Preoperative neoadjuvant chemoradiation for locally advanced gastric adenocarcinoma

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ABSTRACT

AIMS AND BACKGROUND: To evaluate toxicity and the radical resection rate in gastric adenocarcinoma treated with preoperative neoadjuvant chemoradiation.

MATERIALS & METHODS: 32 patients, 22 males and 10 females with gastric adenocarcinoma, were treated with chemoradiation and hyperthermia.

RESULTS: The neoadjuvant regimen was completed as planned in 19/32 (59 %) patients; in the remaining patients the intensity of chemotherapy had to be reduced because of haematological and gastrointestinal toxicity. Surgical stage was as follows: 2 patients pathologically complete response, 3 patients AJCC stage I.A, 5 patients stage I.B, 7 patients stage II, 7 patients stage III.A, 1 patient stage III.B, 7 patients stage IV. R0 resection was achieved in 19/32 (59%) patients, R1 in 2/32 (6%) patients and R2 in 11 (34%) patients. Downstaging after neoadjuvant chemoradiotherapy was achieved in 17/32 (53%) patients. At the date of evaluation (31 March 2009), 4 patients were still alive 58, 81, 86 and 98 months from the date of diagnosis. Median survival was 18 months (95% confidence interval: 13–38 months). One-year survival was 69% (95% confidence interval: 53%–85%). Four-year survival was 19% (95% C.I.: 5%–34%).

CONCLUSIONS: Preoperative neoadjuvant chemoradiotherapy has acceptable toxicity, and can lead to a high rate of R0 resections.

KEY WORDS: gastric cancer, preoperative neoadjuvant chemoradiotherapy, hyperthermia

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BACKGROUND

The mainstay of curative treatment of locally advanced gastric adenocarcinoma is radical surgery. Complete surgical tumour removal with microscopically negative margins (R0 resection) is of fundamental importance for the patient's prognosis. Locoregional relapse is a major problem after curative surgery in gastric adenocarcinoma.

Preoperative neoadjuvant chemoradiotherapy has been widely used in the treatment of locally advanced oesophageal and rectal adenocarcinoma, but studies in gastric adenocarcinoma are limited.

Unsatisfactory results of surgery alone in locally advanced gastric adenocarcinoma have led to an increased interest in adjuvant or neoadjuvant therapeutic approaches. According to a meta-analysis published by Hu in 2002, intravenous adjuvant chemotherapy after gastrectomy may have a positive effect on the outcome in gastric cancer [1]. However, the evidence is not strong because of the generally low methodological quality of most of the randomized trials of adjuvant chemotherapy. The principal aim of neoadjuvant therapy is to enable the surgeon to achieve radical resection with microscopically negative margins (R0 resection). Preoperative radiotherapy in gastric cancer has been tested in several non-randomized [2, 3, 4, 5] and randomized studies [6, 7, 8].

AIM

The aim of the present retrospective analysis was to evaluate toxicities and the rate of radical resection with microscopically negative margins (R0 resection) in gastric adenocarci-

noma treated according to a protocol of preoperative neoadjuvant chemoradiation.

MATERIALS & METHODS

Patients

Between March 1999 and December 2003, 32 patients, 22 males and 10 females, median age 63 (range 28–80) years, with gastric adenocarcinoma were treated with neoadjuvant chemoradiation at the Department of Oncology and Radiotherapy, Charles University Medical School Teaching Hospital in Hradec Králové. Initial examinations included case history, physical examination, blood count, biochemistry, lung X-rays, abdominal US, gastroscopy, spiral abdominal contrast CT, endosonography, and endobiopsy. Staging was based on AJCC classification [9]. All patients had histology of adenocarcinoma: 1 patient grade 1, 10 patients grade 2, 17 patients grade 3 and 4 patients grade 4. Pre-treatment stage was as follows: 1 patient AJCC stage I.B, 12 patients stage II, 15 patients stage III.A and 4 patients stage IV.

Anatomical localization of the tumour was as follows: cardia 8 patients, body 6 patients, antrum 5 patients, pylorus 1 patient, lesser curvature 4 patients and greater curvature 8 patients. The median of pre-treatment haemoglobin level was 131 (range 92–163) g/l, leucocytes 7.4 (range 3.2–11.6) 10^9/l and thrombocytes 260 (range 122–438) 10^9/l.

Toxicity was evaluated according to the Common Toxicity Criteria for Adverse Events version 3.0.

Treatment

The following regimens of chemoradiation were used: two 3-week cycles of 5-fluorouracil (5-FU) 200 mg/m^2 continuously days 1–21 with calcium folinate 45 mg per day, cisplatin 25 mg/m^2 days 1, 8, 15, paclitaxel 60 mg/m^2 days 1, 8, 15 and concomitant radiotherapy 30 Gy in 15 fractions (2 Gy daily) of stomach and regional nodes (10 patients; completed in 5/10 patients), in 6/10 patients combined with ultrasound hyperthermia once weekly during the second cycle of chemotherapy (completed in 2/6 patients); 5-FU 200 mg/m^2 continuously 4 weeks and cisplatin 25 mg/m2 days 1, 8, 15, 22, paclitaxel 60 mg/m2 days 1, 8, 15, 22 and concomitant radiotherapy 40 Gy in 20 fractions (2 Gy daily) of stomach and regional nodes (5 patients; completed in 1/5 patients), in 2/5 patients combined with ultrasound hyperthermia once weekly (completed in all patients); 5-FU 200 mg/m^2 continuously 3 weeks and cisplatin 25 mg/m^2 days 1, 8, 15 and concomitant radiotherapy 30 Gy in 15 fractions (2 Gy daily) of stomach and regional nodes (7 patients; completed in 5/7 patients); 5-FU 200 mg/m2 continuously 4 weeks and cisplatin 25 mg/m2 days 1, 8, 15, 22 and concomitant radiotherapy 40 Gy in 20 fractions (2 Gy daily) of stomach and regional nodes (3 patients; completed in all patients); 5-FU 200 mg/m^2 continuously 4 weeks and concomitant radiotherapy 40 Gy in 20 fractions (2 Gy daily) of stomach and regional nodes (7 patients; competed in 5/7 patients). Surgery was performed within 5 weeks after completion of chemoradiotherapy. It consisted of gastrectomy with lymphadenectomy. Histological examination of the resected tissue with lymphatic block and surrounding lymph nodes was performed.

Radiation therapy

External beam radiation was administered concomitantly with the second cycle of chemotherapy.

Radiotherapy with two conformal radiation fields, anterior-posterior and posterior-anterior, involved the entire stomach with perigastric extension and major lymph nodes at risk. Fields were individually modified as it was necessary to spare as much normal tissue as possible, and to shield at least one wholly functional kidney in summation. Function of kidneys was initially evaluated by dynamic scintigraphy. The scheduled dose of radiation was delivered by a linear accelerator (Clinac 600 or Clinac 2100, Varian Medical Systems, Palo Alto, CA, U.S.A.) using 6-MV or 15-MV photons. Radiotherapy was delivered 5 days per week and covered every radiation field. A total dose of 30 Gy in 15 fractions was planned in 17 patients (in 1 of 17 patients the dose had to be reduced because of the haematological and gastrointestinal toxicity of chemoradiotherapy) and 40 Gy in 20 fractions in 15 patients (in 4 of 15 patients the dose had to be reduced because of the haematological and gastrointestinal toxicity of chemoradiotherapy).

Hyperthermia

Hyperthermia was performed using the Sonotherm 1000 Ultrasound Therapy System (Labthermics Technologies, Champaign, IL, U.S.A.) The temperature in the target volume was 41 ºC to 43 ºC for 45 minutes. Tissue up to a depth of 10 cm was heated by an ultrasound frequency of 1 MHz. Temperature was measured by 2 thermometric probes. Hyperthermia was applied during the chemoradiotherapy once weekly after administration of cisplatin and paclitaxel and after radiotherapy. Hyperthermia was planned in 8 patients (in 4/8 it had to be reduced because of the haematological and gastrointestinal toxicity of chemoradiotherapy).

Statistical analysis

Overall survival was analyzed using the Kaplan-Meier method.

RESULTS

Of the 32 patients treated with neoadjuvant chemoradiation, R0 resection was achieved in 19/32 (59%) patients, R1 (microscopic residual tumour) in 2/32 (6%) patients and R2 (macroscopic residual tumour) in 11 (34%) patients. Surgical stage was as follows: 2 patients pathologically complete response, 3 patients AJCC stage I.A, 5 patients stage I.B, 7 patients stage II, 7 patients stage III.A, 1 patient stage III.B, 7 patients stage IV. Downstaging after neoadjuvant chemoradiotherapy was achieved in 17/32 (53%) patients. At the date of evaluation (31 March 2009), 4 patients were still alive 58, 81, 86 and 98 months from the date of diagnosis. The median survival was 18 months (95% confidence interval (C.I.): 13–38 months) [Graph]. One-year survival was 69% (95% C.I.: 53%–85%), two-year survival 50% (95% C.I.: 33%–67%), three-year survival 38% (95% C.I.: 21%–54%) and four-year survival 19% (95% C.I.: 5%–34%). In multivariate analysis, only low grade was an independent indicator of better prognosis (hazard ratio 0.14, 95% C.I. 0.03–0.63, p = 0.01). Among 19 patients 12 patients had a recurrence after R0 resection, including 3 patients with abdominal carcinomatosis, 1 patient with abdominal carcinomatosis and liver metastases, 2 patients with liver metastases, 3 patients with retroperitoneal lymph node metastases, 2 patients with lung metastases and 1 patient with local recurrence and left ovarian metastasis.

Treatment compliance and toxicity

Preoperative neoadjuvant chemoradiotherapy was relatively well tolerated in most patients, and there was no treatment-related mortality. Most adverse events were mild to moderate in intensity, and all of them recovered spontaneously with supportive management. Grade 3–4 leucopenia occurred in 4/32 (13%) patients, grade 3–4 thrombocytopenia in 2/32 (6%) patients, grade 3 anaemia in 2/32 patients (6%), and nausea, vomiting and diarrhoea grade 3 in 5/32 (16%) patients. The median nadir of haemoglobin was 115 (range 65–147) g/l, leucocytes 2.95 (range 0.6–6.3) 109/l and thrombocytes 154 (range 18–259) 109/l. One patient suffered myocardial infarction 28 days after completion of neoadjuvant chemoradiation. The neoadjuvant regimen was completed as planned in 19/32 (59%) patients, but in the remaining patients the intensity of chemotherapy had to be reduced because of haematological and gastrointestinal toxicity. 4/8 (50%) patients did not complete potentiation with hyperthermia and 5/32 (16%) patients did not complete radiotherapy. In 16/32 patients pleural adhesion was observed in the region of the left costophrenic angle on the chest X-ray. In 4 patients this was observed on the baseline staging chest X-ray before the start of neoadjuvant chemoradiotherapy, in 2 patients in the period after the start of neoadjuvant chemoradiotherapy before surgery and in 10 patients after surgery. In 1 patient pleural adhesion was observed in the region of the right costophrenic angle after surgery. Neoadjuvant chemoradiotherapy did not increase surgical mortality. We did not observe hand-foot syndrome in this series of patients. There was no treatment-related death.

DISCUSSION

Present retrospective data indicate the use of neoadjuvant chemoradiation in patients with gastric carcinoma. As expected, tumour grade was an independent prognostic factor in the present cohort. No other independent prognostic indicators were identified, but the size of the cohort was rather limited for multivariate analysis.

In Western countries, the majority of patients diagnosed with gastric carcinoma have locally advanced disease [10]. A curative resection can be performed in about half of these patients, but even after an R0 resection two thirds of the patients will present with recurrence within 2–3 years [10, 11].

The advantage of preoperative radiotherapy, compared with postoperative radiotherapy, is that the target volume is much easier to delineate because the tumour is still in situ. Moreover, tumour downsizing may facilitate surgery [12]. Pathological evaluation of response to therapy adds prognostic information [13]. The neoadjuvant approach allows assessment of pathological response in the treated tumour. The obvious disadvantage is that pretreatment pathological staging is absent [12].

Two randomized trials of adjuvant radiotherapy versus surgery alone were performed [10, 14, 15]. Both trials concluded that there is no evidence of benefit for adjuvant radiotherapy alone in gastric cancer [10, 14, 15]. A three-arm randomized trial, performed by the British Stomach Cancer Group, compared adjuvant chemotherapy, adjuvant radiotherapy and surgery alone [14]. The five-year survival for surgery and adjuvant chemotherapy was 19%, for surgery and adjuvant radiotherapy 12% and surgery alone 20% [14]. In a randomized trial in 115 patients with resectable gastric carcinoma patients received adjuvant intraoperative radiotherapy or surgery alone [15]. There was no evidence of a benefit for adjuvant intraoperative radiotherapy [15].

A prospective randomized Chinese trial in 370 patients compared surgery with preoperative radiotherapy of 40 Gy and surgery alone [6]. The five-year and ten-year survival of the preoperative and surgery group and the surgery alone group were 30% and 20%, 20% and 13%, respectively [6]. Resection rates (90% versus 79%) and radical resection rates (80% versus 61%) also increased after preoperative radiotherapy [6].

In a randomized trial of intensive preoperative radiotherapy with local hyperthermia for the treatment of gastric carcinoma 293 patients were randomized into 3 treatment groups: surgery alone, surgery with preoperative radiotherapy (20 Gy in 4 fractions) and surgery with preoperative radiotherapy (20 Gy in 4 fractions) and hyperthermia [7]. Preoperative radiotherapy did not improve 3- or 5-year survival in gastric cancer patients in comparison with surgery alone [7]. Preoperative radiotherapy in combination with local hyperthermia significantly improved three-year and five-year survival [7]. In unresectable gastric adenocarcinoma patients, radiotherapy and radiotherapy with hyperthermia both increased mean survival [7].

In a Russian trial, 152 patients were randomized between surgery with preoperative radiotherapy (20 Gy in 5 fractions) and surgery alone [8]. The five-year survival of the preoperative and surgery group and the surgery alone group were 39% and 30%, respectively, which was not statistically different [8]. The same authors performed a prospective clinical trial of preoperative radiotherapy (20 Gy in 5 fractions) in combination with a radiosensitizer (metronidazole). Of 91 patients who received preoperative radiotherapy, 67 patients were operated on with curative intent and were eligible for further analysis. Acute gastrointestinal toxicity was significant, but manageable without delaying surgery in most cases. There were 4 postoperative deaths. The five-year and ten-year survival was 46% and 36%, respectively [5].

In a phase I-II study of neoadjuvant radiochemotherapy for locally advanced gastric cancer 19 patients were enrolled and 18 completed neoadjuvant therapy [4]. Patients received 2 cycles of cisplatin on day 1, 5-fluorouracil (5-FU) on days 1 to 4 and leucovorin on days 1 to 4 every 3 weeks, concomitantly with radiotherapy escalated in 3 dose tiers (31.2, 38.4 and 45.6 Gy) [4]. Pathological assessment showed 1 complete and 8 partial responses [4]. Two-year and three-year survival rates were 71% and 59%, respectively [4]. Only 1 patient relapsed locally, and the peritoneum was the most frequent site of relapse [4].

In a pilot study, 24 patients were treated with preoperative external beam radiotherapy (45 Gy) with concurrent 5-FU given as a continuous infusion [16]. Surgical resection and intraoperative radiotherapy to a dose of 10 Gy followed 4–6 weeks after chemoradiotherapy [16]. A pathologically complete response was observed in 2 (11%) of the resected patients and 12 (63%) had pathological evidence of a significant treatment effect [16].

Thirty-four patients were enrolled in a multi-institutional trial of preoperative chemoradiotherapy in patients with potentially resectable gastric carcinoma [2]. Patients received up to two 28-day cycles of induction chemotherapy of 5-FU, leucovorin, and cisplatin, followed by 45 Gy of radiation plus concurrent 5-FU [2]. Twenty-eight (85%) of 33 patients underwent surgery [2]. The R0 resection rate was 70% and the pathologically complete response was 30% [2]. A pathologically partial response was observed in 8 patients (24%) [2]. The median survival time for 33 patients was 33.7 months [2]. Patients achieving a pathologically complete response or pathologically partial response had a significantly longer median survival time (64 months) than those achieving a less than pathologically partial response (13 months) [2]. There were 2 treatment-related deaths [2].

In the study of paclitaxel-based chemoradiation in localized gastric carcinoma 41 patients received two 28-day cycles of induction chemotherapy of 5-FU, paclitaxel, and cisplatin followed by 45 Gy of radiation and concurrent fluorouracil plus paclitaxel [3]. Pathological response and R0 resection were correlated with overall survival and disease-free survival [3].

Forty patients (98%) underwent surgery, and 78% had an R0 resection [3]. There was a pathologically complete response of 20% and a pathologically partial response of 15% [3].

The Southwest Oncology Group (SWOG)/ Intergroup 0116 trial in 556 patients demonstrated that combined chemoradiation following complete gastric resection improves median time to relapse (30 versus 19 months) and overall survival (36 versus 27 months) [17]. Acute toxicity grade 3 was observed in 41% and grade 4 in 32% [17]. Three patients (1%) died from the toxic effects of the chemoradiotherapy [17].

Several phase II studies of combination regimens of paclitaxel plus cisplatin or paclitaxel plus 5-FU for the treatment of advanced gastric cancer patients yielded response rates of 22%–65% and median survival times of approximately 10 months (range 6–14 months) [18, 19, 20, 21]. Although the studies differed with respect to drug regimen and population treated, the regimens were generally well tolerated, with myelosuppression as the most common toxicity [22]. At our department paclitaxel was added in 16 patients.

With the addition of concomitant chemotherapy to radiotherapy, acute toxicity, specifically myelosuppression, increases significantly. The risk of myelosuppression increases with increasing number of chemotherapy agents or with increasing dose intensity.

It has been demonstrated in a meta-analysis of tumours of other primary locations that continuous intravenous infusion of 5-FU is superior to 5-fluorouracil bolus in terms of tumour response, and achieves a slight increase in overall survival [23]. Similarly, haematological toxicity was low in the present cohort of patients. Haematological toxicity is much less important in patients who receive 5-FU as a continuous intravenous infusion, but hand-foot syndrome is more frequent in this group of patients [23]. We did not observe hand-foot syndrome in the present cohort of patients.

Concomitant chemoradiation has several advantages in comparison with both approaches used separately. A synergistic effect within the irradiated volume can be achieved and chemotherapy can affect micrometastases outside the irradiated fields. Chemoradiation has been successful in other gastrointestinal tumours, such as rectal, anal, oesophageal and pancreatic cancers and also in the palliative therapy of gastric cancer.

In our study on preoperative chemoradiation, we used a combination of continuous 5-FU, cisplatin and paclitaxel. Paclitaxel and concurrent application of radiotherapy in patients with inoperable gastric cancer demonstrated substantial locoregional activity [24]. The haematological and gastrointestinal toxicity was lower than reported in the literature [17]. A relatively low dose of radiation was selected because of the fear of complications, but a favourable safety profile may allow for an increase of the dose up to 40 Gy in the future.

CONCLUSION

Neoadjuvant concomitant chemoradiotherapy for locally advanced gastric adenocarcinoma based on application of 5-FU, cisplatin, and paclitaxel, with radiotherapy at a dose of 30–40 Gy is well tolerated and leads to a high percentage of pathological tumour responses and resections with microscopically negative

margins. In part of the presented cohort of patients we later retrospectively investigated the expression of epidermal growth factor receptor (EGFR), p53, p21 and p16 [25, 26].

We conclude that preoperative neoadjuvant chemoradiation using the schedules outlined above is relatively well tolerated, has acceptable toxicity, can lead to a high rate of R0 resections, does not seem to increase the operative risk, and might increase the locoregional control of the disease. An optimal regimen has to be identified in future studies.

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