S-8 [16:20~16:50]

Development of the 3rd Generation Anticancer Platinum Complex as New Drug

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Life Science Research Center of SK Chemicals has developed a 3rd-generation anticancer platinum drug for the first time in the nation's 100-year-old pharmaceutical industry. The Korea Food and Drug Administration (KFDA) approved the sale of "Sunpla" (code name : SKI 2053R, general name : Heptaplatin) on July 14, 1999 for the treatment of advance, metastatic gastric cancer. Cisplatin, the 1st-generation anticancer drug, which was developed by Bristol-Myers of the United States in 1976, is one of the most potent anticancer drugs and is a major component of combination chemotherapy for a variety of human cancers. However its clinical usefulness has frequently been limited not only by undesirable side effects such as severe renal toxicity, nausea, vomiting, ototoxicity, and neurotoxicity but also by the development of resistance. Carboplatin, the 2nd-generation anticancer platinum drug, which was also developed by Bristol-Myers in 1986, has modified the problems of the renal and gastrointestinal toxicities of cisplatin. Carboplatin, however, has no enhanced therapeutic efficacy over cisplatin and does not possess the property to overcome cross-resistance to cisplatin.

In an attempt to develop a new, more potent and less toxic anticancer platinum drug, we designed and synthesized a series of 2-substituted-4,5-bis(aminomethyl)-1,3-dioxolane platinum(II) complexes. Among them, *cis*-malonato[(4R,5R)-4,5-bis(aminomethyl)-2-isopropyl-1,3-dioxolane]platinum(II) (SKI 2053R) was selected for further development on the basis of its high *in vitro* and *in vivo* antitumor activity against a number of murine and human tumor cell lines including cisplatin-resistant L1210 leukemia, its low nephrotoxicity in mice, rats and, dogs and its sufficient solubility and stability in aqueous solution.

On the basis of these preclinical data, a phase I clinical trial of SKI 2053R was performed on 21 patients with malignant tumors to assess its maximum tolerated dose (MTD), toxic effects, pharmacokinetics, and antitumor activity at the Seoul National University Hospital. SKI 2053R was administered intravenously as 1-hour infusion on day 1 and in every four weeks after that. The starting dose of phase I study was 40 mg/m^2, and the dose of drug was increased up to 480 mg/m^2 using modified Fibonacci method. There was no significant toxicity with dosage up to 360 mg/m^2. At 480 mg/m^2, 2/3 patients developed grade 4 hepatotoxicity, grade 3 leukopenia, thrombocytopenia, grade 2 azotemia, and proteinuria. By these result, the initial dose of phase IIa clinical trial was recommended as 360 mg/m^2.

A phase IIa clinical trial was performed on 39 patients with advanced gastric adenocarcinoma that are unresectable or metastatic at the Seoul National University Hospital. Patients received SKI 2053R 360 mg/m^2 by 1-hour infusion on day 1, and courses repeated every 28 days. Thirty-five patients were evaluable for response and toxicity. Six patients achieved a major response (17%), which included 2 complete responses and 4 partial responses. Patients could tolerate the treatment without significant toxicity. No patient had grade 3 or 4 toxicity.

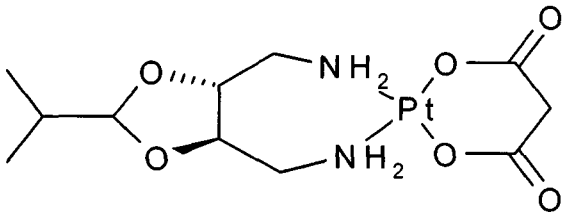
A phase IIb clinical trial of SKI 2053R plus 5-fluorouracil in patients with advanced gastric adenocarcinoma was performed at the eight university hospitals including Seoul National University Hospital. Patients received SKI 2053R 400 mg/m^2 by 1 hour infusion on day 1 and 5-fluorouracil 1,000 mg/m^2/day, 5-day infusion for 12-24 hours, and courses repeated every 3-4 weeks. Sixty-four patients were treated and 50 patients were evaluable for response.. Seventeen patients achieved partial responses (34%), and the median duration of response was 18+ weeks. The anticancer effect of this regimen is comparable to FAM regimen (5-fluorouracil plus adriamycin plus mitomycin C ; 30%) and FP regimen (5-fluorouracil plus cisplatin ; 37%). However, the observed toxicity of the former is quite lower than the latters.

On the basis of these clinical data, SKI 2053R has been approved by KFDA and

marketed in September, 1999. It took almost 10 years for the development of "Sunpla", and 8.1 billion won (about $ 6.7 million) was invested to the drug's research and development.

In our preclinical studies showed that prolonged continuous infusion (over 12-24 hours) of Sunpla was more effective than infusion for a short period (over 1-3 hours). Phase I and II clinical trials with continuous infusion using higher dose of Sunpla are being conducted. In addition, Sunpla is currently undergoing Phase III clinical study in gastric cancer, and Phase I & II studies in the hepatoma, head and neck cancer and lung cancer.

We published 22 scientific papers in international journals enrolled in SCI and received a number of awards based on our outstanding achievements.



Chemical structure of SKI 2053R (Heptaplatin, Sunpla^{TM})

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