Long-term survival of a young patient after multi-disciplinary treatment of initially inoperable stomach cancer with metastases to the liver and visceral lymph node

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ABSTRACT

This paper reports on a 5-year survival of a 30-year-old male patient initially diagnosed with inoperable stomach cancer with metastases to the liver and the visceral lymph node. The systemic treatment regimen (8 cycles of DCF chemotherapy) resulted in an almost complete regression and enabled implementation of a radical resection of the stomach along with the spleen. Eight months into the treatment, the disease progressed producing several metastatic lesions to the liver. The patient received second-line palliative chemotherapy (4 cycles of EOX) which led to a significant reduction of the lesions. This enabled hepatic metastasectomy. The patient has remained in remission for 3 years.

KEY WORDS: inoperable stomach cancer, liver metastases, palliative chemotherapy, regression of lesions, radical resection

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INTRODUCTION

In Poland, malignant gastric tumours are the 6th most common type of cancer in male and 10th in female patients, and represent 6th and 7th cause for cancer-related mortality, respectively. However, morbidity and mortality in both sexes shows a long-term downward trend [1].

The ethiology of stomach cancer has remained unclear for decades. At present, the best known and most researched risk factor is a chronic *Helicobacter pylori* infection, however tumours only occur in very few infected patients [2].

In its early stage, stomach cancer does not produce characteristic symptoms. On the other hand, advanced stomach cancer is associated with upper abdominal pain, dysphagia, odynophagia, vomiting, reduction in body weight and signs of bleeding from the upper gastrointestinal tract.

Unfortunately, stomach cancer is usually diagnosed after it has progressed to an advanced stage when treatment is very difficult or sometimes impossible [2, 3].

Over 90% of all malignant gastric cancers are adenocarcinomas. The type of adenocarcinoma, as determined in accordance with Lauren's histo-clinical classification, is significant in view of the possible surgical interventions and prognosis.

1. Intestinal-type gastric carcinoma represents ca. 50% of all stomach cancers. When looking at its structure, this type of cancer resembles the intestinal mucosa and in built predominantly from glandular structures. It usually co-occurs with atrophic gastritis and intestinal metaplasia. Intestinal-type carcinoma produces expanding infiltrations and is associated with a better prognosis. This type of carcinoma is usually relatively sharply demarcated from the surrounding tissue, which makes it possible to use a 2.5 cm narrower safety margin. Accordingly, it often leads to only a partial resection of the stomach [4, 5].

2. Diffuse-type gastric carcinoma represents ca. 40% of all stomach cancers. It exhibits intramural growth, with diffuse cancerous tissues. Macroscopic infiltration of the normal gastric mucosa occurs often and may extend many centimetres beyond the visible tumour border. For this reason, a much larger safety margin must be used (at least 8 cm). In practice, this translates into a total resection of the stomach. Due to its severe malignancy, this type of gastric tumour is associated with worse prognosis.

Determination of HER2 (human epidermal growth factor receptor 2) status is a significant predictive factor in gastric cancer treatment. The status of this receptor needs to be determined at the time of diagnostic tests as overexpression (HER2+++) may predispose patients to the development of metastases to lymph nodes. This is of particular importance when assessing the patient's eligibility for surgical treatment. HER2 overexpression is mostly identified in the intestinal-type of gastric carcinoma located at the gastroesophageal junction and prepyloric region of the stomach [4, 5].

CASE REPORT

A 30-year-old male patient with no history of prior chronic treatment, working as an architect, with no addictions, presented at the Emergency Room of the hospital in Pruszków (May 2011). The patient reported vomiting for nearly 3 weeks, and choking for the last 2 days on every attempt at eating and drinking, with no reduction in body weight and not signs of bleeding from the gastrointestinal tract. Based on the physical exam, a slight soreness in the upper middle abdomen was identified. No abnormalities were found in the laboratory test results, the thoracic X-ray image and the ECG. A gastroscopy and an X-ray scan of the gastrointestinal tract with a contrast agent were performed. At the cardia of the stomach, a hard, spontaneously bleeding organic infiltration was discovered which produced resistance when the end of the gastroscope was passed through. Right below the cardia, on the greater-curvature side, a bulge made of reddened and swollen mucous membrane was seen. Multiple samples were taken from the lesion for histopathological examination. The abdominal ultrasound scan showed a well demarcated focal lesion measuring approx. 27 mm in the right lobe of the liver. No CT scan was performed at that time due to the presence of the contrast agent in the upper gastrointestinal tract. The histopathological study of the sample obtained during gastroscopy showed G3 adenocarcinoma of intestinal-type, according to Lauren's classification. Adenocarcinoma infiltration was found in the gastric mucosa and under the multi-layer flat epithelium. The abdominal CT scan showed a significantly thickened wall of the cardia (up to 20 mm) with a probable infiltration of the left side of the diaphragm; it was in contact with the edge of the liver and the aortic wall, with no signs of their infiltration. The subcardial lymph node was enlarged (approx. 21 mm). Metastatic lesions were present in the liver, including three foci measuring ca. 27 mm, 15 mm and 13 mm in segment VIII and a single focus measuring approx. 20 mm in segment VII.

The patient presented to the Białystok Cancer Centre in a good general condition in June 2011 to undergo causal treatment. He reported vomiting, choking and difficulties with swallowing solid food. Physical examination did not reveal any significant abnormalities. The patient mentioned a history of cancer in the family (his grandfather had cancer of the larynx and grandmother had cervical cancer).

Laboratory test results did not show any abnormalities. Tumour marker tests (CEA, Ca 19.9) were within the normal range, and the level of Ca 72.4 was elevated at 11.66 U/ml (normal range: 0.0–6.7 U/ml). PET-CT (positron emission tomography – computed tomography) scan was performed which confirmed presence of carcinoma in the lower section of the oesophagus and the gastric cardia, whose stage was assessed at IV B according to PET, with metastases to the liver and the visceral lymph node. The patient's general condition prior to treatment was good (WHO 0). The patient was referred for palliative chemotherapy based on cisplatin and 5-fluorouracil in a full dose per BSA (body surface area) 2.0 m^2 every 21 days (160 mg intravenous cisplatin once daily and 8000 mg 5-fluorouracil in a 96-hour continuous intravenous infusion). The patient tolerated the treatment well. Two days after the completion of chemotherapy, the patient experienced nausea and vomiting assessed at G1 according to WHO.

Upon admission for the second cycle of treatment, the patient reported a significantly improved ability to swallow which made it possible for him to ingest solid food. The HER2 test result was negative. For this reason, trastuzumab was not an option to consider (in Poland, this substance is only used in patients diagnosed with HER2+++ overexpression and no history of prior chemotherapy for metastatic disease). A decision was made to combine the existing regimen with 150 mg intravenous docetaxel (75 mg/m^2) once daily.

After three cycles of treatment, the patient had a port placed with access from the internal jugular vein.
After four cycles of chemotherapy, a follow-up abdominal CT scan showed a reduction in the gastric wall thickness to 9 mm and a regression of the metastases to the liver, with only a single lesion measuring 17 × 12 mm present in the right lobe. A decision was made to administer 2 further cycles of treatment after which an evaluation was performed. PET-CT and CT scans showed a significant regression of the lesions in the gastric cardia as well as reduction in the metastases to the liver and the visceral lymph node.

The patient was referred for a surgical consultation to the General Surgery, Transplantology and Liver Chair and Clinic of the Faculty of Medicine at the Warsaw Medical University to assess his eligibility for a surgical intervention. Upon consultation with a clinical transplantology surgeon, given the spectacular regression of the lesions, the chemotherapy was extended to 8 cycles. After completion of treatment, a PET-CT scan was performed. It showed residual lesions in the stomach and liver, which attested to the positive response to treatment.

While receiving chemotherapy, the patient did not receive any agents for prevention of neutropenic fever. CBC was recommended to be made every 5 and 10 days upon completion of each cycle of treatment. The leukocyte and neutrophil levels were not decreased, there were no signs of infection and the other blood counts were also normal.

While in a very good condition, the patient was assessed as eligible for surgery which took place at the Independent Public Central Clinical Hospital of the Warsaw Medical University in April 2012.

According to the surgery records, no metastases and nodular lesions were identified in the abdominal cavity. A palpation revealed no focal lesions in the liver. The entire stomach with the omentum and spleen were removed. The oesophagus was anastomosed with the loop of small intestine prepared employing the Roux-Y method. As the hepatic metastases were neither visible nor palpable, the scope of the surgery was not expanded at that point. The extensive nature of the surgery and prior long-lasting cytostatic treatment were factored in. A decision was made to postpone a debate on a possible liver resection (the original metastasis site) after evaluation of the post-surgery course of the disease and its progression a few weeks later. No complications occurred during the surgery.

In the late June / early July 2012, a follow-up PET-CT scan was performed which confirmed a continued complete remission of the disease. The patient was closely monitored (appointments at the cancer outpatient clinic scheduled every 3 months and image scans performed every 6 months).

In November 2012, scans (CT and PET-CT) of the liver showed a hypodense lesion measuring 54 × 44 mm in segment V and VI which resembled a metastasis. Tumour markers (CEA, CA 19.9 and Ca 72.4) were within the normal range. Due to evident progression of the disease with metastases present in the liver,

the patient was referred for second-line palliative chemotherapy, possibly to be followed by a metastasectomy.

The patient kept working and asked for one-day oral therapy. He was initiated on EOX regimen recalculated for full doses per BSA 2.0 m² (100 mg intravenous epirubicin once daily, 260 mg intravenous oxaliplatin once daily, 2500 mg oral capecitabin /24 h for 14 days), with cycles scheduled every 21 days. After three cycles of treatment, an abdominal CT scan showed a partial response to treatment (the focal lesion in segment V and segment VI reduced in size to 43 × 37 mm) and small hypodense lesions in segment IV and segment VI, almost too small to be detected. No prophylaxis against neutropenic fever was used but the patient's blood count was checked every week. In total, 4 cycles of EOX chemotherapy were administered.

In March 2013, the patient was considered eligible for hepatic metastasectomy to be performed at the same surgery clinic where the patient had undergone the previous surgery.

According to the surgery records, no metastases were identified in the abdominal cavity. A metastasis with a diameter of approx. 4 cm was detected in the central part of the right hepatic lobe. Above that lesion, in segment VIII, close to the border of segment VII, a small lesion suggestive of another metastasis was seen. Based on that information, a decision was made to perform a right hemihepatectomy. The surgery was performed without complications, with a transient impairment of liver function.

Eight weeks after the surgery, a follow-up abdominal and pelvic CT scan was performed. The scan showed two hypodense areas measuring 11 and 9 mm in segment IV of the liver that resembled cysts. No other focal lesions were present.

Taking into account the successful outcome of the treatment to date, a multidisciplinary council, including a clinical oncologist, oncologist surgeon, radiotherapist, pathomorphologist and radiologist, resolved to monitor the patient only until progression of the disease. The patient was recommended to present for follow-up appointments at a cancer outpatient clinic and have image studies made every 3 months.

The disease has been in remission for 3 years, without any clinical symptoms present. The patient lives an active life. Lab test results, including tumour marker tests, remain within the normal range. The last thoracic, abdominal and pelvic CT scan (June 2016) showed no abnormalities. Hypodense areas measuring 8 and 9 mm (unchanged from previous scans) were seen in the liver (segments IV and V). The rectal wall was found to be thickened and an endoscopic examination was ordered for the patient.

DISCUSSION

A gastric cancer is known to have poor prognosis, with very few patients able to experience long-term survival. In the West, nearly two-thirds of patients suffer from locally advanced or metastasized disease. The median survival for gastric cancer patients is approx. 10 months, with less than 10% patients able to survive 5 years. Moreover, despite radical combination treatment (perioperative chemotherapy followed by a surgery) approx. 50–60% patients experience a local recurrence or distant metastases [6, 7].

The standard of care for metastatic gastric cancer is systemic therapy. According to historic data, the median survival for untreated patients is 3 months and for patients receiving the standard-of-care therapy is 7–15 months. Survival beyond 3 years is rare and survival beyond 5 years occurs in only approx. 2% cases [8]. Use of palliative chemotherapy in advanced stomach cancer improves survival rates and the quality of life when compared to symptomatic treatment.

When combined with DCF chemotherapy (5-FU and cisplatin), docetaxel shows the highest efficacy in metastatic gastric cancer and improves survival in comparison to two-drug therapy [4, 12].

In a prospective Phase III trial comparing different regimens in treatment of advanced gastric cancer, the median overall survival for EOX regimen was 11.2 months and the 1-year survival rate was 47%. Replacement of 5-FU with capecitabin and substitution of oxaliplatin for cisplatin does not adversely affect outcomes, is better tolerated by the patients and does not require intravenous hydration and continuous infusions [3, 4, 11]. Due to increased toxicity of treatment, primary prophylaxis based on granulopoietins is recommended. Only some patients with stage IV gastric cancer who received systemic treatment are eligible for a radical surgical intervention [2].

At present, metastasectomy of hepatic lesions in the course of gastric cancer is not considered to be a standard course of action. The vast majority of patients experience multiple hepatic

metastases, with implants and dissemination into the peritoneal cavity and metastases to visceral lymph nodes. These patients are not suitable candidates for surgery [9].

An analysis was made by Feng Tao et al. to compare 1-year, 3-year and 5-year survival rates in patients receiving systemic treatment combined with gastrectomy and hepatic metastasectomy (R1 or R1 resections) and patients receiving systemic treatment alone in Western and Southern Europe and Asia (Japan, China and Korea). The comparison was made in 1994–2015 and enlisted 678 patients diagnosed with gastric cancer metastasized to the liver. The results were verified by the GYMSSA trial, and the overall survival rate was 96% vs. 38% (systemic treatment vs. gastrectomy); 70.4% vs. 14% (systemic treatment vs. hepatic metastasectomy); and 42% vs. 0% (systemic treatment vs. systemic treatment alone) [9]. However, most of the analysed data did not have a control counterpart, and the limited number of long-term survivals was attributed to the group which had undergone resection of hepatic metastases. However, one must note that the outcomes of multidisciplinary treatment seem to be promising [10].

SUMMARY

In the discussed case, the patient received treatment for stage IV gastric cancer. A histopathologic study confirmed that the patient had adenocarcinoma of G3 malignancy class, and Lauren's intestinal type. Five-year survival for this type of gastric carcinoma is known to be better than for the diffuse type. The patient did not show HER2 overexpression. It is not known whether he had ever suffered from a *H. pylori* infection, which usually occurs more often in the intestinal-type of gastric cancer. Multidisciplinary treatment was implemented, with palliative chemotherapy and a surgery (complete gastrectomy and splenectomy), followed by second-line chemotherapy and metastasectomy of hepatic lesions, which lead to a 5-year survival so far. The factors that affected the course of the highly malignant disease in the young patient are difficult to determine (malignant tumours are usually more aggressive in young patients) because we still know too little about the biologic features of most carcinomas, including gastric carcinoma.

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