Future ONCOLOGY

EDITORIAL

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Metastatic gastric cancer in the last two decades: goals achieved and future promises




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Advances in clinical research, driven by an enhanced understanding of the background biology, have led to notable progresses in the treatment of advanced gastric cancers (GCs). While chemotherapy seems to have reached a plateau in both first- and second-line settings, novel emerging drugs have provided promising results. Ramucirumab, a new angiogenesis inhibitor and pembrolizumab, a human PD-1-blocking antibody, are the most interesting novelties in this field. We present a short viewpoint on the advances medical oncologists witnessed in the last two decades and depict the most relevant compounds that may impact on the clinical practice in the near future.

KEYWORDS

• angiogenesis • gastric cancer • pembrolizumab • ramucirumab • target therapy • translational research

The optimal treatment of metastatic GC up to 2010

GC ranks third among the most prevalent malignancies and remains a global healthcare problem. In the USA, around 25,000 new cases are expected in 2015 [1]. In Europe, approximately 95,000 new cases are diagnosed every year with a 75,000 deaths.

Overall survival (OS) of patients with advanced GC (AGC) remains poor, despite the introduction of new drugs and treatment strategies. Many randomized Phase III trials assessed the efficacy of chemotherapy (CT) for the treatment of AGC, concluding that standard of care is the combination of cisplatin and a fluoropyrimidine within a two- or three-drug regimen [2]; yet, the role of anthracyclines (doxorubicine or epirubucine) still remains unclear. Other agents, such as docetaxel, oxaliplatin, irinotecan, capecitabine and S-1 have all been tested in randomized trials providing interesting results [3]. In the REAL-2 Phase III trial, Cunningham *et al.* suggested that oxaliplatin and capecitabine could replace cisplatin and infusional 5-fluorouracil, respectively [4]. Based on the results of SPIRITS trial, S-1 plus cisplatin has become the standard of care in Japan [5].

At disease progression, about 50% of the patients are fit and can receive second-line chemotherapy. Although drugs such as paclitaxel, docetaxel and irinotecan were shown to improve survival in

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randomized trials, such benefit was too limited, with improvements in absolute OS shorter than 2 months [6–8]. Despite these important improvements in systemic therapy, the prognosis of patients treated with CT remains poor, and median OS does not exceed 12 months.

The current scenario: biologics in GC & the dawn of a new age

A clear example of the importance of identifying different subsets of AGC patients based on the molecular profiling of the tumor itself, is provided by the results of ToGA trial, a large international randomized Phase III study that compared the efficacy and safety of chemotherapy alone or in combination with trastuzumab for the upfront treatment of HER2-positive AGC patients [9]. The addition of trastuzumab to chemotherapy significantly prolonged the median OS (13.8 vs 11.1 months; hazard ratio [HR]: 0.74; 95% CI: 0.60–0.91). A subanalysis of data excluding patients with IHC 0–1+ FISH+ tumors found a more remarkable gain in median OS (+4.2 months; HR: 0.65) [9]: patients with IHC3+ FISH+ AGC treated with trastuzumab and chemotherapy obtained the greatest benefit compared with chemotherapy alone (median OS: 17.9 vs 12.3 months). On these premises, platinum-based chemotherapy plus trastuzumab has become the standard of care for patients with HER2-positive AGC.

"The main challenge in identifying active and effective target therapies in gastric cancer patients is represented by tumor heterogeneity."

With bevacizumab failing to provide any benefit when combined with chemotherapy in the AVAGAST Phase III trial, the implementation of angiogenic inhibitors in the treatment of AGC has suffered a setback [10]. Ramucirumab is a monoclonal antibody that binds to VEGFR-2 and prevents its activation and downstream signaling thus inhibiting angiogenesis and lympho-angiogenesis [11]. REGARD study was a double-blind, placebo-controlled, Phase III study in pretreated patients with AGC. Patients with disease progression after first-line platinum-containing or fluoropyrimidine-containing chemotherapy were randomized in a 2:1 ratio to receive best supportive care plus either ramucirumab (8 mg/kg given every 2 weeks) or placebo. Median OS was significantly longer in the treatment group (5.2 vs 3.8 months: HR: 0.77; 95% CI: 0.60–0.99; p = 0.047) [12], and this survival benefit did not change after adjusting for other prognostic factors. Ramucirumab was well tolerated, although a higher rate of severe hypertension was reported. The subsequent RAINBOW trial of paclitaxel (80 mg/sqm on days 1, 8 and 15 every month) plus ramucirumab (8 mg/kg given every 2 weeks) versus paclitaxel plus placebo for pretreated AGC confirmed the survival advantage provided by this agent in GC. Patients treated with ramucirumab plus paclitaxel had a statistically significant and clinically meaningful improvement in OS compared with those who received chemotherapy alone (9.6 vs 7.2 months; HR: 0.807; 95% CI: 0.678–0.962; p = 0.0169) [13].

Future directions according to disease biology

Over the last few years, another important achievement is the improved understanding of the biology of GC, which is now known to be a very heterogeneous disease with different histological and clinical features. The recent genomic and molecular characterization reported by The Cancer Genome Atlas (TCGA) project identifies four different subtypes of GC providing compelling information on the heterogeneity and potential targeted therapeutics. This valid classification which includes Epstein–Barr virus-positive tumors, microsatellite instable tumors, genomically stable tumors and tumors with chromosomal instability, will necessarily have to be considered for future trial design and development of novel therapeutics [14]. Similarly, many pathways have been extensively investigated, such as ERBB2, EGFR and PI3K–AKT–mTOR, with novel molecules being evaluated in numerous clinical trials.

After the failure of cetuximab [15] and panitumumab [16], the strategy to inhibit EGFR in this disease has been abandoned. Conversely, positive results were reported in the JOSHUA trial, which evaluated the pharmacokinetics of two different doses of pertuzumab in the first-line setting. Based on these results, the ongoing Phase III trial JACOB (NCT01774786) is comparing trastuzumab, fluoropyrimidine and cisplatin, with or without pertuzumab, as first-line treatment in patients with HER2-positive GC and gastro-esophageal junction cancer (GEJC).

Although HGF/cMet overexpression appeared to be a promising target also in GC with positive results initially reported, subsequent randomized trials testing MET-inhibitors, such as rilotumumab, onartuzumab and AMG337, were all disappointing [17].

In order to investigate epithelial-mesenchimal transition, FGFRs pathways have been studied. In preclinical models, different TKIs such

as PD173074, KI23057, SU5402, cediranib (AZD2171), dovitinib (TKI258) and ponatinib (AP24534) were shown to inhibit cell growth by preventing FGFR2 phosphorylation [18]. SHINE is the only ongoing Phase II study (NCT01457846) evaluating the efficacy and safety of AZD4547 compared with paclitaxel in GC patients.

Nanotechnology has developed systems of delivery of chemotherapeutic agents enhancing pharmacokinetics, efficacy and tolerability profiles. Trastuzumab–emtansine (T-DM1), an anti-HER2 trastuzumab combined with the cytotoxic antimicrotubule DM1 is being evaluated in a Phase II/III trial in HER2-positive GC (NCT01641939). Patients will be randomized to one of the three treatment arms: arm A: T-DM1 3.6 mg/kg every 3 weeks; arm B: T-DM1 2.4 mg/kg weekly; arm C: standard taxane therapy. At the end of the first stage of the study, the dose and schedule of T-DM1 that will be used in the second stage of the study will be selected. Additional patients will be then recruited and randomized to either the selected regimen of T-DM1 or to standard taxane-based chemotherapy.

Immunotherapy is also rapidly developing in GC. A Phase II randomized trial (NCT01585987) is evaluating the role of the CTLA4 antibody ipilimumab as maintenance therapy in advanced GC or GEJC without progression after first line chemotherapy with fluoropirimidine and platinum doublet. Of note, the monoclonal antibody anti-PD1, pembrolizumab (MK-3475), provided a manageable toxicity profile in a Phase I study [19]. Authors reported a significant association between PD-L1 expression and ORR with a surprising OS rate (69%). A Phase III randomized trial (KEYNOTE-61) comparing pembrolizumab to paclitaxel in pretreated GC or GEJC has been planned [20].

The main challenge in identifying active and effective target therapies in GC patients is represented by tumor heterogeneity. So far, only a few patients have tumors with specific molecular alterations or pathways leading to cell growth, apoptosis, angiogenesis, invasion or metastasis that may be targeted. As a matter of fact, the exploratory research program of GRANITE-1 [21], a Phase III trial comparing everolimus versus placebo as second-line therapy, represents one of the attempts to overcome this obstacle evaluating a panel of predictive biomarkers in order to select responsive patients.

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