TRASTUZUMAB, AN ANTI-HER2 ANTIBODY MODULATES CYTOTOXICITY AGAINST CHOLANGIOCARCINOMA (CCA) VIA MULTIPLE MECHANISMS

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Background Trastuzumab (Tras) monoclonal antibody targets the extracellular domain of human epidermal growth factor receptor 2 (HER2). FDA approved Tras for the treatment of HER2 positive breast cancer. Cholangiocarcinoma (CCA) is a cancer forms in the bile ducts. Several CCAs are multifocal and cannot be completely removed by surgery and are incurable. Combination of gemcitabine and cisplatin is a standard first line therapy for patients with advanced CCA. Nowadays, the precision medicine and immunotherapy has been playing remarkable roles for cancer treatment. In this study, we found that HER2 expression is relatively high in CCA PDX and cell lines from Thailand. We hypothesized and speculated that Trastuzumab could be a promising antibody immunotherapy for CCAs.

Methods We examined surface HER2 expression on 5 CCA cell lines (M213B, D068, D113, RBE, YSCCC) and patient-derived cell (PDC) by Flowcytometry. We defined the activities of antibody-dependent cytotoxicity (ADCC) and antibody-dependent cell phagocytosis (ADCP) by using FcR-bearing recombinant Jurkat T cell expressing firefly luciferase gene under the control of NFAT response elements. ADCC was then confirmed by using CD16-transduced NK cell line (KHYG-1) and NK cells from a healthy donor. Rabbit and human serum were administered to test CDC activity of Tras. To clarify ADCP activity, we used mouse peritoneal macrophages and monocyte-derived macrophages from healthy donor as effector cells. Moreover, we performed MTT assay to investigate the direct effect of Tras. Finally, we evaluated the efficacy of Tras in vivo xenograft and PDX model.

Results Flowcytometric analysis and immunohistochemistry revealed high expression of HER2 in CCA cells. Tras conferred ADCC, ADCP, CDC, and direct effect to induce CCA cell death. Tras demonstrated potent in vivo inhibitory effect using PDX model.

Conclusions Tras indicates multi-activities against CCA. Tras can be considered as a promising antibody immunotherapy for the treatment of HER2 expressing CCA.

Ethics Approval The use of human materials is approved by Kumamoto University’s ethical committee (ID: 30-78-20-20201119). Animal experiments are approved by Kumamoto University’s animal ethics committee (ID: A2021-053)