IMPACT OF CYTIDINE DEAMINASE (CDA)-RELATED BIOMARKERS ON CLINICAL OUTCOMES OF GEMCITABINE-BASED CHEMOTHERAPIES

Nahoko Kaniwa¹ and Hideki Ueno²
¹National Institute of Health Sciences, Setagaya-ku, Tokyo 158-8501, Japan and ²National Cancer Center Hospital, Chuo-ku, Tokyo 104-0045, Japan

Gemcitabine (2',2'-difluorodeoxyctydine) is a nucleoside anti-cancer drug that has a broad spectrum of antitumor activity against various solid tumors such as pancreatic and non-small cell lung cancers. Gemcitabine is phosphorylated first by deoxycytidine kinase (dCK) and subsequently by UMP-CMP kinase and nucleoside diphosphate kinase to its active forms, gemcitabine diphosphate and triphosphate. Gemcitabine is rapidly metabolized by cytidine deaminase (CDA) to its inactive metabolite, 2',2'-difluorodeoxuryridine (dFdU), and more than 90% of administered gemcitabine is recovered as dFdU in the urine. Therefore, CDA activity may be a key factor affecting safety and efficacy in gemcitabine-based chemotherapies. Two nonsynonymous single nucleotide polymorphisms (SNPs) of CDA, 79A>C (Lys27Gln) and 208G>A (Ala70Thr), have been reported to show altered deamination activity in vitro or in vivo.

Recently, we have performed an association study of CDA related biomarkers with pharmacokinetics and clinical outcomes of gemcitabine to provide basic information for personalized gemcitabine-based chemotherapies, in which 256 Japanese cancer patients participated.¹ In our study, CDA*2 (79C) did not show clear effects on pharmacokinetic parameters of gemcitabine and plasma CDA activity. On the contrary, CDA*3 (208A)-dependent decreases in gemcitabine clearance and plasma CDA activities were clearly observed (Table 1). As shown in Table 2, the incidence of grade 4 neutropenia was significantly high in patients carrying *3 in the combined chemotherapy group. A patient with homozygous *3 showed five times higher AUC value than the average value of patients without *3 and encountered life-threatening toxicities including grade 4 neutropenia and grade 3 anemia.² We concluded that extremely high exposure to gemcitabine due to the decreased deamination activity caused the life-threatening severe toxicities in this patient. In spite of increased incidence of grade 4 neutropenia in the combined chemotherapies, heterozygous *3 was significantly associated with prolonged overall survival time in the monotherapy of advanced pancreatic cancer patients as shown in Table 1. The lower plasma CDA activity and dFdU levels were also significantly associated with longer overall survival time.

Gemcitabine dose reduction will be necessary for patients carrying homozygous *3. However, the dose reduction for patients carrying heterozygous *3 is not recommended, at least in the monotherapy, because they may have good clinical outcomes.

| Table 1 Effects of CDA*3 on median pharmacokinetic parameters, plasma CDA activities and overall survivals (MST) |
|----------|----------|----------|----------|----------|----------|
| Diploftype | n*        | AUC (hr·mg/L) | CL (L/hr/m²) | n*        | Plasma CDA activity (Unit) | n* | MST (Month) |
| non*3/non*3 | 231 | 9.86 | 101.53 | 102 | 6.6 | 67 (2)* | 5.4 |
| non*3/*3 | 17 | 12.8 | 77.93 | 17 | 3.14 | 6 (1)* | 17.3 |
| *3/*3 | 1 | 52.86 | 18.92 | 1 | 0.74 | |
| p-value | Kruskal- | Wallis test | <0.0001 | <0.0001 | Kruskal- | Wallis test | <0.0001 | Kaplan- | Meier test | 0.031 |

* Patients receiving monotherapy and combined chemotherapies were included.
* Patients with pancreatic cancer at stage IV receiving monotherapy were included.
* Number in the parenthesis shows the number of patients alive at the last follow-up

| Table 2 Effect of CDA*3 on the incidence of grade 4 neutropenia |
|----------|----------|----------|
| Diploftype | Monotherapy | Combined chemotherapies |
| n | Incidence | n | Incidence |
| non*3/non*3 | 167 | 0.40 | 53 | 0.09 |
| non*3/*3 | 10 | 0.60 | 6 | 0.50 |
| *3/*3 | 1 | 1.00 |
| p value by Fisher's exact test | 0.205 | 0.0072 |

* Two groups with and without *3 were compared.