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The diagnosis and management of gastric cancer: expert discussion and recommendations from the 12th ESMO/World Congress on Gastrointestinal Cancer, Barcelona, 2010

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Well-recognized experts in the field of gastric cancer discussed during the 12th European Society Medical Oncology (ESMO)/World Congress Gastrointestinal Cancer (WCGIC) in Barcelona many important and controversial topics on the diagnosis and management of patients with gastric cancer. This article summarizes the recommendations and expert opinion on gastric cancer. It discusses and reflects on the regional differences in the incidence and care of gastric cancer, the definition of gastro-esophageal junction and its implication for treatment strategies and presents the latest recommendations in the staging and treatment of primary and metastatic gastric cancer. Recognition is given to the need for larger and well-designed clinical trials to answer many open questions.

methods

At the 2010 Barcelona European Society Medical Oncology/World Congress Gastrointestinal Cancer (ESMO/WCGIC) meeting a panel of invited experts involved in the care of gastric cancer conducted a structured discussion on the different aspects of gastric cancer care. The panel is composed of experts from the different disciplines involved in the care of gastric cancer: gastroenterologists, medical oncologists, radiation oncologists and oncological surgeons. Experts were selected on their scientific merits and their recognition as international opinion leaders. The panel was presented with a detailed questionnaire prior to the meeting. Answers are summarized and then discussed in an extended forum. Conclusions of the recommendations and expert opinion are based on the published data and on clinical experience. The expert opinion recommendations do not therefore represent an official guideline or true consensus statements. The publication aims to guide clinicians in the hands on decisions encountered in the management of gastric cancer.

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introduction

Gastric adenocarcinomas are anatomically divided into true gastric cancer, also referred as gastric, non-cardia cancers, which still comprises the majority of cases, and gastro-esophageal junction (GEJ) adenocarcinomas, also referred as proximal gastric or cardia carcinomas. The GEJ cancers and non-GEJ cancers clearly vary in incidence trends, geographical distrubition, proposed etiology, clinical presentation and treatment strategies.

Gastric carcinoma is the fourth most common malignancy worldwide [1] and it is the second most common cause of death [2]. Incidence varies greatly across the different world regions with a predominance of 26.9 per 100 000 per year (PY) in Asian males as opposed to 7.4 per 100 000 PY in their North American counterparts [1]. The decrease in incidence described in the past few decades reflects mainly the decrease in non-cardia cancers while the GEJ cancers are stable or even clearly more frequent in some parts of the world [3–4]. A recent account of the trends in the USA gathered from the Surveillance, Epidemiology and End Results (SEER) data

between 1977 and 2006 revealed a decline in the rate of non-cardia carcinomas among all race and age groups except for whites aged 25–39 years, where an increase in incidence rate was seen. No clear explanation for this phenomenon is yet available [5].

It is believed that the different trends in the incidence rates in the different geographical regions, as well as the different trends in the anatomical localization of gastric adenocarcinomas are rooted in the rate of exposure to the various causal factors. Non-cardia tumors are attributed to lower socioeconomic background, exposure to *Helicobacter pylori* (HP) infection, smoking, high intake of salty and smoked food and a low intake of fresh fruit and vegetables. The decrease in its incidence is attributed to the decrease in exposure to these risk factors, with better food preservation, reduced smoking, increased consumption of fresh food and very importantly a decrease in HP infection rates [6–8]. Risk factors related to cardia cancers include gastro-esophageal reflux disease (GERD), male gender, white race, smoking and obesity [9–12]. The association of GEJ adenocarcinomas with HP infection remains unclear with conflicting reports of a possible protective role [13–14].

Additional risk factors include atrophic gastritis, familial clustering and genetic syndromes, such as Lynch's syndrome [hereditary non-polyposis colorectal cancer (HNPCC) syndrome].

Survival rates from gastric cancer have improved over the last few decades. Five-year overall survival (OS) in the Western world is estimated at ∼20%. Fewer patients are referred for surgery, but those who undergo resection have a higher survival rate, which reaches 50%, possibly due to more accurate preoperative staging and improved imaging techniques. In Asia large-scale screening programs, detection at earlier stages and more aggressive surgical approaches, including more frequent D2 lymph node resection, contribute to high OS rates of ∼60% [15–17].

Treatment strategies in gastric cancer incorporate a multidisciplinary approach and require the co-operation of gastroenterologists, surgeons, medical and radiation oncologists, pathologists and radiologists. Great importance for optimal outcome is given to referral and treatment in high-volume centers that can incorporate all these different disciplines [18, 19].

familial predisposition

Several syndromes are associated with familial predisposition of gastric cancer. These can be divided according to the histology such as familial diffuse gastric cancer, which is associated in ∼25% of cases with a germline E-cadherin/CDH1 mutation and familial intestinal gastric cancer. Further specific genetic syndromes are also associated with an increased gastric cancer risk, mainly Lynch's (HNPCC) syndrome, but also others, such as Li–Fraumeni syndrome, familial adenomatous polyposis (FAP) syndrome and Peutz–Jeghers syndrome [17].

An occurrence of two or more cases of gastric cancer in the family, especially of the diffuse type in young individuals, should prompt reference for genetic counseling and a search for E-cadherin mutation and HNPCC syndrome (see recommendations in Figure 1). E-cadherin carriers are recommended to undergo regular gastroscopies, every 1–2 years at least from the age of 40 or earlier, specifically if cancers occurred at a young age in the family. Preventive gastrectomy should be considered.

With familial predisposition, HP screening and eradication is advised. In countries with a high incidence of gastric cancer, such as Japan or Korea, familial clustering is sufficient to implement yearly screening gastroscopy.

HP eradication

The correlation between HP infection and the incidence of gastric cancer has been demonstrated by several epidemiologic studies [20–22]. However, no clear benefit is seen with HP eradication for primary prevention of gastric cancer. A systematic review of the literature on the prevention of gastric cancer by HP eradication recently published by Takata et al. [23] suggested that HP eradication can decrease the gastric cancer prevalence by a third, but this observation is supported only by Japanese publications and not by those in other regions.

Which advice for patients with familial predisposition?

- HP screening and eradication
- In Japan and Korea: gastroscopy every year in patients with familial incidence
- Genetic counseling
  - Search for E-cadherin mutation and HNPCC syndrome
  - Search for E-cadherin in families with ≥2 cases (with diffuse-type gastric cancer), especially at younger age
- Gastroscopy every 1–2 years (some specified after age 40) in E-cadherin mutation carriers
- Consider gastrectomy in selected patients with E-cadherin mutation

Figure 1. Recommendations for evaluation in suspected familial predisposition of gastric cancer.

Further randomized trials examining the impact of systemic HP eradication in high-risk regions are ongoing. The eradication of HP in patients without underlying premalignant conditions is not generally recommended at present.

Fukase et al. [24] performed a randomized controlled trial investigating the need for HP eradication after endoscopic mucosal resection (EMR) of early gastric cancer. Eradication resulted in odds ratio for metachronous gastric carcinoma of 0.353 ($P = 0.009$) for the intent to treat group. No randomized trials examined the need for eradication after partial gastrectomy, though an evaluation of the gastric mucosa in patients undergoing partial gastrectomy for early cancer revealed a reduction in mucosal damage of potential pre-cancerous risk [25]. HP eradication is recommended following resection of gastric cancer by EMR or partial gastrectomy.

staging

The diagnosis of gastric adenocarcinoma has to be confirmed by biopsies, performed during upper gastrointestinal endoscopy. Accurate staging is very important since it determines the treatment strategy as well as the outcome of patients with gastric cancer.

A general clinical evaluation, including organ function, is warranted in every patient with gastric cancer. The most useful serum tumor markers are carcinoembryonic antigen (CEA) and CA19-9. Preoperative marker levels have a prognostic value. In a large study, preoperative CEA level was elevated in 249 (28.8%) out of 865 patients with gastric cancer. The CEA levels significantly correlated with stage and a multivariate analysis showed a significant correlation with survival. A significant difference was seen between patients with CEA levels <10 ng/ml as opposed to those >10 ng/ml [26]. A few smaller studies suggested a prognostic role for preoperative CA72.4 levels [27–29]. In general CEA and CA19-9 levels are determined preoperatively in patients with resectable gastric cancer and the marker if initially elevated, is used in the surveillance of these patients.

Available imaging techniques include endoscopic ultrasound (EUS), computerized tomography (CT), magnetic resonance imaging (MRI) and fluorodeoxyglucose F-18 positron emission tomography (FDG-PET). A systematic review of the T staging evaluation by EUS, CT and MRI showed a similar accuracy between these techniques (65%–92.1%, 77.1%–88.9%, and 71.4%–82.6%, respectively). Serosal involvement assessment also showed similar sensitivity and specificity across trials, although it is specified that greater experience is available with EUS [30].

CT remains the imaging method of choice for the evaluation of local extension and of distant metastases. There is no uniform consensus on the role of EUS, although there may be an important role when a decision needs to be made regarding preoperative treatment in patients with superficial disease or in case of linitis plastica. In specific cases FDG-PET may offer some additional information for inderterminate lesions to verify or exclude metastases (mainly in GEJ tumors), although it has been reported that up to one-third of metastatic gastric cancers are FDG-PET negative, especially in the diffuse-type histology [31–33]. A meta-analysis examining the detection of liver metastases in colorectal, gastric and esophageal cancer showed its advantage as compared with US, CT or MRI [31, 32]. MRI is not done routinely for the staging of gastric cancer.

A role for staging laparoscopy, eventually combined with peritoneal lavage, has been suggested in the staging of gastric cancer. Some series suggest up to 20% detection of unsuspected peritoneal metastases, not diagnosed by CT [34, 35]. The prognostic value of cytological examination of intraoperative washings in potentially resectable gastric cancer remains controversial. Hence, this technique has not been routinely implemented in many of the centers especially with preoperative chemotherapy incorporated as a therapeutic option in resectable patients. Recommendations for staging by the panel are presented in Figure 2.

treatment of resectable disease

adjuvant and neoadjuvant treatment

Several treatment strategies have been shown to be efficacious in the treatment of non-metastatic gastric cancer and are accepted as a standard of care option. There is a large regional variation in the adjuvant and neoadjuvant treatment of gastric cancer. The highest level of evidence is available for the strategy of perioperative chemotherapy and postoperative chemoradiotherapy. There is also some evidence for the benefit of postoperative chemotherapy, mainly from recent meta-analyses.

Indications for the use of adjuvant or neoadjuvant treatment vary, but are mainly selected for T3/T4 and/or N-positive tumors.

Perioperative chemotherapy has been implemented in most European countries following the results of the MAGIC trial. The trial demonstrated an increase in 5-year OS from 23% to 36% with the perioperative (pre- and postoperative) ECF [epirubicin, cisplatin, 5-fluorouracil (5FU)] regimen as opposed to surgery alone [36]. Recently, two meta-analyses examined the role of neoadjuvant chemotherapy versus primary surgery; one demonstrated a 5-year OS hazard ratio (HR) of 0.68 [95% confidence interval (CI) 0.48–0.97, $P = 0.03$] in favor of chemotherapy [37]. The other with a survival HR of 0.82 (95% CI 0.73–0.91, $P = 0.0002$), performed a subset analysis demonstrating an advantage only in GEJ tumors and not in gastric tumors ($P = 0.007$, $P = 0.31$, respectively). The researchers stated, however, that the power of the analysis was too low to reach significance [38].

Based on the results of the REAL-2 trial in metastatic gastric cancer, showing the non-inferiority of oxaliplatin compared with cisplatin and of capecitabine compared with 5FU, the panel believes these drugs are accepted alternatives for perioperative treatment as well [39, 40]. A recently published French study validated the concept of perioperative treatment in gastric cancer with 5FU and cisplatin without epirubicin [40]. Insufficient data are available to incorporate docetaxel or biologicals in the perioperative setting.

Adjuvant chemotherapy is the current standard in East Asia. The recent GASTRIC meta-analysis demonstrated an absolute survival benefit of 5.8% at 5 years (from 49.6% to 55.3%) and 7.4% at 10 years (from 37.5% to 44.9%) with adjuvant

- Evaluation of organ function
- Tumor markers: CEA and CA 19-9: recommended
- Further technical examinations:

Gastroscopy with biopsies

Spiral CT scan abdomen with appropriate contrast and chest X-ray or preferably CT thorax

EUS; no complete consensus, although there may be a role when a decision has to be taken on preoperative treatment in patients with superficial disease or in cases of linitis plastica

High resolution CT scan: same information as EUS

No systematic role for MRI

FGG-PET: very selected patients, mainly GE junction (1/3 of gastric cancers: PET negative)

Staging laparoscopy ± peritoneal lavage: not done routinely because no clear therapeutic implications

Figure 2. Recommended primary staging procedures.

chemotherapy compared with surgery alone. Overall HR of death was 0.82 (95% CI 0.76–0.90; $P < 0.001$) [41]. The current regimen implemented in Asia of S1 given for 1 year following surgery, has shown a 3-year OS increase from 70% to 80% when compared with surgery alone [42]. The most frequently used regimens are S-1 in East Asia and Japan and a 5FU/platin-based regimen in the West.

The INT0116 (SWOG 9008) randomized phase III trial is the basis for the current adjuvant chemoradiotherapy often used in the USA. The last update with >10 years follow-up further substantiated the advantage of the 5FU plus radiotherapy protocol over surgery alone. The HR for survival was 1.32 ($P = 0.004$) and for disease-free survival (DFS) 1.51 ($P < 0.001$) in favor of adjuvant chemoradiotherapy. A subset analysis showed a benefit to all subgroups with the exception of a diffuse-type histology [43]. There is no evidence yet that intensifying the chemotherapy with the addition of other cytotoxics to 5FU improves the outcome further. Postoperative chemoradiotherapy is recommended for locally advanced patients demonstrating on pathology-positive lymph nodes, positive margins, inadequate staging or suboptimal surgery, if neoadjuvant chemotherapy was not administered.

radiotherapy regimen

The standard radiotherapy protocol implemented in the adjuvant treatment of gastric cancer reflects the schedule used in the INT0116 (SWOG 9008) trial. Despite the use of bolus 5FU in the trial, the panel recommends the use of a continuous infusion regimen, as this administration is more tolerable and at least as effective. This has been recently incorporated in several small trials that attempted to add different combination cytotoxic agents to the protocol, without success until now [44, 45].

Experience and a quality assurance system is required in the planning of the radiotherapy fields with the use of modern techniques such as three-dimensional conformal radiotherapy (3D-CRT) or intensity-modulated radiation therapy (IMRT) to reduce toxicity. A total dose of 45 Gy should be given in 25 fractions of 1.8 Gy. Delineation of volumes should comply with the published guidelines from the Radiation Therapy Oncology Group (RTOG) and European Organisation for Research and Treatment of Cancer (EORTC) (including tumor bed, celiac and upper para-aortic lymph nodes).

Preoperative radiotherapy has been limited to pilot studies. If implemented, care should be taken as radiated volumes are different from the postoperative ones [46].

nutritional scheme

A nutritional scheme adapted to each patient by a dietician is advised. Caloric intake should aim at a minimum input of 1500 kcal/day. Following gastrectomy inadequate caloric intake or postgastrectomy syndrome is frequent. Total gastrectomy will require intramuscular vitamin B12 supplements. In the case of postoperative chemoradiotherapy, a percutaneous enteral feeding tube may be needed to maintain adequate caloric intake.

GEJ adenocarcinoma

GEJ tumors are categorized according to the Siewert classification into distal esophageal adenocarcinoma (Type I), true carcinoma of the cardia (Type II) and subcardial gastric cancer (Type III) [47]. Some series suggest that stage distribution, as well as long-term survival rates, are different amongst the different classes [48].

There is no consensus available on the treatment strategy of GEJ adenocarcinoma. These tumors are incorporated in esophageal cancer trials dominated by preoperative

chemoradiation, as well as the gastric trials with their various approaches, as specified earlier.

The German Oesophageal Cancer Study Group attempted a phase III comparison between neoadjuvant chemotherapy and neoadjuvant chemotherapy followed by chemoradiotherapy in GEJ adenocarcinoma. The trial unfortunately was closed early due to low accrual. The addition of preoperative radiation increased the 3-year survival rate from 27.7% to 47.4% but the study lacked the necessary power for statistical significance ($P = 0.07$, HR 0.67, 95% CI 0.41–1.07) [49] .

The strategy for the treatment of GEJ cancer can therefore be guided by the 'oesophageal' approach, focusing on preoperative chemoradiotherapy or by the 'gastric' approach with perioperative chemotherapy or to a lesser extent postoperative chemoradiotherapy. This has been thoroughly discussed recently in a review by Power and Reynolds [50].

resection procedures for mucosal tumors

The choice of resection techniques for a mucosal tumor should be based on a multidisciplinary discussion. A growing body of evidence supports the use of EMR in mucosal tumors (Tis–T1a), as only 3%–5% of these will demonstrate invaded lymph nodes if gastrectomy with lymph node resection is performed. When submucosal invasion (T1b) is present, lymph nodes are involved in 25%–28% of patients. This would entail more extensive surgery [51, 52]. Some series suggest that endoscopic submucosal dissection (ESD) would reduce the risk of local recurrence, which remains high with EMR (18% compared with 3.7%, respectively, $P < 0.001$) although this has yet to be proved in randomized clinical trials [53].

resection procedures for advanced, non-metastatic tumors

Surgery is the cornerstone for curative treatment of advanced, non-metastatic resectable gastric cancer. Several Western studies have addressed the extent of lymphadenectomy, comparing D1 with D2 lymph node dissection [54–56]. Postoperative mortality was significantly higher after a D2 dissection, while none of these studies revealed an improvement in OS with D2 lymphadenectomy. However, a recent update of the Dutch D1D2 study showed that the gastric cancer-related death rate after a median follow-up of 15.2 years was significantly higher in the D1 group (48%) compared with the D2 group (37%) [57]. A small Italian study comparing D1 with D2 dissection found very low 30-day mortality rates for both D1 and D2 lymph node dissection (3.0% compared with 2.2%, $P = 0.722$) in experienced centers [58], but survival results of this trial have to be awaited. Other studies focus on procedural volumes as markers for quality of care, and find lower mortality rates and higher survival in centers with a high annual caseload [59–61].

In Asian countries, D2 lymphadenectomy is considered standard therapy for advanced resectable gastric cancer. A small Taiwanese study compared D1 with D3 lymphadenectomy in 221 patients and found a significant improvement in 5-year survival [62]. A Japanese study compared D2 with D2 combined with para-aortic node dissection and found no difference in survival, with more surgery-related complications in the para-aortic group [63].

Based on these results, D2 lymphadenectomy is the recommended type of surgery, and should be performed in experienced centers with high annual caseloads.

surveillance after treatment with curative intent

Several series examined the efficacy of a follow-up scheme or early discovery of an asymptomatic recurrence in gastric cancer. These studies showed no survival advantage [64, 65]. Therefore, no systematic surveillance scheme can be proposed by the panel. No randomized trials, however, attempted to answer this dilemma especially in light of improved modern imaging techniques and improved chemotherapy. Physicians may therefore agree with the patients on an individual surveillance program, taking into account the risk of recurrence, patient's expectations and concomitant pathology.

prognostic markers in resectable disease

Most series investigating possible prognostic factors in primary gastric cancer validate the importance of the TNM staging system [66–69]. Several studies showed a prognostic role for the ratio between dissected nodes and involved ones [70, 71].

Elevated tumor markers, as well as tumor size and Lauren histology, have been shown to be prognostic for recurrence and survival in some series [68, 69, 72].

Asians with gastric adenocarcinoma have superior outcomes in Los Angeles County. These outcomes verify disparities in gastric cancer survival between different races and ethnicities independent of established clinical and pathologic factors [73].

Age has been suggested as a prognostic factor for recurrence and survival following primary treatment of gastric cancer [70, 74]. However, in multivariate analyses, this was not an independent factor [68, 72]. Other patient-related clinical prognostic factors have also failed to show independent prognostic significance in multivariate analysis in these series [75]. However, the incorporation of these into a prognostic nomogram did show a prognostic role.

The prognostic nomogram offered by MSKCC incorporated age, sex, primary site (distal one-third, middle one-third, GEJ and proximal one-third), Lauren histotype, number of positive lymph nodes resected, number of negative lymph nodes resected and depth of invasion. The predictive ability of the nomogram was shown to be superior to TNM staging alone in R0 tumors [76]. The nomogram, however, is not in common clinical use, although the different variables suggested by it are considered.

Series investigating MSI in gastric cancer patients suggest a distinct phenotype characterized by older age, antral localization of the tumor and intestinal Lauren subtype. The prognostic correlation with survival, however, is conflicting [77–80]. Preliminary results in small series suggest a prognostic role for p53 expression [81, 82].

Recently a prognostic association was presented between MMP-9 mRNA expression level and survival in metastatic gastric cancer patients in an Arbeitsgemeinschaft Internistische

Onkologie (AIO) phase III cohort and a possible correlation with chemotherapy resistance [83–85].

treatment of metastatic disease

first-line treatment

The administration of chemotherapy has a clear OS advantage compared with best supportive care (BSC) (HR = 0.39; 95% CI 0.28–0.52) [86]. The advantage of combination versus single-agent treatments, mainly 5FU, was also evident (HR = 0.83; 95% CI 0.74–0.93). It must be emphasized that this applies to patients fit for clinical studies with preserved organ function and a good performance status (PS).

The backbone of chemotherapy for patients with metastatic gastric is 5FU and cisplatin. Following the REAL-2 and other smaller trials [39, 87] demonstrating the non-inferiority of capecitabine compared with 5FU and oxaliplatin compared with cisplatin, the reference chemotherapy in the Western world has become fluoropyrimidine/platinum based. The FOLFOX regimen using biweekly oxaliplatin and continuous infusion 5FU/folinic acid has shown safety advantages compared with 5FU/cisplatin in several phase II trials [88–90]. In Japan and many Asian countries the reference treatment for metastatic gastric cancer is often oral fluoropyrimidine, either S1 or capecitabine based. It is, however, unclear whether S1 is more active than the other fluoropyrimidines in Asian patients. A small Korean study showed similar activity of S-1 and capecitabine. Fit patients are treated in some Asian countries with a capecitabine- or S-1-based doublet (most frequently cisplatin) [91, 92]. The pharmacology of S-1 is different between Asian and Caucasian patients [93]. Recently, the FLAGS multinational phase III trial compared the S1/cisplatin combination with 5FU/cisplatin in non-Asian patients. Similar efficacy was noted with an improved toxicity profile when S1 was administered; including less grade 3/4 neutropenia and fewer treatment-related deaths (32.3% compared with 63.6%, 2.5% compared with 4.9%; $P < 0.05$, respectively) [94].

Docetaxel added to 5FU/cisplatin increases the activity compared with the doublet 5FU/cisplatin according the V325 study: longer progression-free survival, OS and a higher response rate are reported for the triplet cytotoxic combination compared with the doublet [95]. The high toxicity of the three weekly regimen leads, however, to recommendations to add docetaxel only in selected patients with a good PS and good organ function and using a modified regimen with reduced dose, or with weekly or biweekly regimens or integrating oxaliplatin instead of cisplatin [96].

There was also agreement among the experts, based on the lack of demonstration of the additional activity of epirubicin in combination regimens, to not recommend systematically epirubicin in combination regimens for metastatic gastric cancer.

It was recommended by the panel to test metastatic gastric adenocarcinoma for HER2. In the ToGA (Trastuzumab for GAstric cancer) study, from 3665 analyzed tumor samples, 810 (22.1%) were HER2 positive according to protocol requirements (IHC 3+ or FISH positive). Rates of HER2 overexpression/amplification were similar between patients from Europe and Asia, but higher in patients with intestinal versus diffuse-type tumors (32.0% versus 6.1%) and GEJ versus gastric tumors (32.2% versus 21.4%). In the ToGA trial trastuzumab was added to chemotherapy (fluoropyrimidine, either 5-FU or capecitabine plus cisplatin) in patients with advanced gastric or GEJ cancer ($n = 584$) with overexpression /amplification of HER2. The primary endpoint was OS. The combination of chemotherapy plus trastuzumab was shown to be statistically superior to chemotherapy alone, with an increased median OS of nearly 3 months (13.8 compared with 11.1 months without trastuzumab). Moreover, increased benefit from trastuzumab was seen in patients who had higher levels of HER2 protein expression, including subgroups with IHC score 2+/FISH+ and IHC score 3+. In these patients, median OS increased from 11.8 months for the chemotherapy treatment arm to 16.0 months for the chemotherapy with trastuzumab arm. The combination of chemotherapy plus trastuzumab also prolonged the progression-free survival and increased the response rate without adding clinically relevant toxicity to the treatment [97].

All patients with metastatic gastric adenocarcinoma who are candidates for first-line chemotherapy should therefore be tested for HER2-neu status and patients with a tumor overpresssing the HER2 receptor should be treated with the cisplatin/fluoropyrimidine plus trastuzumab combination. Trastuzumab does not increase the toxicity of the chemotherapy backbone. It is, however, not advised to combine trastuzumab with anthracyclines based on increased cardiac risk observed in breast cancer patients [98].

HER2-neu-negative patients should be considered for combination therapy. The choice between a doublet or a triplet combination should be directed by PS, general condition of the patient and the expectations and wishes of the patient. In elderly patients a single-agent regimen (fluoropyrimidine) can be considered, although a combination regimen can also be considered for fit patients [99].

Other targeted biological agents are at the moment still investigational. The recently presented AVAGAST trial investigating first-line capecitabine and cisplatin plus bevacizumab or placebo failed to show a statistically significant survival advantage in the intent to treat population, although the progression-free survival and response rate were improved with the addition of the anti-VEGF antibody. Moreover, a geographical difference was found and in the subset analysis of European and American patients a significant survival advantage was found, but not in Asian patients [100]. The addition of cetuximab to a cytotoxic doublet is currently being investigated in the phase III EXPAND trial.

second-line treatment

Administering second-line therapy is accepted in most centers for selected patients with a good performance status. Only an early stopped German randomized clinical trial of irinotecan plus BSC against BSC has been conducted in this setting. The trial was early stopped due to low-rate recruitment, but it showed a median OS of 2.4–4.0 months (HR 0.48; 95% CI 0.23–0.92; P 0.023 [101].

Accepted variables predicting survival with second-line treatment are PS, baseline hemoglobin levels, time to

progression (TTP) on first-line chemotherapy [102–104]. An analysis published by an Italian group exploring the clinico-pathologic variables predicting a survival analysis found PS 2, hemoglobin ≤11.5 g/l, CEA >50 ng/ml, three or more metastatic sites, TTP in first-line treatment of ≤6 months to be independent of adverse prognostic factors for survival. Having no risk factors resulted in 12.7 months median OS while having three or more resulted in 3.3 months [102].

The choice of agents to be given in second-line therapy depends on earlier lines with acceptable options being irinotecan [101], FOLFIRI (irinotecan, 5FU/folinic acid) [105], docetaxel [106] and paclitaxel [107, 108].

In some trials second-line therapy has been more frequently used in East Asia including Japan and Korea compared with Western countries. Longer survival of Asian patients in some trials was at least in part attributed to more common use of second-line therapy.

Further lines can be discussed with patients in good performance status although evidence of efficacy is lacking. The combination of mitomycin C and capecitabine is optional again with little evidence [109]. Participation in clinical trials should be encouraged.

disclosure

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