Radiotherapy and chemoradiotherapy as a novel option for the treatment of locally advanced inoperable gastric adenocarcinoma: A phase II study

JERZY WYDMANSKI, KINGA GRABINSKA, PAWEŁ POLANOWSKI, AGNIESZKA NAMYSŁ-KALETKA, RAFAL KAWCZYNSKI, MALGORZATA KRASZKIEWICZ and WOJcieCH MAJEWSKI

Department of Radiotherapy, Maria Sklodowska-Curie Memorial Cancer Center and Institute of Oncology, Gliwice Branch, 44-101 Gliwice, Poland

Received May 8, 2014; Accepted June 23, 2014

DOI: 10.3892/mco.2014.348

Abstract. This phase II trial aimed to evaluate the tolerance and efficacy of radical radiotherapy or chemoradiotherapy in patients with primarily inoperable gastric cancer. The analysis was based on 13 patients with primarily inoperable gastric cancer. A total of 6 (46.2%) patients refused surgery and 7 (53.8%) had contraindications to anesthesia due to cardiological or respiratory reasons (4 and 3 patients, respectively). The treatment regimen consisted of radiotherapy and chemotherapy based on 5-fluorouracil. Half of the patients were not qualified to receive chemotherapy due to the presence of comorbidities. A total dose of 45 Gy was administered in 25 fractions. Of the 13 patients who started treatment, 12 (92.3%) completed radiotherapy. Local treatment response was observed in 6/12 patients (50%), with 5/12 (41.7%) displaying clinical complete response and 1/12 (8.3%) partial response. The 1- and 3-year overall survival rates and the median survival were 59 and 48% and 17.1 months, respectively. In conclusion, radical radiotherapy, either alone or in combination with chemotherapy, is safe for patients with inoperable locally advanced gastric cancer and may prolong survival.

Introduction

In patients with gastric cancer, both the stage of the cancer and the patient’s performance status (PS) are taken into consideration when selecting the treatment regimen. In elderly patients, the number of coexisting diseases, the history of the disease and the extent of the planned surgery may limit the possibility of general anesthesia and are associated with a high risk of life-threatening perioperative complications. The proportion of patients with gastric cancer who did not undergo surgery increased from 8% prior to 1970 to 29% in 1990, due to improved pretreatment selection (1). It was estimated that ~10% of patients with locally advanced gastric cancer are not eligible for surgery due to their poor general condition or contraindications to general anesthesia. In such patients, chemotherapy is also usually contraindicated. A proportion of elderly patients do not agree to surgery due to their concerns regarding postoperative complications. For this group of patients, best supportive care (BSC) is the treatment of choice. BSC may improve the quality of life, but offers no survival benefits. There is a lack of alternative treatment regimens for this group of patients. Palliative radiotherapy provides relief of symptoms in the majority of patients and marginally prolongs survival (2-7). In our institution, over the last 10 years neoadjuvant chemoradiotherapy has been used in patients with operable gastric cancer (8). This type of therapy appears to be well tolerated, even by older patients. A high rate of pathological response and R0 resection, low rate of local recurrence and high percentage of 2-year survival were observed and these results prompted us to attempt the use of radical radiotherapy/chemoradiotherapy in patients with inoperable gastric cancer. Such treatment may increase the chance of a cure. The aim of this study was to present our experience with treatment tolerance and patient outcomes with this regimen.

Materials and methods

Patient population. Patients with biopsy-proven locally advanced inoperable gastric adenocarcinoma, with no evidence of distant metastases, were treated with radiotherapy or chemoradiotherapy. All the patients were required to have a Eastern Cooperative Oncology Group (ECOG) PS of 0-2, to be aged 20-85 years, have serum creatinine levels <1.5 mg/dl, serum bilirubin levels <2.0 mg/dl, a granulocyte count >1,500 cells/µl and a platelet count >100,000 cells/µl.

The pretreatment staging included a complete physical examination, oesophagogastroscopy with biopsies, chest X-ray or computed tomography (CT) and CT of the abdomen. Endoscopic ultrasonography is not yet available in our institution. The patients were not staged with laparoscopy. This staging was focused on identifying patients with distant...
metastases, who were excluded from this study. The study was performed in accordance with the Good Clinical Practice guidelines and the Declaration of Helsinki.

A total of 13 patients were investigated, 3 women (23.1%) and 10 men (76.9%), with a median age of 74 years (range, 52-83 years). Patients were enrolled in the study from February, 2008 to June, 2013. A total of 6 patients (46.2%) refused surgery and 7 (53.8%) had contraindications to anesthesia due to cardiological or respiratory reasons (4 and 3 patients, respectively). A total of 6 patients (46.1%) had an ECOG PS of 0, 5 (38.5%) had an ECOG PS of 1 and 2 (15.4%) had an ECOG PS of 2. The tumors were located predominantly in the cardiac region in 9 patients (69.2%), in the body of the stomach in 3 (23.1%) and in the antral region in 1 patient (7.7%). The pretreatment tumor stages were as follows: T1-2, 5 patients (38.5%) and T3, 8 patients (61.5%). There was no nodal involvement (N0) in 8 patients (61.5%) and N1-3 disease was found in 5 patients (38.5%). The median tumor volume was 89 cm³ (range, 25-211 cm³).

A total of 4 patients lost >10% of their weight. A reduced serum albumin level to <3.5 g/dl caused by malnutrition was observed in 2 patients (15.4%). A total of 38% of the patients were found to be anemic (hemoglobin concentration <12 g/dl). The incidence of thrombocytosis, defined as platelet count >400,000 cells/µl, was 23.1%. Carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (CA 19-9) were found to be anemic (hemoglobin concentration <12 g/dl). The incidence of thrombocytosis, defined as platelet count >400,000 cells/µl, was 23.1%. Carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (CA 19-9) levels were elevated above the cutoff level in 30.8 and 46.1% of patients, respectively. The patient characteristics are listed in Table I.

Radiotherapy. The treatment regimen consisted of radiotherapy and chemotherapy administered for 35 days. The total dose of 45 Gy was administered in 25 fractions, with 5 fractions per week for 5 weeks. The biologically effective dose (BED), calculated using the linear-quadratic formalism (9) and an α/β ratio of 10 for early responding-tissues (tumor), was 53.1 Gy. The tumor volume and location were defined on the basis of CT scans of the abdomen and upper gastrointestinal endoscopy reports. The treatment fields encompassed the stomach and regional lymph nodes (gastric, celiac, gastroduodenal, porta hepatitis, splenic, suprapancreatic, retropancreaticoduodenal and lower oesophageal). The longitudinal margins of the esophagus or duodenum (5 cm) were included when the tumor involved the cardia or the gastro-duodenal junction (10). Radiation therapy was delivered with a high-energy linear accelerator (Clinac 23EX; Varian Medical Systems, Palo Alto, CA, USA) using 6-20 MV photons. Three-dimensional conformal treatment planning was used for all the cases in this study. Radiotherapy was performed using intensity-modulated radiation therapy (8 patients), four-field isocentric technique (3 patients) and tomotherapy (1 patient).

Concurrent chemotherapy. The concurrent chemotherapy regimen was based on 5-fluorouracil (5-FU). Chemotherapy was administered at least 1 h prior to starting irradiation. 5-FU was administered intravenously as a 10-min bolus injection. Patients routinely received prophylactic antiemetic support. Bolus infusions of 5-FU (325 mg/m² of body surface area) were administered intravenously on days 1-5 and 29-33. Complete blood cell (CBC) count, liver and renal tests were monitored prior to each course. CBC counts were evaluated at least once per week. Over half of the patients were not qualified to receive chemotherapy due to comorbidities. Five patients (38.5%) received 2 cycles of concurrent 5-FU during radiotherapy and 1 patient (7.7%) received 2 cycles of epirubicin, oxaliplatin and capcitabine prior to qualification for radiotherapy.

Toxicity criteria and tumor response. Treatment-related toxicity was classified according to the Common Terminology Criteria for Adverse Events, version 3.0 (11). Nausea, vomiting, diarrhea, leukopenia, granulocytopenia, lymphocytopenia and thrombocytopenia were assessed weekly. The quality of life was assessed using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30. Tumor response was assessed based on CT scans.

Statistical analysis. The survival function was computed using the Kaplan-Meier method. The overall survival (OS) was calculated from the start of the radiation therapy. Comparisons of survival curves were performed using the Cox’s F-test and P<0.05 was considered to indicate a statistically significant difference. The Chi-square or Fisher's exact tests were used to assess the association between clinical factors and clinical response rates after therapy. All the statistical computations were performed using Statistica software, version 10 (StatSoft, Inc., Tulsa, OK, USA).

Follow-up. Each patient was assessed every 3 months after treatment for 5 years or until death from any cause. The follow-up evaluations included physical examination, oesophagogastrscopy, chest X-ray, transabdominal ultrasonography or CT scans of the abdomen, CBC count, CEA and CA 19-9 levels, liver and renal function tests.

Results

Tolerance and response to treatment. All 13 patients were assessed for tolerance to treatment and survival and 12 patients were assessed for clinical complete response. Of the 13 patients who started treatment, 12 (92.3%) completed radiotherapy. In 1 case (7.7%), radiotherapy was discontinued after 27 Gy due to worsening of a coexisting condition and the patient soon succumbed to the disease despite intensive hospital treatment. In 2 patients (15.4%), treatment was interrupted for a few days, due to hematological adverse events in one and due to worsening of a coexisting condition in the other patient. All 5 patients who were qualified for concurrent chemotherapy received 2 cycles of 5-FU as planned.

The incidence of the treatment-related adverse effects is shown in Table II. A total of 12 patients (92.3%) experienced a maximum of grade 3 or 4 lymphocytopenia. The median of decrease in the concentration of hemoglobin was -0.7 g/dl (range, -3.9-1.1 g/dl). Other hematological toxicities were infrequent. Only 1 patient developed grade 3 nausea/vomiting. There were no cases of grade 4 gastrointestinal toxicities. Tumor regression was assessed in the 12 patients (92.3%) who completed the radiotherapy. Of these 12 patients, 6 (50%) exhibited local response to treatment, with 5/12 (41.7%) displaying clinical complete response and 1/12 (8.3%) displaying partial response. Local progression and stable disease were observed in 4 (33.3%) and 2 (16.7%) patients, respectively (data not shown).
Survival and pattern of failure. The survival analysis was based on all 13 patients in the group studied. The median follow-up for surviving patients was 30.1 months (range, 7.3-65.4 months). No patients were lost to follow-up. At the time of the analysis, 7 (53.9%) of 13 patients were alive, 4 (30.8%) without signs of disease and 3 (23.1%) with local progression of the tumor. Among the 6 (46.1%) deceased patients, 2 (15.4%) succumbed to tumor progression, 2 (15.4%) succumbed to distant metastases, 1 (7.7%) succumbed to tumor progression and distant metastases and 1 (7.7%) died during radiotherapy due to worsening of a coexisting disease. The 1- and 3-year OS rates and median survival were 59 and 48% and 17.1 months, respectively. The survival curve is depicted in Fig. 1.

Prognostic factors. Among the different clinical factors affecting the OS rate, lower tumor stage (T1-2 vs. T3, P<0.031), lymph node metastasis (present vs. absent, P<0.021) and complete or partial tumor regression following therapy (yes vs. no, P<0.019) were statistically significant (data not shown). The following clinical characteristics were not found to be prognostic: gender, age, PS, histology, tumor location, tumor volume, type of treatment (radiotherapy vs. chemoradiotherapy), pretreatment hemoglobin concentration, CEA and CA 19-9 levels.
patients. Neoadjuvant treatment in 35% of patients was considered good PS. Multidrug chemotherapy used in patients (12) reported a survival improvement, with a median actuarial OS of 17.1 months. The survival benefit observed in a study assessing the feasibility and efficacy of radical radiotherapy was similar to those reported by Saikawa et al. (13), who evaluated preoperative chemoradiotherapy for unresectable or incurable gastric cancer. Better results were observed in trials comparing radiotherapy to neoadjuvant chemoradiotherapy followed by surgery for operable gastric cancer (8,14-18). High-dose chemotherapy may be a suitable palliative treatment only for patients exhibiting a good PS. Multidrug chemotherapy used in patients with unresectable or metastatic gastric cancer appears to be intolerably toxic for patients with medically inoperable gastric cancer. In our group, over half of the patients were disqualified from 5-FU alone administered at low doses as a radiosensitizer. However, our results demonstrated that even radiotherapy alone exerted a beneficial effect on treatment outcome.

Radiation therapy may be considered an effective treatment for gastric cancer. In our study, a complete or partial tumor regression following radiotherapy was observed in half of the patients. Suzuki et al. (12) reported that 35% of the patients achieved a clinical complete response. Unfortunately, in our study, no parameters were identified which could be used to predict the degree of clinical tumor response. In the other study, the patients who achieved clinical complete response exhibited a longer OS (12). None of our patients underwent surgery and, therefore, the percentage of pathological response cannot be determined. Neoadjuvant treatment was found to induce a high rate of pathological response, ranging between 6 and 36% (14-18). As expected, in our study, tumor stage and lymph node status affected the OS.

The tolerance to treatment was satisfactory, with a toxic death rate of 7.7% (1/13). Despite intensive hospital treatment, the PS of the patient deteriorated and he succumbed to the disease 2 weeks after the discontinuation of radiotherapy (after 27 Gy). We cannot unambiguously determine the cause of death. The patient was the oldest among the group and had a pretreatment PS of 2. The severity of the side effects was the highest among all the patients: grade 3 nausea/vomiting, grade 2 diarrhea and grade 3 lymphocytopenia. This case highlights the need for careful qualification of patients aged >80 years with a PS of 2. In previous palliative studies there was no reported treatment-related mortality (2,3). However, Saikawa et al. (12) reported 1 case (3%) of lethal events following radical chemoradiotherapy. Myelosuppression was the most commonly observed toxicity. Almost all the patients developed grade 3 or 4 lymphocytopenia. Co-trimoxazole was used as a prophylaxis against Pneumocystis carinii pneumonia when lymphocytopenia was <500 cells/μL. There were no observed grade 3 or 4 granulocytopenia or thrombocytopenia. In palliative studies, the incidence of grade 3 or 4 hematological toxicities was low (2,3). In our study, other observed treatment toxicities included mild nausea/vomiting and diarrhea. Other authors reported grade 3 gastrointestinal toxicity ranging between 3 and 14% (2,3). The toxicity in our study was comparable to that reported regarding neoadjuvant therapy.
chemoradiotherapy (8,13). Modern individual treatment planning based on CT scans and multi-field conformal techniques allow the reduction of the risk of localization errors and enable sparing of normal tissues (kidneys, spinal cord, liver and bowel), while maintaining a relatively high local control rate. The present study demonstrated that the prescribed schedule of radiotherapy and chemoradiotherapy was relatively well tolerated and the complication rate was considered acceptable; however, it is our opinion it may be better administered under hospitalization in elderly patients. In conclusion, inoperable gastric cancer is considered to be an incurable disease. Our results demonstrated that such an approach may be inaccurate and requires revision. Radical radiotherapy, alone or in combination with chemotherapy, is a safe and well-tolerated treatment modality for patients with primarily inoperable gastric cancer and may prolong survival.

Acknowledgements

This study was supported by The National Science Centre of Poland (grant no. NN 403 238 140).

References