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302 INVITED

Optimal treatment for gastric cancer: Tailor made surgery

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Radical surgical dissection of gastric cancer is the basis of cure in this disease. However, because most patients in the Western world present with advanced stages, surgery alone provides long-term survival in only 20−30% of patients. Western series report locoregional failures in about 60% of patients with positive lymph nodes or involvement of the serosa. This high relapse rate has initiated a whole spectrum of more aggressive treatments which did not result in favorable survival until the introduction of combined chemoradiation in the adjuvant setting.
Prospective randomized trials have investigated the role of more extensive lymph node dissection (D2) in comparison with the standard D1 lymph node dissection in which only the perigastric nodes are removed. In the Dutch Gastric Cancer Group trial, 711 patients treated with curative intent were randomized between D1 and D2 lymph node dissection. After a follow up of 15 years there is now a significant difference in favor of D2 of gastric cancer related mortality. Morbidity (25 vs. 43%;$p < 0.001$) and mortality (4 vs. 10%; $p = 0.004$) however, were significantly higher in the D2 group.
The only study demonstrating an overall survival benefit from extended lymphadenectomy (D3) has been published by Wu et al.
In 2005 the final results of the MAGIC-study on perioperative chemotherapy have been presented. In this large multicentre study patients were randomized between surgery only and 3 cycles preoperative ECF (epirubicin, cisplatin, 5-FU) followed by surgery and another 3 cycles of ECF chemotherapy. This regimen resulted in a 10% higher resectability rate and a significant survival benefit of 13% (23% vs. 36%) at 5 years.
In 2001, with the introduction of postoperative combined chemotherapy, a substantial improvement in survival and locoregional control has been described for the first time. An impressive increase in median overall survival was obtained in the chemoradiotherapy group; 36 months versus 27 months in the surgery only group. More relapse free survival was prolonged from 19 months in the surgery only arm to 30 months in the chemoradiotherapy arm. This postoperative chemoradiotherapy regimen has become standard treatment in the US. Nevertheless this study has been criticized because of suboptimal surgery, concerns about toxicity, an outdated chemotherapy regimen and suboptimal radiotherapy techniques. Indeed, 54% of all patients underwent a D0 lymph node dissection, which in it self could be one factor in undermining survival.
Taken together the abovementioned pivotal MAGIC and SWOG/Intergroup studies, the important question that needs to be answered is whether postoperative chemoradiotherapy improves survival and/or locoregional control in patients receiving neoadjuvant chemotherapy followed by an adequate resection. We therefore conduct a prospective randomized multicenter phase III trial (CRITICS; ChemoRadiotherapy after Induction chemoTherapy In Cancer of the Stomach) addressing this important question. In the adoption of the surgical procedure on the basis of imaging and molecular staging will be discussed.

303 INVITED

Perioperative treatment – current standards and next steps

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Surgery is the main treatment for cancer without distant metastases, however most patients develop recurrences despite R0 resection. Consequently, many attempts have been made to prevent recurrences and improve overall survival. Adjuvant chemotherapy (CT) has not been accepted as standard treatment and is applicable only in 50% of the patients (Braga M. et al Br. J. Surg. 75:477−80 (1988); its benefit is less than 10% increase in overall survival (OS) in the recent and appropriate meta-analyses using, individual data (HR = 0.81; $p < 0.0001$) (Sakamoto J, Paoletti X, GASTRIC. abstract ASCO, JCO 2008 # 4543). The adjuvant chemo-radiotherapy (US standard) is active but has the same drawback as only patients in excellent post-operative nutritional status are able to receive it.
The reasons to develop peri-operative chemotherapy are: low efficacy of adjuvant CT, high percentage of patients unable to receive an adjuvant treatment after gastric surgery, testing CT efficacy before surgery, and possibility of down-staging (Rougier P, et al. Eur J Cancer 1994;30A:1269–75).
Two randomized trials have demonstrated the efficacy of this approach:
– the MAGIC trial has evaluated the impact of the addition of a perioperative chemotherapy (epirubicin, cisplatin and (protracted continuous infusion of 5FU), on the survival of 503 patients with resectable gastro-oesophageal cancer (stomach adenocarcinomas: 74% of patients). It reported an increased overall survival in the group receiving a perioperative chemotherapy with a 5-year survival rate of 36% versus 23% (HR for death, 0.75; $p = 0.009$) and in the progression-free survival (HR for progression or death, 0.66; $p < 0.001$). (Cunningham D, et al. N Engl J Med 2006;355:11−20.)
– The FNLCC-FFCD trial conducted on 224 untreated patients with resectable adenocarcinoma of the lower oesophagus and oesophagogastric junction (74% of cases) or stomach cancer (26% of cases) randomized to receive a preoperative chemotherapy (CS group: 2−3 cycles: 5-fluorouracil over 5 days plus cisplatin 100 mg/m^2 on day 1) every 28 days) followed by surgery (n = 113) followed by postoperative chemotherapy in case of efficacy and good tolerance compared to surgery alone (S group; n = 111). The neoadjuvant CT results in a better overall survival (5-year survival rate 38% versus 24%; hazard ratio-HR-for death: 0.69; $p = 0.02$); and of disease-free survival (5-year disease-free survival 34% versus 19%; HR 0.65; $p = 0.003$). In the multivariate analysis of survival, neoadjuvant chemotherapy ($p = 0.01$) and distal site of the stomach cancers ($p < 0.01$) were the only 2 independent prognostic factors. In this trial preoperative chemotherapy significantly improved the curative resection rate (84% *versus* 73%, $p = 0.04$) and its tolerance was acceptable with grade 3/4 toxicity observed in 38% of CS patients (mainly neutropenia) and no increase in postoperative morbidity (Boige V et al; abstract: J Clin Oncol 2007;25:4510; manuscript submitted for publication).

From these two studies we can conclude that for potentially resectable gastro-oesophageal adenocarcinoma, preoperative cisplatin based chemotherapy significantly increased the curative resection rate, disease-free and overall survivals.
The next steps are:
1. to develop better tolerated and more efficient chemotherapy (Cunningham MD, et al. J Clin Oncol 2006;24:LBA4017.) and to test the benefit of adding biologics like antiangiogenic (bevacizumab presently tested in MAGIC2 trial) or tratuzumab in HER2 positive patients.
2. To test the feasibility and efficacy of different combinations of chemo and radiotherapy in preoperative.

304 INVITED

Current chemotherapy options for advanced disease

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Patients with gastric adenocarcinoma present frequently with large, unresectable or metastatic tumours at the time of diagnosis. For these patients, treatment is palliative and, in most cases, options are limited to systemic chemotherapy or supportive care.
Conventional cytotoxic chemotherapy as compared to Best Supportive Care (BSC) can improve the overall survival, quality of life and symptom-free period in carefully selected patients with advanced gastric cancer or gastro-esophageal junction adenocarcinoma. A benefit of a chemotherapy combination has been demonstrated over single-agent regimens in term of overall survival. Many studies evaluate the activity of doublets or triplets. Amongst the agents used in these combination regimens are the fluoropyrimidines (5-FU, capecitabine or S1 in parts of Asia), the platinums (cisplatin or oxaliplatin), the taxanes (docetaxel or paclitaxel), epirubicin and irinotecan. The fluoropyrimidines are often a partner in these combination regimens; it has been shown that 5-FU and capecitabine have a similar activity in advanced gastric cancer. The trials with S1 in Western patients were disappointing. The platinums are also very often used in the combination regimens: several studies have also shown that cisplatin and oxaliplatin have a similar activity. Docetaxel has been studied more extensively than paclitaxel. Adding docetaxel to 5-FU and cisplatin increases the activity (DCF regimen), but also the toxicity. Irinotecan has not been approved for advanced gastric although, it is also active in gastric cancer regimens. Epirubicin is also combined with a fluoropyrimidine and

a platinum in some centers, based on UK trials. Therefore several options can be proposed as reference regimens: the doublets of a fluoropyrimidine (5-FU or capecitabine) plus cisplatin (or oxaliplatin) or triplets of DCF or ECF (or ECC or EOC). The median survival is however usually still in the range of 8−11 months in most modern trials. Recently, the benefit of second line chemotherapy has been also demonstrated with a modest, but clear impact of a second line regimen (irinotecan) compared to BSC.
Although gastric cancer is relatively chemosensitive (RR 30−40%), the outcome remains poor. The complete response rate is extremely low and the response duration is short. Moreover the combinations regimens are relatively 'heavy' for patients often in poor general condition. There is therefore a clear need for better treatment options. The research on targeted agents has been intensified recently. The doublet of 5FU/capecitabine and cisplatin serves often as a backbone for the combination with novel targeted agents. A significantly longer survival has been shown for the combination of a fluoropyrimidine/cisplatin plus trastuzumab in patients with a HER-2 positive gastric or gastro-esophageal junction adenocarcinoma compared to the cytotoxic doublet alone. Several other targeted agents are under investigation in combination with cytotoxics (angiogenesis inhibitors, epidermal growth factor inhibitors or other anti-HER2 inhibitors) or also as monotherapy (mTOR inhibitor everolimus) and offer the hope for an improved outcome.

305 INVITED

Integration of targeted therapies

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Gastric cancer (GC) is the second leading cause of cancer mortality in the world. Advanced GC patients have a poor prognosis. Palliative chemotherapy improves survival, as compared with best supportive care. Although oxaliplatin, docetaxel and capecitabine have demonstrated activity in recent phase III trials the median overall survival (mOS) remains poor [1−2], therefore novel treatment options are urgently needed. New biological therapies aim to inhibit different targets of signal transduction pathways that are thought to be functionally selective or overexpressed in certain tumor types. GC belongs to these tumor models with overexpressed signal transduction pathways that are potential targets of a number of new drugs that are currently being in clinical development (see Table).
Recognition of the vascular endothelial growth factor (VEGF) pathway as a key regulator of angiogenesis has led to the development of several VEGF-targeting agents. At present, available clinical data on the use of angiogenesis inhibitors are limited to nonrandomized phase II trials. The combination of bevacizumab and chemotherapy showed encouraging efficacy results: response rate (RR) ~65%, median time to progression (mTTP) ~8 months and mOS greater than 12 months [3−4]. However, the favorable efficacy results were counterbalanced by bevacizumab-related toxicities: gastric perforation, thromboembolic events and hemorrhage. An ongoing international phase III trial (AVAGAST) will elucidate the role of bevacizumab in the first-line setting. Sunitinib and sorafenib, two multi-tyrosine kinase inhibitors (TKIs), are being tested in the first- and second-line setting with promising preliminary results.
The epidermal growth factor receptor (EGFR) is a tyrosine kinase receptor that belongs to the ErbB family. EGFR is highly expressed in patients with advanced GC. Several phase II studies combining cetuximab with either irinotecan/5-fluorouracil(5-FU)- or oxaliplatin/5-FU-based chemotherapy have demonstrated encouraging activity: RR $\approx$ 50−65%, and mOS of 9.5−11.7 months [5−6]. Unfortunately, all these trials are limited by their nonrandomized design. An ongoing international phase III trial (EXPAND) will define the role of cetuximab in combination with capecitabine and cisplatin in the first-line setting. EGFR inhibitors are also being evaluated as second-line treatment in advanced GC. The human epidermal growth factor receptor 2 (HER2) is overexpressed in ~22% of GC patients. In an international phase III trial of patients with AGC the addition of trastuzumab to standard first-line chemotherapy showed a statistically significant improvement in the mOS of patients with HER2-positive GC. Trastuzumab in combination with chemotherapy (5-FU or capecitabine and cisplatin) has become a new standard option for the first-line treatment of HER2-positive GC patients.
Other potential targets, including other receptors (c-Met, IGF-1R), proteins involved in cell cycle regulation, proteasome, matrix metalloproteinases, histone deacetylases and chaperone proteins, have been demonstrated to be critical in the balance of the tightly regulated pathways that promote either cell survival or cell death. New drugs are being developed against those specific targets and preliminary clinical and clinical evaluation of these compounds is expected in the near future.

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Scientific Symposium (Thu, 24 Sep, 09:00−11:00)
Fertility and sexuality: the development of oncosexology

306 INVITED

Fertility: Understanding the options after cancer treatment

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Because most people with cancer are over age 50, fertility is mainly a concern for those diagnosed in childhood, adolescence, or young adulthood. It is interesting to compare the explosion of interest and research funding focused on fertility preservation, compared to the relatively small increase in attention to assessing or treating sexual dysfunction in men and women with cancer–problems that affect at least 50% of survivors, are profound, and do not improve over time without intervention.
However, cancer-related infertility also can cause profound emotional distress that does not disappear with time. In a recent survey of over 250 women diagnosed at age 40 or less, those who desired a child at the time of cancer diagnosis and were unable to have one were significantly more distressed at a mean of 10 years after cancer treatment than women whose childbearing was not interrupted. Smaller studies of men also have suggested long-term grief over infertility after cancer.
Fortunately, sperm banking is a practical option for 90% of men diagnosed with cancer. Although the choices for women are more expensive and less reliable, recent advances in vitrification of oocytes, use of immature oocytes matured in the laboratory, and banking/autotransplantation of ovarian tissue are gradually approaching the efficacy of ovarian stimulation with cryopreservation of embryos. Some cancer treatments have also been modified to spare fertility, for example less toxic chemotherapy for Hodgkin disease, ovarian transposition before pelvic irradiation, or conservative surgeries like trachelectomy or removal of only one ovary for low-stage ovarian cancer.
A major problem is that choices about preserving fertility must be made at the time of maximum stress, when a cancer diagnosis is recent and treatment planning is underway. It is difficult for younger patients to understand their disease and treatment plan, let alone to take the time to weigh the costs and benefits of options to store gametes or embryos for the future. Parents may also have to make decisions for their very young children that involve an additional minor surgery to collect tissue. Most settings do not have counselors with time to teach patients about their options much less to help them sort out their emotions.
After cancer treatment, some men and women will remain fertile or will recover fertility. They often have intense anxiety about whether their offspring will have special risks for cancer or will have a greater chance of a birth defect related to the parent's cancer treatment. Those relatively few who carry a mutation involved in a hereditary cancer syndrome now have the option of using prenatal diagnosis or preimplantation genetic diagnosis to avoid passing on their damaged gene. For women, another worry is whether pregnancy could provoke a cancer recurrence. Women are less aware of risks that subclinical cardiac or pulmonary impairment could become life-threatening during the stress of a pregnancy.
For those who remain infertile, adoption is not easy. International adoption countries may exclude cancer survivors, make them wait 5 years out, or want a letter from the oncologist. Domestic agencies and birth mothers also may be loathe to give a child to a couple when one spouse has had cancer. Adoption is also quite expensive in most Western countries. Third-party reproduction includes use of donated sperm, oocytes, or embryos, and/or a gestational carrier. Only a minority of cancer survivors are willing to consider these paths to parenthood.

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Talking about sex: identifying psycho-sexual concerns in the clinic

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Background: Multi-modal cancer therapy has led to significant improvements in disease control and survival. However this comes at a price in