Overview on Gastric Cancer

Chapter 4

Recent Research and Review Works in the Field of Gastric Cancer

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Abstract

Gastric cancer is one of the leading causes of cancer-related death worldwide. Many patients have inoperable disease at diagnosis or have recurrent disease after resection with curative intent. Gastric cancer is separated anatomically into true gastric adenocarcinomas and gastro-oesophageal-junction adenocarcinomas, and histologically into diff use and intestinal types. Gastric cancer should be treated by teams of experts from diff erent disciplines. Surgery is the only curative treatment. For locally advanced disease, adjuvant or neoadjuvant therapy is usually implemented in combination with surgery. In metastatic disease, outcomes are poor, with median survival being around 1 year. Targeted therapies, such as trastuzumab, an antibody against HER2 (also known as ERBB2), and the VEGFR-2 antibody ramucirumab, have been introduced. In this review, we mainly resent an update of the treatment of gastric cancer.

1. Introduction

Gastric cancer is an important health problem, being the fourth most common cancer and the second leading cause of cancer death worldwide. More than 950,000 new diagnoses are made every year. An estimated 720,000 patients died from gastric cancer in 2012 [1]. Gastric cancer is separated anatomically into true gastric adenocarcinomas (non-cardia gastric cancers), of which there were 691,000 new cases in 2012, and gastro-oesophageal junction adenocarcinomas (cardia gastric cancers), of which there were 260,000 new cases in that year [2]. Despite a decline in incidence and mortality and despite important advances in the understanding of the epidemiology, pathology, molecular mechanisms, and therapeutic options and strategies, the burden remains high.

Gastric cancer is a main contributor to the global burden of disability-adjusted life-years from cancer in men and accounts for 20% of the total worldwide, following lung and liver cancers, which, respectively, account for 23% and 28% [3]. The burden of gastric cancer remains very high in Asia, Latin America, and central and eastern Europe, whereas in North America and most western European countries, it is no longer a common cancer [4]. Nevertheless, the decline in the incidence of gastric cancer has gradually lessened in some countries, particularly the USA. In other countries, such as France, mortality is predicted not to decrease further in the middle-aged population [4]. This slowing of change is probably explained by long-term low and stable prevalence of Helicobacter pylori infection in these countries [4]. By contrast, the incidence of gastro-oesophageal-junction adenocarcinomas is increasing sharply [5].

2. Surgical Treatment

Adequate surgical resection is the only curative therapeutic option for gastric cancer [6, 7]. Endoscopic resection might be suitable as an alternative to surgery for small well differentiated early-stage tumours [8,9]. Advances in technology and minimally invasive strategies have created new opportunities for surgery in gastric cancer. Minimally invasive procedures are associated with reduced surgical trauma and immunosuppression compared with conventional open surgery and, therefore, might improve quality of care as long as the principles of surgical oncology are respected.

The extent of surgery is determined by tumour stage, diameter, location, and histological type. Adequate surgery in the stomach is defined as complete resection of the primary cancer with tumour-free surgical margins of at least 4 cm and adequate lymphadenectomy. In practice, these requirements correspond to total gastrectomy for gastric cancers with signet-ring cells (linitis plastica), and those located in the upper third of the stomach or with atrophic gastritis. Cancer in the lower two-thirds of the stomach can often be treated with subtotal gastrectomy. Surgery in Japan and east Asia has traditionally been more extensive and aggressive than that in other developed countries. Although there is no worldwide consensus on the degree of lymphadenectomy, D2 lymphadenectomy (perigastric [D1] plus coeliac artery and its branches) is generally recommended if the associated postoperative morbidity and mortality rates are acceptably low-for instance, in high-volume hospitals with experienced surgeons [10]. This approach has contributed to improved cure rates in various registries and studies, from 30% to up to 55% in the past decade. Other reasons are stage migration because of improved methods for staging, increased use of adjuvant and neoadjuvant therapies, and centralisation of surgery, which has led to improvements in postoperative mortality [11]. At least 16 lymph nodes should be removed to enable adequate tumour staging and ensure optimum surgical resection.

Trans abdominal total gastrectomy is the standard surgical approach to treat patients with Siewert type II or III cancer of the gastro-oesophageal junction. The procedure is extend-

ed with a transhiatal resection of the distal oesophagus and lymphadenectomy of the lower mediastinum and the abdominal D2 nodal compartment. A thoracoabdominal approach in these patients can increase the risk of morbidity without improving survival and, therefore, is not usually recommended to treat cardia (type II) or subcardia (type III) gastric cancers [12].

Early gastric cancer is limited to the mucosa or submucosa (pathologically staged as T1 or lower), regardless of nodal status. Even in early gastric cancer, use of a multidisciplinary approach to determine the best therapeutic strategy (ie, endoscopic or surgical resection) is mandatory because lymph-node metastases occur in up to 20% of patients and correlate well with tumour penetration of the stomach wall and large tumour diameter [13,14]. Endoscopic versus surgical management of early gastric cancer has not been studied in randomised clinical trials, but surgical resection is viewed as the gold standard and is associated with 5-year recurrence-free survival of up to 98% [15]. For patients with early disease and suspected or histologically proven lymph-node metastasis, endoscopic resection should not be attempted. For mucosal gastric carcinoma, endoscopic resection is deemed sufficient in all European guidelines because the incidence of lymphnode metastatic disease is very low [9,14]. If the histopathological findings confirm a submucosal carcinoma after endoscopic resection, surgical resection that includes systematic lymphadenectomy has to be done, because lymph-node involvement is seen in up to 20% of these patients. Endoscopic resection of early gastric cancer should be done as a complete en-bloc resection to allow full histological assessment of the lateral and basal margins [9]. Patients who have endoscopic resection should be monitored frequently by endoscopic surveillance.

Most patients with locally advanced gastric cancer, which invades the muscularis propria and beyond (pathologically staged as T2 or higher), present with metastases in lymph nodes, distant organs, or both. Locally advanced gastric cancer might need en-bloc resection of involved structures. Prophylactic splenectomy is discouraged because it increases the risk of operative morbidity and mortality without any survival benefit, but might be necessary if the spleen or its hilar lymph nodes are affected [16]. Only patients without metastatic disease are potential candidates for surgical management with curative intent, although selected patients with peritoneal carcinomatosis or positive peritoneal cytology might benefit from aggressive surgery in expert centres [17]. Several randomised clinical trials and cohort studies have addressed the use of cytoreductive surgery with hyperthermic intraperitoneal chemotherapy for prevention and treatment of peritoneal carcinomatosis from gastric cancer. A systematic review and meta-analysis of 20 prospective randomised clinical trials involving 2145 patients suggested that cytoreductive surgery with hyperthermic intraperitoneal chemotherapy was associated with improved overall survival at 1, 2, and 3 years, but not at 5 years [18]. Most of the trials, however, did not fulfi l high-quality standards. With modern combination systemic chemotherapy regimens and biological agents, well designed randomised clinical trials with

robust methods are needed to confirm the potential benefits of this approach.

Over the past decade, minimally invasive surgery by laparoscopy has gained widespread acceptance in surgical oncology. The procedure seems to be feasible and safe and can represent an alternative to treat early and advanced gastric cancers in expert centres. A meta-analysis and systematic review 72 of studies with 3411 patients showed that laparoscopic distal gastrectomy compared with open surgery was associated with similar lymph-node dissection and long-term survival and with reduced intraoperative blood loss, postoperative complications, analgesic consumption, and length of hospital stay. Another meta-analysis 73 of data from 1819 patients in ten eligible studies showed similar overall and disease-free survival for laparoscopic and open gastrectomy in expert centres. Laparoscopic gastrectomy was also associated with similar lymph-node dissection and reduced intraoperative blood loss, postoperative complications, and length of hospital stay. However, because of potential study biases and notable heterogeneity between studies assessing short-term and long-term outcome measures in gastric cancer, data from well designed randomised clinical trials with robust methods should be awaited before laparoscopic gastrectomy is implemented in daily clinical practice.

3. Adjuvant and Neoadjuvant Therapies in Locally Advanced Disease

Adjuvant and neoadjuvant therapies are generally accepted to improve disease-free survival and overall survival in patients who have undergone adequate complete surgical resection (R0) of locally advanced gastric cancer by eradicating microscopic disease locoregionally and at a distance from the primary tumour. 5-year overall survival is increased by 10–15% with the addition of these treatments, but there is no global consensus about the optimum strategy. Perioperative chemotherapy additional to R0 is the most popular strategy in Europe, whereas in the USA it is postoperative chemoradiotherapy, and in Asia it is postoperative chemotherapy [6,7]. Adjuvant and neoadjuvant therapies are generally recommended for patients with T3, T4, or node-positive tumours.

Two European studies have shown improved outcomes with perioperative chemotherapy, including fluoropyrimidine-based and platinum-based chemotherapy, and with postoperative chemotherapy. In the MAGIC trial [19], treatment with three cycles of the epirubicin, cisplatin, and fluorouracil regimen before and after surgery was compared with surgery alone in patients with resectable stage II and III gastric cancers. In the chemotherapy group, 5-year overall survival was 36%, compared with 23% in the surgery alone group. A French study of perioperative fluorouracil and cisplatin showed similar results [20]. Fluorouracil is frequently replaced by capecitabine on the basis of findings from several studies, as discussed later in this Seminar. Subgroup analyses suggested the largest benefits are achieved in patients with gastro-oesophageal-junction tumours. Potential advantages of preoperative chemotherapy include the possibility of reducing tumour size and burden, controlling microscopic disease, and increas-

ing the likelihood of achieving an R0 resection.

The US 0116 trial randomised patients with T3, nodepositive, or both, gastric cancers to undergo surgery alone or with postoperative chemoradiation (bolus fluorouracil and leucovorin before, during, and after radiotherapy of up to 45 Gy in 1–8 Gy fractions) [21]. The potential advantage of the postoperative treatment is that patients are surgically and pathologically staged before it is started. The goal of postoperative radiation is to eradicate microscopic disease remaining in the surgical bed. By adding chemotherapy, malignant cells in the irradiated volume are radiosensitised and microscopic deposits outside are treated. Adjuvant chemoradiotherapy was associated with substantial reductions in overall and locoregional relapse. Subset analyses showed robust treatment benefits in all subgroups except patients with diff use histology [22], although this finding has been criticised, mainly because surgery was suboptimum (54% of patients underwent less than D1 dissection).

The ARTIST trial in South Korea was done to assess the efficacy of postoperative chemotherapy with capecitabine and cisplatin, with or without radiation to 45 Gy, in patients who underwent D2 lymph-node dissection [23]. Overall, the addition of radiotherapy to chemotherapy did not significantly extend disease-free survival or overall survival, but in patients with pathologically proven lymph-node metastasis, disease free survival was longer in those who received chemoradiation than in those who received chemotherapy alone (estimated 3-year disease-free survival 77.5% vs 72.3%, p=0.0365). The ARTIST-II trial is underway and is randomising patients with lymph-node-positive gastric cancer to receive postoperative chemotherapy or chemoradiation (NCT01761461). In the CRITICS study, being done in Europe, all patients with stage Ib–IVa nonmetastatic gastric cancer are being assigned to receive preoperative chemotherapy followed by at least a D1 resection, then random assignment to postoperative chemotherapy or chemoradiotherapy (NCT00407186).

Asian studies have shown traditionally larger benefits from an adjuvant chemotherapy than have those in developed countries. The Japanese ACTS-GC trial showed a survival benefit with the oral fl uoropyrimidine derivative S-1 after D2 resection [24], and the Korean CLASSIC trial [25] showed improved overall survival and disease-free survival with postoperative combined capecitabine and oxaliplatin. Moreover, although most other randomised studies showed no signifi cant benefit in overall survival with adjuvant chemotherapy, a large meta-analysis confirmed a 6% absolute survival benefi t with fluorouracil-based postoperative chemotherapy compared with surgery alone in all subgroups assessed [26].

Preoperative chemoradiotherapy is frequently used in patients with oesophageal and gastro-oesophageal junction tumours, although results from randomised trials of preoperative chemoradiotherapy in gastric cancer are not yet available. Preoperative chemoradiation has clear potential advantages. Delineation of the target for radiation is easier when the tumour is

still in place, and generally leads to smaller irradiated volumes and thus less acute and fewer late toxic effects than postoperative chemoradiation. Moreover, preoperative treatment leads to downstaging and downsizing, which increase the possibility of achieving an R0 resection. In theory, the tumour bed is better vascularised before than after surgery, which increases drug exposure and radio sensitivity. The Australian and European TOP GEAR phase 2/3 trial is being done to compare perioperative chemotherapy with preoperative chemoradiotherapy followed by postoperative chemotherapy (NCT01924819).

4. Chemotherapy Management in Gastric Cancer

The gastric cancer has a high recurrence rate after operation, especially in advanced stages. Patients with AGC whose performance status is adequate would normally be treated by systemic chemotherapy, aiming at improving cancer-related symptoms and extending life.

There is no international established standard chemotherapy regimen in current use, but several chemotherapeutic agents have been investigated for GC during the past several years, including platinum-based compounds (cisplatin and oxaliplatin), fluoropyrimidines (5-fluorouracil; capecitabine andS-1 in Asiatic countries), docetaxel (D), and the anthracycline asepirubicin (EPI) [27,28], but fluorourpyrimidine and platinum-based combininations are the most widely used in the world [27]. It remains controversial whether a triplet regimen is needed because the triplet regimen tend to bring out a higher toxicity profile and dissatisfactory of Overall Survival. A meta-analysis showed significant benefits from adding an anthracycline to a platinum and fluoropyrimidine doublet, and ECF (epirubicin plus cisplatin plus protracted infusion 5- fluorouracil) is among the most active and well-tolerated regimen [29].

A meta-analysis of gastric cancer trails has made a comparion between the triplet of DCF(docetaxel, cisplatin and 5-fluorouracil) and the triplet of ECF (epirubicin, cisplatin and 5-fluorouracil). The results suggest a similar activity of docetaxel and epirubicin. Evidence showed oxaliplatin was as effective as cisplatin and associated with lower toxicity and a slight survival benefit in patients who are older than 65 years. capecitabine, an oral fluoropyrimidine, was not inferior to fluorouracil in terms of progression-free and overall survival [30].

S-1 is a combination of tegafur, another orally active prodrug of 5-FU, combined with 5-chloro-2, 4-dihydropyrimidine, which prolongs the bioavailability of tegafur, and potassium oxonate, which reduces gastrointestinal. S-1 has shown benefit in advanced gastric cancer. In the multicentre, Phase III randomized trial, 1053 patients with advanced gastric or esophagogastric junction adenocarcinoma were randomized to either cisplatin plus S-1 or cisplatin plus 5-fluorouracil. The results showed no difference in median overall survival (8.6 months and 7.9 months, respectively), but cisplatin and S-1 were associated with a significantly better safety profile [31]. In Japan, the first-line regimen of chemotherapy for advanced gastric cancer is S-1 plus cisplatin. Whereas in the United States and Europe, S-1 remains unlicensed

because the Western FLAGS study showed no improvement in outcome with S-1 substituted for 5-FU in combination with cisplatin.

Irinotecan , a topoisomerase I inhibitor, was less toxic (improved tolerance) and can be an alternative when platinum-based therapy cannot be delivered. Several studies suggest that FOLFIRI (irinotecan with 5-FU) has activity as a first-line regimen [32]. Therefore irinotecan would be considered as reference regimens for second-line studies of novel agents.

5. Radiotherapy using in Gastric Cancer

Radiotherapy is used as important treatment for uncontrolled gastric bleeding and unresectable tumours. In these cases, radiotherapy did not improve survival, but locoregional control rates of 70% were reported. Importantly, due to the high incidence of locoregional failures after surgical treatment, radiotherapy has been regarded as an promising method for curative treatment of gastric cancer. Radiotherapy can be given intra-operatively, or preoperatively, or postoperatively (with or with out concurrent chemotherapy) with external beam radiotherapy.

There are trials suggesting that intra-operative radiotherapy can improve control of locoregional disease and lower locoregional recurrence rates. However, because most patients in countries without screening programmes present with advanced disease, overtreatment will happen in few patients.

Recently, a meta-analysis included 1581 patients, 507 in the intraoperative radiotherapy (IORT) group and 1011 in the control group. There was no significant difference in overall survival (OS) between the IORT group and control group (HR=0.91, 95% CI=0.73-1.13; P=0.38). And IORT showed favorable effects for patients with cancer in stage 2 and stage 3 and have the advantage of locoregional control [33]. Now a days, the radiotherapy is usually combined with chemotherapy to improve locoregional recurrence and offer a better life.

6. Targeted-Therapy Implement in Gastric Cancer

As in other solid tumours, the use of targeted agents that block these signalling pathways has recently emerged as a strategy for the treatment of advanced. GC. Up to now, just trastuzumab and ramucirumab have been shown to significantly improve survival in advanced GC patients.

Trastuzumab, a monoclonal antibody against HER-2 receptor, was the first targeted agent approved by FDA in GC patients. It has been considered as an effective targeted drug to improve overall survival when combined with systemic chemotherapy (cisplatin and a fluoropyrimidine) in advanced HER2-positive gastric cancer. In the Trastuzumab for Gastric Cancer (ToGA) trial, the addition of trastuzumab to chemotherapy significantly improved OS compared with chemotherapy alone in patients with HER2- positive AGC, achieving a median OS

of 13.8 months in the trastuzumab plus chemotherapy group. Tumour response rate, time to progression and duration of response were significantly improved in the experimental group compared with the CT alone group [34]. Recently, Primary and secondary resistance to trastuzumab has become a major problem and new strategies to overcome this resistance are needed. The other anti-EGFR mAbs, such as Cetuximab, matuzumab, Panitumumab , have not demonstrated improvements in survival among advanced GC patients effective “targeted therapies” in the treatment of AGC.

Ramucirumab, a completely humanized monoclonal antibody against VEGFR2, demonstrated either alone or in combination with paclitaxel (RAINBOW Trial) survival and disease control rate benefit as second-line regimen for non-Asian GC patients. In the phase 3 REGARD trial, 117 patients with metastatic gastric cancer progressive after first-line chemotherapy (a fluoropyrimidine and a platinum) were randomly assigned to receive ramucirumab or placebo plus best supportive care. ramucirumab group has showed a significantly better Overall surviva, with a similar survival benefit to that seen with conventional second-line chemotherapy . Ramucirumab combined with first-ling chemotherapy has become a useful option in second-line treatment in patients with good performance status scores and organ function [35].

With the understand of the tumor biology and cellular and molecular mechanisms responsible for malignant proliferation and tumor growth, new and more effective mocular targeted drugs needed to be found.

7. Conclusion

In a word, multidisciplinary synthetic therapy Should be used in treatment of gastric cancer. Besides, individual therapy is also important and should be payed more attention In gastric cancer treatment. Progress has been made in understanding the pathogenesis and the molecular biology of gastric cancer and in optimising the available treatment options and modalities. However, in the future, the focus should be on further unravelling the taxonomy of gastric cancer, fine-tuning treatment strategies, and developing new drugs for patients with advanced gastric cancer.

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