Recent advances in gastric cancer treatment

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ABSTRACT

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INTRODUCTION

Gastric cancer is the fifth most common cancer in the world and it is the third most common cause of cancer related death [1]. Many studies on comparing different interventions including type of surgical resection, perioperative chemotherapy regimen, radiation protocols and imaging protocols have been conducted to improve the quality of life and extend the survival rates of patients. Promising developments have been made in recent years. This editorial presents the innovations discussed in recent studies.

Developments in the TNM staging for gastric cancer

There are two major staging systems for gastric cancer. The first system is Japanese Gastric Carcinoma Classification (JGCC). This is based on the location of the metastatic lymph node [2]. Second is the Union Internationale Contre le Cancer/American Joint Committee Cancer (UICC/AJCC) TNM staging system, it is based on the number of metastatic lymph node [3]. The TNM classification system was merged with JGCC in 2009 in the 7th edition [4].

The 8th edition AJCC gastric cancer staging manual was refined using Japanese and Korean data from the

International Gastric Cancer Association (IGCA). This 8th edition differed in that T1–T3 disease was upstaged with N3b, T4aN3a was down staged from IIIC to IIIB, and T4bN0 and T4aN2 were down staged from IIIB to IIIA [5]. Many studies have compared the survival in patients based on AJCC 7th and 8th edition. Important message conveyed by these studies is that ‘personalized medicine’ is the key for good oncological outcomes.

Endoscopic interventions for early gastric cancer

Surgical resection is the primary treatment for gastric cancers. Endoscopic treatment is less invasive, do not have any negative impact on oncologic outcomes, preserve physiological functions, and improve the quality of life in carefully chosen patients. Endoscopic resection (ER) techniques can be divided into two main categories: endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD). Major gastric cancer treatment guidelines such as National Comprehensive Cancer Network (NCCN), the European Society for Medical Oncology (ESMO), the European Society of Surgical Oncology (ESSO) and the European Society of Radiotherapy and Oncology (ESTRO) have suggested that obtaining negative horizontal and vertical margins with endoscopic resection is adequate protocols for the treatment of gastric cancers that are < 2 cm, are well/moderately differentiated, have no lymphovascular invasion and are not located under the submucosa [6].

Minimally invasive surgery for gastric cancer

Minimally invasive surgery for gastric cancer includes laparoscopic surgery, reduced port surgery (RPS) and robotic surgery [7]. Laparoscopic surgery for gastric cancer (LAG) offers better pain control and a shorter postoperative hospital stay as it is less invasive. Importantly, because of better magnification lymph node dissection is better so oncological outcomes can be enhanced as compared with open gastrectomy. Reduced port surgery (RPS) involves fewer ports than standard

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Received: 20 November 2017

Published: 01 January 2018

laparoscopic surgery and can allow for narrower ports by involving single-incision laparoscopic surgery (SILS). The SILS is performed from a single incision at the umbilicus and is considered the ultimate reduced-port technique. Reduced port surgery has been developed to reduce the invasiveness of laparoscopic surgery. So far, there have been a few reports on reduced port surgery reduced port surgery for gastrectomy for gastric cancer [8]. However, it has remained unclear that reduced port surgery has the advantages compared with LAG, and further randomized controlled trials are awaited. Robotic assisted gastrectomy (RAG) has technical advantages of three-dimensional image and allowing for precise movement. In a meta-analysis by Xiong et al., laparoscopic gastrectomy and robotic assisted gastrectomy were compared; robotic assisted gastrectomy group had less intraoperative blood loss with comparable mortality and morbidity rates. As expected the operation time in robotic assisted gastrectomy was significantly longer than laparoscopic gastrectomy and open gastrectomy [9].

Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy

Cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) were developed as a combined treatment modality from the results of experimental and clinical studies on ovarian malignancy. Complete cytoreduction must be performed before HIPEC is administered. Hyperthermia increases the antitumor activity and penetration of chemotherapeutics [10]. Prominent centers have reported that the median survival time ranged between 11 and 16 months in patients who underwent HIPEC with partial or complete cytoreduction [11]. Desmoplastic stroma and poor vascularization impeding drug delivery especially in

diffuse form of gastric cancer provides a reasonable rationale for this intervention [12]. Currently, there is limited data and literature defining a role for CRS and HIPEC in the management of patients with advanced gastric cancer, and further clinical research on this approach is still needed [13].

Neoadjuvant chemotherapy and immunotherapy for gastric cancer

Medical Research Council Adjuvant Gastric Infusion Chemotherapy (MAGIC) study established the role of preoperative chemotherapy in treatment protocol for curable gastric cancers. In this study, perioperative chemotherapy with epirubicin, cisplatin and 5-FU (ECF), significantly increased overall and cancer free survival compared to the surgery group alone (HR: 0.75, 95% CI: 0.60–0.93, $p = 0.009$) [14]. A practice changing perioperative chemotherapy trial, FLOT4 trial compared perioperative chemotherapy with standard ECF [epirubicin, cisplatin, and 5-fluorouracil (5-FU)] versus FLOT (combination of preoperative infusional 5-fluorouracil, leucovorin, oxaliplatin, and docetaxel) in 716 patients with esophagogastric junction (56%) or gastric cancer (44%). Patients treated with FLOT had a higher rate of curative resection versus ECF (84 versus 77%, $p = 0.011$) an overall survival (50 versus 35 months, hazard ratio 0.77, $p = 0.012$) [15].

Immunotherapy

Currently, numerous targeted therapies belonging to different classes of drugs have been investigated as therapeutics in gastric cancer, starting with preclinical studies and continuing into clinical trials. Table 1 depicts the immunotherapeutic agent and phase of development.

Table 1: Targeted agents reaching clinical development, summarized according to the histological subtype in which the molecular target is most frequently present

Molecular target	Histology in which molecular target is more prevalent	Mechanism of action	Targeted agent	Phase of development
HER2	Proximal nondiffuse	HER2 monoclonal antibody	Trastuzumab	III
		HER2 dimerization inhibitor	Pertuzumab	II
		HER2, EGFR TKI	Lapatinib	III
		Pan-HER TKI	PF 00299804	II
EGFR	Proximal nondiffuse	EGFR monoclonal antibody	Cetuximab, Panitumumab	III
		EGFR TKI	Erlotinib, gefitinib	II
MET	Proximal nondiffuse	MET TKI	Foretinib, crizotinib	I–II
VEGF	Distal nondiffuse	VEGF monoclonal antibody	Bevacizumab	III
VEGFR	Distal nondiffuse	VEGFR2 monoclonal antibody	Ramucirumab	III
		MTI	Sunitinib, sorafenib	II
FGFR	Diffuse	MTI	AZD2171, dovitinib	II
mTOR	Diffuse	mTOR inhibitor	Everolimus	III
MMP	Diffuse	MMP inhibitor	Marimastat, prinostat	III

Trastuzumab for gastric cancer deserves a special mention. It is a monoclonal antibody that interacts with human epidermal growth factor (HER) 2 and is related to gastric carcinoma [16]. Trastuzumab for gastric cancer (ToGA) phase III International multicenter randomized controlled trial compared the clinical effect and safety of trastuzumab with that of standard chemotherapy (capecitabine or intravenous 5-fluorouracil and cisplatin). Survival after treatment with trastuzumab was significantly longer than that with only standard chemotherapy (13.8 mo vs 11.1 mo, respectively, $p = 0.0046$) [17]. Treatment with trastuzumab is standard for the HER2 (+) patients (IHC score +3 and/or FISH) in the USA and Japan. Trastuzumab is recommended for patients with an IHC score of 2+/positive FISH or an IHC score of 3+ with high HER2 protein expression, according to the ToGA study in Europe. The evaluation of HER2 is essential for trastuzumab treatment.

CONCLUSION

Gastric cancer remains a major global health problem; therefore, efficient treatments are needed to achieve improved prognosis. Although promising developments have been made in recent years, the obtained results have limited reliability and benefits. We believe that significant improvements in the treatment of gastric cancer will be developed according to the long-term results of ongoing randomized clinical trials.

Keywords: Endoscopic resection, Gastric cancer, Gastric carcinoma, Surgical resection, Treatment

How to cite this article

Gogna S, Goyal P, Sodhi A. Recent advances in gastric cancer treatment. Int J Case Rep Images 2018;9(1):5–8.

Article ID: Z01201801ED10014SG

doi: 10.5348/ijcri-201802-ED-10014

Author Contributions

Shekhar Gogna – Substantial contributions to conception and design, Acquisition of data, Analysis and interpretation of data, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published

Priya Goyal – Substantial contributions to conception and design, Acquisition of data, Analysis and interpretation of data, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published

Annie Sodhi – Substantial contributions to conception and design, Acquisition of data, Analysis and interpretation of data, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published

Guarantor of Submission

The corresponding author is the guarantor of submission.

Source of Support

None

Conflict of Interest

Authors declare no conflict of interest.

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