Alpha-fetoprotein expressing metastastic adenocarcinoma of the esophago-gastric junction responding favorably to capecitabine and oxaliplatin

Melanie Kripp[a], Philipp Ströbel[b], Dietmar Dinter[c], Nadine Lukan[a], Andreas Hochhaus[a] and Ralf-Dieter Hofheinz[a]

Alpha-fetoprotein-producing metastatic adenocarcinoma of the stomach or the esophago-gastric junction usually exhibits either no or only short-term remission while receiving palliative chemotherapy. We report on a 76-year-old male patient suffering from an unresectable α-fetoprotein-producing adenocarcinoma of the esophago-gastric junction with several liver metastases. He was treated with capecitabine and oxaliplatin-based combination therapy. A long-lasting major remission was observed resulting in a survival of 18.5 months.

Anti-Cancer Drugs 2009, **20**:75–78

Keywords: adenocarcinoma of the esophago-gastric junction, alpha-fetoprotein expression, capecitabine, oxaliplatin

[a]Onkologisches Zentrum, III. Medizinische Klinik, [b]Institut für Pathologie and [c]Institut für Klinische Radiologie und Nuklearmedizin; Medizinische Fakultät Mannheim der Universität Heidelberg, Mannheim, Germany

Correspondence to Melanie Kripp, MD, Onkologisches Zentrum, III. Medizinische Klinik, Medizinische Fakultät Mannheim der Universität Heidelberg, Theodor-Kutzer-Ufer, D-68167 Mannheim, Germany
Tel: +49 621 383 2854; fax: +49 621 383 2488;
e-mail: melanie.kripp@med3.ma.uni-heidelberg.de

Received 30 June 2008 **Revised form accepted** 28 July 2008

Introduction

Alpha-fetoprotein (AFP)-expressing adenocarcinoma of the stomach or the esophago-gastric (EG) junction is a rare but well-defined entity. It is characterized by a distinct morphology and immunohistochemistry [1]. On account of poor differentiation and aggressive behavior with early hematogenous (chiefly liver) metastases it reportedly shows poor prognosis [2]. Once beyond the control of surgery palliative chemotherapy is the mainstay of treatment. Yet, distinct prospective clinical trials for patients with AFP-producing tumors of the stomach or the EG junction have not been conducted thus far. A few case reports describe the potential efficacy of cisplatin-based or 5-fluorouracil (5-FU)-based chemotherapy (e.g., using the FLEP regime, i.e., 5-FU, folinic acid, epirubicin, and cisplatin) but responses are usually short lasting [3–6].

In the treatment of AFP-negative adenocarcinoma of the EG junction or the stomach, three randomized trials have recently shown that 5-FU may be replaced by capecitabine and cisplatin by oxaliplatin in combination regimens in view of the superior toxicity profile of both new drugs [7–9]. For AFP-positive tumors no data on the use of both drugs have been published thus far. Here we report on a case of an AFP-producing metastatic adenocarcinoma of the EG junction exhibiting remarkable response to a combination of capecitabine and oxaliplatin.

Case report

We report a case of a 76-year-old man who presented with anorexia and weight loss of 5 kg. No sign of ethylism was observed but his nicotine abuse amounted to 100 pack-years. He had a history of carcinoma of the urinary bladder successfully treated with transurethral resection in 1989 and a carcinoma of the prostate gland in 1992 (treated with transurethral resection as well). A Barrett's esophagus had been diagnosed in 1998. Physical examinations did not show any abnormalities.

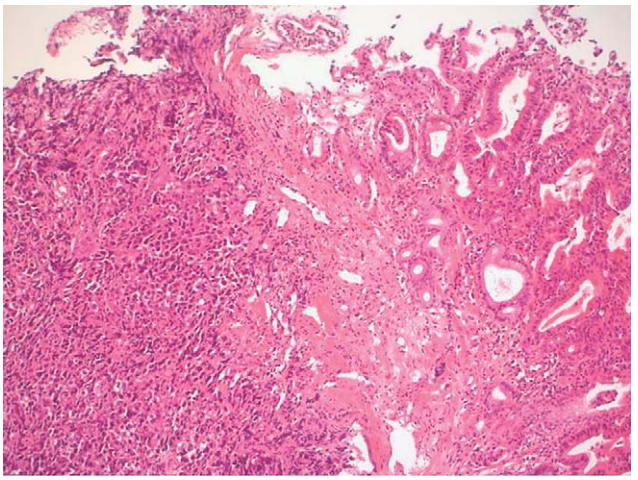
Endoscopy revealed a semicircular ventral growing ulcerating lesion 28–36 cm from the upper incisors (endoscopic ultrasound uT3 uN positive). On biopsy the lesion was diagnosed as a poorly differentiated adenocarcinoma (G3) arising in Barrett's esophagus (Fig. 1). Immunhistochemical examination for AFP showed weak staining in the cytoplasm of cancer cells (Fig. 2). Thus, the tumor was classified as an AFP-producing adenocarcinoma of the EG junction (Siewert I).

The magnetic resonance imaging (MRI) showed enlarged paragastral and paraaortal lymph nodes as well as multiple liver metastases (more than six lesions) in both lobes of the liver with a maximum diameter of 4.0 cm (index lesion; Fig. 2).

Laboratory studies including liver function tests were normal. Serum levels of tumor markers were as follows: carcinoembryonic antigen 1.6 μg/l (within normal ranges), carbohydrate antigen 19–9 was 10.0 kU/l (within normal ranges), and cancer antigen 72–4 was 24.9 kU/l (upper level of normal range 6.7 kU/l). In addition, the serum AFP level was 5453 μg/l, showing pronounced elevation (upper level of normal range 13 μg/l).

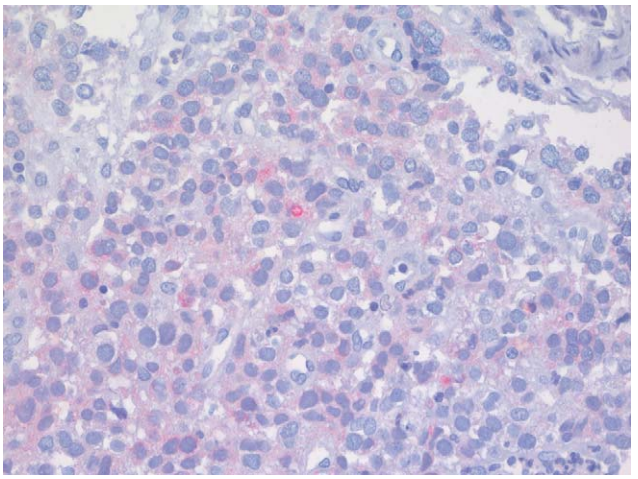
0959-4973 © 2009 Wolters Kluwer Health | Lippincott Williams & Wilkins DOI: 10.1097/CAD.0b013e328312659a

Fig. 1



Primary tumor, haemotoxylin and eosin staining.

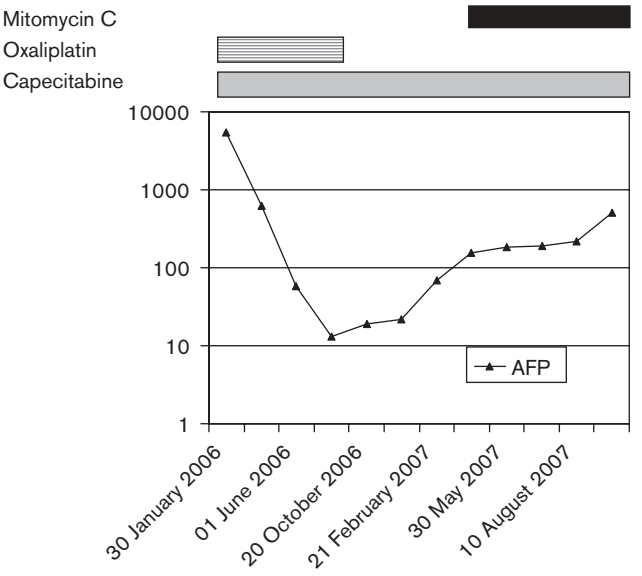
Fig. 2



Primary tumor, α-fetoprotein staining.

Chemotherapy was initiated using XelOx regimen on 10 March 2006: capecitabine (1000 mg/m^2 twice daily; days 1–14; repeated day 22) and oxaliplatin (130 mg/m^2; day 1; repeated day 22). Four weeks after the start of the therapy AFP level had decreased to 632 µg/l. Figure 3 illustrates the administered treatment along with the AFP values. A dose reduction by 25% of both drugs was applied because of grade 3 diarrhea, which occurred during the second XelOx cycle. Treatment was continued and the AFP level decreased further (1 June 2006; 59 µg/l). A total of seven oxaliplatin administrations (total cumulative oxaliplatin dose of 750 mg/m^2) were applied until July 2006. Oxaliplatin was then omitted because of allergic reactions and treatment with capecitabine was continued.

Fig. 3



Time course of α-fetoprotein (AFP) levels (micrograms/liter) in correlation to the administered treatment. Note: AFP values are plotted logarithmically.

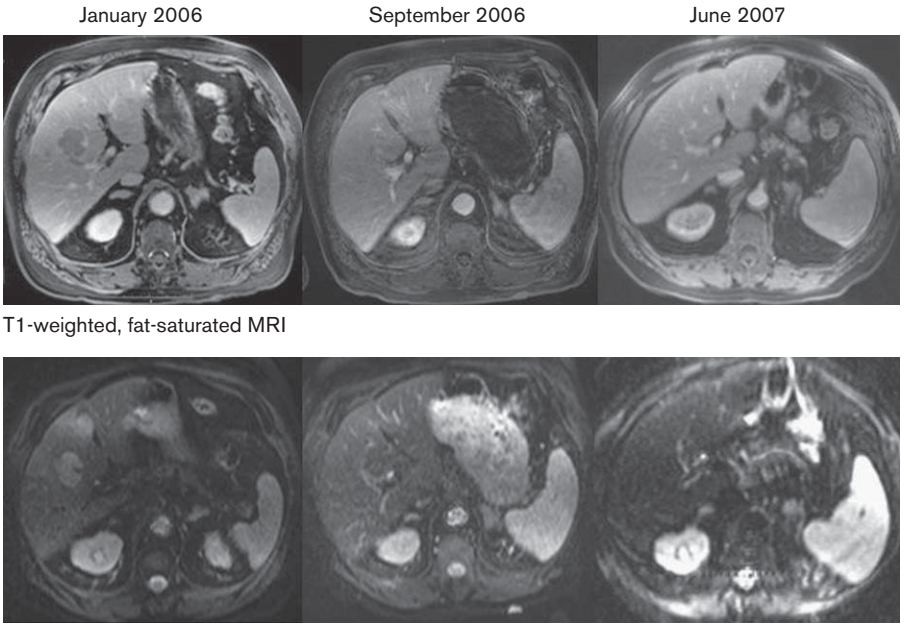
Restaging in September 2006 revealed remarkable tumor regression observed endoscopically (endoscopic ultrasound staging uT2 uN1) as well as in the MRI. The size of the liver metastases and lymph nodes had decreased by more than 75% and the index lesion had disappeared (Fig. 4). Accordingly, the serum level of AFP had normalized (13 µg/l).

On account of increasing AFP levels despite continued capecitabine treatment, mitomycin C (8 mg/m^2; day 1, repeated day 22) was added to the capecitabine regimen starting in April 2007. At 27 June 2007 another MRI confirmed the major remission of the liver metastases with the complete disappearance of the index lesion (Fig. 4). Nevertheless, the primary tumor progressed and AFP serum levels increased. At the patient's request chemotherapy was stopped in July 2007 and best supportive care was provided. The patient died on 26 October 2007, 18.5 months after the diagnosis of metastatic disease.

Discussion

AFP-positive adenocarcinoma of the stomach or the EG junction is a rare but well-defined entity. The incidence of AFP-producing gastric cancer has been estimated to be 1.3–1.5% considering all patients with gastric cancer [10–12]. Nevertheless, AFP immuno-staining is not part of the standard work-up of pathological specimen of cancers of the stomach or the GE junction. Thus, the estimated number of unreported cases might be higher. In an analysis of AFP expression in 25 patients immunohistochemical AFP expression in paraffin-embedded

Fig. 4



T1- and T2-weighted MRI with fat saturation, demonstrating the index lesion in segment 5/4 before treatment (January 2006), and after treatment with capecitabine and oxaliplatin (complete remission first documented in September 2006). The complete remission was confirmed in June 2007.

specimens was found in two patients (8%) and AFP-mRNA was detected in three patients (12%) [13]. It has been reported that AFP-producing gastric cancer has high proliferative activity, weak apoptotic activity, and rich neovascularization compared with AFP-negative gastric cancer [14]. Some factors associated with mitosis, cell movement, proliferative activity, and tumor progression such a Ki-67, hepatocyte growth factor and its receptor, c-Met and vascular endothelial growth factor (VEGF) were found to be highly expressed in AFP-producing gastric cancer [14–16]. These markers may explain the poor prognosis and drug resistance of this tumor. To estimate the aggressiveness of this entity Ishigami *et al.* [2] retrospectively analyzed its clinical features. Five hundred and fifty-six patients with gastric cancer underwent preoperative measurement of AFP levels, 97 of whom, in addition, had immuno-histochemical evaluation of AFP and p53 expression in the primary tumor. AFP positivity was detected in 25 of 556 patients. These patients displayed deeper tumor invasion, increased nodal involvement and venous invasion. Surgical outcomes were significantly worse ($P < 0.05$), and all recurrences involved hepatic metastases. Abnormalities of p53 were more frequent compared with AFP-negative gastric cancers.

On account of aggressive behavior and early hematogenous metastases liver involvement is frequent. Few successful treatment options exist for AFP-producing gastric cancer. Surgical resection is considered to be curative in approximately 50% of patients [17]. Once beyond the control of curative surgery only few cytostatic drugs – among them 5-FU, cisplatin, and paclitaxel – were reported to have antitumor activity in case reports or at best in case series [3–6]. Usually these responses are short lasting. Moreover, AFP-producing tumors were found to have a higher likelihood of expression of chemoresistance-related proteins. Using immunohistochemistry Kamoshida *et al.*, analyzed 12 AFP-positive and 94 AFP-negative patients with gastric cancers. High expression of thymidine phosphorylase (TP) – an enzyme that converts the prodrug capecitabine to the active 5-FU – was found in 30% of AFP-negative tumors, but in none of the AFP-positive tumors ($P = 0.03$). Moreover, metallothionein – a protein associated with resistance to cisplatin because of its high affinity for heavy metal ions – was observed in 30% of AFP-negative tumors but in only one AFP-positive tumor (10%). The TP-low and metallothionein-low phenotype was noted in 92% of AFP-positive tumors and in 46% of AFP-negative tumors ($P = 0.004$). These data suggest that AFP-producing adenocarcinoma of the stomach should be sensitive to cisplatin but resistant to fluoropyrimidine prodrugs that are converted to 5-FU by TP, for example, capecitabine [18].

In contrast to these preclinical data we observed long-lasting remission using capecitabine in conjunction with oxaliplatin in this case. It is unlikely that oxaliplatin

would have led to a remission to the same extent because oxaliplatin is virtually ineffective as monotherapy. The remission was chiefly observed in the liver exhibiting a near-complete disappearance of all liver metastases for almost 18 months (until the patient's death, which was caused by progressive primary and mediastinal lymph node metastases and pneumonia).

In conclusion, we observed a long-lasting remission using capecitabine and oxaliplatin in this AFP-producing cancer of the EG junction. Following the trend to use capecitabine instead of 5-FU and oxaliplatin instead of cisplatin, especially in elderly patients [7] with AFP-negative adenocarcinoma of the stomach or the EG junction, we believe that this combination deserves further studies in AFP-producing cancers as well, ideally within prospective clinical trials.

References

1 Kaiser U, Zugmaier G, Frank M, Riedel I, Neubauer A, Moll R. [AFP-producing adenocarcinoma of the stomach. A rare tumor with poor prognosis]. *Pathology* 2003; **24**:141–145.

2 Ishigami S, Natsugoe S, Nakashima H, Tokuda K, Nakajo A, Okumura H, *et al*. Biological aggressiveness of alpha-fetoprotein (AFP)-positive gastric cancer. *Hepatogastroenterology* 2006; **53**:338–341.

3 Chiba N, Yoshioka T, Sakayori M, Mikami Y, Miyazaki S, Akiyama S, *et al*. AFP-producing hepatoid adenocarcinoma in association with Barrett's esophagus with multiple liver metastasis responding to paclitaxel/CDDP: a case report. *Anticancer Res* 2005; **25**:2965–2968.

4 Shimakawa T, Ogawa K, Naritaka Y, Wagatsuma Y, Katsube T, Hamaguchi K, *et al*. Alpha-fetoprotein producing Barrett's esophageal adenocarcinoma: a case report. *Anticancer Res* 1999; **19** (**5C**):4369–4373.

5 Kochi M, Fujii M, Kaiga T, Takahashi T, Morishita Y, Kobayashi M, *et al*. FLEP chemotherapy for alpha-fetoprotein-producing gastric cancer. *Oncology* 2004; **66**:445–449.

6 Takeyama H, Sawai H, Wakasugi T, Takahashi H, Matsuo Y, Ochi N, *et al*. Successful paclitaxel-based chemotherapy for an alpha-fetoprotein-producing gastric cancer patient with multiple liver metastases. *World J Surg Oncol* 2007; **5**:79.

7 Al-Batran SE, Hartmann JT, Probst S, Schmalenberg H, Hollerbach S, Hofheinz R, *et al*. Phase III trial in metastatic gastroesophageal adenocarcinoma with fluorouracil, leucovorin plus either oxaliplatin or cisplatin: a study of the Arbeitsgemeinschaft Internistische Onkologie. *J Clin Oncol* 2008; **26**:1435–1442.

8 Cunningham D, Starling N, Rao S, Iveson T, Nicolson M, Coxon F, *et al*. Capecitabine and oxaliplatin for advanced esophagogastric cancer. *N EnglJ Med* 2008; **358**:36–46.

9 Kang Y, Kang WK, Shin DB, Chen J, Xiong J, Wang J, *et al*. Randomized phase III trial of capecitabine/cisplatin (XP) vs. continuous infusion of 5-FU/cisplatin (FP) as first-line therapy in patients (pts) with advanced gastric cancer (AGC): efficacy and safety results. *J Clin Oncol (Meeting Abstracts)* 2006; **24** (**18_Suppl**):LBA4018.

10 McIntire KR, Waldmann TA, Moertel CG, Go VL. Serum alpha-fetoprotein in patients with neoplasms of the gastrointestinal tract. *Cancer Res* 1975; **35**:991–996.

11 Chang YC, Nagasue N, Abe S, Taniura H, Kumar DD, Nakamura T. Comparison between the clinicopathologic features of AFP-positive and AFP-negative gastric cancers. *Am J Gastroenterol* 1992; **87**:321–325.

12 Chang YC, Nagasue N, Abe S, Kohno H, Kumar DD, Nakamura T. alpha Fetoprotein producing early gastric cancer with liver metastasis: report of three cases. *Gut* 1991; **32**:542–545.

13 Chen J, Rocken C, Treiber G, Jentsch-Ulrich K, Malfertheiner P, Ebert MP. Clinical implications of alpha-fetoprotein expression in gastric adenocarcinoma. *Dig Dis* 2003; **21**:357–362.

14 Koide N, Nishio A, Igarashi J, Kajikawa S, Adachi W, Amano J. Alpha-fetoprotein-producing gastric cancer: histochemical analysis of cell proliferation, apoptosis, and angiogenesis. *Am J Gastroenterol* 1999; **94**:1658–1663.

15 Amemiya H, Kono K, Mori Y, Takahashi A, Ichihara F, Iizuka H, *et al*. High frequency of c-Met expression in gastric cancers producing alpha-fetoprotein. *Oncology* 2000; **59**:145–151.

16 Kamei S, Kono K, Amemiya H, Takahashi A, Sugai H, Ichihara F, *et al*. Evaluation of VEGF and VEGF-C expression in gastric cancer cells producing alpha-fetoprotein. *J Gastroenterol* 2003; **38**:540–547.

17 Kono K, Amemiya H, Sekikawa T, Iizuka H, Takahashi A, Fujii H, *et al*. Clinicopathologic features of gastric cancers producing alpha-fetoprotein. *Dig Surg* 2002; **19**:359–365; discussion 365.

18 Kamoshida S, Suzuki M, Sakurai Y, Ochiai M, Kimura F, Kuwao S, *et al*. Expression of chemoresistance-related proteins in alpha-fetoprotein-producing adenocarcinoma of the digestive organs. *Oncol Rep* 2006; **16**:721–727.