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Letter to the Editor

Can grapefruit juice decrease the cost of imatinib for the treatment of chronic myelogenous leukemia?

Imatinib, a selective inhibitor of Bcr-Abl tyrosine kinase, has dramatically changed the treatment of chronic myelogenous leukemia (CML). The estimated 6-year overall survival is 95% when only CML-related deaths were considered [1]. However, imatinib is a very expensive agent (standard daily dose (400 mg) costs 12,512 yen = 140 US$ in Japan). Therefore, in developing countries, allogeneic hematopoietic stem cell transplantation is still performed as a first-line treatment for CML, since many patients are unable to afford the continuing treatment with imatinib.

Grapefruit juice has been found to increase blood concentrations of several clinically important drugs such as nifedipine, cyclosporine, midazolam and triazolam by reducing the level of CYP3A4. Imatinib is also metabolized by CYP3A4. Therefore, the plasma concentration of imatinib may be increased when imatinib is coadministered with drugs that inhibit CYP3A4 activity [2]. Ingestion of grapefruit juice with imatinib may also increase the concentration of imatinib. However the interaction between imatinib and grapefruit juice has not been analyzed. If the concentration of imatinib is stably increased by grapefruit juice, the dose and cost of imatinib can be decreased. In this study, therefore, we investigated the effect of grapefruit juice on imatinib pharmacokinetics in CML patients.

Patients with CML in chronic phase, who had been taking imatinib at 400 mg daily for more than 6 months without significant adverse events (less than grade 2 adverse events evaluated by CTCAE v3.0), were included. Patients who were taking medications which may interfere with imatinib metabolism such as azole antifungal agents, rifampicin, St. John's wort and anticonvulstant agents [2], were excluded. This prospective study was approved by the Institutional Review Board of Saitama Medical Center, Jichi Medical University and Saitama City Hospital. Each patient provided their written informed consent to be enrolled in the study (clinical trial registration number: UMIN-CTR R000003274).

Patients recorded the following items in a diary; daily imatinib ingestion time for 1 week until the blood test, other prescribed medicine or over-the-counter drug if they took during the study period and if any, newly developed symptoms. On the first blood sampling day, patients came to our center without ingesting imatinib and were obtained the blood samples approximately 24 h after the last imatinib ingestion for measuring the trough concentration. Then, patients took imatinib with water as usual. Three hours later, blood sampling was performed again, which was regarded as the sample for the peak concentration of imatinib based on the pharmacokinetic data which showed that time to reach peak concentration in steady state was 3.3 ± 1.1 h [2]. The second blood sampling day, when patients ingested imatinib with grapefruit juice (Tropicana® 100% juice 250 ml, Kirin Tropicana, 100 yen = 1.1 US$ per pack), was scheduled between one and three months after the first one. Seven packs of grapefruit juice were sent to the patients in advance. Patients took imatinib with grapefruit juice for 1 week until the second blood sampling day. The patients were obtained blood samples in the same way for trough and peak concentrations of imatinib. Imatinib concentration was measured by liquid chromatography/tandem mass spectrometry in BML (Tokyo, Japan).

We planned to enroll ten patients, but the study was terminated early when we obtained the results of the first 4 patients (all males) from November 2009 through July 2010. Patient characteristics and imatinib pharmacokinetics are shown in Table 1. The median age was 44 years (range, 41–62 years old) and the median weight was 69 kg (range, 63–74 kg). All patients successfully completed the study and there were no serious adverse events. Median trough concentration of imatinib with grapefruit juice (C(GF)min) was 1102 ng/ml (range, 772–1450 ng/ml), which was not different from the trough concentration with water (C(W)min) (median, 1080 ng/ml; range, 1060–1360 ng/ml; $P = 0.715$). Median peak concentration of imatinib with grapefruit juice (C(GF)max) was 2455 ng/ml (range, 1870–2750 ng/ml), which was not also different from the peak concentration with water (C(W)max) (median, 2495 ng/ml; range, 2380–2680 ng/ml; $P = 0.715$).

We expected the imatinib concentration to be increased when it was taken with grapefruit juice due to the inhibition of CYP3A4, which might be used as imatinib sparing agent. We selected Tropicana® grapefruit juice because inhibition of CYP3A4 was reported to be the strongest among various kinds of grapefruit juices [3]. The results of this study, however, showed no significant effect of grapefruit juice on imatinib pharmacokinetics. A plausible explanation of this is that grapefruit juice mainly inhibit gut CYP3A4 but has little influence on hepatic CYP3A4 at least by the amount in this study. In fact, drugs which have been reported to have interaction with grapefruit juice are orally administered and undergo significant pre-systemic extraction by enteric CYP3A4. For example, grapefruit juice had no effect on pharmacokinetic parameters of intravenous cyclosporine. After oral administration of cyclosporine, however, blood concentration was increased by 40% [4]. Because the absolute bioavailability of imatinib is nearly 100% [2], inhibition of gut CYP3A4 could not increase imatinib absorption. On the other hand, Dutreix et al. reported that ketoconazole, which was also a potent CYP3A4 inhibitor, increased the peak imatinib concentration by 26% [5]. This was probably because ketoconazole had significant influence on hepatic CYP3A4 and inhibited drug metabolism.

In conclusion, 250 ml per day of grapefruit juice had no significant effect on imatinib pharmacokinetics in CML patients. In other words, ingestion of such amount of grapefruit juice might be safe in patients taking imatinib.

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Table 1
Patient characteristics and imatinib pharmacokinetics.

Patient	Age (year)	Sex	Weight (kg)	Imatinib concentration with water (ng/ml)		Imatinib concentration with GFJ (ng/ml)	
				C(W) min	*C*(W) max	*C*(G) min	*C*(G) max
1	62	M	64	1060	2680	953	1870
2	40	M	74	1070	2390	772	2640
3	41	M	63	1090	2380	1450	2750
4	46	M	74	1360	2600	1250	2270

Abbreviations: C_{min}, trough concentration; C_{max}, peak concentration; GFJ; grapefruit juice.

Conflict of interest

The authors declare no conflict of interest.

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