Gastric Cancer (2015) 18:205–209
DOI 10.1007/s10120-014-0437-0

EDITORIAL

Gastric cancer: past progress and present challenges

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Received: 2 July 2014 / Accepted: 5 October 2014 / Published online: 26 October 2014

In recent years the evolution of treatment options for gastric cancer has resulted in diverging management paradigms based on apparent variations in epidemiology, biology and clinical practice in the context of a different demographic as well. Differences in the timing of systemic therapy, extent of surgery and inclusion of radiotherapy are key questions in management of locally advanced gastric cancer. In more advanced/metastatic disease, systemic therapy is the mainstay of treatment, with new agents raising challenges around patient selection and integration into local treatment practices.

Although cytotoxic agents have formed the backbone of systemic therapies for advanced/metastatic disease for many years [1], it is only recently that a survival advantage for second-line systemic therapy has been demonstrated [2–5]. Once a survival benefit in patients receiving first-line chemotherapy had been demonstrated for combinations of cytotoxics in the late 1990s [6–8], subsequent trials primarily built on this progress by substituting newer cytotoxic agents. Initial combinations saw 5-fluorouracil combined with either leucovorin and etoposide as used by Glimelius et al. [7], or methotrexate and an anthracycline (doxorubicin, epidoxorubicin) [9, 10]. As newer agents became available, they were subsequently incorporated into these regimens, some with more success than others. Platinum compounds established their place in initial therapy, firstly cisplatin [11], then oxaliplatin [12]. The utility of epirubicin remains controversial; it remains a component of European but not Asian or pan-American treatment protocols. Following evidence of activity in early-phase studies, the taxanes have been incorporated into treatment of gastric cancer. For fit patients, the addition of docetaxel to first-line cisplatin and 5-fluoruracil therapy improved overall survival compared with doublet therapy, and is considered a standard treatment [13]. Not unexpectedly, the triplet was associated with increased toxicity, and alternative schedules, including weekly docetaxel therapy have demonstrated reasonable activity with decreased haematological toxicities [14].

A decade after the utility of first-line systemic therapy was established, the oral fluoropyrimidines were introduced into the treatment paradigm for gastric cancer [4, 15]. Two large trials established the non-inferiority of capecitabine in comparison with 5-fluorouracil administered by continuous infusion when used in combination with either cisplatin or oxaliplatin. Another oral fluoropyrimidine, S-1, failed to demonstrate superior survival in Western countries (although the data in Asian countries are much more convincing), but was more tolerable than 5-fluorouracil administered by continuous infusion [16]. The current standard of care in first-line therapy revolves around platinum compound and fluoropyrimidine combinations, with the type of platinum compound (cisplatin, oxaliplatin) and fluoropyrimidine (5-fluorouracil, capecitabine, S-1) dictated by regional experience and availability as well as the toxicity profile and individual patient and clinical preference.

This comment refers to the article available at doi:10.1007/s10120-014-0351-5.

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Even as the benefits from traditional cytotoxic agents were being established, it was noted that not all patients derived benefit from therapy [5]. Research into prognostic and predictive factors, coupled with an increased understanding of tumour biology, heralded the new era of biologic agents. Intensive efforts to exploit aberrant signalling pathways have focused on the epidermal growth factor receptor (EGFR), mammalian target of rapamycin (mTOR) and tumour (neo)angiogenesis. Success has been mixed, with only one randomised phase III trial demonstrating a survival benefit for the addition of 'targeted' therapy in the first-line setting [17].

The addition of trastuzumab to platinum compound and fluoropyrimidine combination therapy in the first-line treatment of advanced gastric cancer is now standard therapy for patients whose tumours overexpress human HER2 following the results of the ToGA trial. In this randomised phase III open label trial, Bang et al. [17] demonstrated improved overall survival with the addition of trastuzumab to chemotherapy compared with chemotherapy alone [hazard ratio 0.74; 95 % confidence interval (CI) 0.60–0.91; $p = 0.0046$]. The limitations of this strategy include its cost (it is prohibitively expensive in several countries) and the relatively small proportion of patients for whom this therapeutic option is applicable (up to 22 % of all patients with metastatic gastric cancer) [18]. Trastuzumab remains the only biologic therapy in gastric cancer for which a predictive biomarker exists. Whether continued HER2 targeting following progression of disease after first-line therapy is as successful in gastric cancer as in breast cancer remains to be seen. Newer agents, in particular TDM1, hold particular promise in this setting either as first-line therapy or as salvage therapy in patients with tumours overexpressing this biomarker. An antibody–drug conjugate, this first-in-class agent delivers higher concentrations of intracellular chemotherapy than traditional taxanes, with seemingly minimal toxicity [9]. Another novel agent acting on HER2, pertuzumab, is also of interest. This humanised monoclonal antibody binds to HER2 and prevents heterodimerisation of HER2 with other members of the HER family (HER1, HER3 and HER4) and blocks ligand-activated downstream signalling [19].The addition of pertuzumab to transtuzumab therapy and chemotherapy in HER2-overexpressing gastric cancer is under investigation in a randomised phase III trial in metastatic disease [20]. Further exploration of this class of agents is certainly warranted, as is the routine testing of all biopsy specimens (obtained from a metastatic site rather than a primary site as in the past) for HER2 in patients with advanced gastric cancer.

Agents targeting other EGFRs have been less successful. Two large phase III trials exploring the addition of an anti-EGFR antibody to first-line chemotherapy not only failed to demonstrate benefit but reported worse outcomes in the experimental arm [21, 22]. The EXPAND [23] and REAL-3 [24] trials coupled cetuximab and panitumumab therapy, respectively with a platinum compound and fluoropyrimidine combination, the latter trial also including an anthracycline. Both trials included unselected populations, and neither trial was able to identify predictive biomarkers for benefit (or harm) from the addition of EGFR antibodies to chemotherapy in gastric cancer. Similarly, trials using lapatinib have not fulfilled their promise of further increasing survival. The TyTAN and TRIO-013/LOGiC phase III studies aimed to improve overall survival with the addition of lapatinib to second-line paclitaxel therapy [25] or first-line capecitabine and oxaliplatin therapy [21] for patients with HER2-amplified advanced gastric cancer. The reasons for the failure of lapatinib to improve patient outcomes in these trials is unclear, but may relate to the interaction between a tyrosine kinase inhibitor (TKI) and chemotherapy.

Another agent which failed to demonstrate efficacy in late-phase trials despite a promising biologic rationale and earlier evidence of activity is everolimus. The mTOR/AKT/phosphatidylinositol 3-kinase (PI3K) pathway is known to be associated with drug resistance [26], and PI3K/AKT and mTOR are known to be upregulated in a proportion of gastric cancers [27]. Despite promising results in a phase II study, everolimus did not demonstrate a survival benefit in pretreated advanced gastric cancer when compared with placebo (hazard ratio for overall survival, 0.90; 95 % CI, 0.75–1.08; $p = 0.124$) [28].

Although successful in other solid tumours such as colorectal, hepatocellular and renal cell carcinomas, targeting angiogenesis has been a less successful strategy in gastric cancer. Without neovascularisation, it is thought that tumour growth will be arrested, with many solid tumours known to overexpress vascular endothelial growth factor (VEGF), which stimulates angiogenesis through a complex signalling cascade. Several isoforms of VEGF exist (VEGF-A, VEGF-B, VEGF-C, VEGF-D, and VEGF-E), along with multiple receptors [VEGF receptor (VEGFR) 1, VEGFR-2, and VEGFR-3], mediators (placental growth factor) and coreceptors (neuropilin 1 and neuropilin 2) [29]. Increased expression of VEGF by tumours is associated with poorer prognosis, and agents targeting one or more of these receptors have been evaluated in clinical studies in gastric cancer, with mixed results.

Bevacizumab, a monoclonal antibody against the VEGF-A isoform, has been evaluated in the first-line setting in advanced gastric cancer. Despite bevacizumab showing promise in earlier-phase trials, the randomised phase III AVAGAST trial failed to meet the primary end point of improved overall survival when bevacizumab was added to cisplatin and fluoropyrimidine combination

therapy [30]. This trial notably demonstrated an improved response rate and progression-free survival benefit in the bevacizumab arm. It has been hypothesised that the increased use of second-line chemotherapy in patients treated in Asia (66 % vs 21 % in pan-America) may explain why the pan-American patients appeared to derive an overall survival benefit which was not seen in those treated in Asia in a post hoc subgroup analysis. Despite extensive exploration, no predictive biomarker has yet been identified to determine which patients may benefit from bevacizumab therapy [29].

Recently, ramucirumab, a fully human IgG1 monoclonal antibody to VEGFR-2, has demonstrated single-agent activity in the second-line setting, both alone and in combination with weekly paclitaxel therapy, and two large randomised phase III trials have reported survival benefits [31, 32]. Efforts to improve outcomes in the first-line setting by combining ramucirumab with combination chemotherapy (5-fluorouracil and oxaliplatin) have been less successful, with a recently reported randomised phase II trial failing to demonstrate an improvement in median progression-free survival from the addition of ramucirumab therapy [33]. Toxicity is comparable to that of similar agents in the same class, although a higher rate of treatment discontinuation for reasons other than progression was noted in the latter trial. As with bevacizumab, no predictive biomarker has been discovered to determine which subgroup of patients might derive the most benefit from this approach.

Other agents with demonstrated antiangiogenic activity in various solid tumours are being evaluated in gastric cancer. Multitargeted TKIs targeting the VEGFR family include sorafenib, sunitinib, apatinib and regorafenib. Both sorafenib and sunitinib have been evaluated in phase II trials, with results demonstrating only modest activity; the former as combination therapy in the first-line setting with docetaxel and cisplatin [34], and the latter as a single agent in the second-line setting [35]. Apatanib, an oral TKI of VEGFR-2, is the first agent to improve overall survival compared with placebo following failure of two separate lines of chemotherapy (hazard ratio 0.71; 95 % CI 0.54–0.94; $p < 0.016$) [36]. Regorafenib, which has demonstrated a survival benefit in the last-line treatment of colorectal cancer [22] and GIST [37], is currently under evaluation by the Australasian Gastrointestinal Trials Group in a phase II trial in the second-line or third-line setting [38].

In this issue, Shen et al. [REF] report a phase III study comparing bevacizumab with placebo in combination with capecitabine and cisplatin for treatment of advanced gastric cancer patients from China. Consistent with the earlier AVAGAST study, this trial did not demonstrate an improvement in overall survival, the primary end point. This study was designed to determine whether differences in biology might result in greater benefit from bevacizumab in a purely Asian (Chinese) population, given this subgroup represented only a fraction of the patients in the earlier study. Unfortunately, issues with this study, albeit encouraging, limit the ability of clinicians to draw general conclusions about the efficacy of bevacizumab in this setting; the study is underpowered to detect a significant benefit in survival, and only a small proportion of patients received second-line chemotherapy in either arm.

In addition to EGFR, other cellular membrane proteins have been identified that are overexpressed and represent potential targets [39, 40]. Agents targeting c-MET and fibroblast growth factor receptor 2 are currently being evaluated. One such agent is rilotumumab, a monoclonal antibody against hepatocyte growth factor, a ligand for MET, which has recently been reported to show promising early-phase results in combination with epirubicin, cisplatin and capecitabine [41]. Placebo-controlled phase III trials combining rilotumumab or placebo with standard first-line chemotherapy are currently under way in advanced/metastatic disease overexpressing c-MET [42, 43]. Determining whether c-MET is indeed a target has been a challenge, and hence the results of such studies are eagerly awaited.

An increased understanding of tumour biology, particularly predictive biomarkers, is essential if we are to address the many hypotheses that the new generation of therapeutics have raised. The era of targeted therapy has yielded a number of successes, but several disappointments. Recent successes have come with limitations; the only predictive marker that has been successfully identified for gastric cancer (HER2 overexpression) applies to only a small proportion of patients. There has been much investment into targeting angiogenesis, with mixed results, and as yet no predictive biomarker predicting a benefit from antiangiogenic agents has been identified. Future strategies need to include identification of predictive biomarkers to allow better selection of patients for treatment.

Conflict of interest Katrin M.Sjoquist, clinical lead and investigator for the Australasian Gastrointestinal Trials Group, led the INTEGRATE trial. She received a gastrointestinal cancer preceptorship (2013) funded by Hoffman-LaRoche, and has received funding from a Cancer Australia programme grant. John R. Zalcberg has received research support from Eli Lilly, Bayer, Merck and Roche as well as having been compensated for talks or Advisory Boards by Eli Lilly, Bayer and Roche. He has also received travel support from Merck Serono, Bayer and Roche and served as an expert witness for Bayer.

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