Editorial

Ataxia telangiectasia mutated (*ATM*), could it be another useful biomarker for the successful treatment with the poly (ADP-ribose) polymerase inhibitor?

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Gastric cancer is one of threatening health problems worldwide with poor treatment outcomes (1). Importance of selection of patients has been proposed as a key factor in improving outcomes of treatment with targeted therapies in patients diagnosed as advanced gastric cancer (AGC) due to its biological heterogeneity. The significance of use of appropriate biomarkers in application of targeted therapies was highlighted in the ToGA trial, in which clinical benefit of trastuzumab was achieved by using immunohistochemistry (IHC) of human epidermal growth factor receptor 2 (HER2) as a biomarker in treatment of patients with AGC (2).

The DNA damage response is a vital signaling pathway involved in detection and repair of damaged DNA leading to maintenance of genomic stability (3). Many genes including *ATM* and *BRCA1* or *BRCA2*, have been known to play a role in repairing DNA double strand breaks (DSBs) by homologous recombination (HR), and their altered functions are known to be associated with development of several types of malignancies (4-6). Ataxia telangiectasia mutated (ATM) is a serine/threonine kinase which belongs to the phosphatidylinositol 3-kinase-related kinase family contributing to regulation of DNA damage response. Upon induction of DNA DSBs, ATM is recruited to the sites of DNA damage and activates downstream targets such as p53 which subsequently acts as a transcription factor and induces expression of proteins working for activation of the cell cycle checkpoint (7,8). Targeting the DNA damage response pathway has been an appealing therapy in treatment of cancers as a sensitizer for tumor cells to chemotherapy or radiotherapy to improve efficacy of these modalities or overcome resistance. Because it has been reported deregulated DNA damage response pathway by overexpression of components involved in the pathway is one of mechanisms for development of resistance against genotoxic therapies in various tumor cells, inhibition of regulators of the pathway can enhance efficacy of DNA damage inducing therapies (7,8). The DNA damage pathway can also be an attractive target by virtue of another mechanism, synthetic lethality. Synthetic lethality refers to the situation when a mutation or defect of either of two genes results in no effect on cell survival, while defects in both genes at the same time lead to cell death (9). The concept of synthetic lethality was first introduced in treatment of patients with breast or ovarian cancer harboring *BRCA1/2* mutations in clinical trials (10,11). Poly [adenosine diphosphate (ADP)-ribose] polymerase (PARP) is an enzyme that catalyzes production of large branched chains of poly (ADP) ribose from nicotinamide adenine dinucleotide (NAD+). DNA alteration such as single strand breaks (SSBs), the most common DNA abnormality, is mainly repaired by base excision repair (BER) and PARP is an important mediator for the repair. After the induction of SSBs, PARP-1 binds to the breaks and activates catalysis which results in other DNA repair proteins (12-14). Inhibition of PARP leads to an increase of SSBs that collapse replication folks to generate DSBs which is repaired by HR. Inability of repair of DSBs by means of HR in BRCA deficient cells are easily led to cell lethality (15). Several studies have also reported the similar effect resulting from synthetic lethality interaction

was also observed in cells deficient of proteins involved in HR including ATM, suggesting ATM as a potential useful biomarker in application of the PARP inhibitor to enhance efficacy of the agent (16,17).

Since the experience from a lot of failed clinical trials performed with targeted agents in patients AGC, necessity of development of a novel biomarker to improve efficacy in treatment with targeted agents has been consistently suggested. Kim *et al*. recently reported significance of expression level of ATM as a prognostic marker in gastric cancer. Results in this study showed low ATM expression was associated with worse clinical characteristics and lower disease-free survival and overall survival (OS). Higher portion of tumors with low ATM expression was observed in microsatellite stable (MSS) or microsatellite instability (MSI)-low tumors than in MSI-high tumors. The study reported a subgroup of low ATM expression and MSI-negative (MSS and MSI-low) showed the most dismal prognosis in terms of disease free survival and OS (18). In addition, depletion of p53 is reported to promote olaparib (Lynparza; AstraZeneca, London, UK) sensitivity in gastric cancer cell lines in which ATM was depleted by a small molecule ATM inhibitor or shRNA (19). Because p53 protein is a component of the ATM mediated DNA damage response pathway that acts downstream of ATM, activation of p53 independently from activation of ATM could result in primary resistance against agents targeting the DNA damage response pathway.

Bang *et al*. combined olaparib, an orally active small molecule which inhibits PARP and interferes with repair of SSBs, with paclitaxel for treatment of patients with gastric cancer who progressed after first line chemotherapy in a randomized, double-blind phase II trial. They adopted expression level of ATM accessed with IHC as a biomarker in application of a PARP inhibitor and suggested the possibility of treatment by means of synthetically lethality therapies in patients with refractory AGC (20). The primary end point of the study was progression-free survival (PFS), and the study failed to meet the primary objective [hazard ratio (HR) 0.80; 80% confidence interval (CI): 0.62–1.03; P=0.131, one-sided] (20). A subset of patients with low expression of ATM also showed no significant difference in PFS (HR 0.74; 80% CI: 0.51–1.08; P=0.157, one-sided). However, OS of olaparib/paclitaxel group was significantly improved compared with placebo/paclitaxel group. Based on the previous study on patients with breast cancer treated with olaparib and paclitaxel and current guideline for treatment of metastatic gastric cancer progressed to first line therapy, paclitaxel was chosen for the combination therapy with the PARP inhibitor in Bang *et al*.'s study with refractory gastric cancer (21).

Because ATM is a major checkpoint protein acting at the G1/S cell cycle, the combination therapy of olaparib and taxane might not be the best in order to maximize the effect of synthetic lethality in tumor cells expressing low level of ATM. A recent study reported administration of taxane with a small molecule inhibitor acting against checkpoint with forkhead and ringfinger domains (CHFR) increased the efficacy of the chemotherapeutic agent. *CHFR* is a gene acting as the mitotic checkpoint and known to play a role in mediating resistance against taxane, microtubule-targeted agents (22). The study showed interaction between PARP1 and PAR-binding zinc finger (PBZ) domain of CHFR and degradation of CHFR by disruption of the interaction. Loss of expression of CHFR by interrupting interaction of CHFR and PARP1 is expected to lose its function acting at the antephase checkpoint, which subsequently leads to overcome resistance and sensitize the cytotoxic effect of taxane. Considering results from these studies, adoption of additional biomarkers other than ATM expression level or appropriate combination of chemotherapeutic agents which can maximize synthetic lethality interaction should have been considered in the treatment with olaparib.

Although small sample size is another hurdle that had to be overcome for reliable statistical results as the authors mentioned, PFS in the phase II trial was consistent to that of other studies with metastatic gastric cancer patients treated in second line therapy. A previous phase III study comparing irinotecan with paclitaxel in patients with AGC whose diseases progressed after first line chemotherapy reported median PFS as 3.6 months, an equivalent result to Bang' s study (23). The response rate presenting in the phase II trial was also consistent to the results on PFS. Overall response rate in the subset of patients with low expression level of ATM is 34.6% in the olaparib administration group and 26.1% in the placebo group with no statistical significance. Significant benefit in OS was observed in patients who received olaparib, and discrepancy of results between PFS and OS was explained by investigators with postprogression synergism with irinotecan. The genes for carcinogenesis might act on different steps of behavior of cancer cells. Some genes dominantly act on proliferation of cells and other genes show their action on invasion and migration of cancer cells (24). So mechanism of action of olaparib on gastric cancer cells should be investigated with further studies. The validation of the response rate as an evaluation

method in studies on targeted agents is also needed to consider for future clinical trials.

The study performed by Bang *et al*. has certainly contributed to bring advancement by introducing a new class of targeted agent in treatment of patients with refractory gastric cancer. The only targeted agent approved in those patients as second line therapy with proven clinical benefit is ramucirumab, an anti-angiogenic agent. Although the phase II trial with olaparib did not meet the primary endpoint, the enhanced OS left hope to connect to the next step, and phase III trial is now being performed. Achievement of additional beneficial chemotherapeutic regimen is meaningful given that the limited numbers of chemotherapeutic agents we can adopt in the salvage therapy in recurrent gastric cancer. Introduction of a new biomarker in evaluating the efficacy of olaparib in gastric cancer is another point to be praised. Selection of patients for the targeted therapy has been regarded as a critical issue to be addressed for the successful treatment. The biologically heterogeneity of gastric cancer, which has always been an obstacle in application of targeted agents, has seemed to be solved by a recent study which divided the cancer into four molecular classification, tumors positive for Epstein-Barr virus, microsatellite unstable tumors, genomically stable tumors, and chromosomal instability tumors (25). Nevertheless, application of the classification in clinical trials is still an assignment that has yet to be solved.

In summary, although the randomized phase II clinical trial examining the efficacy of olaparib combined with paclitaxel comparing with placebo plus paclitaxel did not meet the primary endpoint, PFS, olaparib still remains attractive as a targeted agent for metastatic gastric cancer and should be evaluated with larger number of patients to achieve uniform and statistically reliable results. Application of an appropriate biomarker to select patients who can benefit from the target agent was a remarkable point considering the successful outcomes of ToGA study. Given that previous studies on ATM, however, use of only one biomarker for treatment with olaparib might not be the best way to achieve significant results. In addition, a sophisticated combination of the targeted agent with chemotherapeutic agents based on the precise mechanism of action of each agent would lead to promising outcomes.

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Footnote

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