ISP-12-9 TAS-117, a novel allosteric AKT inhibitor, shows potent antitumor activity on ovarian clear cell adenocarcinoma cells from fresh surgical samples in 3-dimentional culture

Taiho Pharmaceutical CO. LTD.[1], Keio University[2], St. Marianna University[3]
Kohji Tsuta[1], Eiichiro Tominaga[2], Akiko Tozawa[3], Tomoko Akahane[2], Atsushi Uekawa[3], Tatsuru Ohara[3], Hiroyuki Nomura[2], Fumio Kataoka[2], Akira Hirasawa[2], Kouji Banno[2], Nao Suzuki[3], Daisuke Aoki[2]

[Objective] Activation of PI3K/AKT pathway is thought to be one of the possible mechanisms of intrinsic or acquired chemoresistance of ovarian clear cell carcinoma (OCCC). We have previously reported TAS-117 showed potent activities on ovarian serous carcinoma cells from ascites in an AKT2 -dependent manner. We have examined AKT2 in OCCC and evaluated growth inhibitory effects of TAS-117 alone and combined with paclitaxel and carboplatin (TC) on OCCC under 3-dimentional culture condition for the first time. [Methods] With the approval of the institutional review board, 70 paraffin-embedded and 4 fresh surgical samples were applied. AKT isoforms (AKTs) were measured by qRT-PCR. Cancer cells were isolated from fresh samples and cultured in collagen gel with TAS-117, GDC-0068 (ATP-competitive AKT inhibitor) and TC. [Results] In OCCC, AKT2 expression was higher than other AKTs and this expression pattern of AKTs was different from the other histological subtypes. TAS-117 showed high effects with mean growth inhibition rate of 59% (47-70%) at 0.1 μM, clinically achievable concentration, while that of TC was only 32% (16-48%). TAS-117 combined with TC showed higher effects than TC or TAS-117 alone in 3 of 4 cases. Further, the effects of TAS-117 were higher than GDC-0068 in 2 cases. [Conclusion] TAS-117, especially when treating in combination with TC, may be suitable treatment for OCCC.

ISP-12-10 Identification through a functional genomics screen of factors whose down-regulation enhances the cancer stem cell population in ovarian cancer

Kyoto University
Koji Yamanoi, Noriomi Matsumura, Kaoru Abiko, Ken Yamaguchi, Junzo Hamanishi, Tsukasa Baba, Masafumi Koshiyama, Ikuo Konishi

[Objective] Cancer stem cells (CSC) are regarded as the cause of tumor recurrence. We aimed to identify genes whose downregulation increase CSC phenotype of serous ovarian cancer through a functional genomics screening. [Methods] Using a library of 81,000 shRNA lentiviral plasmids (Cellecta) targeting 15,000 genes and two serous ovarian cancer cell lines, CH1 and SKOV3, which harbor minimal side population (SP) fractions (less than 0.1%), we detected genes whose downregulation markedly increased SP. In addition, we examined the functions of SP, such as sphere formation ability, single cell clonogenicity and in vivo tumorigenicity. [Results] Suppression of *GeneA, GeneB and GeneC* markedly increased the SP in CH1 cells (control ; 0.08% vs *GeneA* ; 1.1%, *GeneB* ; 1.0%, *GeneC* ; 2.0%). Suppression of *GeneD, GeneE and GeneF* markedly increased the SP of SKOV3 cells (control ; 0.07% vs *GeneD* ; 1.4%, *GeneE* ; 1.1%, *GeneF* ; 1.0%). All generatad SP cells had significantly high ability of sphere formation, single cell clonogensity and in vivo tumorgenesity compared to major population cells ($p<0.05$, respectively). Overexpression of all six genes markedly decreased the SP in A2780 and IGROV 1 cells ($p<0.0001$). [Conclusion] We identified six genes whose downregulation increased the CSC phenotype of serous ovarian cancer. Our findings may be important to reveal molecular mechanisms of tumor recurrence.

ISP-13-1 The usefulness of ultrasonographic evaluation of malignant ovarian tumors by IOTA (International Ovarian Tumor Analysis) study

Showa University[1], Showa University Northen Yokohama Hospital[2], NTT Medical Center Tokyo[3]
Kanae Shimada[1], Takashi Mimura[1], Tetsuya Ishikawa[1], Chiaki Iitsuka[1], Shingo Miyamoto[1], Kiyotake Ichizuka[2], Hajime Tsunoda[3], Akihiko Sekizawa[1]

[Objective] To clarify the usefulness of ultrasonographic evaluation by using IOTA study for malignant ovarian tumors. [Methods] We compared the rate of proper diagnosis of ovarian tumors by using both ultrasonography and MRI scans from Feb. 2014 to May 2015 with approval of IRB. We used IOTA criteria as the tool for ultrasonographic evaluation. On the basis of the previous research, we set 0.1 of the probability of malignancy (POM) as the cutoff value. Then, we diagnosed malignant ovarian tumors when the POM was over 0.1. When it was under 0.1, we considered benign tumor. [Results] Out of 165 ovarian tumor surgeries, 142 were benign, 19 were malignant and 4 were borderline malignancy by pathological study. The median percentage of POM in benign and malignant ovarian tumors were 0.017 and 0.78, respectively. We set 0.78 as the cutoff value. There were 27 cases which were over 0.1 of the POM. 23 cases were malignant, and 4 cases were benign. The ovarian tumors which were under 0.1 of the POM were all benign. We pre-diagnosed that 30 ovarian tumors might be malignant using MRI scans before surgery. After surgery, 22 were malignant and 8 were benign. [Conclusion] When diagnosing ovarian tumors, ultrasonography is easy and useful. It is concluded that ultrasonography is not inferior to MRI scans when diagnosing ovarian tumors.