Poster

[P26-8] P26-8: Oncologic drugs (4): Pharmacokinetics, TDM practice

Chair: Kohji Naora, Japan

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[P26-8-10] The relationship between hepatotoxicity and pazopanib trough plasma concentration in patients with renal cell carcinoma and soft tissue sarcoma

Takeshi Aoyama[1], Takako Karaki[2], Kazuyuki Ito[3], Keiichi Azuma[4], Koki Hashimoto[5], Ryota Furutani[6], Kazuyoshi Kawakami[7], Kenichi Suzuki[8], Kenji Nakano[9], Junichi Tomomatsu[10], Naoki Fukuda[11], Takeshi Yuasa[12], Erika Sugiyama[13], Hitoshi Sato[14], Shunji Takahashi[15], Toshihiro Hama[16] (1.The Cancer Institute Hospital, Japanese Foundation for Cancer Research, 2.The Cancer Institute Hospital, Japanese Foundation for Cancer Research, 3.The Cancer Institute Hospital, Japanese Foundation for Cancer Research, 4.The Cancer Institute Hospital, Japanese Foundation for Cancer Research, 5.The Cancer Institute Hospital, Japanese Foundation for Cancer Research, 6.The Cancer Institute Hospital, Japanese Foundation for Cancer Research, 7.The Cancer Institute Hospital, Japanese Foundation for Cancer Research, 8.The Cancer Institute Hospital, Japanese Foundation for Cancer Research, 9.The Cancer Institute Hospital, Japanese Foundation for Cancer Research, 10.The Cancer Institute Hospital, Japanese Foundation for Cancer Research, 11.The Cancer Institute Hospital, Japanese Foundation for Cancer Research, 12.The Cancer Institute Hospital, Japanese Foundation for Cancer Research, 13.Showa University, 14.Showa University, 15.The Cancer Institute Hospital, Japanese Foundation for Cancer Research, 16.The Cancer Institute Hospital, Japanese Foundation for Cancer Research)

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Background

Pazopanib is a tyrosine kinase inhibitor approved for the treatment of renal cell carcinoma (RCC) and soft tissue sarcoma. The most common adverse events are hypertension, diarrhea, fatigue, nausea, vomiting, and hepatotoxicity. In particular, hepatotoxicity causes treatment discontinuation. In the pivotal trial for soft tissue sarcoma patients, the Common Terminology Criteria for Adverse Events (CTCAE) grade 3/4 alanine-aminotransferase elevation was observed in 2.5 % (6/240) of the whole patients, with 1% (1/31) of the Japanese patient. However, in the phase 3 trial for RCC, the incidence was 10% (55/554) of the whole patients, with 24 % (7/29) of the Japanese patients. Although, the incidence of hepatotoxicity is reportedly higher especially in the Japanese RCC patients, the cause remain largely unknown, and the pharmacokinetic investigation has not been performed.

Methods

We analyzed plasma trough concentration of pazopanib in patients with RCC and soft tissue sarcoma. Patients' blood samples were collected on day 16 or later from pazopanib initiation. Trough concentrations of pazopanib was evaluated by high performance liquid chromatography photodiode array analysis.

Results

The mean plasma trough concentration of pazopanib was higher in the RCC patients than the soft tissue sarcoma patients (57.2 vs. 41.0 μg/mL, P <0.03). The incidence of dose reduction or treatment discontinuation were also higher in the RCC patients than soft tissue sarcoma patients (85.7 % vs. 9.1 %, P

<0.01). The main reason for dose reduction and treatment discontinuation was hepatotoxicity. Furthermore, trough concentration of pazopanib found to be correlated with the elevation of serum liver enzyme levels.

Conclusions

Pazopanib plasma trough concentration was higher in the patients with RCC than with soft tissue sarcoma, suggesting that the higher pazopanib exposure was associated with the incidence of hepatotoxicity.