patients receive either another 3 courses of ECC chemotherapy or CRT. Currently, over 400 patients have been entered in the study. In conclusion, there is no evidence that CRT can replace D2 dissection. More importantly, it seems that CRT will have its best effect after optimal surgery.

Reference(s)

[1] Hartgrink HH, Jansen EP, van Grieken NC, et al: Lancet 374:477–490, 2009.
[2] Songun I, Putter H, Kranenbarg EM, et al: Lancet Oncol 11:439–449, 2010.
[3] Jensen LS, Nielsen H, Mortensen PB, et al: Eur J Surg Oncol, 2010.
[4] Cunningham D, Allum WH, Stenning SP, et al: N Engl J Med 355:11−20, 2006.
[5] Macdonald JS, Smalley SR, Benedetti J, et al: N Engl J Med 345:725–730, 2001.
[6] Hundahl SA, Macdonald JS, Benedetti J, et al: Ann Surg Oncol 9:278–286, 2002.
[7] Kim S, Lim do H, Lee J, et al: Int J Radiat Oncol Biol Phys 63:1279–1285, 2005.
[8] Jansen EP, Boot H, Dubbelman R, et al: Br J Cancer 97:712–716, 2007.
[9] Jansen EP, Boot H, Saunders MP, et al: Int J Radiat Oncol Biol Phys 69:1424–1428, 2007.
[10] Jansen EP, Boot H, Dubbelman R, et al: Ann Oncol 21:530–534, 2010.
[11] Dikken JL, Jansen EP, Cats A, et al: J Clin Oncol 28:2430–2436, 2010.

PG 9.04 SPEAKER ABSTRACT

Oesophagogastric cancer: A case for perioperative chemotherapy

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Although the global incidence of gastric adenocarcinoma is declining in western countries, the incidence of gastroesophageal junction (GEJ) tumors has risen faster than other GI adenocarcinoma over the last quarter century [1].

For resectable desease, the use of adjuvant chemotherapy has been disappointing and has never been adopted as a standard of care. In 2001, Macdonald reported a positive phase III trial for a post operative radiochemotherapy regimen, but associated to a high digestive toxicity and a low quality of surgical procedures.

After several phase II trials of Neoadjuvant chemotherapy, the results of a large phase III study (MAGIC) were published in 2006 [2]. Five hundred and three patients with resectable stomach (74%), lower oesophagus or GEJ adenocarcinoma were randomized between surgery alone and perioperative chemotherapy using ECF regimen. A significant improvement of TN stage and R0 resection was obtained in the chemotherapy group and resulted in a better Progression Free Survival (HR 0.66) and a better 5 year overall Survival (36%versus 23%). The surgical mortality was not affected by pre-operative chemotherapy but only 55% of operated patients could initiate post-operative chemotherapy.

More recently, a French trial published in 2011 [3] confirms these results using another chemotherapy regimen with 5-Fu (800 mg/m^2/day day 1−4 in CI) and Cisplatin (100 mg/m^2 day 1 or 2) every 4 weeks. Two hundred and twenty four patients were randomized between surgery alone (n = 111) and perioperative chemotherapy (n = 113). At the opposite of the MAGIC trial, a majority of patients (75%) had a tumor located to lower oesophagus or GEJ.

No significant difference was obtained in pathological T or N staging but the neoadjuvant chemotherapy improved the R0 resection rate (84% versus 74%). The post operative fatal complications were similar in the two groups and only 50% of the patients could receive at least one cycle of postoperative chemotherapy.

The 5-year Disease Free Survival and Overall Survival were significantly improved in the chemotherapy arm, respectively 34% vs 19% and 38% vs 24%.

These two randomized trials support the use of peri-operative chemotherapy as a standard of care for resectable Oesophagogastric adenocarcinoma.

Some questions are still pending for the chemotherapy regimen: the role of Epirubicin, the possibility to replace Cisplatin by Oxaliplatin and intravenous 5FU by Capecitabine, the place of Taxanes.

Other questions have to be adressed in future trials: the early selection of good candidates to neoadjuvant chemotherapy (PET, Biomarkers, . . .), the place of Biologic drugs (Trastuzumab in HER-2 positive tumors, c-met inhibitors, . . .) or the role of pre-operative radiotherapy.

Reference(s)

[1] Botterweck AA, Schouten LJ, Volovics A, et al: Trends in incidence of adenocarcinoma of the oesophagus and gastric cardia in ten European countries. Int J Epidemiol 29:645–654, 2000.
[2] Cunningham D, Allum WH, Stenning SP, et al: Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. N Engl J Med 355:11−20, 2006.
[3] Ychou M, Boige V, Pignon JP, et al: Perioperative chemotherapy compared with surgery alone for resectable gastroesophageal adenocarcinoma: an FNCLCC and FFCD multicenter phase III trial. J Clin Oncol 29:1715–1721, 2011

Friday, 23 March, 16:00−17:30

Session VIII. Gastric Cancer

PG 10.01 SPEAKER ABSTRACT

Predicting the response to neoadjuvant chemotherapy I (Who profits from neoadjuvant chemotherapy)

C. Mariette. *Service De Chirurgie Digestive Et Générale Hôpital Claude Huriez, University Hospital of Lille, Lille, France*

Despite a decline in the overall incidence, gastric adenocarcinoma remains the second most common cause of cancer death worldwide and thus a significant global health problem. Even in early-stage locoregional confined disease the 5-year survival rarely exceeds 25−35%. Randomized trials have demonstrated a benefit from neoadjuvant and perioperative chemotherapy. However the optimal approach in individual patients is not clear and remains controversial. A consistent finding is that patients who have a histopathological response to neoadjuvant therapy are more likely to receive a survival benefit. These clinical data provide a strong argument for the urgent development of methods to predict histopathological response to neoadjuvant therapies for gastric adenocarcinomas. Published data demonstrate that clinino-pathological features (tumour histology and location), imaging through metabolic response by FDG-PET and tissue/molecular biomarkers may have all a predictive value for neoadjuvant therapies. However it is still uncertain from published data whether or not they will be useful for clinical decision making in individual patients. Existing candidate biomarkers need to be properly qualified and validated and novel biomarkers are required and an optimal approach should involve the combination and integration of clinical, imaging, pathological and molecular biomarkers.

PG 10.02 SPEAKER ABSTRACT

Predicting the response to neoadjuvant chemotherapy II (Ability of pretherapeutic parameters to predict response and prognosis early in patients with locally advanced gastric cancer)

S. Lorenzen. *NCT Nationales Centrum für Tumorerkrankungen, UNI-Klinikum Heidelberg, Heidelberg, Germany*

Introduction: Response to neoadjuvant chemotherapy is an independent prognostic factor in locally advanced gastric cancer. However, no prospectively tested pretherapeutic parameters predicting response and/or survival in gastric cancer are available in clinical routine.

Patients and Methods: We evaluated the prognostic significance of various clinicopathologic parameters in 410 patients who were treated with neoadjuvant chemotherapy followed by gastrectomy. Clinical and histopathological response evaluation was performed using standardized criteria. A prognostic score was created on the basis of the variables identified in the multivariate analysis.

Results: Three pretherapeutic parameters were identified as positive predictive factors for response and prognosis: tumor localization in the middle third of the stomach ($p = 0.001$), well differentiated tumors ($p = 0.001$) and intestinal tumor type according to Laurén's classification ($p = 0.03$). A prognostic index was constructed, dividing the patients into three risk groups: low (n = 73), intermediate (n = 274) and poor (n = 63). The three groups had significantly different clinical ($p = 0.007$) and histopathological response rates ($p = 0.001$) and survival times, with a median survival time that was not reached in the low risk group, 39.2 months in the intermediate risk group and 20.5 months in the poor risk group. The corresponding 5 year survival rates were 65.3%, 41.2%, and 21.2% ($p < 0.001$), respectively.

Conclusion: A simple scoring system based on three clinicopathologic parameters, accurately predicts response and prognosis in neoadjuvant treated gastric cancer. This system provides additional useful information that could be applied to select gastric cancer patients pretherapeutically for different treatment approaches. However, prospective testing of the score in an independent patient cohort is warranted.

PG 10.03 SPEAKER ABSTRACT

Lessons from the GASTRIC metaanalysis of adjuvant treatment

P. Rougier. *Digestive Oncology, Hopital Ambroise Paré, Boulogne Billancourt, France*

Background: Despite potentially curative resection of stomach cancer, 50−90% of patients die of disease relapse. Numerous encouraging phase II and phase III trials compared surgery alone to adjuvant chemotherapy, but definitive evidence is lacking. These trials generally used the overall survival at 5 years as the primary endpoint leading to long and costly trials. Our group has

initiated an individual patient data (IPD) based meta-analysis of all randomized clinical trials in the adjuvant gastric setting with two main objectives: (1) To quantify the potential benefit of chemotherapy after complete resection over surgery alone and to further study the role of various treatments including mono-chemotherapy, combined chemotherapy with FU derivatives, mitomycin-C (MMC), anthracyclines, taxanes, or irinotecan. (2) To validate disease free survival (DFS) as a surrogate endpoint of overall survival (OS) for randomized trials in the adjuvant setting.
Methods: All randomized controlled trials (RCTs) closed to patient accrual at the end of 2005 were eligible. Trials testing radiotherapy, intraperitoneal chemotherapy, or immunotherapy were excluded. The primary endpoint was overall survival (OS), the secondary endpoint disease-free-survival (DFS).
Results: The gastric group set up the largest database of patients treated with adjuvant treatment for gastric cancers. Thirty-two eligible trials (7,517 patients) were identified. As of June 2011, individual patient data were available from 18 trials (4,945 patients, 66% of the targeted data) carried out in 11 different countries (Europe, Asia, USA), with a median follow-up exceeding 7 years. They were the opportunity to gather experts from 12 different cooperative groups in 4 investigators meeting where results were discussed. These data, carefully checked using statistical diagnostic tools, were analysed using meta-analytic techniques to provide robust results: (1) There were overall statistically significant benefits in favour of adjuvant therapy in terms of OS (HR = 0.80, 95% CI 0.77–0.84, $p < 0.0001$) and DFS (HR = 0.79, 95% CI 0.74–0.84, $p < 0.0001$). No statistical heterogeneity in the treatment effect could be detected neither across the included trials nor across the four pre-defined types of regimen. Adjuvant 5FU based regimens appeared to be superior to surgery alone and was recommended as a valid standard for further clinical trials. (2) DFS (rank correlation coefficient, 0.976; 95% CI, 0.965, 0.987) was strongly associated with OS at the individual level. On average, there was also a very high correlation at the trial level between the log hazard ratios log HR_{OS} and log HR_{DFS}. Trial-level R^2 was estimated to 0.989 (95% CI = 0.978, 1.0). Considering the high correlation at both levels, we computed the surrogate threshold effect (STE = 0.90), meaning that a HR_{DFS} of 0.9 predicts a HR_{OS} of 1. Unfortunately, despite implication of the steering committee, it was not possible to collect 33% of the targeted data and some collaborative groups refused to join this international collaboration. Last, but not least the time to constitute the database lead to delay that may slow down the enthousiasm of the participants. Yet, this is a unique ressource to adress numerous questions of interest. We now invite proposals for specific studies using the database from our colleagues in cancer research.

PG 10.04 SPEAKER ABSTRACT
Adjuvant chemotherapy: an option for Asian patients only?

Y.-J. Bang. *Internal Medicine, Seoul University Hospital, Seoul, Korea*

Recently we presented the results of the CLASSIC trial, an Asian phase III randomized trial testing the effectiveness of adjuvant chemotherapy with capecitabine and oxaliplatin (XELOX) after D2 gastrectomy in patients with stage II or III gastric cancer. This study demonstrated that 8 cycles of XELOX following D2 gastrectomy is superior to surgery alone in terms of disease-free survival, the primary endpoint of the study. Our findings are consistent with the Japanese ACTS-GC trial, in which adjuvant chemotherapy with S-1 for 1 year after D2 gastrectomy was tested. These two studies show that adjuvant chemotherapy following D2 gastrectomy improves outcomes in patients with resectable gastric cancer. A key question would be how generalizable the results of these studies are to other regions of the world. A notable finding from the CLASSIC trial is the good patient outcomes; the 3-year overall survival rate in the surgery-alone group (78%) was considerably higher than those in the US Intergroup-0116 and UK MAGIC populations (30% to 40%). Somebody could argue that the good clinical outcomes in our study are caused by differences in patient populations. However, we believe that the favorable outcomes are a result of the consistent use of D2 resection and the high quality of the surgery. Now that D2 gastrectomy is standard of care in both Europe and the US, we suggest that our study findings are highly relevant for other regions and may be generalisable to Western patients when D2 surgery is performed by surgeons experienced with this type of surgery.

PG 10.05 SPEAKER ABSTRACT
Selecting the best treatment for an individual patient

S. Cascinu. *Oncologia Medica – Azienda Ospedaliera Di Ancona, Universita' Politecnica delle Marche, Torette – Anco, Italy*

Goals: Several factors concur in determining outcome for locally advanced gastric cancer patients. Shockingly, geographical origin of the patient seems to play a major role. In Eastern countries, the high level of surgery that can be expected grants a high percentage of success in a strategy that employs surgery as immediate treatment followed by adjuvant chemotherapy, mainly based on oral fluoropyrimidines (S-1 or Capecitabine), with satisfactory results. In Western countries, the expertise of the surgeon maintains its role as predictor of high likelihood of cure.
Methods: In patients who obtain a good surgical outcome, the benefit of the addition of adjuvant chemotherapy is still debatable: the gain in survival seems to be small (around 8% at 5 years) and with noticeable toxicities. On this basis, neoadjuvant treatment is a promising option even if there is a general lack of conclusive data regarding which is the best regimen to use. Even with the limitation of a small number of studies, neoadjuvant chemotherapy is usually feasible, allows for a greater chance of receiving chemotherapy at all, and opens the possibility of a downstaging and downsizing of the tumour, allowing a easier surgery.
Results: Regarding this strategy preliminary results have also been presented about the addition of monoclonal antibodies. For example, in the TOGA trial, a significant benefit in terms of overall survival, response rate and progression free survival was observed also for patients with locally advanced gastric cancer and not just for the metastatic ones. In the AVAGAST trial also, the addition of Bevacizumab failed to determine a significant improvement in the primary outcome, overall survival, for patients treated with the combination, but in the subgroup analysis, patients with locally advanced gastric cancer had a significantly better overall survival and response rate.
Conclusion: Finally, an increasing interest in the use of hyperthermic intraperitoneal chemotherapy in other types of solid tumours (including those of the gastrointestinal tract) has led to evaluate this treatment modality in gastric cancer patients with peritoneal involvement. It should be noted that it is still to be considered a experimental approach, even though it would be intriguing to evaluate if a particular subset of patients, those who are more likely to develop peritoneal metastasis, may benefit from this technique in the adjuvant setting. It should be considered that other than histologic subtype (diffuse vs intestinal) there seems to be a series of polymorphisms of genes usually involved in cell interaction and migration that can explain a different metastatic pattern in resected patients. Further research on these determinants of metastatic spread could be used to select those patients who may benefit from HIPEC and those who may benefit from standard adjuvant or that gain no benefit at all.