Early drop in serum lactate dehydrogenase concentrations as a predictor of tumor response to ongoing anti-epidermal growth factor receptor antibody treatment

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Abstract
Prediction of tumor responses before and during treatment for unresectable advanced and/or metastatic colorectal cancer is important to maximize treatment benefit to individual patients. In the present case series, we introduce the potential of using serum lactate dehydrogenase (LDH) concentrations to predict the tumor responses during treatment with anti-epidermal growth factor receptor antibody. Based on our observations, an early drop in serum LDH concentrations predicts tumor shrinkage, whereas maintenance of LDH concentrations presages a moderate response to treatment or tumor progression.

Keywords: panitumumab, liver metastasis, LDH, positive marker

Introduction
Anti-epidermal growth factor receptor (EGFR) antibody treatment significantly improves the prognosis of unresectable advanced and metastatic colorectal cancer (mCRC)1. Recent advances in our understanding of tumor biology suggest that detection of RAS mutations is indicative of a negative tumor response to treatment1. However, even in the case of ‘RAS wild-type’ tumors, tumor shrinkage by anti-EGFR antibody treatment is not guaranteed2,3. For example, first-line cetuximab monotherapy in patients with wild-type Kirsten rat sarcoma viral oncogene homologue (KRAS) mCRC is associated with only a 10% response rate, with a disease control rate of 44%-4. Thus, most patients experience treatment-related adverse events, such as acneiform eruption, paronychia, and xerosis cutis, without any actual benefits of treatment5.

Herein we report on four patients with hepatic metastatic tumors from colorectal cancer. These patients had elevated serum lactate dehydrogenase (LDH) concentrations in common. In three patients, serum LDH concentrations decreased early after the initiation of anti-EGFR antibody treatment, and significant tumor shrinkage was observed on computed tomography (CT) during treatment. In the fourth patient, serum LDH concentrations remained high, and disease progression was confirmed radiologically 7 weeks after the start of anti-EGFR antibody treatment. Based on these observations, we suggest that changes in LDH concentrations may be useful in predicting tumor responses to ongoing anti-EGFR antibody treatment.

Case presentation
Case one
A 68-year-old male presented with abdominal distension. Enhanced CT revealed obstructive sigmoid colon cancer with hepatic metastasis. The largest two hepatic tumors had maximum diameters of 134.0 and 141.8 mm. After sigmoidectomy to resolve the obstruction, SOX (TS-1 and oxaliplatin) combined with panitumumab was initiated for RAS wild-type metastatic colon cancer (Figure 1). The serum LDH concentration dropped from 1201 U/L (upper normal limit: <229 U/L) to 419 U/L in 2 weeks, and was nearly within the normal range within 4 weeks. Pretreatment serum carcinoembryonic antigen (CEA) concentrations were 174.1 ng/mL (normal range: <3.2 ng/mL), and had decreased to 30.2 ng/mL in 4
weeks. After four cycles of treatment, CT revealed a partial response of the tumor, with the maximum diameters of the two largest tumors shrinking to 98.9 and 84.2 mm, respectively. After a further two cycles of treatment, the patient underwent hepatectomy.

**Case two**
A 72-year-old male presented with melena, and medical examination revealed sigmoid colon cancer with hepatic metastasis. Enhanced CT revealed that the diameter of the largest two tumors in the right hepatic lobe was 108.2 and 51.0 mm. The primary tumor was resected to treat the melena, followed by chemotherapy. Pretreatment serum LDH and CEA concentrations were 609 U/L and 5624 ng/mL, respectively (Figure 2). Two weeks after the first treatment with FOLFOX (bolus/infusion 5FU, leucovorin, and oxaliplatin) and panitumumab, the patient’s CEA concentrations remained high, although they had decreased to 2169 ng/mL. Notably, the LDH concentration decreased to 194 U/L. After six cycles of treatment with FOLFOX and seven cycles of panitumumab, the diameter of the two largest tumors had decreased to 32.4 and 19.6 mm, respectively, indicating a partial response.

**Case three**
An 80-year-old female presented with bowel obstruction. Rectosigmoid colon cancer was diagnosed after medical examination. Enhanced CT revealed a large hepatic tumor in the right hepatic lobe measuring 107.8 mm. Resection of the primary tumor to treat the obstruction was performed and peritoneal dissemination was diagnosed. The pretreatment concentrations of LDH and CEA were 549 U/L and 17.8 ng/mL, respectively (Figure 3). Two weeks after the first treatment with panitumumab alone, the patient’s concentrations of LDH had dropped to 293 U/mL. After two cycles of treatment, CEA concentrations had marginally decreased to 7.0 ng/mL. After eight cycles of panitumumab, the diameter of the tumor was 68 mm, indicating a partial response. The tumor continued to shrink up until the 12th treatment cycle. However, after that the treatment regimen was changed due to skin toxicity.

**Case four**
An 81-year-old female with rectal cancer was treated surgically. Nine months after surgery, multiple lung metastases and liver metastasis were diagnosed on CT. The patient was started on capecitabine and oxaliplatin, which was eventually discontinued due to tumor progression. Because the patient’s preference was not to use irinotecan because of the potential for hair loss, cetuximab monotherapy was initiated (Figure 4). At that time, the

![Figure 1](image_url)
Figure 2  Treatment course of Case two
After preoperative evaluation with computed tomography (CT), the patient underwent surgical resection of the primary tumor (white arrow). Serum lactate dehydrogenase (LDH) concentrations remained high after resection of the primary tumor. However, 2 weeks after initiating treatment with FOLFOX with panitumumab, serum LDH concentrations had decreased significantly (blue circle), almost to within the normal range. In contrast carcinoembryonic antigen (CEA) concentrations at the same time were still high. The relevant CT images are shown in the right-hand panels.

Figure 3  Treatment course of Case three
After preoperative evaluation with computed tomography (CT), the patient underwent sigmoidectomy (white arrow). Two weeks after panitumumab monotherapy was initiated, serum lactate dehydrogenase (LDH) concentrations had decreased significantly (blue circle), and were within the normal range within 4 weeks. At the same times, carcinoembryonic antigen (CEA) concentrations remained high, but decreased steadily throughout treatment to be within the normal range. The results of radiological examinations were consistent with LDH and CEA results. (The results of CT performed between initial treatment and the last evaluation are not shown.)
patient’s serum LDH concentration was slightly elevated at 339 U/mL, and the CEA concentration was 466 ng/mL. Despite cetuximab treatment, the elevated serum LDH concentrations continued to rise, and the progression of the disease was confirmed on CT 7 weeks after the initiation of treatment. The patient was then started on next-line treatment with irinotecan and bevacizumab.

**Discussion**

An extensive tumor burden poses treatment difficulties because of the decreased function of vital organs and performance status. In such patients in particular, a delay in treatment or continuation of inappropriate treatment may lead to the complete loss of an opportunity to receive other potential treatments. Because thus far it is not possible to predict the tumor response before starting treatment, prompt decision making concerning continuation of ongoing treatment is extremely important. In the clinical setting, enhanced CT with the aid of serum tumor markers is an established method to evaluate tumor responses. However, frequent evaluation by CT at intervals <2 months or by tumor markers at intervals <1 month is not common practice in Japan. Moreover, it remains unknown as to whether early and frequent evaluation with CT and/or tumor markers is really correlated with future tumor responses.

In this context, our findings that changes in serum LDH concentrations may predict the tumor response are clinically important. In the present study, an early drop in serum LDH concentrations was demonstrated in patients with tumors that were susceptible to ongoing anti-EGFR antibody treatment. In contrast, the LDH concentration remained high in a patient with tumors that were resistant to treatment. These findings are supported, in part, by known tumor biology and the mechanisms underlying the antitumor activities of anti-EGFR antibodies.

Glucose is an indispensable energy source for human cells, and the metabolism of glucose in tumor cells differs from that in normal cells. Tumors have more glucose reflux and rely on anaerobic glycolysis compared with normal tissue under the same conditions. In tumor cells, LDH-5, which is regulated by hypoxia-inducible factors (HIF), plays a key role in anaerobic glycolysis. One study revealed that cetuximab downregulates HIF-1α protein by inhibiting the phosphatidylinositol 3-kinase/Akt and mitogen-activated protein kinase (MEK)/extracellular signal-regulated kinase (Erk) pathways. Consequently, the expression of LDH-5 can be reduced by cetuximab treatment.

In conclusion, the observations reported herein suggest that serum LDH concentrations may be useful in predicting the tumor response to chemotherapy with anti-EGFR antibody treatment. Further studies using LDH isozymes and upstream molecules are warranted to establish predictive markers for tumor responses to anti-EGFR antibody treatment.

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**References**


