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Review

Advanced gastric cancer: the value of systemic and intraperitoneal chemotherapy

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Summary. Several possibilities in treating advanced gastric cancer exist. Radical surgery associated with chemotherapy represents the cornerstone. Which one is more effective among neoadjuvant, adjuvant or perioperative chemotherapy is still a matter of debate. Several innovative results showed the necessity to keep increasingly into consideration the intraperitoneal administration of chemotherapies. Moreover, classical drugs and their ways of administration should be combined with the new ones to improve results. Lastly the prevention of recurrence should be considered: one possibility is to administer intraperitoneal chemotherapy earlier in the therapeutic algorithm. (www.actabiomedica.it)

Key words: advanced gastric cancer, chemotherapy, hipec, intraperitoneal, surgery, carcinosis, metastasis

Introduction

Several possibilities exist in treating advanced gastric cancer (AGC). Radical surgery associated with chemotherapy (CT) represents the cornerstone. Several innovative results showed the necessity to keep increasingly into consideration the intraperitoneal administration of chemotherapies (IPC). Moreover, and their ways of administration should be combined with the new ones to improve results. Lastly the prevention of recurrence should be considered: one possibility is to administer intraperitoneal chemotherapy earlier in the therapeutic algorithm.

The CT can be administered through different ways and at different time points. The present review aims to give a comprehensive overview of the different possibilities in treating AC.

Neo-adjuvant chemotherapy

The primary aim of neo-adjuvant chemotherapy (NACT) is to reduce the tumoral extension to potentially increase the effects of a radical surgery and to reduce the biological potential of tumor cells with particular attention to subclinical micrometastases. One possible disadvantage of NACT could be to delay the surgical intervention.

The EORTC 40954 trial (1) showed an increased rate of R0 resections in NACT group, more frequent postoperative morbidity and positive hazard ratio in favor to NACT with regards to survival although not significantly. Few randomized studies were closed prematurely with no favorable results. The FAMTX trial (2, 3) gave no survival differences related to NACT. However, several evidences exist about the value of this

kind of CT. A recent meta-analysis including 15 randomized controlled trials (RCTs) and involving 2001 patients showed that the NACT does not give any adverse effect during the perioperative period. In fact, it does not increase the risk of complications nor the post-operative mortality rate. Furthermore, the effect on early gastric cancer (EGC) and AGC was positive in term both of survival and recurrence rate (4).

Perioperative chemotherapy

Perioperative chemotherapy consists in combining CT before surgery and post-operative CT with interval surgery. The concept at the base of this combined approach is to obtain the advantages of neoadjuvant schemes in reducing tumor size and facilitating radical surgery associated to the advantages offered by post-operative drug administration. In Europe, this approach is diffused, and several trials have been published.

The MAGIC trial enrolled gastric or distal esophagus adenocarcinoma (5). Preoperative CT improved R0 resection rate; almost half of the patients who received preoperative treatment completed the postoperative CT. Perioperative CT reduced the risk of relapse and improved median overall survival.

The ACCORD07 RCT enrolled patients with gastro and gastro-esophageal junction cancer (6). Perioperative CT resulted in higher rates of R0 resection, in reduction of the risk of relapse and of the risk of death.

A Cochrane single patient data meta-analysis on the perioperative CT in resectable gastric adenocarcinoma (7) included 14 RCTs. The cumulative analysis showed an increase in overall survival (OS), R0 resection and longer disease-free survival (DFS) with no differences in term of mortality and morbidity. Advantages of the perioperative scheme were more pronounced in gastro-esophageal junction cancers. When radiotherapy was added, a better OS was obtained. The best effect was found in younger patients, whereas no survival benefit was demonstrated for elderly patients.

Another British study (8) demonstrated a considerable gain in DFS in neoadjuvant and adjuvant treatment in comparison with those who didn't receive postoperative CT. OS was not significantly different.

A recent meta-analysis of RCT, involving 1240 patients comparing prognosis and safety between perioperative CT and adjuvant chemotherapy (ACT), showed an improved survival for patients treated with perioperative CT. In addition, combination CT resulted in better survival compared to monotherapy in the NACT regimens (9).

Adjuvant chemotherapy

ACT is the most applied scheme throughout the world. Many colleagues from surgical and oncological department prefer to face cancer primarily with the surgical intervention, as surgery is universally considered the main curative option in gastric cancer.

The single patient data meta-analysis by the GASTRIC group (10) analyzed 17 RCTs (3838 patients). Results showed as ACT improved 5-years survival with similar DFS. No differences were found regarding the several fluoropyrimidine based drug regimens applied (i.e. mono-, poly-chemotherapy). Further studies, the ACTSGC study (11) and the CLASSIC study (12), (13), confirmed the results.

A recent RCT did not find a significant survival benefit to be associated with ACT with fluoropyrimidines in patients with stage IB-IIIA gastric cancer. However, patients with stage II disease and those receiving uracil-tegafur treatment in the adjuvant group showed significantly better prognosis than those in the surgery-alone group (14).

S-1 is an orally active combination of tegafur, a prodrug that is converted by cells to fluorouracil, gimeracil, which inhibits dihydropyrimidine dehydrogenase, and oteracil, which inhibits the phosphorylation of fluorouracil in the gastrointestinal tract, thereby reducing the toxic gastrointestinal effects of fluorouracil (15). In Japan ACT using S-1 has become a standard treatment in patients treated by curative gastrectomy for stage II or stage III gastric cancer on the basis of results from a randomized phase III study comparing surgery plus adjuvant S-1 with surgery alone (ACTSGC trial) (16, 17).

New agents

Tumor biology and the cellular and molecular mechanisms of malignant proliferation have been studied deeply, leading to the comprehension of part of their

pathways. This permitted to develop targeted therapies against specific mechanisms. Target therapies permitted to decrease toxicity of traditional chemotherapy agents and improve survival. In gastric cancer HER-2/neu (ERBB2) has demonstrated to be the principal molecular target where monoclonal antibodies have showed their efficacy. HER2 is over-expressed in 10-40% of gastric cancer. Data from a few meta-analyses defined the prognostic role of HER2 over-expression in gastric cancer. However contrasting results have been published (18-22) depending from the diagnostic technique. Trastuzumab (Herceptin®, Genentech) demonstrated its efficacy against HER2. The ToGA trial (23) reported a reduced relative risk of death by the addiction to the traditional CT scheme of the monoclonal antibody. This result was even more evident in the HER2-enriched population, with 3+ or 2+ immunohistochemistry and FISH-positive. Several countries routinely use this drug as standard treatment in AGC.

Lapatinib is another tyrosinkynase inhibitor against Epithelial Grow Factor Receptor (EGFR), usually applied in the treatment of breast cancer. The phase II trials that tested it for AGC showed no increase in OS (24, 25).

EGFR over-expression in gastric cancer is happens in 30-50% of cases (25, 26) and tests of new drugs against this agent have been done only in metastatic or inoperable cancers. Cetuximab (Erbitux®) and Panitumumab (Vectibix, Amgen) usage brought discordant results but it seems to slightly improve the progression free survival in AGC (26, 27). Several trials are needed to estimate the real benefit and the eventual translation in operable gastric cancer in perioperative settings. Other molecules have demonstrated their ineffectiveness in gastric cancer (Gefitinib (Iressa®, AstraZeneca Pharmaceuticals) and Erlotinib (Tarceva®, Roche-Genetech) (26).

The role of angiogenesis in tumoral growth and survival and metastatic diffusion are well known pathogenetic factors. For this reason vascular endothelial growth factor (VEGF) and its receptors (VEGFR-1 and VEGFR-2) are main molecular targets of some novel drugs. Bevacizumab, a monoclonal antibody against VEGF, was at the beginning applied in colorectal, lung, ovarian, and renal cell cancers. Two randomized phase III trial, the AVAGAST and the AVATAR trials studied its application in advanced gastric cancer (28, 29). Bevacizumab insertion in treatment algorithm of AGC showed no difference in overall survival but improved progression free survival and overall response rate.

Intra-peritoneal chemotherapy

Gastric cancer cells diffuse mainly through lymphatic flow and via cell seeding after serosa invasion. The 53-60% of patients affected by AGC present peritoneal carcinosis (PC) (stage III-IV), and the 40% hepatic metastases (30) (31). Moreover, the main cause of death is PC, despite R0 resections associated to systemic CT and/or radiotherapy (30, 32-34).

A meta-analysis (32) evaluated the effect of intraperitoneal chemotherapy (IPC) associated to cytoreductive surgery (CRS) compared with surgery alone, in patients with AGC with or without peritoneal, nodal and distant metastasis. This analysis of 20 RCTs (2145 patients) reported an increase in morbidity rate in the IPC group, but also an improvement in OS, in overall recurrence rate, in hematogenous metastasis rate and in peritoneal recurrence rate in the IPC group. No statistically significant difference in lymph nodal recurrence rate was found.

Another meta-analysis (33) reported the effects of IPC and R0 resections on patients with AGC without PC compared with surgery alone. 16 RCTs (1906 pts.) were included. An increase in survival rate at 1, 2, 3, 5, 9 years and a significant reduction in recurrence rate after 2, 3, 5 years were reported in IPC group. No increase in anastomotic leakage, ileus, bowel perforation, myelosuppression, gastrointestinal reaction and hepatic failure were associated to IPC, only an increased the incidence of abdominal pain.

Lastly, another meta-analysis (35) reported an increased OS in IPC group particularly compared to surgery alone in patients with serosal invasion with no macroscopic spread of disease.

From these data results the feasibility of prophylactic IPC associated to neoadjuvant chemotherapy in order to increase the DFS and OS in patients with AGC without PC.

IPC was considered also in a neoadjuvant setting. In 2012 Yonemura et al. (36) (37) proposed a new

therapeutic approach called "bidirectional chemotherapy" which consisted in a neoadjuvant intraperitoneal and systemic chemotherapy (NIPS) that can act on PC from the inside of peritoneum and from the subperitoneal blood vessels. He proposed a drug regimen with oral S-1, i.v. taxotere and cisplatinum and intraperitoneal cisplatinum and docetaxel with good result in terms of CC-0 achievement during surgery, DFS and OS.

The role of intra-peritoneal cytology

The finding of free intraperitoneal tumor cells (FITC) has a fundamental importance in defining the prognosis of patients with AGC (38-40). Positive cytology is described in 11 to 27% of patients with gastric cancer (41).

When gastric serosa is involved, PC could be considered practically unavoidable (32). In case of free peritoneal tumor cells in abdominal cavity the natural evolution in PC occur in 80% of cases, with a distant survival near to 0% (42). PC was considered the more important prognostic factor (more than T or N) for advanced disease, early recurrence, and decreased disease-specific survival following curative resection in patients with AGC (38). In the AJCC-NCCN TNM classification, the positive cytology at the staging laparoscopy is considered as M1 disease (43-45).

The main criticism of peritoneal washing cytology remains its low sensitivity (14-70% reported in the literature, but these rates are in heterogeneous cohort of patients and stage of disease) (39). To improve sensitivity, Homma et al. (40) suggested to perform the washing in multiple cavities (in the right and left subphrenic space, inside the omental bursa, and in the Douglas pouch), and not only in the Douglas pouch (41). Furthermore, with the introduction of new molecular techniques, some studies directly compared cytology by Papanicolaou staining with molecular detection by PCR. Detection methods using PCR offer considerably higher sensitivity and a marginally lower specificity (46).

A meta-analysis including 12883 patients revealed FITC to be associated with poor overall survival poor peritoneal recurrence free survival, regardless of the detection method (47).

Then FITC represents an "*in fieri*" PC, practically comparing patients with FITC to those with PC in terms of survival. A meta-analysis focusing on the effect of IPC on patients with AGC with FITC and without macroscopic PC showed that 2- and 5-years survival was increased by IPC (RR=1.62, RR=3.10). Two- and 5-years survival was further increased by IPC associated with peritoneal lavage (PL) (RR=2.33, RR=6.19). Furthermore, peritoneal recurrence was reduced by IPC (OR=0.45) and by IPC with PL (OR=0.13) (48).

Conclusions

Gastric cancer is an aggressive disease with a high risk of peritoneal dissemination even at early stages. The surgical therapy of gastric cancer should be based on radical surgery aiming to eradicate all the macroscopic disease and perform adequate lymphadenectomy. As the peritoneal dissemination of gastric cancer is the main cause of long-term failure of the treatment, a peritoneal fluid cytology should always be done. However, the uncertainty of its results suggests preventing peritoneal dissemination and subsequent carcinosis with an early use of the intraperitoneal CT. Moreover, the use of perioperative and bidirectional CT should be considered. AGC with invasion of serosa and/or positive cytology at stadiation laparoscopy should be treated in experienced centers in order to introduce the use of "prophylactic IPC" even in absence of macroscopic peritoneal dissemination associated to perioperative CT regimen.

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