Optimising treatment regimens for the management of advanced gastric cancer

Systemic chemotherapy for advanced gastric cancer (AGC) has been demonstrated to improve survival and quality of life compared with best supportive care and is routinely offered to patients of adequate performance status (PS) [1, 2]. Combination chemotherapy results in superior outcomes compared with monotherapy [2] and several large randomised controlled trials have been conducted over the past few decades in an attempt to define the optimal first-line regimen. Despite this, to date no chemotherapy regimen has been universally accepted as standard first-line therapy for AGC. Unresolved issues include which drug combinations are best to use upfront, triplet versus doublet therapy, and whether results can be translated between Eastern and Western populations. Additionally, results of recent trials have reinforced the importance of careful patient selection in order to minimise treatment-related toxicity, precipitating the evaluation of treatment options with more favourable toxicity profiles and with more convenient methods of drug delivery.

In this edition of *Annals of Oncology*, Kang et al. publish the results of the multicentre ML17032 trial which was designed with a primary end point of noninferiority for the progression-free survival (PFS) of capecitabine + cisplatin (XP) compared with a 3-weekly regimen of 5-fluorouracil + cisplatin (FP). Three hundred and sixteen patients were randomly assigned 1:1 to receive XP (160 patients) or a 3-weekly regimen of FP (156 patients). Measurable disease was mandatory for entry into the study and tumour assessments were carried out every two cycles. In the intent-to-treat population, median PFS for XP was 5.6 months compared with 5.0 months for FP, corresponding to an unadjusted hazard ratio (HR) of 0.80 (95% confidence interval (CI) 0.63–1.03) therefore meeting the predetermined noninferiority margin of 1.25. Overall survival (OS) was also noninferior with XP compared with FP (10.5 versus 9.3 months; HR 0.85, 95% CI 0.64–1.13; per-protocol population), although not statistically significant for superiority (P = 0.2650). Overall response rate was significantly higher in the XP arm (P = 0.02). Grade 3/4 treatment-related toxic effects were similar between the two arms, although notably, rates of catheter-related complications have not been reported.

A nonstandard 3-weekly FP regimen was used in this study; however, the authors considered this regimen to have equivalent dose intensity to standard 4-weekly FP regimens. Importantly, the 3-weekly FP regimen was well tolerated and efficacy was comparable to historical controls, resulting, in fact, in a longer median OS compared with the FP arms in a number of previously reported studies [3,4,5].

So how do the results of ML17032 advance us in the first-line treatment of metastatic gastric cancer?

Without a doubt, capecitabine can replace infused 5-fluorouracil (5-FU) in the treatment of AGC without compromising efficacy. The results from the ML17032 study confirm the results from the REAL-2 [Randomised study of Epirubicin, Cisplatin, Fluorouracil (ECF) for Advanced or Locally advanced oesophagogastric cancer (OG)] study, to date the largest randomised first-line trial for advanced OG cancer, which demonstrated that in triplet combination chemotherapy regimens for the end point of OS: capecitabine is noninferior to infused 5-FU and oxaliplatin is noninferior to cisplatin [6]. The HR of 0.86 (95% CI 0.80–0.99; noninferiority margin 1.23) for the capecitabine–fluoropyrimidine comparison was similar to the HR of 0.85 reported in the current study [7]. In the REAL-2 trial, 10% of patients receiving 5-FU developed catheter-related complications requiring removal of the device. Oral capecitabine abrogates the routine use of central venous access devices and is therefore a more convenient mode of administering fluoropyrimidine chemotherapy. In a meta-analysis of the two studies, compared with 5-FU regimens, capecitabine-containing combinations resulted in superior OS (HR 0.87, 95% CI 0.77–0.98; P = 0.02) and response rates (odds ratio 1.38, 95% CI 1.10–1.73; P = 0.006) [8].

In Japan, the phase III SPIRITS (S-1 plus cisplatin versus S-1 alone for first-line treatment of AGC) trial also evaluated the benefits of an oral fluoropyrimidine plus platinum combination [9]. S-1 + cisplatin resulted in superior OS compared with S-1 alone (HR 0.77, 95% CI 0.61–0.98; P = 0.04), with an impressive median OS of 13.0 months. These results have not, however, been reproduced in a Western population and S-1 is not currently licenced for use in Europe or North America. Interestingly, the OS results achieved within both the SPIRITS trial and the earlier JCOG 9912 study [10] occurred despite relatively short median PFS. Whether this reflects differing cultural views with regards to initial resectability/unresectability, different biology of the disease, high uptake of participation in second-line studies, or a combination of these and other factors is unknown. Outside Japan, the multinational FLAGS trial failed to demonstrate superiority for S-1 + cisplatin over 5-FU + cisplatin. Median OS for S-1 + cisplatin was 8.6 months, highlighting the need to exercise caution before extrapolating efficacy data between Eastern and Western populations [11].

Based on the results of the current study, XP can be considered a standard doublet regimen for AGC. ML17032 does not, however, address the ongoing question of triplet versus doublet therapy. The only recent randomised phase III trial addressing this issue is the V-325 trial which directly compared a standard 4-weekly FP regimen with a 3-weekly...
triplet combination of docetaxel, cisplatin and 5-fluorouracil (DCF) [4]. The triplet combination of DCF resulted in a statistically significant improvement in time to progression, survival, and response rate. This was, however, at the cost of increased toxicity, including complicated neutropenia (29%) and diarrhoea (all grades 75%, grade 3/4 19%), and 13 patients (3% of those randomised) suffered toxic deaths due to infection. These adverse events occurred in spite of a generally young patient population with good PS (median age 55 years, Karnofsky PS 80% in 99% of patients) and permissive use of granulocyte colony-stimulating factor as prophylaxis. Whether sequential administration of CF followed by docetaxel could achieve similar OS as DCF (median OS 9.2 months) with less toxicity is unknown. The efficacy of second-line docetaxel monotherapy is currently being evaluated in phase III trials.

In an update of their meta-analysis of chemotherapy regimens in AGC, Wagner et al. [12] have demonstrated that triplet combinations comprising 5-FU, anthracycline, and cisplatin result in superior OS when compared with doublet regimens of either 5-FU/cisplatin or 5-FU/anthracycline. The combination of ECF was the best tolerated of the evaluated triplet regimens. Although meta-analyses lack the robustness of a prospective randomised controlled trial, until recently, ECF has been regarded as a standard of care in many oncology centres, particularly in Europe.

Two trials have subsequently demonstrated that oxaliplatin can be substituted for cisplatin [6, 13]. Substituting oxaliplatin for cisplatin has the potential advantage of reducing demands on hospital resources, as cisplatin hydration schedules often mandate hospitalisation or prolonged treatment periods in day centres and, compared with ECF, oxaliplatin-containing regimens appear to have significantly lower rates of thromboembolic adverse events (7.6% versus 15.1%; P < 0.0001) [6]. Additionally, of the four drug regimens evaluated in REAL-2, epirubicin and oxaliplatin plus capcitabine (EOX) resulted in the longest median OS (11.2 months compared with 9.6 months for ECF; P = 0.02) [6]. The survival and safety profile of the EOX regimen has led to increasing adoption of this regimen as standard triplet therapy over ECF. Neither EOX nor ECF have been compared with cisplatin–fluoropyrimidine doublets or docetaxel-containing regimens in the context of a randomised phase III trial.

The Royal Marsden Hospital Prognostic Index, originally published in 2004, identified Eastern Cooperative Oncology Group PS of two or more, liver metastasis, peritoneal metastasis, and serum alkaline phosphatase ≥2100 U/l as poor prognostic factors in locally advanced and metastatic OG cancer [14]. OS significantly correlated with the number of risk factors (RFs) present, with good (0 RF), moderate (1 RF), and poor (3–4 RFs) risk groups corresponding to 1-year survival of 48.5%, 25.7%, and 11%, respectively. These data have recently been validated using the REAL-2 dataset and should therefore be considered a useful tool for selection of treatment of individual patients and stratification of patients in future clinical trials [15]. Applying this prognostic index to the M1L7032 and V-325 trial populations, it is possible that due to the baseline characteristics, in particular PS, these patients may have had an inherently more favourable prognosis. Equally, the good PS and younger median age of the patients is likely to have improved tolerability of the treatment regimens and hence the toxicity associated with the V-325 DCF regimen is particularly concerning. On the other hand, in both these studies, unlike REAL-2 and SPIRITS, measurable disease was required for study entry and a large proportion of patients had two or more metastatic sites at entry, possibly reflecting a larger burden of disease. Regardless, consideration should be given to the baseline characteristics of populations in clinical trials since results may not necessarily be transferable to the general oncology population, which is often older and of poorer PS.

To date, there have been no phase III randomised controlled studies establishing a standard second-line treatment regimen for AGC. Administration of second-line therapy to patients with AGC can be challenging, predominantly due to poor or rapidly declining PS. Despite this, several phase II trials have demonstrated efficacy for a number of chemotherapy agents including irinotecan, docetaxel, and paclitaxel [1]; prompting further evaluation of these drugs in randomised phase III trials. For patients with a long progression-free interval, consideration should be given to rechallenging with the therapeutic agents used in the first-line setting.

Unlike other solid tumour types, a definitive role for targeted therapies in gastric cancer has not yet been established. A number of current phase III trials (Table 1) are evaluating the addition of mAbs to standard chemotherapy regimens. Results from the first of these studies, the ToGA (trastuzumab with chemotherapy in HER-2-positive advanced GC) trial, are expected this year. Extrapolating from data in breast cancer, where HER-2 positivity is predictive of response to trastuzumab as well as prognostic, patients treated within ToGA were specifically selected for HER-2 positivity. Data from ToGA have reported a HER-2 positivity rate of 21.9% among the 2484 samples screened, a rate not dissimilar to that observed in breast cancer [16]. ToGA is the first phase III study in AGC using a molecular marker to preselect patients for treatment with a targeted agent.

In contrast, the incidence of both KRAS and BRAF mutations in AGC appear lower in gastric cancer compared with colorectal cancer. In a retrospective analysis of 43 patients treated with cetuximab-containing regimens, the frequency of KRAS and BRAF mutations were 11.6% and 2.4%, respectively [17]. KRAS and BRAF mutations did not appear to correlate with response to cetuximab-containing regimens (P = 0.846). Although these data are insufficient to determine whether these tumours are responsive or refractory to epidermal growth factor receptor (EGFR) antibodies, importantly, cetuximab...
combined with chemotherapy did not have a detrimental effect on patients with KRAS or BRAF mutations. It is expected that the analysis of tissue samples prospectively collected within current phase III trials such as REAL-3 will identify potential prognostic and predictive biomarkers. In the meantime, however, the presence of such mutations should not preclude patients from treatment within clinical trials in AGC incorporating EGFR antibodies.

The potential increased risk of bleeding and perforation associated with bevacizumab has not prevented evaluation of the antibody in AGC. Results from phase II studies investigating bevacizumab in combination with chemotherapy have been reported [18, 19]. In the first of these studies, bevacizumab combined with cisplatin and irinotecan resulted in a median time to progression of 8.3 months (95% CI 5.5–9.9 months), meeting the primary end point of a 50% improvement in time to progression over historical values. The observed rate of gastric perforation (two patients) or near perforation (one patient) was 6% and one patient experienced a significant upper gastrointestinal bleed. Grade 3/4 thromboembolic events were noted in 23% of patients [18]. More recently, a trial evaluating bevacizumab combined with a modified regimen of DCF reported a 6-month PFS rate of 79% and a median OS of 16.3 months. The rates of both perforation and bleeding were 2%, and 31% of patients experienced grade 3/4 thromboembolic event [19]. Whether or not these adverse events are entirely attributable to the addition of bevacizumab is unknown, although the rates of thromboembolism are markedly higher than those observed in any arm of the REAL-2 trial. A randomised phase III trial evaluating XP ± bevacizumab has completed recruitment and will provide further information regarding efficacy and safety of bevacizumab in AGC.

Increasing interest in small-molecule inhibitors has prompted a growing number of phase II studies evaluating these agents, particularly in chemorefractory AGC patients. Early results of trials evaluating everolimus (RAD001) and sunitinib indicate that these agents are generally well tolerated in chemorefractory patients with good PS [20,21,22]. Although objective response rates with these drugs are low, reported disease control rates in assessable patients are 55% for everolimus (29 of 53 patients) [20] and 47%–35% for sunitinib (17 of 36 and 5 of 14 patients) [21, 22]. As seen in other tumour types, for these newer agents, antitumour activity may be reflected by tumour stabilisation [20, 21, 22]. As seen in other tumour types, for these newer agents, antitumour activity may be reflected by tumour stabilisation rather than objective response rates. Further evaluation of these drugs in AGC is therefore warranted.

In summary, in conjunction with REAL-2, the results of ML17032 firmly establish the role of capecitabine in the treatment of AGC. Trials comparing capecitabine-based regimens to 5-FU regimens are no longer warranted. By inference, oral capecitabine can also replace infused 5-FU in the perioperative management of gastric cancer. Platinum/fluoropyrimidine-based therapies form the backbone of first-line chemotherapy regimens and current data indicate that triplet regimens result in superior outcomes compared with doublets. DCF is efficacious, but routine use is limited by treatment-related toxicity. On the other hand, EOX is a well-tolerated triplet regimen and has been selected as the control arm for the multicentre REAL-3 trial which is evaluating the addition of panitumumab to chemotherapy. It is hoped that in the first-line setting, the addition of targeted agents to chemotherapy will result in clinical significant improvements in survival and results from recent studies in chemorefractory patients indicate that some of the newer small-molecule-targeted agents may have activity in this disease. Concurrently, translational research is vital to identify prognostic and predictive markers to guide treatment and aid the development of new therapeutic agents. Through these collaborative efforts, the optimal treatment regimens for patients with AGC can be defined and ultimately individualisation of patient therapy can occur.

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