New possibilities for the treatment of gastric cancer

Nowe możliwości leczenia raka żołądka

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Abstract

Most cases of gastric cancer in Europe are detected in the advanced stages. The recommendations concerning diagnostic and therapeutic procedures currently in effect were presented during the 1st St. Gallen EORTC Gastrointestinal Cancer Conference in St. Gallen, in March 2012. The indispensable diagnostic tests are endoscopy with histopathological assessment of endoscopic biopsies, and CT scan of the abdomen and the chest. In the case of locally advanced gastric cancer the basis of treatment is a resection procedure. The type of surgery performed depends on the size of tumour (cT) and the state of lymph nodes (cN). In tumours cT2-4a and/or cN+ a total or subtotal gastrectomy is an obligatory step. Clinical studies carried out recently have confirmed that patients with locally advanced tumours – depth of invasion T2, T3, T4 and/or N+, without the presence of distant metastases – should be eligible to receive neoadjuvant chemotherapy. Adjuvant therapy following surgical resection after the resection surgery consists in the continuation of chemotherapy or application of radiotherapy. Postoperative chemotherapy prolongs the 5-year survival rate by 13–14%, and the use of adjuvant radiochemotherapy increases the percentage of overall survival by 11%.

Streszczenie

Rak żołądka w większości przypadków wykrywany jest w Europie w stadiach zaawansowanych. Aktualnie obowiązujące zalecenia dotyczące postępowania diagnostyczno-terapeutycznego zostały przedstawione podczas pierwszej konferencji EORTC w St. Gallen w marcu 2012 r. Koniecznymi badaniami diagnostycznymi są endoskopia z oceną histopatologiczną wycinków oraz tomografia komputerowa jamy brzusznej i klatki piersiowej. Podstawą leczenia w przypadkach miejscowo zaawansowanego raka żołądka jest zabieg resekcyjny. Rodzaj operacji zależy od wielkości guza (cT) oraz stanu węzłów chłonnych (cN). W guzach cT2-4a i/lub cN+ obowiązuje całkowita lub prawie całkowita resekcja żołądka. W przeprowadzonych w ostatnich latach badaniach klinicznych dowiedziono, że pacjentów z miejscowo zaawansowanymi nowotworami – głębokie T2, T3, T4 i/lub N+, bez przerzutów odległych należy kwalifikować do neoadjuwantowej chemioterapii. Leczenie uzupełniające po zabiegu resekcyjnym polega na kontynuowaniu chemioterapii lub zastosowaniu radiochemioterapii. Chemioterapia okołooperacyjna zwiększa odsetek 5-letnich przeżyć o 13–14%, a zastosowanie radiochemioterapii uzupełniającej zwiększa odsetek przeżyć całkowitych o 11%.

Introduction

Gastric carcinoma is among the most common cancers. Ninety-five percent of cancers of the stomach are adenocarcinomas, and the remainder are lymphomas, neuroendocrine tumours and tumours arising from the lining of the gastrointestinal tract [1].

In Poland, a decrease has been observed in both morbidity and mortality rates due to gastric cancer. According to the 2010 National Cancer Register, 3,399 cases of gastric malignant cancers in males, and 1,877 in females, were registered in Poland, which constitutes 4.85% and 2.66% of morbidity due to all malignant tumours. In that year, 3,486 deaths among males, and 1,878 deaths in females were noted, i.e. 6.73% and 4.6% of deaths due to malignant cancer [2].

In the 2010 statistics concerning morbidity due to malignant gastrointestinal cancer, gastric cancer constituted the second most common malignancy among males (following colon cancer), and the third in females (following colon and rectal cancer). Con-

sidering mortality, this was the second most common cancer in males (following colon cancer), and the third in females (following colon and pancreatic cancer) [2].

The detection of gastric cancer at early stages of advancement is relatively low; exceptions are countries with high morbidity rates – Japan and Korea, where screening tests have been introduced. In Poland, gastric cancer is most often diagnosed at an advanced stage, and less than half of patients are qualified for radical treatment.

Precise determination of the stage of advancement of the cancerous disease conditions the type of therapy applied. Inadequate assessment results in the undertaking of improper therapy – in the case of understaging this leads to unnecessary laparotomies and, in consequence, non-radical resections and increase in the probability of complications [3], while overstaging results in referring a patient with potentially resectable cancer for palliative care.

Diagnostics

The basis for the diagnostics of gastric cancer is histopathological assessment of endoscopic biopsies. This allows one to make a diagnosis of the tumour and determine the prognostic and predictive factors which exert a significant effect on the selection of an adequate method of treatment.

In order to determine the stage of advancement of the disease it is necessary to perform auxiliary tests. In practice, the following tests are performed: endoscopic ultrasound (EUS), computed tomography scan, magnetic resonance imaging, positron emission tomography-computed tomography (PET-CT), cytological examination of the peritoneal fluid, examination of circulating tumour cells, and bone marrow tests in order to diagnose the presence of micrometastases.

The recommendations concerning the diagnostics and treatment of gastric cancer currently in effect were established during the 1st St. Gallen EORTC (European Organisation for Research and Treatment of Cancer) Gastrointestinal Cancer Conference in St. Gallen in March 2012. Endoscopic examination of the abdomen with histopathological assessment of endoscopic biopsies, and computed tomography scan of the abdomen and the chest were considered as necessary tests to be performed. In the case of EUS, it was stated that this test is necessary when qualifying minor endoscopic lesions for resection, while it is hardly reliable in the diagnostics of the lymph nodes. No recommendations were found for performing routine PET-CT. Cytological examination of the peritoneal fluid was considered as redundant, because, according to the experts, it does not change the procedure. The identification of tumour cells circulating in peripheral blood proved to be useful. This test, due to the possibility of diagnosing the diffusion of the disease, exerts an important effect on the type of treatment undertaken. Diagnostic laparoscopy is important in the assessment of tumours cT3 and cT4, and the determination of the presence of metastatic lesions [4–6].

Positron emission tomography-computed tomography and exploratory laparoscopy, in combination with the cytological examination of peritoneal fluid, are highly valued by Japanese researchers. With PET-CT the possibility of detecting metastatic lesions that are not visible in CT and magnetic resonance (MR) is emphasized, as well as diagnosing metastases in the bone system, which occur in 0.7–1.4% of patients with gastric cancer. Minimally invasive exploratory laparoscopy allows one to reveal metastatic changes in the peritoneum that are not imaged in other tests. In combination with cytological examination of the peritoneal fluid, it enables correct cancer staging, and in consequence, the implementation of adequate treatment [4, 7].

The identification of tumour cells circulating in peripheral blood is a useful method in the determination of advancement, monitoring the course of the disease, evaluation of treatment and prognosis in many types of cancer, including gastric cancer. The presence of circulating tumour cells indicates the diffusion of the cancerous disease, and in consequence, changes the stage of advancement of the disease and significantly affects the selection of the therapeutic procedure. Various methods of detection of these cells are applied. The best known techniques are aimed at the identification and isolation of tumour cells circulating in peripheral blood: density gradient centrifugation, direct filtration, immunomagnetic separation, flow cytometry, real time polymerase chain reaction (RT-PCR), and the microchip method. The first method is based on the theory that various types of cells may be separated according to their density; however, it is difficult to isolate cancer cells due to their migration capability. Also, this method requires the use of special kits. A commonly applied technique is RT-PCR, due to its high sensitivity and specificity; however, due to its high sensitivity this method may provide false-positive results. At present, the method which is most often used is an immunomagnetic technique – cells are identified using antibodies against the epithelial marker epCAM (a protein known as epithelial cellular adhesion molecule), and viewed using a fluorescence microscope. This method is also burdened with error – it may provide both false-positive and false-negative results. Considering the lack of an ideal method of identification of circulating tumour cells, attempts are being undertaken to seek other, more precise methods. In one of these methods, a phenomenon of high telomerase activity was used – an enzyme playing an important role in the development, invasion, and metastasis of cancer, the activity of which is elevated in cancer cells [8].

Treatment

The basis for the treatment of patients with locally advanced gastric cancer is surgical resection. The selection of the type of surgery depends on the stage of clinical advancement determined based on additional tests – size of tumour (cT), and the assessment of the state of the lymph nodes (cN). The possibility of applying local therapy – endoscopic submucosal dissection – is limited to patients with cT1 sm1 stage gastric cancer, in intestinal type carcinomas, smaller than 3 cm in diameter. In such a case, the risk of the presence of metastases to the locoregional lymph nodes is assessed as being lower than 3%. In the remaining stages of advancement of gastric cancer without the diagnosis of distant metastases, radical surgery should be performed [6]. There are significant differences in the approach to gastric cancer surgery between Eastern countries (Japan, Korea), and Western countries (USA, Canada, Western Europe).

The results of treatment are definitely better in the East. This is due not only to the genetic differences and the stage of advancement of the disease, but also the extent of resection of lymph nodes – in Japan, D2 lymphadenectomy is preferred, and in selected cases D3, while in the USA D1 is preferred. Lymphadenectomy is aimed at the stage of advancement of cancer, and the quality of its performance exerts an effect on the development of local metastases and overall survival (OS). Examination of at least 16 lymph nodes is also recommended [9]. The studies showed that with examination of less than 10 lymph nodes it is impossible to reliably assess the N stage. Dissection and examination of an insufficient number of lymph nodes leads to understaging of the disease, and in consequence, inappropriate qualification for adjuvant therapy [10].

The scope of gastrectomy depends on the size of the tumour, its location, infiltration depth and tumour type according to Borrmann's classification. Maintenance of adequate resection margins is necessary. In the case of T1 carcinoma, the close margin should be at least 2 cm, in tumours of T2–T4, type I and II according to Borrmann's classification – 3 cm, and type III and IV – 5 cm. The most common operations are total and subtotal gastric resection. Distal gastrectomy, proximal gastrectomy, pylorus-preserving gastrectomy, segmental or local resection are more rarely performed. In the case of tumours cT2-4a and/or cN+ stage of advancement, a total or subtotal gastric resection is an obligatory step. With cT1 changes not eligible for endoscopic submucosal resection, there is a possibility to perform surgery with a smaller scope of resection. The location of the tumour in the central part of the stomach, at a distance larger than 4 cm from the pylorus, enables the performance of pylorus-preserving gastrectomy, whereas the location of the tumour in a proximal part allows the performance of proximal gastric resection, and while maintaining adequate margins, the preservation of more than half of the stomach. Segmental and local resections still remain an object of clinical studies.

The scope of resection of the lymph nodes depends on the stage of clinical advancement of the cancer, and variation in its histopathological features. In all cases with cT2-T4 and cT1N+ stage, lymphadenectomy D2 is an obligatory step. Lymphadenectomy D1 may be performed only in cT1a carcinomas not eligible for endoscopic procedure, and histologically varied cT1b of a diameter not larger than 1.5 cm. In the remaining cases of cT1N0 gastric cancer, lymphadenectomy D1+ is necessary [11].

The outcomes of gastric cancer treatment are better in Asian countries due to other aetiological factors of the disease, implementation of screening tests, use of extended lymphadenectomy, and beginning chemotherapy immediately after surgery. These differences cause difficulties in the comparison of the results of clinical studies with those obtained in Europe and the United States, and with the application of these treatment schemes outside Asia [12, 13].

In order to improve the outcomes of treatment which still remain unsatisfactory, in recent years attention has been focused on peri-operative therapy, especially pre-operative therapy. In many clinical studies and meta-analyses the value of neoadjuvant and adjuvant chemotherapy and radiotherapy in the treatment of resectable gastric cancer was assessed. The results of studies were often contradictory. Therefore, the question arises whether patients with resectable gastric cancer should receive systemic treatment and what this treatment should be – neoadjuvant or adjuvant [12–14].

While comparing the above-mentioned methods of therapy in the treatment of patients with locally advanced gastric cancer, a positive effect of pre-operative chemotherapy has been confirmed.

This beneficial effect consists in the following: better tolerance of pre-operative than post-operative treatment, a greater possibility to apply a complete dose of drugs; reduction of tumour size, and consequently a decrease in the stage of advancement and an increase in the percentage of resectability; early treatment of micrometastases; possibilities of evaluation of the effectiveness of neoadjuvant therapy based on clinical, radiological and histopathological response; distinguishing of a group of patients with rapid progression of the disease, who would not benefit from surgical treatment [13, 15].

The beginnings of the application of pre-operative chemotherapy in gastric cancer go back to the 1970s. At that time in Japan, phase I studies were conducted consisting in the infusion of methotrexate, vinblastine or mitomycin, or a combination of these drugs, into the gastroepiploic artery. The study covered 62 patients, and the infusion was performed for 7 days before the surgery. An increase in the percentage of

3-year survival was observed, compared to the control group. Patients with tumours at pT4a stage of advancement benefited most from this treatment [16].

Subsequently, the focus of interest became the application of systemic chemotherapy in the treatment of primarily non-resectable cases of gastric carcinoma.

In 1989, phase II studies were published, using the EAP scheme (etoposide, Adriamycin, cisplatin) in 34 patients who had previously undergone laparotomy, with primarily non-resectable gastric carcinoma. The percentage of responses reached 70%; in 19 patients gastric resection was performed, including R0 in 15, and R1 in 3 [17].

In 1991, Plukker *et al.* published phase II studies, where treatment with methotrexate and 5-fluorouracil was applied in a group of 20 patients with non-resectable gastric cancer. After 4 cycles of chemotherapy it was possible to perform gastrectomy in 8 patients (40%) [18].

In the same year, Ajani *et al*. presented studies conducted in a group of 25 patients who received pre- and post-operative chemotherapy according to the PFP scheme (etoposide, 5-fluorouracil and cisplatin). Two cycles of chemotherapy were administered before surgery and 3 cycles after the surgery. Responses to treatment were obtained in 20 patients (80%), while in 1 patient progression of the disease was observed. All patients were qualified for laparotomy. R0 resection for gastric carcinoma was performed in 18 cases (72%), while in the remainder it was not possible to perform radical surgery due to the presence of metastases [19].

In 2006, the clinical study MAGIC (Medical Research Council Adjuvant Gastric Infusional Chemotherapy) was published. This is the largest randomized study conducted to date concerning the use of peri-operative chemotherapy. The study included 503 patients who were divided into two groups – the first group, where peri-operative chemotherapy was implemented based on etoposide, cisplatin, and 5-fluorouracil, and the second group, where a surgical procedure was the only treatment applied. This study enrolled patients with gastric adenocarcinoma, cancer of the gastroesophageal junction and in the lower third of the oesophagus, type I and II of clinical advancement, without distant metastases, also with primarily non-resectable tumour. The patients received 3 cycles of chemotherapy prior to surgery and 3 cycles after the surgery. The surgical procedure was performed – in the case of patients not covered by the systemic treatment – 6 weeks after randomization, and in the case of chemotherapy treatment 3-6 weeks after completion of the third cycle. The subsequent cycle of chemotherapy was administered 6–12 weeks after surgical treatment.

The overall survival time was assessed in the study, then survival time to progression was considered, reduction in the stage of advancement of the disease (down-staging), and the quality of life [20, 21].

The 5-year survival of patients who were treated with peri-operative chemotherapy was 36.3%, while among those who received surgical treatment it was only 23.0%. The percentage of local metastases remained at the level of 14.4% and 20.6%, respectively [12].

In the MAGIC study, an improvement in survival was confirmed in patients who received peri-operative chemotherapy, compared with those treated with surgery only, by 13% within 5 years, which is equivalent to a reduction in death risk by 25% [20, 21].

The MAGIC study was compared with the FAMTX Dutch study (Dutch Gastric Cancer Group), where patients were administered 4 courses of pre-operative chemotherapy with 5-fluorouracil, doxorubicin and methotrexate. This study covered a small group of patients (59). No prevalence of combined treatment over surgical treatment only was confirmed – the median survival of patients who had undergone surgery not preceded by chemotherapeutic treatment was 30 months, while among patients who received systemic treatment prior to surgery it was 18 months [13, 20, 22].

It was possible to perform a complete MAGIC study protocol in 42% of patients. The remainder did not receive post-operative chemotherapy due to early progression of the disease, post-operative complications, or their resignation from participation in the study. Nevertheless, the prevalence of combined treatment over exclusively surgical treatment was confirmed. The results of treatment of patients who received 3 courses of chemotherapy and those covered with complete pre- and post-operative treatment were not compared. Since the time of acceptance of chemotherapy according to the MAGIC protocol, new preparations have been implemented into treatment. Thus, an oral precursor of fluoropyrimidine – capecitabine – may replace 5-fluorouracil, and oxaliplatin, which shows lower nephrotoxicity, may replace cisplatin [20, 21].

Adjuvant treatment in patients who have undergone surgical resection consists in the application of chemotherapy or radiochemotherapy. In the case of patients who received pre-operative chemotherapy, it is possible, according to the histopathological result, to apply radiochemotherapy, or to continue treatment according to the MAGIC protocol. In Poland, patients in whom a surgical procedure was the first phase of treatment are qualified, according to the pTNM stage of advancement, for adjuvant radiochemotherapy, or are under observation. Radiochemotherapy is a more beneficial option in patients with full thickness infiltration of the abdominal wall (pT3, pT4), with metastases to the lymph nodes, as well as after an insufficient lymphadenectomy and R1 resection when, for various reasons, re-surgery is not possible [6, 22, 23].

The most commonly used scheme of radiochemotherapy is based on the study by MacDonald, which confirmed prolongation of the median survival time of patients by 9 months, and increase in the 3-year

asymptomatic survival rate from 31% to 48%, compared to patients who received surgical treatment only. This consists in the application of 5-fluorouracil and leucovorin, and irradiation of the tumour bed, locoregional lymph nodes, an area 2 cm beyond the proximal and distant resection margin, and the lymph nodes: peripancreatic, visceral, periaortic, spleen, hepatic-duodenal or hepatic-portal, pancreatic-duodenal, and in the case of gastric cardia cancer also pericardial and peri-oesophageal.

In the study there also participated patients who had undergone gastric resection with lymphadenectomy D0 – 54%, D1 – 36% and D2 – 10%. Considering the very low percentage of patients after D2 lymphadenectomy, there are doubts concerning benefits from the adjuvant treatment of these patients. Despite this, adjuvant radiochemotherapy is a standard treatment in the United States and Europe [23].

Taking into account the fact that the results of the Intergroup 0116 and MAGIC studies cannot be directly compared, further clinical trials have been planned aimed at obtaining an improvement in the survival of patients who had undergone surgical procedures due to gastric cancer. This study (the CRITICS trial) compared overall survival, disease-free survival, toxicity of treatment, and the quality of life of patients treated with chemotherapy prior to radical surgery (epirubicin cisplatin capecitabine – ECC), who after the surgery are classified into two groups: in the first group chemotherapy is continued (3 cycles of ECC), while in the other group patients are treated with chemotherapy (cisplatin capecitabine) in combination with radiotherapy [24].

In 2012, the results of Phase III of a study were published (the ARTIST trial) concerning the application of capecitabine with cisplatin, compared to the use of capecitabine and cisplatin in combination with simultaneous radiotherapy in patients who had undergone a total gastric resection with D2 lymphadenectomy, who did not receive systemic treatment prior to surgery. It was also found that the additional application of radiotherapy did not significantly prolong disease-free survival time (DFS). A statistically significant prolongation of DFS was observed only in the subgroups of patients who were randomly assigned to each of the groups where metastases to the lymph nodes were observed. Therefore, it is planned to conduct the ARTIST-II clinical study in order to compare the use of radiochemotherapy and post-operative chemotherapy in patients after total gastric resection with D2 lymphadenectomy, in whom metastases to lymph nodes were diagnosed [25].

Summing-up

In the case of patients with gastric cancer, an algorithm for the diagnostic and therapeutic procedure should be based on endoscopy and computed tomography. The remaining additional tests available are applicable in selected cases. An adequate assessment of the stage of advancement of the disease results in proper qualification for combined treatment.

In recent years, progress has been achieved in the combined treatment of gastric cancer. In patients who received peri-operative chemotherapy an increase has been obtained in 5-year survival rates by 13–14%, and the use of supplementary radiochemotherapy resulted in an increase in overall survival by 11%. Patients with locally advanced cancer – deep T2, T3, T4 and/or N+, without the presence of distant metastases, in a general good condition – should be qualified for neoadjuvant chemotherapy. Peri-operative chemotherapy, according to the ECF scheme (epirubicin, cisplatin, fluorouracil), prolongs overall survival and progression-free survival in patients with locally advanced gastric adenocarcinoma, cancer of the gastroesophageal junction and in the lower part of the oesophagus. Such treatment should be applied in patients with malignant cancer in these locations [5, 13, 20].

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