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MINIREVIEWS

HER2 therapies and gastric cancer: A step forward

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Abstract

Gastric cancer usually is diagnosed in advanced stages and thus current medical practice affords limited therapeutic options. However, recent studies established the role of human epidermal growth factor receptor 2 (HER2) in clinical management. Trastuzumab, an anti-HER2 monoclonal antibody, acquired a main role in advanced gastric cancer harboring HER2 overexpression and/or amplification improving survival to 17.1 mo according to trastuzumab for gastric cancer phase Ⅲ trial results. Also, new promising drugs, such as c-Met inhibitors, are in development and assessment for this setting. Certainly, novel drugs will emerge in the next feel years for help oncologists improve clinical management of advanced gastric cancer providing higher survival and quality of life. In this mini-review we will discuss some issues in this regard and provide an actual overview of this setting.

Key words: Gastric cancer; Trastuzumab; c-Met; Human epidermal growth factor receptor 2; Lapatinib; Pertuzumab

Core tip: Approaches for treatment advanced gastric cancer are object of interesting debates toward scientific community worldwide over the last 20 years. Chemotherapy based on platinum and fluoropirimidine agents remained up to now the standard of care for those patients, otherwise triplet therapy either an anthracycline or taxane may be considered. Herein we provide an additional discussion regarding the role of biologic agents, such as trastuzumab and novel therapies for improve survival in this field.

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INTRODUCTION

Gastric cancer (GC) is one of the leading types of cancer worldwide. Although the trend in death rates[1] for GC is decreasing, this tumor continues to have a poor prognosis and few efficacious therapeutic options particularly in advanced stages. Since most of symptoms for this type of cancer are nonspecific and screening strategies in many countries are absence, GC is usually diagnosed in advanced stages. The predominant histological type of GC is adenocarcinoma (95% of tumors) and the main adenocarcinomas sub-types are intestinal, diffuse and mixed type. Recent studies showed the human cancer is the human epidermal growth factor receptor in advanced GC personalizing treatment[2-5]. Herein we will discuss issues concerning novel biologic agents for advanced gastric cancer, focusing in anti-human epidermal growth factor receptor 2 (HER2) therapies, such as trastuzumab, and promising novel agents.

HER2 AND GASTRIC CANCER

Treatment depends on the site and extent of the tumor[4,6,7]. Treatment objectives vary from through curative approaches, such as curative surgery, radiotherapy and perioperative chemotherapy, that may improve the survival rate of operable GC patients; to palliative approaches in advanced stage patients or those who are subject to relapse after prior curative surgery[7,8]. For advanced patients, 5-fluorouracil (5-FU) plus platinum remain standard treatment regimens, with or without an anthracycline or taxane[9]. This therapeutic regimen offers a response rate of 30%-50% with 9-11 mo median overall survival (OS)[10]. Given these poor results, an investment in new treatment weapons is required. One of the most considerable innovative targets in human cancer is the human epidermal growth factor receptor (EGFR) family[11]. The human HER family includes four structurally related members, HER1 (ErbB1, also known as EGFR), HER2 (ErbB2), HER3 (ErbB3) and HER4 (ErbB4)[12]. Relatively to HER2, this is highly expressed in a significant proportion of GC[13] and thus it is nowadays considered an excellent therapeutic target. GC harboring HER2 overexpression was shown to have a worse prognosis[14]. In HER2-amplified patients the median survival was 5.5 mo compared with 12.6 mo in non-amplified patients. HER2 overexpression was more commonly seen in the intestinal-type than diffuse-type cancers (32% *vs* 6%)[15-17].

HER2 MOLECULAR TESTS AND TRASTUZUMAB

HER2 overexpression can be determined by immunohistochemistry (IHC) using a monoclonal antibody or by the detection of HER2 gene amplification through fluorescent *in situ* hybridization (FISH)[18-20]. Thus, it is current practice to test all new diagnoses of GC for HER2 by IHC[21,22]. Tumors can be classified by IHC as IHC 0/1+, negative resulted; IHC2+, equivocal resulted and it is recommended FISH testing, and IHC3+, positive resulted[18,23].

In the trastuzumab for gastric cancer (ToGA) trial[2], trastuzumab, a recombinant humanized monoclonal antibody that targets the extracellular domain Ⅳ of the HER2 protein, was evaluated in HER2 overexpressing gastric and gastroesophageal junction (GEJC) cancer. In the mentioned study, patients with GC or GEJ that showed HER2 overexpression were eligible for the analysis and randomized in two arms. To one arm standard chemotherapy alone (5-FU/capecitabine plus cisplatin) was administered while to the other arm it was administered chemotherapy plus transtuzumab. Median OS was 13.8 mo in those assigned to trastuzumab plus chemotherapy compared with 11.1 mo in those assigned to chemotherapy alone[24]. The median of progression-free survival (PFS) was increased with the addition of transtuzumab to standard chemotherapy: 6.7 mo in the transtuzumab arm and 5.5 mo in the chemotherapy alone arm. The overall response rate was 47.3% *vs* 34.5% in transtuzumab plus chemotherapy and chemotherapy, respectively. The toxicity did not increased substantially with transtuzumab addition; however, the most common grade 3/4 adverse reactions associated with trastuzumab in metastatic GC were neutropenia, diarrhea, fatigue, anemia, stomatitis, weight loss, upper respiratory tract infections, fever, thrombocytopenia, mucosal inflammation, nasopharyngitis and dysgeusia. Thus, the ToGA trial showed that trastuzumab in combination with chemotherapy can be considered as a new standard option for patients with HER2-positive advanced GC or GEJC. So, trastuzumab was approved by the Food and Drug Administration and the European Medicines Agency (EMA) for patients with HER2-positive metastatic GC or GEJ who have not received previous anticancer therapy for metastatic disease.

NOVEL AGENTS AND PROMISING MOLECULES

Nevertheless, others monoclonal antibodies have been developed as an alternative to transtuzumab[25-28]. For example, HER dimerization inhibitor, such as pertuzumab, which in combination with the transtuzumab has shown to have a promising effect in experimental models of GC[29,30]. In addition, some studies with anti-HER2 combination treatments indicate that the use of more than one HER2-targeted therapy was superior to one of these agents alone, particularly in breast cancer (BC) HER2 positive[31-33]. For instance, the CLEOPATRA[34] phase Ⅲ trial compared the efficacy and safety of pertuzumab, trastuzumab, and docetaxel with placebo, trastuzumab, and docetaxel in patients with HER2-positive first-line metastatic breast cancer, showed a significant improvement in OS with addition of pertuzumab. So, there is need for planning studies to assess the safety and efficacy of the pertuzumab in the GC HER2 positive[35,36].

However, when the patients acquire resistance to transtuzumab, what to do? The molecular mechanisms underlying trastuzumab resistance in GC are still unknown, but intra-tumoral heterogeneity of this tumor may contribute to this resistance[12,37-39]. There are some mechanist theories in a study that attempted to explain this phenomenon, *e.g.*, that catecholamine-induced β2-AR activation mediates desensitization of GC cells to trastuzumab through up regulation of the MUC4 expression[40,41]; or that interaction between HER2 and insulin-like growth factor 1 receptor in trastuzumab-resistant breast cancer cells and involved in cross-talk that results in p27 downregulation[42]. Furthermore, hepatocyte growth factor (HGF) and its receptor, the trans-membrane tyrosine kinase c-Met, promote cell proliferation, survival, motility and invasion as well as morphologic changes that stimulate tissue repair and regeneration in normal cells but can be co-opted during tumor growth[28]. Previous studies reported that high levels of HGF or c-Met are associated with poor prognosis in gastric can-

cer, due to gene amplification and protein overexpression of c-Met drive resistance to epidermal growth factor receptor family inhibitors, both in preclinical models and in patients[21,27,28,43,44]. Only a few phase I - Ⅱ trials[26,45] recently assessed the role of c-Met inhibitors, such as crizotinib[46] and foretinib[26], in gastric cancer setting. In a studied by Lennerz *et al*[46] two patients harboring MET amplification were treated with crizotinb and presented tumor shrinkage (-30% and -16%) and experienced progression after 3.7 and 3.5 mo. Shah *et al*[26] reported 67 advanced gastric cancer patients who were treated with foretinib irrespective of c-Met status. Best response was stable disease (SD) in 10 (23%) patients receiving intermittent dosing and 5 (20%) receiving daily dosing; SD duration was 1.9-7.2 mo (median 3.2 mo). Of 67 patients with tumor samples, 3 had MET amplification, one of whom had SD. Treatment-related toxicity occurred in 91% of patients[26]. Thus, the response to this dilemma is not to simple and current there are many options for explore in this regard.

In this regard, others classes of targeted drugs, including tyrosine kinase inhibitors, such as lapatinib[47] and dacomitinib[48], mammalian target of rapamycin pathway inhibitors, such as everolimus[49], have also been investigated. Lapatinib inhibits the catalytic activity of the EGFR and it is also a HER2 inhibitor; thus, it is a dual tyrosine kinase inhibitor of both EGFR and HER2. The SWOG S413 trial[47] analyzed lapatinib in the first line therapy in patients with advanced or metastatic GC showing 9% response rate (11% overall response rate) and a median OS of 4.8 mo. In summary, lapatinib as a single agent presents reduced responses, but in combination with other chemotherapeutic agents may have additional benefits. Dacomitinib[18] is a pan-HER inhibitor with potential use in cancer treatment via mutations or overexpression/amplification of HER family members or their target molecules alone or in combination with chemotherapeutic and/or molecular-targeted agents, however, there are no clinical trials phase Ⅱ/Ⅲ to justify its use in GC patients.

CONCLUSION

Nowadays, an interesting biologic option is available, such as trastuzumab, for combination with platinum-5-FU for prolongs OS in a sub-set of patients. However, only 20% of advanced GC harbor with HER2 overexpression and thus a large number of patients will not acquire benefit from this innovative option. Thus, further alternatives are warranted for overcome this issue. Others biological agents are under investigation, but without immediate results for the current clinical practice. Crizotinib, foretinib and pertuzumab seems to be promising due to preliminaries small studies. However, results from larges phase Ⅲ trials are still need to determine whether those innovative agents would be place in the current scenario. In conclusion, HER2 targeted therapy is responsible for a significant increase in survival of patients with GC in advanced stages. Unfortunately, the GC continues to still have a poor prognosis. In the future it is intended to develop new trials and look for other genetic alterations that may be highly specific therapeutic targets and less toxic as well.

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