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A phase 1 study of S-1 with 3-week schedule in patients with biliary tract cancer of normal and varying degrees of liver dysfunction

D.H. Yoon[1], H.J. Lee[1], S.S. Lee[2], J.R. Lee[1], H.M. Chang[1], M.H. Ryu[1], Y.K. Kang[1], J.S. Lee[1], T.W. Kim[1]. *[1]Asan Medical Center, Oncology, Seoul, South Korea; [2]Yonsei University, Oncology, Seoul, South Korea*

Background: Hepatic dysfunction is common in patients with biliary tract cancer due to the obstructive jaundice and high incidence of liver metastases. S-1 has a favorable toxicity profile and could be safely administered to biliary tract adenocarcinoma with hyperbilirubinemia (Park et al, Oncology 2009;76:126). However, the optimal tolerable dose of S-1 with 3-week schedule in normal and hepatic dysfunction has not been defined yet.
Mateiral and Methods: Forty-six patients with biliary tract adenocarcinoma with normal and varying degrees of liver dysfunction were entered between February 2006 and December 2008 and stratified into four groups according to serum total bilirubin and AST by National Cancer Institute Organ Dysfunction Working Group liver dysfunction classification. S-1 was given from day 1 to day 14 of a 21-day cycle with 3−3 dose escalation scheme to define MTD and DLT. Pharmacokinetic study was not conducted in this study.
Results: All the patients were assessable for toxicity. In the normal hepatic function group, DLT was not observed up to 45 mg/m^2. At the prespecified maximal dose of 50 mg/m^2, a grade 3 abdominal pain and a grade 3 vomiting occurred in each patient among twelve patients establishing the dose to be MTD. No DLT was observed among six at the 40 mg/m^2 dose level which is the predefined maximal dose in the mild hepatic dysfunction (HD) group to define the dose to be MTD. In the moderate HD group, a grade 3 confusion occurred in one of eight patients at the dose 35 mg/m^2. The MTD was 35 mg/m^2 because DLT of a G3 stomatitis with G3 diarrhea and a sepsis occurred in each patient out of six at the dose of 40 mg/m^2. Two out of six experienced DLT of grade 3 vomiting at the dose of 30 mg/m^2 in the group of severe HD and none of three showed DLT at the dose of 25 mg/m^2. Thus, MTD should be less than or equal to 25 mg/m^2 in the group of severe HD.
Conclusions: TS-1 starting doses that seem to be safe for hepatically impaired patients treated with 3-week schedule are 50, 40, 35 and less than or equal to 25 mg/m^2 in the normal, mild, moderate and severe HD groups, respectively.

	Dosage of S-1 (mg/m^2)					
Group	25	30	35	40	45	50
Normal	–	–	–	3* (0 DLT)	3 (0 DLT)	12† (2 DLTs)
Mild HD	–	–	–	6*† (0 DLT)	–	–
Moderate HD	–	–	8*† (1 DLT)	5 (2 DLTs)	–	–
Severe HD	3 (0 DLT)	6* (2 DLTs)	–	–	–	–

*: starting dose, †: maximal tolerated dose, HD: hepatic dysfunction, DLT: dose-limiting toxicity.

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Combination of platinum standard first front line chemotherapy and anti-idiotype 1E10/aluminum vaccine in patients with advanced non-small- cell lung cancer (NSCLC)

A. Macias[1], D. Toledo[1], E. Santiesteban[2], F. Aguirre[2], X. Popa[1], A. Vazquez[3], Z. Mazorra[1], T. Crombet[1], R. Perez[3]. *[1]Center of Molecular Immunology, Clinical Immunology, C. Havana, Cuba; [2]Jose Ramon Tabranes Hospital, Oncology Unit, Matanzas, Cuba; [3]Center of Molecular Immunology, Antibody Engineering, C. Havana, Cuba*

The combination of vaccines and chemotherapy holds promise for cancer therapy, but the effect of cytotoxic chemotherapy on vaccine-induced antitumor immunity is unknown.
1E10/aluminum is an anti-idiotype vaccine that mimics N-glycolylated gangliosides tumour antigens in humans.
An exploratory phase I study was conducted to assess the feasibility of combining 1E10/aluminum vaccine with the standard first line chemotherapy used in advanced NSCLC patients and determine the effect on 1E10-specific humoral immune responses.
Twenty patients with histological confirmed NSCLC stages IIIB/IV were treated with cisplatin/vinblastine as standard first front line therapy according the treatment established in the Oncology Therapeutic Guidelines (NCCN v3.2009). The vaccination schedule consisted in the administration of 1 mg of 1E10 by intradermic route. The first 5 doses were administered every 14 days concomitantly with the first line chemotherapy and the rest every 28 days beyond progression, until unacceptable toxicity or patients worsening performance status.
Humoral immune responses against 1E10 anti-idiotype and NeuGcGM3 antigen were measured by standard ELISA assays, and changes in lymphocyte cells subpopulations were measured by flow cytometry analyses (FACS).
The distribution of these patients by clinical stage at inclusion was: 8 in stage IIIB, 12 in stage IV. The combination (CT plus vaccine) responses were evaluated according the RECIST Criteria, and 19 patient achieved control disease. The 20 patients were included in an evaluation of survival (Kaplan Meier estimate), after a follow up of at least 10 months. Median survival has not been reached and the mean survival is 12.94 months. The combination was safe. Not serious adverse events (SAEs) were observed (CTC-NCI Criteria v 3.00).
All patients developed high antibody responses against 1E10 MAb during the vaccination schedule. IgM and IgG antibody response against NeuGcGM3 antigen was obtained, as in the standard not concomitant vaccination schedule used in other clinical trial protocols. Moreover, an early onset kinetics IgG isotype antibody response specifically for NeuGcGM3 was detected
The combination of 1E10/aluminum vaccine and systemic platinum chemotherapy has an acceptable safety profile. The data suggest that chemotherapy does not inhibit 1E10 vaccine-mediated immune response and provide further support for evaluating novel combinations of chemotherapy and 1E10 vaccine for NSCLC and other cancers.

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Phase I study of intra-tumoral injection of a newly developed enzyme-targeting radiosensitizer (KORTUC) containing hydrogen peroxide & sodium hyaluronate for unresectable and/or recurrent malignant neoplasms

Y. Ogawa[1], K. Kubota[1], H. Ue[1], K. Miyatake[1], M. Tadokoro[1], K. Tsuzuki[1], S. Yaogawa[1], S. Kariya[1], A. Nishioka[1], T. Sasaki[1]. *[1]Kochi Medical School, Radiology, Nankoku, Japan*

Background: Using a currently used linear accelerator, our intent was to inactivate peroxidase/catalase in tumor tissue by the application of hydrogen peroxide, which is degraded to produce oxygen, thus reoxygenizing the tumor tissue. In this way, we can convert radioresistant tumors into radiosensitive ones, based on our experimental results (Ogawa Y et al. Int J Mol Med 12: 453–458, 845–850, 2003, 14: 397–403, 2004). The purpose of this study was to evaluate safety and effectiveness of KORTUC for patients with unresectable and/or recurrent neoplasms.
Materials and Methods: Based on our clinical exepriences using KORTUC I (Ogawa Y et al. Oncol Rep 19: 1389–1394, 2008), we developed a new radiosensitizer containing hydrogen peroxide & sodium hyaluronate for intra-tumoral injection for various types of tumors which are not superficially exposed, and the method was named KORTUC II (Ogawa Y et al. Int J Oncol 34: 609–618, 2009, Raiother Oncol 90: S73, 2009). KORTUC II was approved by our local ethical committee for advanced skin cancer including malignant melanoma, bone/soft tissue malignant neoplasms, breast cancer, and metastatic lymph nodes. A maximum of 6 ml of the agent was injected into tumor tissue two times per week under ultrasonographic guidance, just prior to each administration of radiation therapy. The agent is composed of 0.5% hydrogen peroxide & 0.83% sodium hyaluronate, which is safe for injection, effectively preserving oxygen concentration in the tumor tissue for more than 24 hours following intra-tumoral injection of the agent (Tokuhiro S et al. Radiother Oncol 90: S73, 2009).
Results: Treatment was well tolerated, with a minimum of adverse effects. Fifty patients including 29 with unresectable and/or recurrent breast cancer, 8 with soft tissue neoplasms, 4 with cervical lymph nodes metastases, and 9 with another types of neoplasms were enrolled in the KORTUC II trial upon fully informed consent. 28 of the 50 patients (56%) showed a complete response (CR), and 12 (24%) showed a partial response (PR), and another 10 (20%) showed a no change (NC). Concering breast cancer, patients under 75 years old also undertook systemic chemotherapy (EC) prior to the KORTUC II treatment.
Conclusions: This new enzyme-targeting radiosensitization treatment named KORTUC II may be indicated for various types of locally advanced neoplasms, including soft tissue neoplasms and breast cancers. KORTUC II has great potential to become a viable noninvasive replacement for surgical procedures and a valuable radiosensitizer for low LET-radioresistant neoplasms.