State-of-the-art Progress of Anticancer Agents for Advanced Gastric Cancer

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Advanced gastric cancer (AGC) has achieved major success in prolongation of overall survival (OS) through the progress of chemotherapies, molecularly targeted agents (MTAs), and immune checkpoint inhibitors (ICIs), etc.

For the 1st-line therapies, combinations of fluoropyrimidines and platinums (cisplatin or oxaliplatin) are standard treatments. Our unique regimen using weekly 24-hour infusion of high-dose 5-fluorouracil (5-FU) and leucovorin regimen [acronym, HDFL] has *satisfactory* single-agent activity with *minimal*myelosuppressionand *mild* toxicity. HDFL-based doublet combinations (cisplatin-HDFL, oxaliplatin-HDFL) have become the cornerstone regimens with high efficacy and low toxicity. Trastuzumab, a humanized human epidermal growth factor receptor-2 (HER2) monoclonal antibody (mAb), can be added to platinum-fluoropyrimidine doublets in HER2-overexpressing AGC with improved OS in 1st-line setting [ToGA study].

For the 2nd-line therapies, taxanes (docetaxel or paclitaxel), or irinotecan, are considered as standard treatments. Ramucirumab (RAM), a vascular endothelial growth factor receptor-2 (VEGFR-2) mAb, has demonstrated that RAM monotherapy[REGARD study], or RAM plus paclitaxel [RAINBOW study] improved survival in 2nd-line setting.

For the 3rd-line therapies, inhibitors of angiogenic receptor tyrosine kinases (TKIs) (apatinib, regorafenib) have shown OS prolongation. Immune checkpoint inhibitors (ICIs), anti-PD-1 (pembrolizumab, nivolumab) and anti-PD-L1 (MPDL3280A, MEDI4736) mAbs, are under activeevaluation in AGC. Pembrolizumabmonotherapy has shown highly encouraging objective response rates of 22% (by central review) in 3rd-line setting [KEYNOTE-012 study, AGC cohort].

It is crucial to identify useful *predictive* biomarkers for *precision medicine* of MTAs and ICIs in the state-of-the-art treatment of AGCs.