Editorial

Different regimens of perioperative chemotherapy for esophagogastric and gastric adenocarcinoma: does a triplet therapy with taxane generate a survival benefit?

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With new diagnoses in more than 39,000 patients annually, esophagogastric cancer (EGC) is the seventh most common cancer worldwide and a serious health problem. It is a highly lethal disease, causing more than 25,000 deaths per year (1). Surgery with a radical lymphadenectomy is the mainstay of therapy for operable adenocarcinoma of the esophagogastric junction cancer (EGJC) and gastric cancer not involving the GE-junction cancer (GC) but many patients relapse and the 5-year survival rate remains low (2). Because of the poor prognosis of locally advanced disease, additional therapy besides oncologic surgery is required to improve patient outcome. Recent studies demonstrated that preoperative chemotherapy improves overall survival (OS) of patients with locally advanced EGJC/GC and histopathologic response was identified as an independent prognostic parameter in these patients (3,4). Several neoadjuvant chemotherapy regimens are under discussion and currently in use but the optimal treatment regimen remains unclear.

The landmark MAGIC-trial recruited patients with resectable EJGC and GC. Here, 503 patients were randomized to either undergo surgery with perioperative chemotherapy or surgery only. The chemotherapy applied in this trial included three preoperative and three postoperative cycles of epirubicin, cisplatin and continuous 5-fluorouracil (5-FU) (ECF-regimen). There was at least no significant difference in postoperative complications and 30-day mortality in both treatment arms (46% *vs.* 45% and 5.6% *vs.* 5.9%, respectively). A clear downstaging effect could be monitored for patients in the chemotherapy arm. The resected tumors in that group were significantly smaller and less advanced. OS as well as progression-free survival (PFS) of patients receiving perioperative chemotherapy (CTx) were significantly increased compared with patients treated by surgery only (P=0.009 and P<0.001). Results showed that the 5-year survival rate (5YSR) was 36% for patients receiving perioperative CTx and 23% for patients treated by surgery only (P=0.009 and P<0.001) (5).

The chemotherapeutic regimen of the French ACCORD-trial was composed of 2 or 3 cycles of cisplatin/5-FU and was disposed for patients with resectable EGJC/GC. The 224 patients were randomized to receive either preoperative chemotherapy or surgery only. The R0-resection rate among the patients receiving chemotherapy was significantly higher compared to the primary surgery arm (84% *vs.* 73%; P=0.04). A significantly prolonged overall and disease-free survival could be shown after chemotherapy (P=0.02 and P=0.003). The 5YSR largely matched those reported for the MAGIC-trial with 38% in the CTx + surgery and 24% in the surgery only arm (6).

In contrast, the EORTC-trial by Schuhmacher showed a higher R0-resection rate among the patients treated with a neoadjuvant regimen consisting of cisplatin/5-FU/folinic

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acid (PLF-protocol) in contrast to those undergoing primary surgery. The authors were able to demonstrate downstaging and a trend towards extended OS and DFS for the neoadjuvant treatment arm but there was no significant survival benefit. The trial was stopped as a result of insufficient accrual (7).

In a recent article, Springfield and fellow colleagues published their results of a retrospective multicentre study that assessed the influence of different preoperative chemotherapy regimens on patients' response, complication rate and prognosis. A total of 1,051 patients with EGJC/GC receiving neoadjuvant treatment were enrolled in the study. Neoadjuvant chemotherapy was initiated in cT3/cT4/cNany/cM0. The 843 patients included were stratified into four groups. A total of 417 patients in group "A" received a duplet-therapy with cisplatin/5-FU. In group "B" 54 patients were treated with oxaliplatin/5-FU. Group "C" included 190 patients receiving epirubicin/platinum/5-FU. Patients in group "D" were medicated with taxane/platinum/5-FU. The median follow-up was 33 months with a median OS of 39.1 months. In total, 71.8% of the patients revealed EGJC with a median OS of 39.3 months and 23.5% had GC with a median survival of 39.9 months. Surgery was performed 2–4 weeks after the completion of the respective chemotherapy. Comparing the four different groups demonstrated the best clinical response (34.8%) with the longest median OS (53.9 months) in group "D". But there was no significant change in DFS compared to the other groups. Comparing the groups with duplet therapy to that one with the triplet chemotherapy regimen, there was no significant increase in OS, clinical response or any significant increment of overall complications. The triplet therapy group with taxane was the only one to show improved clinical response (34.8% *vs.* 28%) and longer OS (55.9 *vs.* 37.1 months). In EGJC-patients' triplet therapy with taxane indicated a significant rise of median OS and DFS. Among GC-patients this issue could not be confirmed (8).

Conclusively the authors were unable to determine a superior chemotherapeutic regimen that significantly improved clinical response, pathological response or OS in the available datasets. Besides, the potentially more effective triplet therapy with epirubicin or taxane was not able to significantly improve outcome although there was a trend for better clinical response and survival in the taxane-associated group "D" without raising surgical complication rates or mortality (8). The chemotherapeutic regimen was partly influenced by patient's age and general conditions. The patients in the taxane group were younger and the statistical difference was lost when the model was adjusted for age and sex. However, the observed trend for better oncologic outcome was confirmed in a randomized controlled phase 2/3 trial which achieved higher complete tumor regression rates [regression grade 1a according to Becker (9,10)] when a taxane-based regimen was applied (9). They confirmed the hypothesis that FLOT-treatment would result in an increased chance of pathological complete regression by approximately 10% (11). When EGJC-patients and GC-patients were considered separately, a trend for a better clinical response in the taxane group was illustrated for EGJC-patients only by significant longer OS whereas this was not reproducible for GC-patients (8).

The differences in response rates to preoperative chemotherapy with greater benefit for EGJC-patients compared to GC-patients were recently reported (4,12). It was confirmed that histopathological response (HPR) to preoperative chemotherapy is an independent prognostic factor for OS in EGJC and GC (11,13). Nonetheless, this holds true only for EGJC but not for GC. Besides that, a meta-analysis by Ronellenfitsch found an effect of perioperative chemotherapy on OS only for EGJC- but not for GC-patients (14). Cunningham reported the same statement in the MAGIC-trial. It was discussed that there was no clear evidence for a treatment effect related to the primary tumor-site, which indicates that preoperative chemotherapy was more effective in EGJC (8). The question why EGJC are more likely to respond to preoperative/perioperative chemotherapy compared to GC remains still unclear.

There are several clinical problems that should be addressed in the future. The value of the adjuvant part of perioperative chemotherapy remains elusive. Currently there is only one randomized controlled trial investigating on the value of adjuvant *vs.* perioperative chemotherapy for patients suffering from signet ring cell GC (15). The benefit of the FLOT-regimen is currently investigated in the phase III part of the FLOT4-AIO-trial (11).

Further, the benefit of neoadjuvant chemoradiation compared to perioperative chemotherapy has not been completely elucidated yet. The ESOPEC-trial currently investigates the effect of perioperative chemotherapy (FLOT-protocol) to neoadjuvant chemoradiation (CROSS protocol) in multimodal treatment of non-metastasized resectable EGJC (16).

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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