A PHASE I DOSE-ESCALATION AND PHARMACOKINETIC STUDY OF S-1 PLUS NAB-PACLITAXEL IN PATIENTS WITH UNRESECTABLE OR RECURRENT GASTRIC CANCER

Ishido Kenji1, Nakayama Norisuke2, Chin Keisho3, Higuchi Katsuhiko1, Nishimura Ken1, Motomekiya Satoshi2, Azuma Mizutomo3, Takagi Seiichi2, Kumekawa Yosuke2, Tanabe Satoshi4, Inokuchi Yasuhiro2, Koizumi Wasaburo4

1Department of Gastroenterology, Kitasato University School of Medicine, Sagamihara-city, Japan
2Department of Gastroenterology, Kanagawa Cancer Center, Yokohama City, Japan
3Cancer Institute Hospital Department of Gastroenterology, Koto-ku, Japan
4Department of Gastroenterology, Kitasato University School of Medicine, Sagamihara-city, Japan

Introduction: S-1, an oral fluoropyrimidine, plus cisplatin (SP) is a standard regimen for advanced gastric cancer (GC) in East Asia. Nab-Paclitaxel (nab-P) is a treatment option in GC (approved 260 mg/m² q3w dosing schedule in Japan). Since these two agents differ in their mechanisms of action and toxicity profiles, we sought to test their combined activity in a phase I study of S-1/nab-P for GC. No pharmacokinetic (PK) profiles with a co-administration of S-1 and nab-P were reported previously for GC.

Methods: The primary endpoints were to determine the maximum tolerated dose (MTD) and recommended dose (RD) of S-1/nab-P in patients with GC. The secondary endpoints were to evaluate PK parameters of both agents, safety and efficacy. This study was designed to perform stepwise dose escalation study on the basis of standard 3 + 3 method. Patients received treatment on 3 week cycles. S-1 was administered orally at a twice-daily dose of 80 mg/m² for 14 days and nab-P was administered as a 30-minute IV infusion at a dose of 180 mg/m², 220 mg/m² or 260 mg/m² on day 1 (level 1a, 2a or 3a). Dose limiting toxicity (DLT) was defined as follows during the first cycle; Grade 4 neutropenia to continue more than 3 days, febrile neutropenia, Grade 4 hematological toxicity, nonhematological toxicity of grade 3 or higher, and treatment delay more than 8 days on cycle 2 day 1. The MTD was defined as the dose level at which DLT occurred in more than 33% of the patients and the RD defined as the next dose level lower than MTD. Toxicities and tumor responses were evaluated based on CTCAE v4.0 and Response Evaluation Criteria in Solid Tumor (RECIST1.1).

Results: Sixteen patients were enrolled in this study, DLT were observed in 0 of 3 patients at level 1a, 1 of 6 patients at level 2a and 0 of 6 patients at level 3a. The observed DLT was delay of initiation of cycle 2, due to treatment-related adverse event (fatigue, anorexia, hyperkalemia). The MTD was not obtained, and level 3a (S-1 80 mg/m² twice daily plus nab-P 260 mg/m² on days 1) was established as the RD. The toxicity of all grades that occurred in more than 30% of patients was leukopenia, neutropenia, peripheral neuropathy, diarrhea and anorexia. There were no treatment-related deaths. Among the 11 patients who had measurable lesions, the overall response rate was 50% (1 of 2) at level 1a, 50% (3 of 6) at level 2a and 67% (2 of 3) at level 3a. Five patients were evaluable for PK at the RD, and PK of Paclitaxel and 5-FU in the combination therapy were comparable to those in each monotherapy of nab-P or S-1, respectively.

Conclusion: Based on the results of this study, the RD was determined to be dose level 3a (S-1 80 mg/m² twice daily plus nab-P 260 mg/m² on days 1). The study suggests that this combination therapy may be a promising treatment regimen in GC and merits further evaluation.