and (B) after pain monitoring. The arrows indicate the tumor.

## DISCUSSION

Ward pharmacists noticed that her complaints of abdominal pain clearly decreased immediately after starting Pmab infusion. This observation made us think of monitoring her pain during Pmab administration as part of a clinical study. After designing the study, Pmab had to be infused every alternate cycle to reduce skin-related adverse events. Therefore, an interval of 4 weeks between each infusion convinced us of the dramatic analgesic response, because 4 weeks were enough to evaluate NRS profiles as well as to estimate

the Pmab concentrations; the pain-relief effect continued for more than 14 days, after which her pain recurred. If FOLFIRI plus Pmab therapy would have been regularly repeated at 2 week-intervals, her pain might have been masked throughout the course of treatment.

We first aimed to determine the serum concentrations of Pmab to examine the mechanism of pain-relief, but there was no available method. Therefore, we decided to calculate the predictive serum concentrations of Pmab [5]. The profiles of pain

intensity were in parallel to the estimated concentrations. This analgesic action of Pmab was evident, although the intra-abdominal tumor was enlarged as observed on CT scan. Accordingly, the pain-relief action of Pmab was presumed to be dependent on the serum concentrations, but it not mediated through the anti-tumor effect.

We wanted to determine how Pmab infusion could rapidly alleviate somatic pain. Neuropathic pain is well controlled by EGFR inhibition [3, 4]. Mitogen-activated protein (MAP) kinase and Erk1/2 phosphorylation are believed to be important drivers of neuropathic pain [4, 6]. Nerve growth factor and glial cell line-derived neurotrophic factor (GDNF) can activate the signaling of MAP kinase [6]. The secretion of GDNF has been reported to contribute to inflammatory hyperalgesia in animal model [7]. After nerve injury, neurons up-regulated the expression of HER-family receptors, thereby increasing their activation of MAP kinase signaling. Cetuximab could directly inhibit such MAP kinase signals, which is suspected to occur both in neuronal and glial cells [4], leading to the rapid relief of the neuropathic pain triad [8]. Conversely, the pain in this patient was somatic and its intensity further increased with movement, being different from neuropathic pain. Somatic pain is nociceptive and thought to be acute. Recently EGFR-signals were detected in all the sensory neurons in the dorsal root ganglia [9] and EGFR did initiate signaling in nociceptive neurons, but not through Erk1/2 phosphorylation. These findings may suggest that the palliative effect of EGFR inhibition should be mediated by a distinct mechanism from the MAP kinase-involved one [9, 10]. There is another possibility that Pmab might exert its effect through a mechanism different from that of cetuximab. The molecular mechanism of Pmab-induced analgesic response against somatic pain remains to be elucidated.

## COMPETING INTERESTS

The authors declare that they have no competing interests.

## AUTHORS' CONTRIBUTIONS

SY and KI equally contributed to writing the manuscript. SY and MK made a study design and estimated Pmab concentrations. RF, SH, CK, and SN collected the clinical data. All authors read and approved the final manuscript.

## REFERENCES

- [1] Ciardiello F, Tortora G. EGFR antagonist in cancer treatment. *N Eng J Med* 2008; 358: 1160-74. <http://dx.doi.org/10.1056/NEJMra0707704>
- [2] Douillard JY, Siena S, Cassidy J, *et al.* Randomized, phase III trial of panitumumab with infusional fluorouracil, leucovorin, and oxaliplatin (FOLFOX4) versus FOLFOX4 alone as first-line treatment in patients with previously untreated metastatic colorectal cancer. *J Clin Oncol* 2010; 28: 4697-705. <http://dx.doi.org/10.1200/JCO.2009.27.4860>
- [3] Mesía R, Palmero R, Cos M, Vilajosana E, Vázquez S. Rapid palliation of symptoms with platinum-based chemotherapy plus cetuximab in recurrent oral cancer: a case report. *Head Neck Oncol* 2010; 2: 3. <http://dx.doi.org/10.1186/1758-3284-2-3>
- [4] Kersten C, Cameronb MG. Cetuximab alleviates neuropathic pain despite tumour progression. *BMJ Case Rep* 2012; 2012. pii: bcr1220115374. doi: 10.1136/bcr.12.2011.5374
- [5] Doi T, Ohtsu A, Tahara M, *et al.* Safety and pharmacokinetics of panitumumab in Japanese patients with advanced solid tumors. *Int J Clin Oncol* 2009; 14: 307-14. <http://dx.doi.org/10.1007/s10147-008-0855-2>
- [6] Ji RR, Gereau RW 4th, Malcangio M, Strichartz GR. MAP kinase and pain. *Brain Res Rev* 2009; 60: 135-48. <http://dx.doi.org/10.1016/j.brainresrev.2008.12.011>
- [7] Fang M, Wang Y, He QH, *et al.* Glial cell line-derived neurotrophic factor contributes to delayed inflammatory hyperalgesia in adjuvant rat pain model. *Neuroscience* 2003; 117: 503-12. [http://dx.doi.org/10.1016/S0306-4522\(02\)00958-2](http://dx.doi.org/10.1016/S0306-4522(02)00958-2)
- [8] Scolz J, Woolf CJ. The neuropathic pain triad: neurons, immune cells, and glia. *Nature Neurosci* 2007; 10: 1361-8. <http://dx.doi.org/10.1038/nn1992>
- [9] Andres C, Meyer S, Dina OA, Levine JD, Hucho T. Quantitative automated microscopy (QuAM) elucidates growth factor specific signalling in pain sensitization. *Molecular Pain* 2010; 6: 98. <http://dx.doi.org/10.1186/1744-8069-6-98>
- [10] Kersten C, Cameronb MG, Mjålandb S. Epithelial growth factor receptor (EGFR)-inhibition for relief of neuropathic pain—A case series. *Scand J Pain* 2013; 4: 3-7. <http://dx.doi.org/10.1016/j.sjpain.2012.11.011>