Successful treatment of advanced gastric cancer with liver metastasis by S-1 + CDDP and S-1 therapy without surgery

Yuichiro Tanishima^{1,2} · Yuya Nyumura^{1,2} · Tomoko Nakayoshi^{1,2} · Yoshiyuki Hoya² · Tomoyoshi Okamoto^{1,2} · Katsuhiko Yanaga²

Received: 18 November 2018 / Accepted: 11 February 2019 / Published online: 25 February 2019
© The Japan Society of Clinical Oncology 2019

Abstract

It is generally reported that prognosis of patients who have unresectable gastric cancer is from 3 to 5 months with best supportive care. Despite the improvement of survival after the appearance of S-1, the outcome of treatment for advanced gastric cancer is still unfavorable. Here we present a valuable case of advanced gastric cancer with synchronous liver metastasis, which was treated by S-1 + CDDP and S-1 therapy without surgery. A 58-year-old man was referred to our hospital with a diagnosis of advanced gastric cancer with liver metastasis at stage of cT3N0M1. He underwent first-line chemotherapy consisting of S-1 plus cispatin. 3 months later, a follow-up endoscopy revealed complete response (CR) of the gastric lesion. 3 months later, computed tomography (CT) also demonstrated disappearance of liver metastasis. Then he underwent maintenance chemotherapy with S-1 alone for 8 months. To date, there has been no recurrence for 6 years and 6 months since the acquisition of CR.

Keywords Gastric cancer · Liver metastasis · S-1 · CDDP

Introduction

Gastric cancer is one of the most common cancers with 754,000 deaths worldwide in 2015 [1]. In Japan, it ranks high in all causes of death from cancer, in particular second in men. While the prognosis of early gastric cancer has been remarkably good, the one of advanced/metastatic gastric cancer still remains poor.

The treatment of liver metastasis from gastric cancer is still controversial, and current treatment protocols in Japan do not recommend surgical resection for liver metastasis. Although new key medications such as molecular target drugs have been used recently, further development of new anti-cancer drugs and multidisciplinary treatment are urgently required.

Case report

A 58-year-old man was referred to our hospital presenting with hematemesis and tarry stool in March 2012. His height and weight were 164 cm and 62 kg, respectively. He had received medications for hypertension and hyperlipidemia.

Emergency esophagogastroduodenoscopy (EGD) demonstrated a huge gastric ulcerative lesion without severe bleeding. Pathological finding of the lesion demonstrated poorly differentiated adenocarcinoma. Furthermore, abdominal CT, ultrasonography (US) and magnetic resonance imaging (MRI) showed two liver metastases (Figs. 1, 2). Laboratory data showed mild anemia as indicated by hemoglobin of 9.8 g/dl, and mild acute kidney dysfunction (Cr: 1.46 mg/dl, eGFR: 40 ml/min/1.73 m²) in addition to the elevation level of CA19-9 (108 U/ml).

Based on these findings, the patient was diagnosed as an advanced gastric cancer (cStage IV, TNM). Systemic chemotherapy was chosen without gastrectomy because there was no bleeding or stenosis by gastric cancer. He received S-1 (50 mg/body, orally administered twice a day for 21 days followed by a 14-day rest, every 5 weeks [one cycle]) plus cisplatin (75 mg/body, intravenously administered on day 8, every 5 weeks [one cycle]) as the first-line systemic chemotherapy for metastatic

✉ Yuichiro Tanishima
tanishima@jikei.ac.jp

¹ Department of Surgery, The Jikei University Daisan Hospital, Tokyo, Japan

² Department of Surgery, The Jikei University School of Medicine, Tokyo, Japan

Fig. 1 Images on admission. **a** Gastroscopy shows a type 2 tumor in the mid-stomach. **b** Barium contrast study shows deformity at the great curvature of the gastric wall (arrow)

Fig. 2 Images on admission. **a** Enhanced CT shows two irregular masses in the liver (arrows). **b** Ultrasonography shows two irregular hypoechoic areas in the liver (arrows). **c**, **d** Enhanced MRI shows two masses with ringed enhancement (arrows)

gastric cancer. His drug dose was reduced to about 80% due to kidney dysfunction by the reference to SPIRITS trial [2]. After two cycles of chemotherapy, the primary lesion was judged complete response (CR). Endoscopy showed the healing stage of the ulcerative lesion with cancer-negative pathological findings. Furthermore, the level of CA19-9 became normalized (Fig. 3). The size of liver lesions was reduced to be judged as partial response (PR) by CT and US. After two more cycles, the effect of the primary lesion not only maintained CR, but also the one of the liver lesions became CR (Fig. 4). Therefore, the treatment was switched to maintenance chemotherapy with S-1 alone (40 mg/body, orally administered twice a day for 28 days followed by a 14-day rest, every 6 weeks [one cycle]).

After eight cycles (1 year) of maintenance chemotherapy as well as adjuvant chemotherapy according to Japanese gastric cancer treatment guidelines [3], CR was maintained without major side effects, the patient has been alive for 6 years and 6 months with no evidence of recurrence with CR as evidenced by EGD, CT, US, MRI and pathological findings.

Discussion

Although tumor reduction ratio is increasing in chemotherapy for advanced or metastatic gastric cancer, the response has not ultimately led to be sufficient. The median survival

Fig. 3 Treatment and changes in serum tumor markers

time is about 6–13 months and 5-year survivors are rarely observed [2, 4]. The clinical goal of chemotherapy, therefore, is to delay the appearance of disease-related symptoms and/or to prolong survival [5].

Liver metastasis is one of the miserable metastatic diseases of gastric cancer. Although single metastasis is regarded as a good surgical indication [6], extra-hepatic diseases such as peritoneal dissemination, lymph node metastasis, and direct cancer invasion of other organs and/or bilobar liver metastasis frequently occur. Therefore, surgical indication of liver metastasis is rarely indicated [7]. However, no prospective clinical trial investigating

systemic chemotherapy, intrahepatic arterial injection, or radiofrequency ablation (RFA) for liver metastasis from gastric cancer has been reported. Therefore, the treatment of liver metastasis from gastric cancer still remains controversial.

According to Gastric Cancer Treatment Guidelines, S-1 + CDDP is recommended as the first-line standard treatment.

In the current case, the primary lesion disappeared by CT, EGD, US, and pathological finding, and he had 72 months survival after four cycles of chemotherapy.

Few reports of CR and long survival of metastatic or advanced gastric cancer have been published. Masuishi et al. reported a case similar to the current case who had 68-month survival by S-1 alone without surgery for gastric cancer with synchronous liver metastasis [8] which is a rare case with long survival by the treatment of single anti-cancer drug alone. Kitahara et al. reported a case that had survival of 10 months by gastrectomy and hepatectomy after chemotherapy for gastric cancer with synchronous liver metastasis [9]. The metastatic lesion had disappeared by CT before hepatectomy and the postoperative pathological finding revealed CR for liver metastasis. However, whether hepatectomy was necessary or not seems controversial for invisible tumor. Recently, conversion surgery after chemotherapy of gastrointestinal malignancies is a topic, but further research is necessary. Nakada et al. reported a case who had 17-month survival with gastrectomy and RFA of liver metastasis after chemotherapy for gastric cancer with synchronous liver metastasis [10].

Fig. 4 Imaging study at 6 months after chemotherapy. **a** Gastroscopy shows the tumor to have changed to an ulcerative lesion (arrows). **b–d** CT and MRI shows disappearance of two lesions (arrows)

Multidisciplinary treatment including resection and RFA may contribute to prolonged survival.

In four cases including ours with long survival of advanced or metastatic gastric cancer, the effect of chemotherapy appeared in early phase (ex. 3–4 cycles) after starting treatment, the appearance of rapid therapeutic effect as indicated by the early suppression of the tumor marker might suggest good prognosis.

As to adjuvant chemotherapy after CR, few cases have been reported. Therefore, further investigation is needed.

Conclusions

We experienced a case who had long survival for advanced gastric cancer with liver metastasis by S-1 + CDDP and S-1 therapy without surgery. Chemotherapy seems to be the primary treatment to be considered for advanced or metastatic gastric cancer.

Funding Katsuhiko Yanaga received a research grant from Pfizer Japan Inc (Tokyo, Japan) and Taiho Pharmaceutical Co Ltd (Tokyo, Japan).

Compliance with ethical standards

Conflict of interest The other authors have declared no conflict of interest.

Research involving human participants and/or animals For this type of study, formal consent is not required.

Informed consent Informed consent was obtained from the patient included in this report.

References

1. <http://www.who.int/mediacentre/factsheets/fs297/en/>
2. Koizumi W, Narahara H, Hara T et al (2008) S-1 plus cisplatin versus S-1 alone for first-line treatment of advanced gastric cancer (SPIRITS trial): a phase III trial. *Lancet Oncol* 9:215–221
3. Japanese Gastric Cancer Association (2011) Japanese gastric cancer treatment guidelines 2010 (ver. 3). *Gastric Cancer* 14:113–123
4. Bang YJ, Van Cutsem E, Feyereislova A et al (2010) Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer (ToGA): a phase 3, open-label, randomised controlled trial. *Lancet* 376:687–697
5. Japanese Gastric Cancer Association (2018) Japanese gastric cancer treatment guidelines (ver. 5) (**in Japanese**)
6. Kodera Y, Fujitani K, Fukushima N et al (2014) Surgical resection of hepatic metastasis from gastric cancer: a review and new recommendation in the Japanese gastric cancer treatment guidelines. *Gastric Cancer* 17:206–212
7. Koga R, Yamamoto J, Ohyama S et al (2007) Liver resection for metastatic gastric cancer: experience with 42 patients including eight long-term survivors. *Jpn J Clin Oncol* 37:836–842
8. Masuishi T, Sakai Y, Soma T et al (2012) A case of advanced gastric cancer with multiple liver metastases. *Jpn J Cancer Chemother* 39:975–977 (**in Japanese**)
9. Kitahara H, Oki E, Saeki H et al (2013) A case of liver metastasis from gastric cancer responding completely to S-1/docetaxel chemotherapy. *Jpn J Cancer Chemother* 40:1093–1097 (**in Japanese**)
10. Nakada S, Kawamoto J, Yoichi T et al (2015) A case report—a synchronous liver metastasis from gastric cancer treated with chemotherapy. *Jpn J Cancer Chemother* 42:1992–1994 (**in Japanese**)

Publisher's Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.