Current Therapeutic Options for GC

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Cytotoxic chemotherapy (CT) regimens with less toxic agents, which have been shown to provide similar survival as more toxic drugs and better quality of life, are the reference standard for advanced gastric cancer (GC). Although no specific regimen has been universally accepted, a combination regimen with platinum- and fluoropyrimidine-based compounds is optimal first-line treatment [Wagner AD et al. *J Clin Oncol*. 2006]. Florian Lordick, MD, Universität Leipzig, Leipzig, Germany, stated that patients aged > 70 years receive the same benefit from this treatment [Trumper M et al. *Eur J Cancer*. 2006], provided that highly toxic regimens are avoided, and new data show that second-line treatment is effective [Ford HE et al. *Lancet Oncol*. 2014; Thuss-Patience PC et al. *Eur J Cancer*. 2011].

The less toxic platinum compound oxaliplatin (OX) can replace cisplatin (CIS), stated Prof Lordick, with the REAL-2 study showing that it was noninferior (HR, 0.92; 95% CI, 0.80 to 1.10) with a similar 2-year survival [Cunningham D et al. *N Engl J Med*. 2008]. A German Association of Medical Oncology study showed that in patients aged ≥ 65 years, OX versus CIS, combined with 5-FU and leucovorin, significantly improved progression-free survival (PFS; 6.0 vs 3.1 months; p = .029) and improved overall survival (OS; 13.9 vs 7.2 months; p = NS) [Al-Batran SE et al. *J Clin Oncol*. 2008]. Experimental work has suggested that it may be possible to predict which platinum compound is more effective in specific patients; although such effort is hypothesis generating, more work is needed for clinical application. Tan and colleagues [Tan IB et al. *Gastroenterology*. 2011] showed that one genetic subtype (G-intestinal) was more sensitive to 5-FU and OX, while another (G-diffuse) was more sensitive to CIS and that these subtypes correlated, although not completely, with tumor morphology.

Two acceptable less toxic compounds to replace intravenous 5-FU are the oral capecitabine (CAP) and oral S-1 compounds. The randomized REAL-2 study showed a similar survival with CAP and 5-FU [Cunningham D et al. *N Engl J Med*. 2008]. The randomized open-label ML 17032 study showed that the response rate to treatment was better with CAP + CIS (46%) than with 5-FU + CIS (32%; p = .02) and that CAP + CIS was noninferior for PFS (5.6 vs 5.0 months; p < .001) and survival (10.5 vs 9.3 months; p = .008) [Kang YK et al. *Ann Oncol*. 2009]. Two studies showed that the new compound called S-1 (a combination of tegafur, gimeracil, and oteracil) combined with CIS, when compared with CIS alone, improved OS (13.0 vs 11.0 months) and PFS (6.0 vs 4.0 months; p < .0001) [SPIRITS; Koizumi W et al. *Lancet Oncol*. 2008] and that S-1 + CIS was as effective as 5-FU + CIS with a better safety profile [FLAGS; Ajani JA et al. *J Clin Oncol*. 2010].

The MATEO International Study will begin enrollment soon and will explore whether de-escalation maintenance with S-1, as compared with the standard of care of continuing polychemotherapy, is noninferior in terms of OS after 3-month induction therapy. The study will also examine whether there is a relation between tumor gene expression and fluoropyrimidine sensitivity. In mesenchymal-type gene expression, PI3K-AKT-mTOR inhibitors were shown to be more effective, while 5-FU was more effective in the setting of metabolic-type gene expression [Lei Z et al. *Gastroenterology*. 2013].

Triple-drug regimens increase efficacy but also increase toxicity. The TAX-325 study showed that treatment response rate, time to progression, and survival were improved when docetaxel was added to CIS + 5-FU, as compared with CIS + 5-FU, but was associated with a higher rate of treatment-related adverse events [Van Cutsem E et al. *J Clin Oncol*. 2006].

Table 1 summarizes the improvement in survival with second-line chemotherapy. According to these data, both irinotecan monotherapy and taxane monotherapy (either paclitaxel or docetaxel) can be regarded as proven options for the postprogression treatment of advanced GC. Second-line chemotherapy combinations are more toxic but not necessarily more effective and therefore cannot be recommended.

Targeted treatment of GC with first- and second-line regimens have been shown to improve OS and PFS. A large number of targets have been identified, heralding a new era of drug testing for

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Table 1. Effect on Survival and Symptom Control With Second-Line Chemotherapy of Gastric Cancer

Study	Protocol	Survival, mo (p Value)	Symptom Control
Thuss-Patience PC et al. *Eur J Cancer.* 2011 (n = 40)	Irinotecan vs BSC	4.0 vs 2.4 (.012)	44% vs 5% improvement
Kang JH et al. *J Clin Oncol.* 2012 (n = 202)	Irinotecan or docetaxel vs BSC	5.3 vs 3.8 (.007)	No data
Ford HE et al. *Lancet Oncol.* 2014 (n = 168)	Docetaxel vs BSC	5.2 vs 3.6 (.01)	Global QoL unchanged but better symptom control
Hironaka S et al. *J Clin Oncol* 2013 (n = 219)	Paclitaxel vs irinotecan	9.5 vs 8.4 (.38)	No data
Higuchi K et al. *Eur J Cancer* 2014 (n = 130)	Irinotecan + cisplatin vs irinotecan	10.7 vs 10.1 (.9823)	No data

BSC=best supportive care; QoL=quality of life.

GC, and success will be defined by the ability to identify patients who will benefit from particular targeted treatments, said Manish A. Shah, MD, New York-Presbyterian Hospital, New York, New York, USA. The heterogeneity of GC has shown that disease biology is important, and tumors that are proximal versus distal, or diffuse versus nondiffuse, behave differently, along with differential effects of genetic risk, behavior (tobacco use, diet), and the environment.

Data from the ToGA and TyTan studies have validated human epidermal growth factor 2 (HER2) as a target for first- and second-line treatment, respectively. All patients with metastatic GC should be tested for HER2, stated Dr Shah. In ToGA, survival was prolonged with the monoclonal antibody (mAB) trastuzumab added to CT when compared with CT alone in patients with HER2 GC [Bang YJ et al. *Lancet*. 2010]. HER2-targeted treatment is associated with 16-month survival, compared with ~ 11 months with CT alone in the high HER2 overexpressors. In TyTAN, the tyrosine kinase inhibitor lapatinib plus paclitaxel and paclitaxel alone had a similar effect on the primary end point of survival, but there appeared to be a greater effect in patients who were Asian or were HER2 immunohistochemistry 3 positive [Bang YJ et al. *J Clin Oncol.* 2013 (abstr 11)].

Antiangiogenic treatments that target the vascular endothelial growth factor (VEGF) ligands and receptors also show promise. Targeting the VEGF receptor 2 with the mAB ramucirumab (RAM) for second-line treatment in the REGARD trial [Fuchs CS et al. *Lancet*. 2014] and with apatinib in a Phase 3 study conducted in China [NCT01512745] demonstrated an improvement in OS and PFS when compared with best supportive care.

An anticipated standard option for second-line treatment of GC is RAM plus paclitaxel (PTX), based on the results of the RAINBOW study [Wilke H et al. *J Clin Oncol.* 2014 (abstr LBA7)]. The response rate and disease control rate was better with RAM + PTX when compared with placebo + PTX (28% vs 16%; p = .0001; 80% vs 64%; p < .0001, respectively). The main side effects are fatigue, neutropenia, bleeding, and hypertension.

In patients receiving first-line therapy of CAP + CIS for locally advanced or metastatic GC, the addition of bevacizumab (BEV) significantly improved PFS and provided a numeric but not significant improvement in the primary end point of OS (12.1 vs 10.1 months, respectively; HR, 0.87) [AVAGAST; Kang Y et al. *J Clin Oncol.* 2010 (abstr LBA4007)].

A comparison of the results from AVAGAST and RAINBOW suggest that BEV may be effective in non-Asian patients, but this must be tested, stated Dr Shah, and it supports the benefit of BEV in some patients, based on the effect on OS. Furthermore, he said that the PFS results suggest that the 2 mABs may not be the same in Asian patients: BEV is apparently not effective for first-line treatment (HR, .92) in AVAGAST, whereas RAM appears to be effective for second-line treatment (HR, .63) in RAINBOW.

Two candidate biomarkers for greater benefit with BEV are VEGF-A and neuropilin 1, identified in an analysis of AVAGAST, with high levels of the former and lower levels of the latter associated with improved OS [Van Cutsem E et al. *J Clin Oncol.* 2012]. Further validation of these biomarkers is required. Trials are underway or being planned to validate other biologic treatment targets for GC.