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Neoadjuvant chemotherapy in gastric cancer: pro

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Introduction

Gastric cancer (GC) remains one of the leading causes of cancer mortality worldwide even thought its incidence has been decreasing in recent years.

Radical surgery is the only potentially curative treatment option for cancer without distant metastases; however most patients develop recurrence despite R0 resection (1, 2).

Adjuvant chemotherapy

The role of adjuvant therapy in GC has been extensively studied during the past three decades in an attempt to improve the prognosis of patients with GC who have undergone curative surgery.

In caucasian population large clinical trials failed to demonstrate a survival advantage in favor of chemotherapy (CHT) compared with surgery alone (3-7).

Metanalyses of some of these trials found that post-operative CHT led to statistically significant reduction in mortality compared to surgery alone in the range of 18%-28%, corresponding to an absolute risk reduction of not more than 2-4% (8-13).

Recently the ITACAS study was published (14) and established 5-FU adjuvant monotherapy as a new standard in radically resected GC in Europe.

In this trial 1106 patients with resectable adenocarcinoma of the stomach or gastroesophageal junction were randomized to an intensive CHT (FOLFIRI for four cycles followed by docetaxel and cisplatin for three cycles) or De Gramont CHT.

No statistically significant difference was detected for both disease-free [hazard ratio (HR) 1.00; 95% confidence interval (CI): 0.85–1.17; P = 0.974] and overall survival (OS) (HR 0.98; 95% CI: 0.82–1.18; P = 0.865).

In Asian population adjuvant CHT showed excellent result in phase III trials and became the standard of care (15, 16).

Neo-adjuvant chemotherapy

Neo-adjuvant CHT has recently received increasing attention in an attempt to increase the rate of complete tumor resections, to combat systemic micro- metastases, to evaluated in vivo chemosensitivity and to prolong survival in patients with resectable GC.

The available data indicate that neo-adjuvant CHT is feasible, does not increase post-operative morbidity and mortality, and it is able to increase the rate of R0 resection.

In particular, several small phase II trials with different neo-adjuvant cisplatin-based CHT regimens have reported response rates between 40% and 60% and R0 resection rates up to 80%.

The MAGIC trial (17) evaluated the efficacy of a peri-operative CHT.

Five hundred and three patients with potentially resectable GC were randomly assigned to both pre-operative and post-operative cisplatin, epirubicin, and 5FU (ECF) CHT versus surgery alone. The results showed a statistically significant improvement of the ECF arm in PFS (HR: 0.66; 95%CI 0.53–0.81) and

OS (HR: 0.75; 95%CI 0.60–0.93; 5-year OS 36% vs. 23%). The resected tumors were significantly smaller and less advanced in the peri-operative CHT group.

An FNCLCC and FFCD Multicenter Phase III trial randomized 224 patients with resectable adenocarcinoma of the lower esophagus, gastroesophageal junction (GEJ), or stomach to perioperative chemotherapy and surgery (CS) or surgery alone (S).

In this trial perioperative CHT significantly improved OS, PFS and the curative resection rate (18).

In both MAGIC and FNCLCC and FFDC trials only about half of patients were able to receive postoperative CHT underlying the importance of the preoperative component of the treatment.

The EORTC 40954 phase III trial investigated the same patient population as the MAGIC and the FNLCC and FFCD trial, whereas adenocarcinomas of the distal esophagus were excluded. The trial had to be closed early due to poor accrual after inclusion of 144 patients (n = 72 per treat- ment arm), whereas 360 patients were initially planned. This trial solely relied on preoperative CHT with cisplatin, 5-FU and folinic acid. The analysis of the patients included showed a higher R0 resection rate among the patients treated with neoadjuvant CHT compared to those undergoing primary surgery (81.9% versus 66.7%; p = 0.036). A significant survival benefit could not been shown because of the low patient number, but a downstaging and a tendency towards a prolonged OS and PFS for the neoadjuvant treatment arm was observed (p = 0.113 and p = 0.065). Postoperative complications and deaths did not differ significantly. (27.1% versus 16.2%; p = 0.09 and 4.3% versus 1.5%) (19).

Ronellenfitsch and colleagues performed an interesting meta-analysis showing an absolute improvement in survival of 9% at 5 years for patients undergoing perioperative CHT. In addition no increase in postoperative morbidity and mortality as well as duration of hospitalization could be recognized (20).

Conclusion

Neoadjuvant chemotherapy is feasible and well tolerated treatment, and it doesn't increase morbidity and operative mortality.

Peri-operative chemotherapy significantly improved OS, PSF and the chance of getting an R0 resection.

A multidisciplinary effort is necessary to include patients in well designed clinical trials in order to definitively establish the role of neoadjuvant chemotherapy (peri-operative) in patients with resectable gastric cancer.

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