Current Management of Gastric Cancer in Europe

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Abbreviations:

DFS – disease-free survival
OS – overall survival
ORR – overall response rate
CRT – chemoradiotherapy

Rezumat

Managementul actual al cancerului gastric în Europa

Cancerul gastric reprezintă una dintre cele mai frecvente malignități și o problemă majoră de sănătate la nivel global. Tratamentul multidisciplinar reprezentat de chirurgia radicală și chimioterapia perioperatorie oferă cea mai bună șansă de vindecare pentru pacienții cu cancer gastric rezecabil. Date provenind din trialuri clinice randomizate, bine conduse demonstrează ameliorarea supraviețuirii prin utilizarea chimioterapiei în boala metastatică. În ultimii ani, două terapii țintite au fost aprobate în stadiul metastatic. Având în vedere rezultatele promițătoare din trialurile clinice, este probabil ca în viitorul apropiat imunoterapia să fie încorporată în tratamentul multimodal al cancerului gastric.

Cuvinte cheie: cancerul gastric, chimioterapia perioperatorie, chimioterapia adjuvantă, terapia țintă, imunoterapia

Abstract

Gastric cancer is one the most common malignancies and a considerable health problem throughout the world. Multimodal approach, encompassing both radical surgery and perioperative chemotherapy provides the best chance to cure resectable gastric cancer. Data originating from well-conducted randomized trials demonstrate that chemotherapy improves survival in patients with metastatic disease. During the last years, two targeted therapies have been approved in metastatic setting. Based on promising clinical trials results, it is expected for the near future that immunotherapy to be incorporated in the multimodal treatment of gastric cancer.

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Key words: gastric cancer, perioperative chemotherapy, adjuvant, targeted therapy, immunotherapy

Introduction

Despite a gradual decline in incidence reported by recent epidemiological studies, gastric cancer remains one of the leading causes of malignant disease-associated morbidity and mortality worldwide. In Europe, there were reported 140,000 new cases of gastric cancer in 2012 and, according to the same statistics, 107,000 deaths occurred due to this malignancy (1,2). A multidisciplinary treatment approach is now recommended in most European medical guidelines. Surgery is still the cornerstone of curative treatment for locally advanced gastric cancer. However, in the last 15 years, different phase III clinical studies have demonstrated that perioperative strategies, mainly perioperative chemotherapy, adjuvant chemotherapy or chemoradiation improve outcomes in patients with locally advanced gastric cancer. In metastatic setting, molecular targeted therapy has been implemented as standard treatment with or without chemotherapy, to further prolong survival. Moreover, immunotherapy has shown favorable results in phase III trials, having the potential to change the current treatment landscape. Recent advances in molecular subtyping of gastric cancer could also lead to new therapeutic strategies in the next decades. Increased awareness of the high morbidity and mortality associated with gastric cancer changed in the recent years, also in Romania, the landscape of the specific treatment and turned it into a more tailored, modern and according to European guidelines. To our knowledge, several efforts are being made to develop preventive strategies, to implement multidisciplinary teams in every hospital involved in gastric cancer treatment and to decrease variation in care across the country by identifying and spreading best practices (perioperative chemotherapy being one of the most recent, but less implemented treatment strategies). This article aims to give an

overview of the standard management of gastric cancer in Europe, underlying some of the recent therapeutic advances and the most promising treatment perspectives.

Management of Local/Loco-Regional Disease

A multidisciplinary meeting with experts from different specialties involved in the management of gastric cancer (gastric surgeon, pathologist, radiologist, radiation oncologist, medical oncologist, gastroenterologist, dietician) is mandatory before any treatment. There is still a critical need in Romania to enhance the communication between the different medical specialties involved in the treatment of gastric cancers, in order to deliver the best medical care and to improve outcomes of the patients. Although not widely recognized, some hospitals, mainly in small towns are lacking structured, functional multidisciplinary teams (MDT) or are in difficulty to provide regular meetings for the MDT or to refer the patients with gastric cancer to established MDT centers in a timely manner.

Endoscopic Treatment

Less than 15% of gastric cancers in Europe are diagnosed at an early stage (3). Well-implemented screening programs are lacking in Romania and most patients, consequently present with late-stage gastric cancer at diagnosis. More endoscopy departments with adequately trained gastroenterologists are needed for closer monitoring of the population at risk. Although slowly adopted, due to low incidence of early gastric cancer in Western countries, endoscopic submucosal dissection (ESD) is now regarded as a standard treatment option, alongside the more conventional endoscopic mucosal resection (EMR) for early gastric cancers. ESD is recommended by European Society of Gastrointestinal Endoscopy for the

most superficial neoplastic gastric lesions, with very low risk of lymph node metastasis (4). European trials showed an en-bloc resection rate of 98.4%, a R0 resection rate of 90.2%, along with a delayed bleeding rate and perforation rate of 6% and 1%, respectively, results that are largely equivalent with those reported by Eastern Asian centers (5-7). After endoscopic resection, surveillance endoscopies with chromoendoscopy are recommended at 3,6 months after resection, then annually in order to decrease metachronous cancer risk.

Surgical Treatment

Surgical resection is currently the only potential curative treatment for locally advanced gastric cancer. Most of the European guidelines recommend radical gastrectomy with D2 lymph node dissection for stage IB-III gastric cancer, in high volume centers with appropriate surgical expertise (8). As it was showed in a 10-year follow-up of the well-known Dutch trial and in other observational and randomised studies, D2 dissection leads to superior outcomes compared with D1 resection (9,10). Although laparoscopic gastrectomy and laparoscopic D2 lymph node dissection has the potential advantage of decreased postoperative morbidity and reduced recovery time, this procedure requires more confirmation and is considered technically challenging for advanced gastric cases (11). One key recommendation, in order to enable the best possible treatment for Romanian patients with gastric cancer is to facilitate centralization of care, by referring the patients with resectable gastric cancer to centers with extensive expertise in performing radical gastrectomy.

Preoperative and/or Postoperative Treatment

Most experts agree that resectable gastric cancer with clinical stage $\geq$ T1b is best treated with multidisciplinary approaches and particularly within high volume centers (12,13). The main two treatment modalities are perioperative chemotherapy and surgery or up-front surgery and either adjuvant chemotherapy

or chemoradiation. East Asian experts prefer initial surgery and adjuvant therapy, whereas in the US and Europe, the strong preference is for perioperative chemotherapy.

Perioperative Chemotherapy

Perioperative chemotherapy has been widely adopted as the standard of care throughout Europe and evidence for this therapeutic strategy was derived from two phase III trials. The Magic trial randomly assigned 503 patients with resectable adenocarcinoma of the stomach, gastroesophageal junction and lower esophagus to either three cycles of pre- and postoperative epirubicin, cisplatin, 5-Fluorouracil (ECF) and surgery or surgery alone. The perioperative chemotherapy arm showed a significant improvement in disease-free survival, 5-year overall survival rates (5-year OS rates: 36 vs 23%, $p=0.009$)(14). In the FFCD 9703 study, 224 patients with esophago-gastric adenocarcinoma were assigned to receive 18 weeks of perioperative 5-FU plus cisplatin and surgery, with a recommended D2 dissection or surgery alone. The perioperative chemotherapy arm resulted in a significant improvement in curative resection rate (84% vs 73%, $p=0.04$), 5-year disease-free survival rates (34% vs 19%, $p=0.003$) and overall survival (5-year OS rate: 38% vs 24%, $p=0.02$) (15). However, only 50% of patients enrolled in the Magic and FFCD studies, who underwent preoperative chemotherapy and surgery were able to complete adjuvant chemotherapy, suggesting that future strategies should focus on intensifying preoperative approaches.

In the recent FLOT-AIO trial a triplet regimen of perioperative docetaxel, 5-FU and oxaliplatin (FLOT, 4 cycles before and after curative surgery) was compared with the standard after the Magic trial, epirubicin, cisplatin and 5-FU (ECF) or epirubicin, cisplatin and capecitabine (ECX) – 3 cycles preoperative plus 3 cycles postoperative, in 714 patients with gastro-esophageal junction/gastric cancer $\geq$ cT2 and/or cN+. The authors reported that perioperative FLOT improved pathological complete remission rates (pCR:16% vs 6%),

disease-free survival (DFS; 30 vs 18 months), $p=0.004$) and overall survival (mOS; 50 vs 30 months, $p=0.0012$ and 5-year OS rate; 45% vs 36%, $HR=0.77$)(16). FLOT type perioperative chemotherapy can now be considered the Western gold standard treatment in resectable disease.

To date, there is no evidence to support the use of perioperative biologically targeted therapy, including trastuzumab or antiangiogenic compounds, and immunotherapies are currently investigated (17). A number of clinical trials are in progress to evaluate the impact of additional preoperative radiotherapy to perioperative chemotherapy (18).

In recent years, the indication for perioperative chemotherapy was a subject of great debate for Romanian surgeons and medical oncologists. Some of them feared that the almost unavoidable side effects of preoperative treatment might have negative consequences on the patient's performance status, thus influencing the surgical outcomes. Moreover, the potential event of tumor progression to a non-resectable stage during preoperative treatment in cases of initially resectable locally advanced gastric cancer has been considered by surgeons a reason not to refer patients for neoadjuvant / perioperative chemotherapy. Oncologists, who rely heavily on imaging to guide the multimodal treatment raised the problem of restaging after neoadjuvant chemotherapy with CT imaging or PET scan to assess for the presence of interval development of metastatic disease. There is still a great need observed in some centers to include a trained radiologist in the MDT. Moreover, oncologists claimed that the availability of the implantable ports, of the portable infusion pumps for patients who need continuous administration of chemotherapy remains low and the knowledge to insert the ports by interventional radiologists is still missing in some centers. However, the overwhelming evidence of the recently published data have extended the use of perioperative chemotherapy. An increasing number of Romanian oncologists consider that administering chemotherapy first provides a tool for selecting patients with the highest likelihood to benefit from

additional surgery. On the other hand, more surgeons now agree that adequate gastric cancer surgery should be integrated in the setting of multimodal treatment approach.

Adjuvant Treatment

For patients with $\geq$ stage IB gastric cancer, who did not receive preoperative chemotherapy, postoperative adjuvant chemotherapy or chemoradiation is recommended.

Chemotherapy

A meta-analysis of 3838 patients from 17 clinical studies demonstrated a survival benefit of 5-FU-based adjuvant chemotherapy ($HR = 0.82$ (IC 95%:0.76-0.90); $p = 0.001$) (19). The intensification of postoperative chemotherapy with irinotecan followed by docetaxel and cisplatin did not show any survival benefit compared to 5-FU alone (20). Trials in East Asian patients who had undergone a D2 resection proved that there is an overall survival benefit with 1 year adjuvant chemotherapy with S1, with similar findings for 6 months of adjuvant capecitabine-oxaliplatin regimen (21,22). However, because of the similar 10% improvement in 5-year OS observed, it is not clear how much additional benefit derives from adding a platinum to a fluoropyrimidine, even in Asian population.

Following preoperative chemotherapy, the patients who have undergone surgery should complete the preoperative chosen regimen, independent from histopathologic findings.

Chemoradiotherapy

Adjuvant 5-FU/leucovorin plus conventionally fractionated radiotherapy has shown a survival benefit compared to surgery alone and is regarded as standard treatment in the US, but not in Europe. In the United States, the INT 0116 phase III study proved that postoperative chemotherapy reduced local recurrence rates and improved overall survival following D1 dissection or R1 resection (23). Other randomized or non-randomized data

suggested a survival benefit of the postoperative chemo-radiation even after D2 resection. However, the recent international phase III CRITICS study did not show an overall survival advantage of additional postoperative radiotherapy to perioperative chemotherapy and at least D1 surgery (24). Only 52% of patients in the chemotherapy arm and 47% in the chemoradiation arm completed the assigned therapy, due to low postoperative treatment tolerance in Western patients. For this reason, the ongoing Western studies on adjunct treatment (ESOPEC study, Neo-AEGIS study) focus on the preoperative strategies.

Management of Advanced/Metastatic Disease

Data from numerous randomized clinical trials including patients with unresectable locally advanced and/or metastatic gastric cancer showed a statistically significant advantage of palliative chemotherapy in terms of survival and quality of life, compared to best supportive care alone.

First-line Treatment

The platinum/fluoropyrimidine doublet alone or in combination with other compounds (triplet regimen; with epirubicin or with taxanes) have been largely used for fit patients with advanced gastric cancer. The REAL-2 study showed equivalence in terms of efficacy and better tolerability with oxaliplatin replacing cisplatin, and improved OS with capecitabine instead of infused 5-FU (25,26). Adding docetaxel to 5-FU/cisplatin (DCF) demonstrated improved outcomes over cisplatin + 5-FU in V-325 trial, in terms of response rate (37% vs 25%), time-to-progression (5.6 vs 3.7 months) and 2-year survival rate (18% vs 9%), but significantly more hematologic toxicity (27). Infusional 5-FU/leucovorin/irinotecan (FOLFIRI) may be used as an efficient alternative to platinum-based regimens (28).

The phase III ToGA trial demonstrated an increased response rate, progression-free survival and overall survival with the addition of trastuzumab (anti-Her2 monoclonal anti-

body) to the fluoropyrimidine/cisplatin doublet (median OS, 13.8 vs 11.1 months; HR, 0.74 (95% CI 0.60-0.91); $p=0.0046$) (29). This combination is now a standard of care for the 10-15% of the patients with gastric cancer who are Her2 positive.

The addition of other antinangiogenics (bevacizumab), antiEGFR (cetuximab, panitumumab) and antiMET/HGF (onartuzumab, rilotumumab) therapies to first line chemotherapy did not provide any benefit of OS (30-32).

Second-and Further Line Treatment

In second-line, two randomized studies comparing irinotecan monotherapy (AIO trial) or docetaxel (Cougar-02 study) versus best supportive care have shown an improvement of overall survival (similar median OS of 8-9 months) and quality of life in patients with good performance status after failure of fluoropyrimidine /platinum therapy (33,34). Ramucirumab (a VEGFR-2 inhibitor) improved overall survival compared to placebo in two phase III trials, when administered as a single agent (REGARD trial; OS: 5.2 vs 3.8 months) or when added to paclitaxel (RAINBOW trial; mOS: 9.6 vs 7.4 months) (35,36).

Recently, immunotherapy has emerged as one of the most auspicious new area of drug development. Comprehensive molecular characterisation performed by the TCGA group showed a relatively high mutational load in about 34% of gastric cancers and a subset of tumors (22%) with microsatellite instability or with a favorable immune-environment (the „EBV-related” subtype, which presents hallmarks of sensibility to immunotherapy, such as elevated PD-L1/PD-L2 expression, intra- or peritumoral immune cell infiltration), reinforcing the use of immunotherapy in gastric cancer, especially based on immune checkpoint inhibitors (37,38). Pembrolizumab monotherapy demonstrated encouraging efficacy and manageable toxicity in metastatic gastric cancer after more than two prior lines of therapy (mOS: 5.6 months, 12 months OS rate: 23 %). Overall response rate was 15.5% in patients who were PD-L1 positive

and 6.4% in PD-L1 negative (39). Nivolumab, another anti-PD1 monoclonal antibody demonstrated in a large Asian phase III trial (ATTRACTION-2) a significant survival benefit compared with placebo in patients with advanced gastric cancer, who failed two or more lines of treatment (OS: 5.26 vs 4.14 months; HR: 0.63 (95% CI 0.51-0.78); $p=0.0001$ and 12 months OS rate: 26.2%)(40). These results supported approval of nivolumab in Japan as a standard therapy for patients with heavily pretreated advanced gastric cancer. Moreover, these favorable data provided a strong rationale to further investigate nivolumab in Western population with advanced gastric cancers (there are gene expression differences among Asian and non-Asian gastric adenocarcinomas, which might influence clinical outcomes and response to immunotherapy), as well as nivolumab in combination with other immuno-oncology drugs or chemotherapy.

In the palliative setting, Romanian oncologists have the possibility to recommend all of the chemotherapeutic regimens or targeted therapies used across European countries. However, some of them reported experiences with shortage of cisplatin in last years and, consequently, with the use of an alternative drug, such as oxaliplatin, strategy which is proved not to be inferior in metastatic gastric cancer treatment.

Conclusion

Perioperative chemotherapy improves outcomes in patients with resectable gastric cancer and should be considered standard therapy in Europe. Various clinical trials will be conducted in order to strengthen the preoperative treatment. Many more chemotherapy regimens, molecular targeted therapies and immunotherapeutic drugs are now available for the treatment of metastatic gastric cancer, to further improve survival. Research into more effective therapeutic targets, biological mechanisms, predictive biomarkers of response is evolving fast and new standards of care may emerge in the near future.

Conflicts of Interest

No conflict of interest.

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