Tumori, 95: 811-814, 2009

Treatment of advanced gastric cancer with cetuximab plus chemotherapy followed by surgery. Report of a case

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ABSTRACT

The prognosis of patients affected by advanced gastric cancer who did not undergo non-curative resection is extremely poor. We report a case of a 26-year-old woman affected by gastric cancer with peritoneal carcinosis in whom surgical treatment was not considered. The patient was enrolled in the Italian phase II trial of cetuximab (Erbitux, Merck KGaA, Darmstadt, Germany), a monoclonal antibody, in combination with docetaxel and cisplatin chemotherapy. Restaging of the tumor showed progressive regression, so the patient underwent a total gastrectomy. The patient is alive, well and disease-free ten months after surgery. The good result achieved in this patient provides interesting prospects for chemotherapy combined with cetuximab, followed by surgery.

Introduction

Gastric cancer is the second leading cause of cancer-related death worldwide. Recent advances in diagnosis and treatment have improved the prognosis of early-stage gastric cancer, but the prognosis of patients at an advanced TNM stage remains poor[1-4]. In early-stage gastric cancer, surgery is potentially curative, but the majority of patients have advanced-stage disease at diagnosis and are therefore candidates for chemotherapy or palliative care. Moreover, the 1-year survival rate is <50% in stage II-IA and B and <25% in stage IV; the median survival in patients not receiving chemotherapy is 3-4 months[5].

Standard therapy for locally advanced gastric cancer is still controversial. However, R0 resection is an important prognostic factor[6], as is the absence of lymph node involvement and pathological tumor regression after chemotherapy[7].

Curative surgery is usually excluded in patients having gastric cancer with peritoneal involvement. Here we report on a young woman with stage IV gastric cancer who was treated with chemotherapy in combination with cetuximab, followed by "curative" surgery.

Key words: gastric cancer, neoadjuvant therapy, cetuximab, gastrectomy.

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Received January 15, 2009;
accepted April 16, 2009.

Case report

A 26-year woman with a negative remote medical history and a recent finding of epigastric pain, in treatment with proton pump inhibitors, presented to us. Esophagogastroduodenoscopy (EGDS) showed a mass of the body-antrum of the stomach, 7 cm in diameter (Figure 1A), histologically classified as invasive, poorly differentiated adenocarcinoma, diffuse type according to Lauren's classification. Serum tumor marker levels were raised [CA 19-9: 61.8 U/mL (normal value <37 U/mL), CEA: 5.5 ng/mL (normal value <5 ng/mL)]. Computed tomography (CT) showed full thickness involvement of the gastric wall (up to 2 cm), mainly at the level of the anterior wall

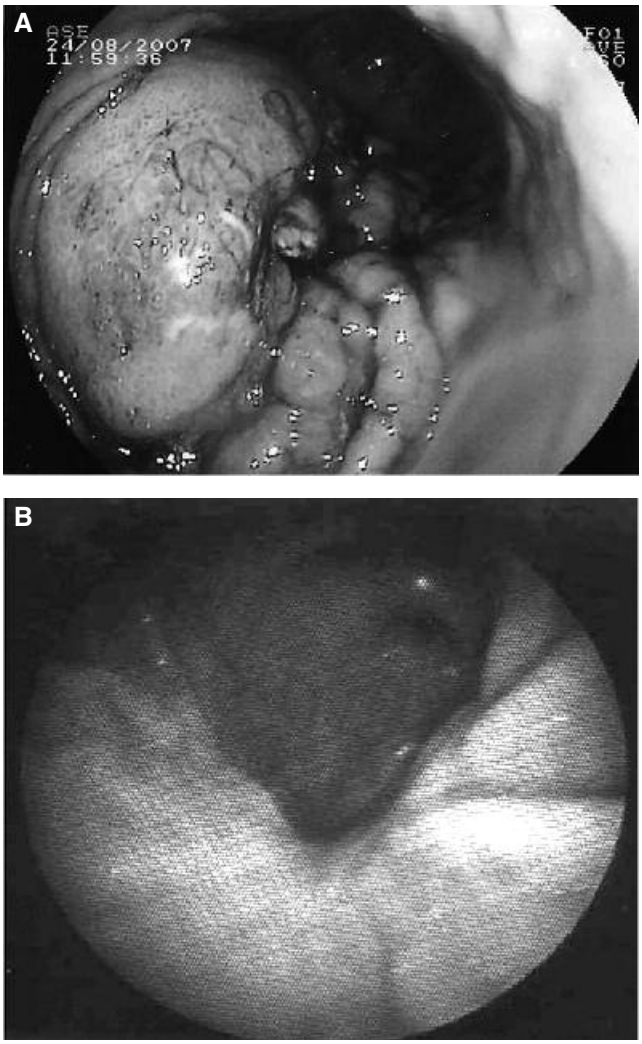

Figure 1 - A) EGDS before neoadjuvant therapy showed a gastric mass of 7 cm in diameter. B) EGDS after neoadjuvant therapy showed the disappearance of the mass and the presence of a fibrous area in the gastric body at the level of the greater curvature.

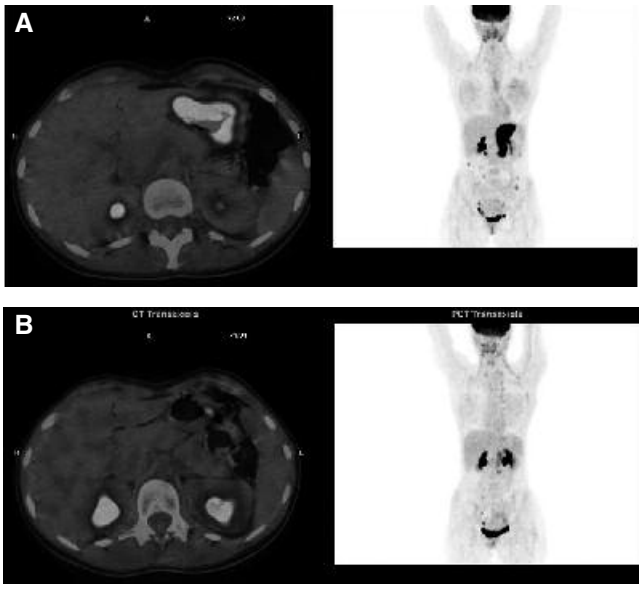

Figure 2 - A) 18F-FDG-PET before neoadjuvant therapy revealed abnormal metabolic activity of the whole stomach (SUV_{max} = 21). B) 18F-FDG-PET after neoadjuvant therapy showed a markedly decreased uptake at the level of the stomach (SUV_{max} = 3.8).

and the greater curvature with an irregular external outline. Moreover, diffuse lymph node involvement, an oval-shaped mass under the stomach (3.2 x 2 cm in diameter) with the appearance of diffuse pelvic carcinosis and intrabdominal effusion were observed. 18F-fluorodeoxyglucose positron emission tomography (18F-FDG-PET) revealed abnormal metabolic activity of the whole stomach, mainly at the level of the gastric body-antrum (maximum standardized uptake value [SUV_{max}] = 21), increased metabolic activity at the lower diaphragmatic surface (SUV_{max} = 8) and diffuse peritoneal masses (SUV_{max} = 4) (Figure 2A). Due to the advanced stage of the disease (stage IV: T3 N+ M+), surgical treatment was not considered.

The patient was enrolled in an Italian phase II study for patients with locally advanced or metastatic gastric and gastroesophageal junction adenocarcinoma. The protocol consisted of the administration of cetuximab, a monoclonal antibody directed to the epidermal growth factor receptor (EGFR) binding site, in combination with cisplatin and docetaxel[8].

The patient received cetuximab weekly at 400 mg/m^2 i.v. loading dose, and then at 250 mg/m^2 i.v. maintenance dose, cisplatin 75 mg/m^2 i.v. and docetaxel 75 mg/m^2 i.v. every 3 weeks, for 6 cycles (18 weeks). She tolerated the therapy very well and presented only low-grade toxicity with cutaneous symptoms and asthenia.

After the first cycle, the patient underwent 18F-FDG-PET, which showed a markedly decreased uptake at the level of the gastric body and antrum (SUV_{max} = 3.8) and almost normal metabolic activity at the lower diaphragmatic area and the peritoneal masses (SUV_{max} <2) (Figure 2B). Therefore, after only 1 month of therapy, the patient showed a complete metabolic response of the peritoneal carcinosis.

Every 2 cycles of therapy, a CT scan was performed, showing a progressive decrease in gastric wall thickness and in the previously described oval-shaped mass (from 3.2 cm to 1.3 cm). The last CT scan showed the complete disappearance of all lesions .

Finally, an EGDS showed a fibrous area in the gastric body at the level of the greater curvature (Figure 1B) and the blood levels of neoplastic markers were normal. Due to the downstaging (TxN0M0), surgical treatment was considered feasible.

Surgery began with an explorative laparoscopy, which did not find any intraabdominal effusion, peritoneal carcinosis or liver metastases. Then a total gastrectomy with D2 lymphadenectomy and Roux-en-Y reconstruction was performed. Histological examination demonstrated 4 mucosal microfoci (2 mm) of diffuse type poorly differentiated adenocarcinoma without nodal metastases, the surgical margins were tumor free and Ki-67 was 50.9% (Figure 3A and 3B). The histopathological regression grade was 1b, according to Becker's scale[7]. The postoperative course was complicated by an anastomotic fistula, successfully treated with medical therapy. Now, 10 months after surgery, the patient is alive, well and disease free.

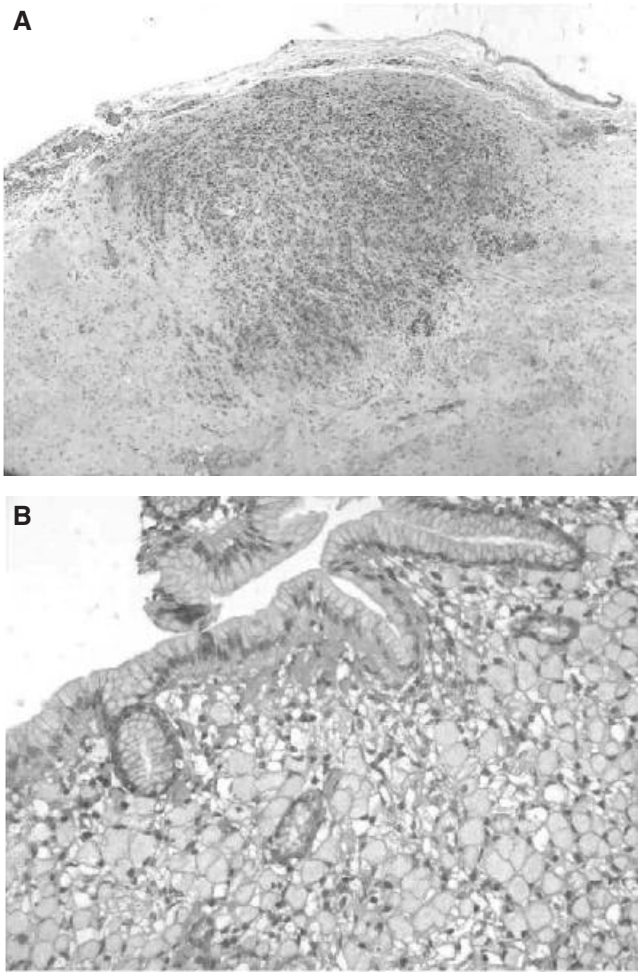

Figure 3 - A) Residual microfoci of diffuse poorly differentiated adenocarcinoma. Section staining with hematoxylin-eosin, low-power amplification. B) Detail of mucosal microfoci (2 mm) of diffuse poorly differentiated adenocarcinoma. Most of the mucin produced is intracytoplasmic, resulting in the typical signet ring cells. Section staining with hematoxylin-eosin, hight-power amplification.

Discussion

Surgery is the only potential curative option for gastric cancer. The R factor, nodal involvement and histopathological tumor regression after neoadjuvant chemotherapy appear to be correlated with survival[6,7,9]. The chance of achieving complete resection of the tumor is less than 50%[10-13] and therefore the majority of patients are candidates for chemotherapy, either neoadjuvant or palliative, according to the patient's performance status. No single regimen of chemotherapy has emerged or been accepted as clearly superior over another and the neoadjuvant use shows no survival benefit compared to surgery alone. A systematic review from the Cochrane Collaboration analyzed the results from the best available evidence comparing neoadjuvant chemotherapy plus surgery *versus* surgery alone. The 2 groups did not show any significant difference for R0 resection rate, morbidity and mortality rates and improvement of survival[14]. Chemotherapy resulted in better quality of life and overall survival when compared with best supportive care in patients with advanced gastric cancer[9,15-17]. In advanced gastric cancer the new chemotherapy regimens TCF (docetaxel-cisplatin-5-fluorouracil) and EOX (epirubicin-oxaliplatin-capecitabine) showed a response rate of 37-48%[18-20]. At present the prognosis of unresectable advanced or metastatic gastric cancer remains poor, with a median survival of 7-10 months[21,22].

Molecular targeting agents are another new approach in the field of cancer therapy and may have a significant impact also on gastric cancer treatment. Preliminary results of ongoing studies of the use of cetuximab in combination with chemotherapy in advanced or metastatic gastric cancer have shown an overall response rate of 44.1% to 54% and a median survival time of 11.4 to 16 months[23,24].

To our knowledge, this is the first case of neoadjuvant targeted therapy combined with chemotherapy in which regression of the disease, in particular of the peritoneal carcinosis, is reported. The downstaging allowed a R0 surgical resection without lymph node involvement. Moreover, histological tumor regression according to the Becker scale was obtained.

More randomized studies are needed, however, to substantiate the evidence of the effectiveness of monoclonal antibody therapy.

References

1. Maruyama K: The most important prognostic factors for gastric cancer patients: a study using univariate and multivariate analyses. Scand J Gastroenterol, 22 (Suppl 133): 63-68, 1987.
2. Nakamura K, Ueyama T, Yao T, Xuan ZX, Ambe K, Adachi Y, Yakeishi Y, Matsukuma A, Enjoji M: Pathology and prognosis of gastric carcinoma: findings in 10,000 patients who

underwent primary gastrectomy. Cancer, 70: 1030-1037, 1992.
3. Maruyama K, Okabayashi K, Kinoshita T: Progress in gastric cancer surgery in Japan and its limits of radicality. World J Surg, 11: 418-425, 1987.
4. Roukos DH, Kappas AM: Perspectives in the treatment of gastric cancer. Nat Clin Pract Oncol, 2: 98-107, 2005.
5. Kelley JR, Duggan JM: Gastric cancer epidemiology and risk factors. J Clin Epidemiol, 56: 1-9, 2003.
6. Persiani R, D'Ugo D, Rausei S, Sermoneta D, Barone C, Pozzo C, Ricci R, La Torre G, Picciocchi A: Prognostic indicators in locally advanced gastric cancer (LAGC) treated with preoperative chemotherapy and D2-gastrectomy. J Surg Oncology, 89: 227-236, 2005.
7. Becker K, Mueller JD, Schulmacher C, Ott K, Fink U, Busch R, Böttcher K, Siewert JR, Höfler H: Histomorphology and grading of regression in gastric carcinoma treated with neoadjuvant chemotherapy. Cancer, 98: 1521-1530, 2003.
8. Pinto C, Di Fabio F, Barone C, Siena S, Falcone A, Cascinu S, Rojas Llimpe FL, Artale S, Schinzari G, Giaquinta S, Mutri V, Martoni AA: Cetuximab in combination with cisplatin and docetaxel as first-line treatment in patients with locally advanced or metastatic gastric or gastroesophageal junction (GEJ) adenocarcinoma (Italian phase II DOCETUX study). J Clin Oncol, 26: 15S, 4575A, 2008.
9. NCCN Gastric Cancer Panel Members: NCCN Clinical Practice Guidelines in Oncology™: Gastric Cancer. Available at http://www.nccn.org (V.2.2009) (accessed December 2009).
10. Cascinu S: Linee Guida AIOM 2006. Neoplasie dello stomaco. Available at http://www.aiom.it (accessed December 2009).
11. Roder JD, Böttcher K, Siewert JR, Busch R, Hermanek P, Meyer HJ: Prognostic factors in gastric carcinoma: results of the German Gastric Carcinoma Study 1992. Cancer, 72: 2089-2097, 1993.
12. Leichman L, Silberman H, Leichman CG, Spears CP, Ray M, Muggia FM, Kiyabu M, Radin R, Laine L, Stain S: Preoperative systemic chemotherapy followed by adjuvant postoperative intraperitoneal therapy for gastric cancer: A University of Southern California pilot program. J Clin Oncol, 10: 1933-1942, 1992.
13. Ajani JA, Mayer RJ, Ota DM, Steele GD, Evans D, Roh M, Sugarbaker DJ, Dumas P, Gray C, Vena DA: Preoperative and postoperative combination chemotherapy for potentially resectable gastric carcinoma. J Natl Cancer Inst, 85: 1839-1844, 1993.
14. Wu AW, Xu GW, Wang HY, Ji JF, Tang JL: Neoadjuvant chemotherapy versus none for respectable gastric cancer. Cochrane Database Syst Rev, 2: CD005047, 2007.
15. Pyrhönen S, Kuitunen T, Nyandoto P, Kouri M: Randomised comparison of fluorouracil, epidoxorubicin and methotrexate (FEMTX) plus supportive care with supportive care alone in patients with non-resectable gastric cancer. Br J Cancer, 71: 587-591, 1995.
16. Murad AM, Santiago FF, Petroianu A, Rocha PR, Rodrigues MA, Rausch M: Modified therapy with 5-fluorouracil, doxorubicin, and methotrexate in advanced gastric cancer. Cancer, 72: 37-41, 1993.
17. Glimelius B, Hoffman K, Haglund U, Nyrén O, Sjödén PO: Initial or delayed chemotherapy with best supportive care in advanced gastric cancer. Ann Oncol, 5: 189-190, 1994.
18. Van Cutsem E, Van de Velde C, Roth A, Lordick F, Köhne CH, Cascinu S, Aapro M; European Organisation for Research and Treatment of Cancer (EORTC)-gastrointestinal cancer group: Expert opinion on management of gastric and gastro-oesophageal junction adenocarcinoma on behalf of the European Organisation for Research and Treatment of Cancer (EORTC)-gastrointestinal cancer group. Eur J Cancer, 44: 182-194, 2008.
19. Van Cutsem E, Moiseyenko VM, Tjulandin S, Majlis A, Constenla M, Boni C, Rodrigues A, Fodor M, Chao Y, Voznyi E, Risse ML, Ajani JA; V325 Study Group: Phase III study of docetaxel and cisplatin plus fluorouracil compared with cisplatin and fluorouracil as first-line therapy for advanced gastric cancer: a report of the V325 Study Group. J Clin Oncol, 31: 4991-4997, 2006.
20. Cunningham D, Starling N, Rao S, Iveson T, Nicolson M, Coxon F, Middleton G, Daniel F, Oates J, Norman AR: Upper Gastrointestinal Clinical Studies Group of the National Cancer Research Institute of the United Kingdom. Capecitabine and oxaliplatin for advanced esophagogastric cancer. N Engl J Med, 358: 36-46, 2008.
21. Yano M, Shiozaki H, Inoue M, Tamura S, Doki Y, Yasuda T, Fujiwara Y, Tsujinaka T, Monden M: Neoadjuvant chemotherapy followed by salvage surgery: effect on survival of patients with primary noncurative gastric Cancer. World J Surg, 26: 1155-1159, 2002.
22. Wagner AD, Grothe W, Haerting J, Kleber G, Grothey A, Fleig WE: Chemotherapy in advanced gastric cancer: a systematic review and meta-analysis based on aggregate data. J Clin Oncol, 24: 2903-2909, 2006.
23. Pinto C, Di Fabio F, Siena S, Cascinu S, Rojas Llimpe FL, Ceccarelli C, Mutri V, Giannetta L, Giaquinta S, Funaioli C, Berardi R, Longobardi C, Piana E, Martoni AA: Phase II study of cetuximab in combination with FOLFIRI in patients with untreated advanced gastric or gastroesophageal junction adenocarcinoma (FOLCETUX study). Ann Oncol, 18: 510-517, 2007.
24. Lordick F, Lorenzen S, Stollfuss J, Vehling-Kaiser U, Kullmann F, Hentrich M, Zumschlinge R, Dietzfelbinger H, Thoedtmann J, Hennig M, Seroneit T, Bredenkamp R, Duyster J, Peschel C: Phase II study of weekly oxaliplatin plus infusional fluorouracil and folinic acid (FUFOX regimen) as first-line treatment in metastatic gastric cancer. Br J Cancer, 93: 190-194, 2005.