

**Regular Article****Prediction of Therapeutic Effect of Rasburicase on Hyperuricemia Associated with Chemotherapy Based on Theoretical Model**Koji Kimura,\*<sup>a</sup> Naomi Kanehira,<sup>a</sup> Risa Takayanagi,<sup>a</sup> Hideto Minohara,<sup>b</sup> Masato Homma,<sup>c</sup> and Yasuhiko Yamada<sup>a</sup>

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Received September 9, 2015; accepted January 16, 2016

**Rasburicase has a strong and fast effect for reducing blood levels of uric acid. However, there have been no reports of theoretical analysis for the rational dose and interval of administration. Thus we constructed a pharmacokinetic and pharmacodynamic model to determine changes in uric acid level after rasburicase administration at various doses and regimens. The time courses of uric acid level predicted using our model were in good agreement with observed data, indicating adequate performance for our model. The therapeutic effects after a single infusion at various rates of generation of uric acid were predicted. The maximum effect was not a large difference, in spite of the generation rate. Then, the therapeutic effects of repeated administrations were predicted. The effect did not change when rasburicase was administered at more than the usual dose. Besides, as the administration interval increased, the difference between minimum and maximum level of uric acid became greater. However, in all doses and regimens, adequate therapeutic effects were obtained. In conclusion, the model was found useful for predicting therapeutic effect of rasburicase and individually determining rational dosage regimen of rasburicase.**

**Key words** rasburicase; pharmacokinetic–pharmacodynamic model; tumor lysis syndrome; hyperuricemia; predicting therapeutic effect

Tumor lysis syndrome (TLS) occurs when a tumor rapidly lyses from the effects of chemotherapy and has been frequently reported to occur after the initial chemotherapy treatment,<sup>1,2)</sup> with an incidence of about 5% reported in patients treated for a hematopoietic organ tumor.<sup>3)</sup> Nucleic acid released in a large amount due to TLS is subsequently decomposed to a large amount of uric acid, which induces crystallization, leading to renal disorder.

Allopurinol, a uric acid production-inhibitory agent, is orally administered for prevention and treatment of hyperuricemia caused by TLS. However, several problems with that treatment have been noted. Uric acid present prior to chemotherapy cannot be decomposed by allopurinol administration,<sup>4)</sup> which is generally performed 2–3 d prior to the start of chemotherapy.<sup>5)</sup> Also, obstructive uropathy is likely to develop, as xanthine crystals are formed from xanthine accumulation and their decomposition to uric acid by xanthine oxidase is inhibited by the action of allopurinol.<sup>4,6)</sup> Dose reduction of inhibitors of purine synthesis, such as 6-mercaptopurine and azathioprine, is required when used in combination with allopurinol.<sup>4,7)</sup> Furthermore, it is difficult to administer allopurinol to patients who have difficulty with oral administration.

Rasburicase is a recombinant uric acid oxidase originally produced by introducing an *Aspergillus flavus*-derived uric acid oxidase gene to a *Saccharomyces cerevisiae* strain.<sup>8)</sup> For its pharmacological action, rasburicase reduces the level of uric acid, as it oxidizes and decomposes uric acid to allantoin.<sup>9)</sup> Rasburicase has a stronger and faster effect for reducing uric acid as compared to allopurinol. Moreover, since it is given as an injection, rasburicase can be administered to patients who have difficulty with oral administration. Fur-

thermore, no dose reduction is necessary even for those with reduced renal function.<sup>10)</sup>

In Japan, rasburicase is normally administered intravenously once a day at a dose of 0.20 mg/kg for a maximum of 7 d based on clinical trials, though a single infusion of 0.15 mg/kg was reported to be effective.<sup>11,12)</sup> The package insert recommends that administration should be limited to the minimum time required, while taking into consideration inter-individual variability in efficacy. There have been no reports presented of theoretical analysis of the minimum required duration of administration, thus it is considered important to perform theoretical evaluations of dose, regimen, and the effects of rasburicase. In the present study, we constructed a pharmacokinetic and pharmacodynamic model to determine the time courses of uric acid level after rasburicase administration, for examination of the effects of the drug in a theoretical manner with a variety of doses and regimens.

**MATERIALS AND METHODS**

**Pharmacokinetic and Pharmacodynamic Data for Analysis** Data regarding the time course of serum concentration following a single infusion of rasburicase at 0.15 and 0.20 mg/kg for Japanese patients who participated in a phase II clinical study were obtained from the Japanese package insert.<sup>13)</sup> Clinical response was evaluated by uric acid level, and the data sources used for analysis were Japanese leukemia and malignant lymphoma patients who participated in the phase II clinical study.<sup>13)</sup> We also obtained data from that study for values representing uric acid level before and at 4, 8, 24, 48, 72, 96, 104, 120, and 168 h after administration (0.15 or 0.20 mg/

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kg, once a day) of rasburicase for Japanese patients. At this point, we converted the graphic data to numerical value by measuring the graph directly.

**Analysis of Time Courses of Serum Concentration of Rasburicase** Previously reported findings obtained from the package insert showed that the clearance of rasburicase is unchanged by increasing the dose (range 0.05 to 0.20 mg/kg), while linear relationships can be observed among dose administered, maximum serum concentration, and area under the curve.

The serum concentration data were obtained from a 0.5 h infusion. Therefore, in the present study, the time courses of serum concentrations after a single infusion of rasburicase were analyzed using the following Eq. 1 during infusion ( $t \leq 0.5$ ) and Eq. 2 after infusion ( $t > 0.5$ ).

$$C_{\text{Ras}} = \frac{R}{Vd \cdot k_e} \cdot (1 - e^{-k_e \cdot t}) \quad (t \leq 0.5) \quad (1)$$

$$C_{\text{Ras}} = \frac{R}{Vd \cdot k_e} \cdot (1 - e^{-0.5k_e}) \cdot e^{-k_e(t-0.5)} \quad (t > 0.5) \quad (2)$$

where  $C_{\text{Ras}}$  ( $\mu\text{g/mL}$ ),  $R$  (mg/h),  $Vd$  (L), and  $k_e$  ( $\text{h}^{-1}$ ) represent the serum concentration of rasburicase, infusion rate of rasburicase, volume of distribution, and elimination rate constant, respectively.

The  $R$  values were analyzed using the following Eq. 3.

$$R = \frac{D \cdot Wt}{T} \quad (3)$$

where  $D$  (mg/kg),  $Wt$  (kg), and  $T$  (h) represent dose (0.20 or 0.15 mg/kg), weight, and infusion time (0.5 h), respectively. At this point, previously reported median weight values (0.15 mg/kg: 57.1 kg, 0.20 mg/kg: 54.5 kg) in the phase II clinical study were adopted.<sup>13</sup> Then, we calculated the  $R$  values (0.15 mg/kg: 17.1 mg/h, 0.20 mg/kg: 21.8 mg/h).

To estimate the pharmacokinetic parameters of  $Vd$  and  $k_e$  in patients receiving the drug, the serum concentration of rasburicase after a single infusion at a dose of 0.15 or 0.20 mg/kg was simultaneously fitted to Eqs. 1 and 2 using the nonlinear least squares method. The nonlinear least squares program MLAB (Civilized Software, Inc.) was used for analysis.

**Analysis of Clinical Response to Rasburicase Using a Pharmacokinetic and Pharmacodynamic Model** A model derived from the pharmacokinetic profile of rasburicase and turnover rate of uric acid is shown in Fig. 1. With this model, we assumed that rasburicase oxidizes and decomposes uric acid to allantoin. In addition, rasburicase becomes free after generating allantoin and is used again in the reaction.

Disappearance from the body of rasburicase occurs by  $k_e$ . Uric acid is generated at a rate constant of  $k_s$  ( $\text{mg} \cdot \text{dL}^{-1} \cdot \text{h}^{-1}$ ) and eliminated at a rate constant of  $k_T$  ( $\text{h}^{-1}$ ), then is oxidized by rasburicase at a reaction rate constant of  $k_{ox}$  ( $\text{mL} \cdot \mu\text{g}^{-1} \cdot \text{h}^{-1}$ ) and decomposed to allantoin. Thus, the concentration of the uric acid of  $C_U$  (mg/dL) was represented as follows:

$$\frac{dC_U}{dt} = -k_{ox} \cdot C_U \cdot C_{\text{Ras}} - k_T \cdot C_U + k_s \quad (4)$$

Furthermore, the value for  $C_U$  in the absence of rasburicase [ $C_U(0)$ ] was expressed using the following Eq. 5:

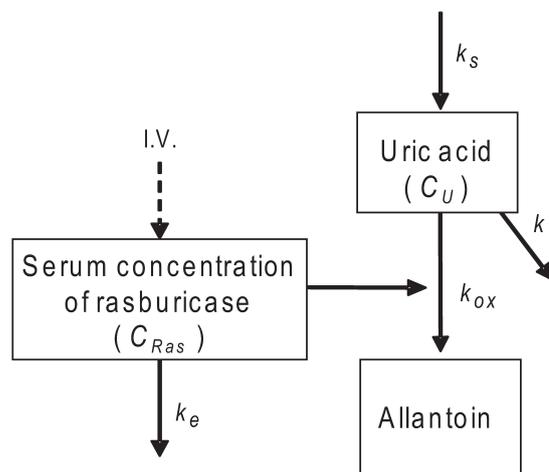


Fig. 1. Pharmacokinetic and Pharmacodynamic Model for Oxidative Degradation and Metabolism of Rasburicase

$$C_U(0) = k_s / k_T \quad (5)$$

At this point, previously reported  $C_U(0)$  values (0.15 mg/kg: 5.18 mg/dL, 0.20 mg/kg: 5.56 mg/dL) in the phase II clinical study were adopted. To estimate the values for  $k_{ox}$  and  $k_T$ , we simultaneously fitted  $C_U$  data from patients repeatedly administered rasburicase for 5 d at a dose of 0.15 or 0.20 mg/kg to Eqs. 1 to 5.

**Predictor of Therapeutic Effects of Rasburicase** Based on our analytical results, uric acid levels over time were predicted to investigate the appropriate administration of rasburicase in consideration of individual differences. Seven and half milligram per deciliter or lower uric acid levels were considered to be a marker for therapeutic effect, as it has been reported that an additional dose is necessary when the level exceeds that value.<sup>11</sup> In the first prediction, we considered patients who had a  $C_U(0)$  value of 7.5, 10, 12.5, or 15 mg/dL, and were given a single infusion of rasburicase at 0.20 mg/kg. In the second, the patients had a  $C_U(0)$  value of 7.5 or 15 mg/dL, and were given rasburicase daily during a 5-d administration at a dose of 1.5, 3.0, 4.5, 6.0, 7.5, 11, or 15 mg. These doses were the quantity of rasburicase with a RASURITEK<sup>®</sup> i.v. injection of 1.5 mg/vial (1, 2, 3, or 4 vials), that of 7.5 mg/vial (1 or 2 vials), or the usual dose (0.20 mg/kg) for a patient weighing 55.3 kg (median weight of all patients in the phase II clinical study). For the third prediction, the patients had a  $C_U(0)$  value of 7.5 or 15 mg/dL and were given rasburicase daily, every 2nd day, or every 3rd day during a 5-d administration at a dose of 0.20 mg/kg.

For these predictions, we considered that the  $k_i$  value obtained in the above mentioned analyses did not change, and that was calculated by using  $k_i$ ,  $C_U(0)$ , and Eq. 5. In addition, we assumed that the calculated  $k_s$  value was also maintained.

## RESULTS

**Analysis of Time Courses of Serum Concentrations of Rasburicase** The time courses of serum concentrations of rasburicase following a single infusion at a dose of 0.15 or 0.20 mg/kg for patients with leukemia or malignant lymphoma, along with fitted curves based on the nonlinear least squares method are shown in Fig. 2. The fitted curves were

well matched to observed data. The estimated  $Vd$  (L) value ( $\pm$ standard deviation (S.D.)) was 2.2 ( $\pm$ 0.018) and the  $k_e$  ( $h^{-1}$ ) value ( $\pm$ S.D.) was 0.066 ( $\pm$ 0.0014).

**Analysis of Clinical Response to Rasburicase Using a Pharmacokinetic and Pharmacodynamic Model** Time courses of uric acid level following repeated administrations of rasburicase as well as fitted curves based on the simultane-

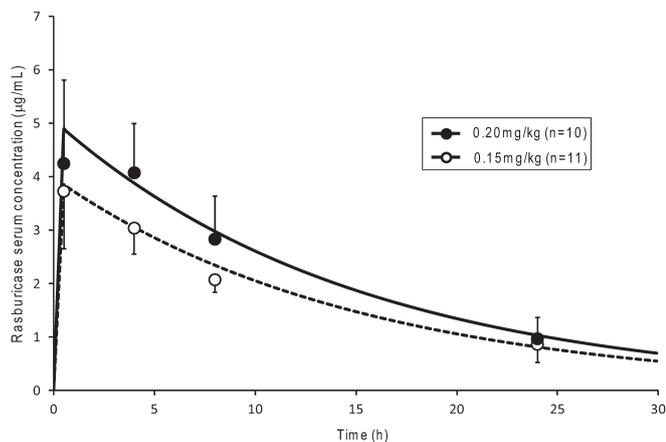


Fig. 2. Time Courses of Serum Concentrations of Rasburicase Following a Single Infusion at a Dose of 0.15 or 0.20 mg/kg for Japanese Patients

Symbols represent actual data (mean $\pm$ S.D.).<sup>13)</sup> The lines shown are fitted curves simultaneously calculated using the nonlinear least squares method.

ous nonlinear least squares method are shown in Fig. 3. The fitted curves were well matched to observed data.

The estimated  $k_{ox}$  ( $mL \cdot \mu g^{-1} \cdot h^{-1}$ ) value ( $\pm$ S.D.) was 0.193 ( $\pm$ 0.012) and the  $k_T$  ( $h^{-1}$ ) was 0.0139 ( $\pm$ 0.0008). Then, the  $k_s$  ( $mg \cdot dL^{-1} \cdot h^{-1}$ ) values calculated from Eq. 5 were 0.0720 (0.15 mg/kg) and 0.0773 (0.20 mg/kg).

**Prediction of Therapeutic Effects of Rasburicase** By using the obtained pharmacokinetic and pharmacodynamic

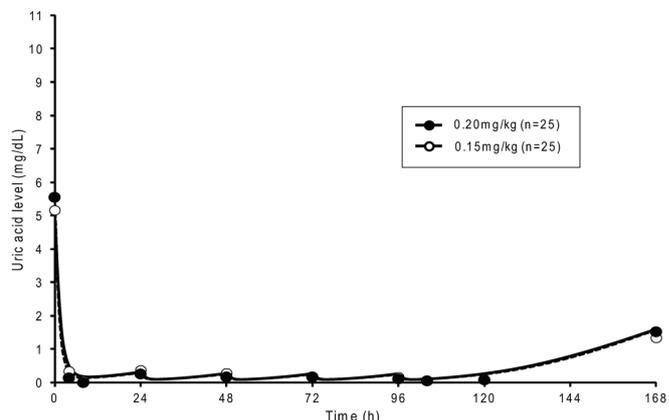


Fig. 3. Time Courses of Uric Acid Level (mg/dL) after Repeated Administrations of Rasburicase for Japanese Patients

Symbols represent actual data (mean).<sup>13)</sup> The lines shown are fitted curves simultaneously calculated using the nonlinear least squares method.

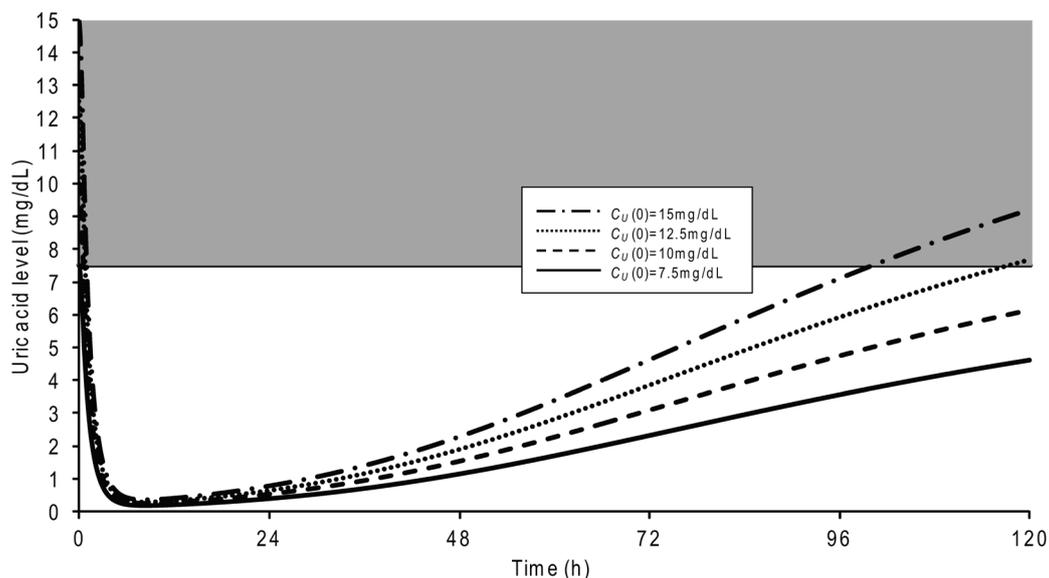


Fig. 4. Prediction of Relationship between Uric Acid Level and Time after a Single Infusion of Rasburicase in Patients Who Had a  $C_U(0)$  Level of 7.5, 10, 12.5, or 15 mg/dL

Gray area indicates the need for a second dose.

Table 1. Parameters after a Single Infusion of Rasburicase in Patients with Various  $C_U(0)$  Values

$C_U(0)$ (mg/dL)	$k_s$ ( $mg \cdot dL^{-1} \cdot h^{-1}$ )	$E_{max}$ ( $mg \cdot dL^{-1}$ )	$T_{E_{max}}$ (h)	Time to additional dosage (h) (Time to $E_{max} \geq 7.5$ mg/dL)
7.5	0.10	0.18	8	582
10	0.14	0.24	8	153
12.5	0.17	0.30	8	117
15	0.21	0.36	8	100

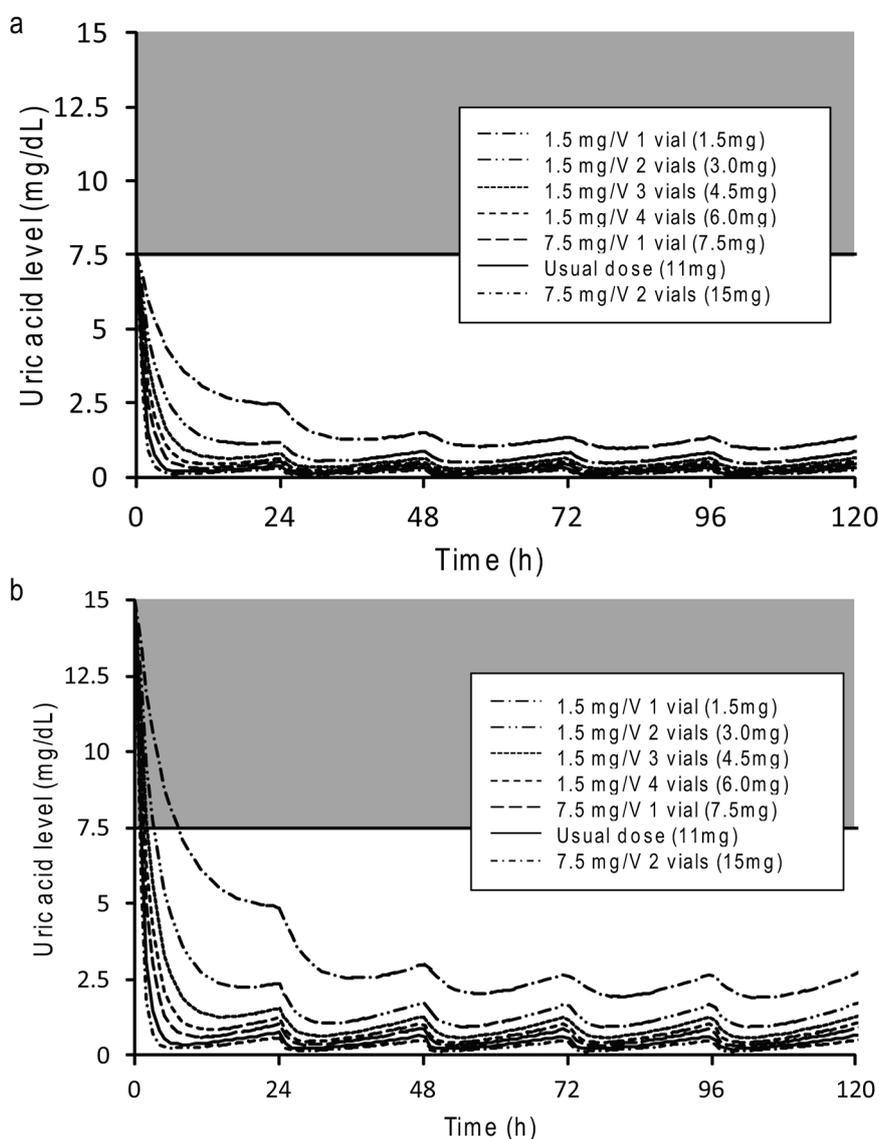


Fig. 5. Prediction of Relationship between Uric Acid Level and Time after Repeated Administrations at the Tested Doses of 1.5, 3.0, 4.5, 6.0, 7.5, 11, or 15 mg in Patients Who Had a  $C_U(0)$  Value of 7.5 mg/dL (a) or 15 mg/dL (b)

Gray area indicates the need for a second dose.

parameters, the therapeutic effects of rasburicase were predicted. First, the therapeutic effects of a single infusion of rasburicase in patients with  $C_U(0)$  values of 7.5, 10, 12.5, or 15 mg/dL were predicted. At this point, the  $k_s$  value of those patients was 0.10, 0.14, 0.17, or 0.21  $\text{mg} \cdot \text{dL}^{-1} \cdot \text{h}^{-1}$ , respectively. The maximum therapeutic effect expressed by the minimum level of uric acid ( $E_{\text{max}}$ ) was 0.18–0.36 mg/dL, which was not a large difference. Furthermore, the time required for uric acid to reach a minimum level ( $T_{E_{\text{max}}}$ ) was 8 h. Meanwhile, the time until an additional administration was necessary (blood level greater than 7.5 mg/dL) were 582 h [ $C_U(0)$ : 7.5 mg/dL], 153 h [ $C_U(0)$ : 10 mg/dL], 117 h [ $C_U(0)$ : 12.5 mg/dL], and 100 h [ $C_U(0)$ : 15 mg/dL] (Fig. 4, Table 1).

Second, the therapeutic effects of repeated administrations of rasburicase at a dose of 1.5, 3.0, 4.5, 6.0, 7.5, 11, or 15 mg in patients weighing 55.3 kg with a  $C_U(0)$  value of 7.5 or 15 mg/dL were predicted. There was no difference when rasburicase was administered at more than the usual dose, in spite of individual differences for rate of generation of uric acid. On

the other hand, the effect of rasburicase became weaker as the dose was lowered. However, with all of the predictions, the  $C_U$  value was reduced sufficiently (Fig. 5).

Third, we examined the therapeutic effects of rasburicase when repeatedly administered with 3 different regimens at a dose of 0.20 mg/kg. Our results showed that as the administration interval increased, the difference between minimum and maximum level of uric acid from 24 to 120 h after the initial dose ( $E_{\text{range}}$ ) became greater. Notably, the minimum uric acid level ranged from 0.11 to 0.16 mg/dL in patients who had a  $C_U(0)$  value of 7.5 and 0.22 to 0.32 mg/dL in those with a  $C_U(0)$  value of 15 mg/dL, which were not significant differences. On the other hand, the maximum uric acid level varied greatly from 0.38 to 2.3 mg/dL in patients who had a  $C_U(0)$  level of 7.5 and from 0.76 to 4.6 mg/dL in those with a  $C_U(0)$  level of 15 mg/dL. However, in all predictions, the uric acid level dropped below 1 mg/dL after each administration and never exceeded 7.5 mg/dL (Fig. 6).

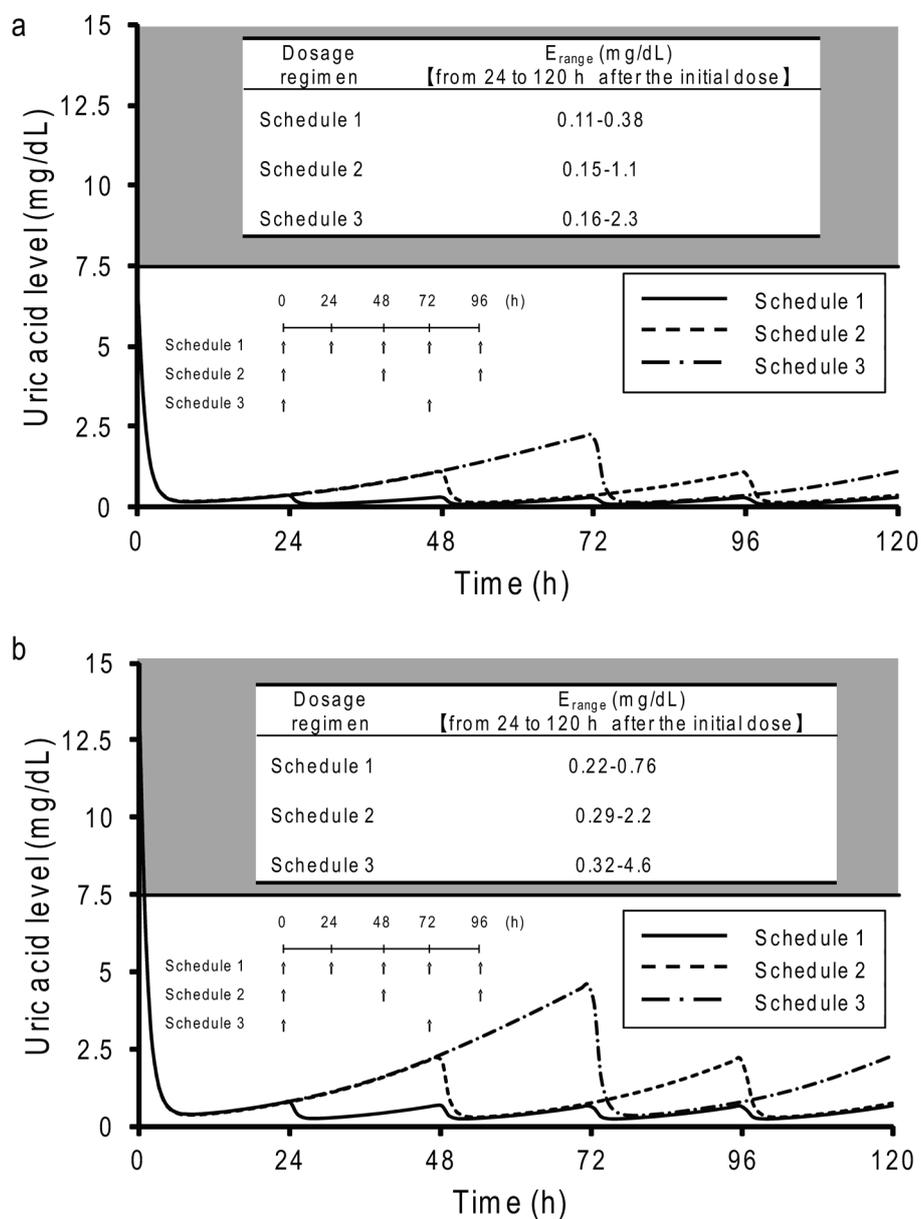


Fig. 6. Prediction of Relationship between Uric Acid Level and Time at the Tested Intervals, and Differences between Minimum and Maximum Level of Uric Acid from 24 to 120h after Initial Dose of Rasburicase ( $E_{range}$ ) in Patients Who Had a  $C_U(0)$  Value of 7.5 mg/dL (a) or 15 mg/dL (b)

Gray area indicates the need for a second dose.

## DISCUSSION

Rasburicase, used as a therapeutic agent for hyperuricemia associated with chemotherapy, is administered intravenously at 0.20 mg/kg once a day for a maximum of 7 d in Japan. However, a single infusion of 0.15 mg/kg has been reported to be effective,<sup>11,12)</sup> thus we considered it important to perform theoretical evaluations of dose and regimen. We collected the data which are the serum concentration and uric acid level after administration of rasburicase for Japanese patients. Then, we constructed a pharmacokinetic and pharmacodynamic model to determine changes in uric acid level over time after rasburicase administration for Japanese patients, and also examined the effects of various doses and regimens. The time courses of uric acid level predicted with our model were in good agreement with observed data,<sup>13)</sup> indicating adequate performance

for our model. We also obtained the following results.

First, the therapeutic effects of rasburicase when administered to patients with a  $C_U(0)$  value of 7.5, 10, 12.5, or 15 mg/dL were predicted (Fig. 4). At this point, the  $C_U(0)$  values exceeding 7.5 mg/dL were reported as 29 of 80 patients in the previous report.<sup>11)</sup> Then, we estimated the  $C_U(0)$  values which were raised by 2.5 mg/dL progressively to 15 mg/dL of the double of 7.5 mg/dL so as to investigate the therapeutic effects of rasburicase when administered to patients with different  $C_U(0)$  values. The prediction resulted in an  $E_{max}$  value range of 0.18–0.36 mg/dL, which were not significantly different. In all cases, the  $T_{E_{max}}$  was 8 h, while the time until an additional administration was necessary ( $C_U$ : exceeding 7.5 mg/dL) were 582 h [ $C_U(0)$ : 7.5 mg/dL], 153 h [ $C_U(0)$ : 10 mg/dL], 117 h [ $C_U(0)$ : 12.5 mg/dL], and 100 h [ $C_U(0)$ : 15 mg/dL]. Therefore, it is suggested that similar clinical responses are provided regardless

of the rate of generation of uric acid immediately following an administration of rasburicase. Furthermore, these results suggested that the inter-individual variability in clinical response increased over time, because of the difference in rate of generation of uric acid.

We considered that the uric acid level elevated along with drug elimination, as  $k_s$  is thought to maintain the blood level of  $C_U(0)$ . On the basis of the  $k_e$  value, the half-life of rasburicase was calculated to be about 10.5 h. Thus, in patients with a  $C_U(0)$  level of 15 mg/dL, the blood level of rasburicase at 52.5 h after infusion drops to about 3% of the level just following the initial infusion and uric acid to 2.7 mg/dL, indicating that 47 h is needed until the uric acid level reaches 7.5 mg/dL. Accordingly, we concluded that some time is needed to recover once uric acid drops to a level of 7.5 mg/dL even after elimination of rasburicase, and that recovery time is increased with a lower  $C_U(0)$  value and higher dosage.

Second, the therapeutic effects of repeated administrations of rasburicase at a dose of 1.5, 3.0, 4.5, 6.0, 7.5, 11, or 15 mg in patients with a  $C_U(0)$  value of 7.5 or 15 mg/dL were predicted. Our results suggested that the effect did not change when rasburicase was administered at more than the usual dose, while it becomes weaker at lower doses. However, the clinical significance of an immediate reduction of  $C_U$  was unidentified at the time of approval of rasburicase. Clinically significant TLS can occur in a spontaneous manner, though it is most often seen at 48–72 h after initiation of chemotherapy.<sup>14,15</sup> It is necessary for the level of uric acid to decrease to adequate level during that period. In this prediction,  $C_U$  was reduced with all doses and a sufficient effect was obtained, in spite of individual differences for the rate of generation of uric acid.

Finally, we predicted the therapeutic effects of a dose of 0.20 mg/kg with repeated administrations at 3 different regimens (Fig. 6). Our findings suggested that the  $E_{\text{range}}$  increased when the interval was increased for up to 120 h after administration. Notably, the minimum uric acid level ranged from 0.11 to 0.16 mg/dL in patients who had a  $C_U(0)$  value of 7.5 and 0.22 to 0.32 mg/dL in those with a  $C_U(0)$  value of 15 mg/dL, which were not significantly different. On the other hand, the maximum varied greatly from 0.38 to 2.3 mg/dL in patients who had a  $C_U(0)$  value of 7.5 and from 0.76 to 4.6 mg/dL those with a  $C_U(0)$  value of 15 mg/dL. However, in all cases, the level of uric acid dropped below 1 mg/dL after each administration and never exceeded 7.5 mg/dL (Fig. 6). Thus, we considered that the response rate of uric acid ( $k_s \cdot C_U \cdot C_{\text{Ras}}$ ) is much higher than the rate of generation of uric acid rate after administration of rasburicase.

At this point, it was considered that the values of pharmacokinetic parameters ( $Vd$  and  $t_{1/2}$ ) were valid because the values of  $C_{\text{max}}$ ,  $AUC$  and accumulation index of rasburicase, which were calculated by using these parameters, were comparable with the actual values (data not shown).

Though our study did not consider the inter/intrasubject variability of rasburicase, our results suggested that clinical efficacy is affected by dose and regimen of rasburicase rather than rate of generation of uric acid. Therefore, even if that generation rate changes during chemotherapy, the clinical efficacy of rasburicase is not largely affected. Though the number of patients in Fig. 2 ( $n=21$ ) and Fig. 3 ( $n=50$ ) was different, these data were obtained from the same phase II clinical study. In addition, it was confirmed that the results of

the pharmacokinetic study ( $n=21$ ) of rasburicase were comparable with those of the clinical study in non-Japanese patients. Therefore, we considered that it was valid to analyze the time courses of uric acid level (Fig. 3) by using pharmacokinetic parameters provided by Fig. 2.

As for applying our findings to clinical practice, the clinical efficacy of rasburicase in individual patients can be predicted by determining the  $C_U(0)$  value, and then using the model and parameters presented in this study. By monitoring  $C_U$  and administering rasburicase based on this model, it would be possible to reduce the dose and to increase the administration interval of rasburicase. Then, the financial burden of patients can be reduced.

In conclusion, the present model was useful for predicting therapeutic effect of rasburicase. Then, based on this model and the value for  $C_U$  in the absence of rasburicase [ $C_U(0)$ ], it would be possible to individually determine rational dosage regimen of rasburicase.

**Conflict of Interest** The authors declare no conflict of interest.

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