EUR. J. ONCOL.; Vol. 20, Suppl n. 1, pp. 18-20, 2015

Neoadjuvant therapy in gastric cancer: surgeon vs oncologist. The point of view of the surgeon

Pierfilippo Crucitti, Giuseppe Mangiameli, Roberto Coppola
Department of Surgery, Campus Bio-Medico University of Rome, Italy

Background

Western countries have not national screening programs therefore gastric cancer is usually diagnosed at an advanced stage due to the lack of early specific symptoms. Despite adequate surgery with R0 resection and radical lymphadenectomy, the prognosis of gastric cancer is still poor. The 5-year survival of patients with early gastric cancer is about 75% while it is 30% or less for patients with extensive lymph node involvement (1). Since the early 1990s the neoadjuvant treatments are increasingly employed in the treatment of locally advanced or initially un-resectable gastric cancer, especially in Europe. The first phase II studies have demonstrated positive results of preoperative chemotherapy (CT) (high R0 resection rates and good survival rate) (2, 3). Subsequently two randomized trials (4, 5) have shown the advantages of perioperative CT (pre- and postoperative) over surgery only. In the setting of neoadjuvant therapy the role of preoperative chemo radiotherapy is not yet full established. A German pilot study (6) was able to demonstrate a high percentage of complete responders from preoperative chemoradiotherapy (CRT), and recent data from a Dutch trial (7) indicate additional positive effects of radiotherapy on overall survival (OS). The present review gives an overview of the already mentioned landmark-studies investigating neoadjuvant therapy in gastric cancer.

Methods

The recent literature on the multimodal treatment of gastric cancer with a particular attention to the randomized studies on neoadjuvant treatment was revisited by the authors.

Results

Neoadjuvant/perioperative chemotherapy

Based on the results of three European randomized phase III trials investigating the results of perioperative CT in the treatment of gastric cancer, perioperative CT should be considered as the standard treatment in Europe. No significant difference in postoperative complications and 30-day mortality in both treatment arms (perioperative CT vs surgery alone) were found in the MAGIC trial (4) and the French FNLCC ACCORD 07 FFCD 9703 trial (5). Both studies were able to show that the R0 resection rate among the patients receiving CT was significantly higher compared with the primary control arm, and OS and DFS were significantly prolonged after CT. The European Organization for Research and Treatment of Cancer (EORTC) 40954 phase III trial investigated the same patient population as the MAGIC and the FNLCC ACCORD 07 FFCD 9703 trial but resection was performed obeying elaborate staging workup (including a standardized staging-laparoscopy) and strict surgical quality standards (including a D2-lymphadenectomy). Interestingly

in this study a significant survival benefit could not been shown but a downstaging and a tendency towards a prolonged OS and DFS for the neoadjuvant treatment arm was observed (8).

Neoadjuvant/perioperative chemo radiotherapy

Based on the results of the German POET trial (6), comparing neoadjuvant CT with neoadjuvant CRT in patients with adenocarcinomas of the EGJ, European guidelines consider neoadjuvant or perioperative CRT an alternative to CT in adenocarcinomas of the EGJ (9, 10). Meanwhile a study from the Netherlands (CROSS trial) investigated the role of neoadjuvant CRT in the treatment of esophageal cancer and cancer of the EGJ in a multicenter, randomized, and controlled, phase III setting (7). Patients with resectable tumors (T1N1 or T2-3N0-1, M0) were randomly assigned to CRT followed by surgery or surgery alone. The R0 resection rate in the CRT group was significantly higher compared with the surgery only group (92% versus 69%, $p < 0.001$) with a pathological complete response in 29% in the former. Median OS was also significantly better after CRT + surgery compared to surgery alone, while postoperative complications and in-hospital mortality (4% in both) were similar in both arms. Table 1 gives an overview on the relevant randomized trials investigating neoadjuvant treatment in locally advanced esophagogastric cancer.

Conclusions

Different approaches in multimodal gastric cancer therapy can be observed in Asia, Europe and US and they reflect differences in epidemiology of gastric cancer and in surgical management. In Europe, due to the absence of national screening program, gastric cancer tends to be diagnosed later compared to Asian countries. In this scenario, since the landmark trial by Cunningham and colleagues (4), perioperative CT is considered the standard of care for patients with locally advanced gastric cancer. However, this trial was criticized because of the rather poor quality of the surgery with inadequate lymphadenectomy. Traditionally, primary surgery with D2 lymphadenectomy is considered as one of the most important criteria for surgical quality when talking about curative gastrectomy for locally advanced gastric cancer. However, the adherence to D2 dissection varies in different parts of the world. Although underpowered and inconclusive, the result of the EORTC 40954 trial (8) did not showed a differences in survival when accurate D2 dissection was performed. Probably, perioperative CT may be an appropriate tool to catch up inadequate lymph-node dissection or a preoperative staging without a systematic laparoscopy to exclude peritoneal carcinosis. Another important point should be made regarding the different epidemiological composition of the studies between the East and the West. The incidence of adenocarcinoma of the lower esophagus and the gastric cardia (AEG I-III) is increasing in most Western populations. There is evidence from a meta-analysis and a retrospective analysis of a large single-center cohort that predominantly patients with cancer of the EGJ seem to benefit from neoadjuvant CT (11). In this setting a legitimate question is whether the positive effects of perioperative CT (with emphasis on the neoadjuvant part) shown in a European population of gastric cancer patients should be correlated with a high

Table 1. RCT investigating the results of neoadjuvant therapy in locally advanced esophagogastric cancer.

Trial	Regimen	Treatment arms	T site	R0 rate	OS	PFS/DFS
Neoadjuvant CT				*p*	*p*	*p*
MAGIC	CT perioperative	res. *vs* mult. treat.	GC+EGJ	0.018	0.009	<0.001
FFCD 9703	CT perioperative	res. *vs* mult. treat.	GC+EGJ	0.04	0.021	0.003
EORTC 40954	CT preoperative	res. *vs* mult. treat.	GC+EGJ	0.036	0.46 n.s.	0.2 n.s.
Neoadjuvant CRT						
POET	C(R)T preoperative	mult. CRT *vs* mult. CT	EGJ			
(AEG I/II/III)	n.s.	0.07 n.s.	0.06 n.s.			
CROSS	CRT preoperative	res. *vs* mult. treat.	Esoph+EGJ	<0.001	0.003	<0.001

percentage of tumors located at the EGJ rather than a less radical lymphadenectomy. Furthermore both landmark trials showing a positive effect of neoadjuvant CRT just included adenocarcinomas of the EGJ (6, 7). In this scenario all the eligible patients for a neoadjuvant treatment have to be determined exactly in terms of tumor location and maybe also Lauren histotype. Recently a French group demonstrated that neoadjuvant CT appears to be ineffective in patients with signet ring cell histology (12).

In conclusions the results of the European randomized phase III trials clearly show that neoadjuvant treatments does not adversely affect the postoperative course in terms of postoperative complications and 30-day mortality. Currently there are no "surgical" contraindications to enroll patients affected by gastric cancer in clinical trials involving multimodal treatments because the most important objective is to ensure the best oncological outcome. On the other hand, although multimodal treatment improves oncologic outcomes, the surgical issues should also be addressed in ongoing trials, especially in the Western world where D2 dissection is still not commonly accepted. In addiction future trails should necessarily include an adequate preoperative staging through explorative laparoscopy to exclude the presence of peritoneal carcinosis. Surgical training of trialists should be enforced in future studies.

References

1. Agboola O. Adjuvant treatment in gastric cancer. Cancer Treat Rev 1994; 20: 217-40.
2. Wilke H, Preusser P, Fink U, *et al*. Preoperative chemotherapy in locally advanced and nonresectable gastric cancer: a phase II study with etoposide, doxorubicin, and cisplatin. J Clin Oncol 1989; 7: 1318-26.
3. D'Ugo D, Rausei S, Biondi A, *et al*. Preoperative treatment and surgery in gastric cancer: friends or foes? Lancet Oncol 2009; 10: 191-5.
4. Cunningham D, Allum W, Stenning S, *et al.* Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. N Engl J Med 2006; 355: 11-20.
5. Ychou M, Boige V, Pignon J, *et al.* Perioperative chemotherapy compared with surgery alone for resectable gastroesophageal adenocarcinoma: an FNCLCC and FFCD multicenter phase III trial. J Clin Oncol 2011; 29: 1715-21.
6. Stahl M, Walz M, Stuschke M, *et al.* Phase III comparison of preoperative chemotherapy compared with chemoradiotherapy in patients with locally advanced adenocarcinoma of the esophagogastric junction. J Clin Oncol 2009; 27: 851-6.
7. Van Hagen P, Hulshof M, Van Lanschot J, *et al.* Preoperative chemoradiotherapy for esophageal or junctional cancer. N Engl J Med 2012; 366: 2074-84.
8. Schuhmacher C, Gretschel S, Lordick F, *et al.* Neoadjuvant chemotherapy compared with surgery alone for locally advanced cancer of the stomach and cardia: European Organisation for Research and Treatment of Cancer randomized trial 40954. J Clin Oncol 2010; 28: 5210-8.
9. Lutz M, Zalcberg J, Ducreux M, *et al.* Highlights of the EORTC St. Gallen international expert consensus on the primary therapy of gastric, gastroesophageal and oesophageal cancer - differential treatment strategies for subtypes of early gastroesophageal cancer. Eur J Cancer 2012; 48: 2941-53.
10. Rivera F, Gravalos C, Garcia-Carbonero R. SEOM clinical guidelines for the diagnosis and treatment of gastric adenocarcinoma. Clin Transl Oncol 2012; 14: 528-35.
11. Reim D, Gertler R, Novotny A, *et al.* Adenocarcinomas of the esophagogastric junction are more likely to respond to preoperative chemotherapy than distal gastric cancer. Ann Surg Oncol 2012; 19: 2108-18.
12. Messager M, Lefevre J, Pichot-Delahaye V, *et al.* The impact of perioperative chemotherapy on survival in patients with gastric signet ring cell adenocarcinoma: a multicenter comparative study. Ann Surg 2011; 254: 684-93.