4

Therapeutic Drug Monitoring of Imatinib for Chronic Myeloid Leukemia Patients

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1. Introduction

Imatinib mesylate (Glivec®; Novartis, Basel, Switzerland), a protein kinase inhibitor of the BCR–ABL fusion protein, has demonstrated significant clinical efficacy in the treatment of Philadelphia (Ph) chromosome-positive chronic myeloid leukemia (CML). Imatinib mesylate (hereinafter shortly referred to as imatinib) produces durable responses and prolonged survival; therefore, it has become the standard of care for this disease (Goldman 2007; O'Brien, et al. 2003a). Notwithstanding the positive effects of imatinib, nearly 20% of the patients who take imatinib fail to achieve a complete cytogenetic response (CCyR); others may develop intolerable side effects or drug resistance overtime. Factors that might be associated with suboptimal responses and failure to treatment include (i) biological factors, such as the baseline presence or later emergence of BCR–ABL mutations or other genetic variants (Gorre, et al. 2001; Radich, et al. 2006), or organic cation transporter-1 (OCT1)-mediated drug influx (White, et al. 2010); (ii) clinical features, such as the disease status of the patients or the Sokal risk score at baseline (Crossman and O'Brien 2004); (iii) pharmacokinetic (PK) factors, such as PK-related interindividual variation affecting imatinib metabolism and drug–drug interactions (Cortes, et al. 2009; Peng, et al. 2004b); and (iv) the patient's compliance with therapy (Marin, et al. 2010).

In this chapter, we review the factors that affect imatinib pharmacokinetics, including the daily dose of imatinib, polymorphisms of imatinib-associated drug transporters, and the currently available methods for quantitative determination of imatinib. Moreover, we discuss the clinical significance of therapeutic drug monitoring (TDM) of imatinib.

2. Relationship between daily dose of imatinib and clinical response

The standard daily dose of imatinib—established by the International Randomized Study of Interferon and STI571 (IRIS)—is 400 mg for patients with chronic phase CML (Druker, et al. 2006; Hochhaus, et al. 2009). However, several studies have suggested that the administration of doses higher than 400 mg improves the response in some patients. Indeed, a better response was observed in accelerated and blast phases of CML with a dose of 600 mg/day (Talpaz, et al. 2002). In another study of 107 Japanese patients with chronic phase CML, patients given higher average daily doses of imatinib (more than 350 mg) not only achieved higher CCyR rate at 12 and 30 months but also had longer CCyR duration than

those given lower average daily doses (Nagai, et al. 2010). Collectively, these results suggest a clear dose-response relationship between daily dose of imatinib and treatment results.

3. Clinical significance of trough imatinib plasma concentrations

The imatinib plasma trough concentration (C_0) appears to affect the clinical response of patients (Table 1) (Ishikawa, et al. 2010; Larson, et al. 2008; Picard, et al. 2007; Singh, et al. 2009; Takahashi, et al. 2010b; Forrest, et al. 2009; Sakai, et al. 2009). Picard et al. reported that a steady-state imatinib C_0 measured after at least 12 months of treatment with a standard imatinib dose correlated with both cytogenetic and molecular responses (Picard, et al. 2007). Takahashi et al. have reported that in multiple analyses, the major molecular response (MMR) is significantly associated with the age of patients and imatinib C_0, whereas CCyR is associated only with daily dose (Takahashi, et al. 2010b). In addition, Picard et al. suggested that the threshold for the imatinib C_0 should be set above 1002 ng/mL, as this level was significantly associated with an MMR based on a concentration-dependent receiver-operating characteristic curve analysis with best sensitivity (77%) and specificity (71%) (Picard, et al. 2007). According to this threshold C_0 of imatinib, clinical responses were evaluated in several reports (Table 2). Takahashi et al. and Marin et al. reported that patients with imatinib C_0 less than 1000 ng/mL have a significantly lower success rate in achieving improved MMR (P = 0.012 and 0.02, respectively) but not CCyR (Marin, et al. 2010; Takahashi, et al. 2010b). Thus, the efficacy threshold C_0 of imatinib should be set above 1000 ng/mL for CML patients.

Reference	N	Response	Responders		Nonresponders		*P* value
			N	Mean C_0 (ng/mL)[1]	N	Mean C_0 (ng/mL)[1]	
Larson et al.	351	CCyR	297	1,009 ± 544	54	812 ± 409	0.01
Takahashi et al.	254	CCyR	218	1,057 ± 585	36	835 ± 524	0.033
		MMR	166	1,107 ± 594	88	873 ± 528	0.002
Picard et al.	68	CCyR	56	1,123 ± 617	12	694 ± 556	0.03
		MMR	34	1,452 ± 649	34	869 ± 427	0.001
Singh et al.	40	Clinical response	20	2,340 ± 520	20	690 ± 150	0.002
Ishikawa et al.	60	MMR	38	1,093 (median)	22	853 (median)	0.002
Sakai et al.	33	Optimal	25	1,242	8	736	0.0087
Forrest et al.	78	CCyR	53	1,010 ± 469	24	1,175 ± 656	0.29
		MMR	51	1,067 ± 473	27	1,063 ± 643	0.74

[1]All values, except those belonging to the studies by Ishikawa et al. and Sakai et al., are presented as the mean ± standard error.
Abbreviations: C_0, plasma trough concentration; CCyR, complete cytogenetic response; MMR, major molecular response

Table 1. Correlation of imatinib pharmacokinetics with clinical response

Reference	N	Response	C_0 (ng/mL)				*P* value
			N	≤1,000	N	>1,000	
Marin et al.	84	CCR	43	23.3%	41	44.4%	0.14
		MMR		60.1%		83.2%	0.02
Takahashi et al.	254	CCyR	146	83.6%	108	88.9%	0.276
		MMR		58.9%		74.1%	0.012
Picard et al.	68	MMR	32	25.0%	36	72.2%	0.03
Ishikawa et al.	60	MMR	29	48.3%	31	77.4%	0.019

Table 2. Clinical response and target plasma trough concentration (C_0)

4. Reported methods for the quantitative determination of imatinib

Table 3 summarizes the available methods, including the internal standard used, for the quantitative determination of imatinib (Bakhtiar, et al. 2002; Chahbouni, et al. 2009; Davies,

Reference	Analyte(s)	IS	Method
Miura et al. (2011)	Imatinib	IS: Dasatinib	HPLC–UV (265 nm)
Roth et al. (2010)	Imatinib	IS: None	HPLC–UV–Diode Array (265 nm)
Davies et al. (2010)	Imatinib, *N*-desmethylimatinib, Nilotinib	IS: Clozapine	HPLC–UV (260 nm)
Chahbouni et al. (2009)	Imatinib (Erlotinib, Gefitinib)	IS: D8-Imatinib	LC–MS/MS
De Francia et al. (2009)	Imatinib (Dasatinib, Nilotinib)	IS: Quinoxaline	HPLC–MS
Rochat et al. (2008)	Imatinib	IS: D8-Imatinib	LC–MS/MS
Oostendorp et al. (2007)	Imatinib, *N*-desmethylimatinib	IS: 4-Hydroxybenzophenone	HPLC–UV (265 nm)
Titier et al. (2005)	Imatinib	IS: D8-Imatinib	LC–MS/MS
Widmer et al. (2004)	Imatinib	IS: Clozapine	HPLC–UV–Diode Array (261 nm)
Velpandian et al. (2004)	Imatinib	IS: None	HPLC–UV (265 nm)
Schleyer et al. (2004)	Imatinib, *N*-desmethylimatinib	IS: None	HPLC–UV (260 nm)
Parise et al. (2003)	Imatinib, *N*-desmethylimatinib	IS: D8-Imatinib	LC–MS
Bakhtiar et al. (2002)	Imatinib, *N*-desmethylimatinib	IS: D8-Imatinib	LC–MS/MS

Abbreviations: IS, internal standard; LC–MS, liquid chromatography with mass spectrometry; LC–MS/MS, liquid chromatography with tandem mass spectrometry; HPLC–UV, high-performance liquid chromatography with ultraviolet detector

Table 3. Analytical methods for the quantitation of imatinib in human plasma

et al. 2010; De Francia, et al. 2009; Miura, et al. 2011; Oostendorp, et al. 2007; Parise, et al. 2003; Rochat, et al. 2008; Roth, et al. 2010; Schleyer, et al. 2004; Titier, et al. 2005; Velpandian, et al. 2004; Widmer, et al. 2004). High-performance liquid chromatography (HPLC) with ultraviolet (UV) detection, liquid chromatography with mass spectrometry (LC–MS), and liquid chromatography with tandem mass spectrometry (LC–MS/MS) have been used in clinical studies to measure the plasma concentration of imatinib. HPLC–UV is less expensive than LC–MS or LC–MS/MS detection and requires equipment that is widely available in hospital laboratories. As such, a validated HPLC–UV assay provides the most practical platform to measure imatinib plasma concentration in actual clinical practice.

5. Interpatient variability of trough imatinib plasma concentration

Despite the linear relationship between imatinib C_0 and its daily dose, substantial interpatient variability is observed (Takahashi, et al. 2010b). Even among patients taking the same 400 mg/day dose, the imatinib C_0 ranges widely (140–3910 ng/mL) (Table 4) (Forrest, et al. 2009; Ishikawa, et al. 2010; Larson, et al. 2008; Marin, et al. 2010; Picard, et al. 2007; Takahashi, et al. 2010b). Factors that could underlie this interpatient variability include body size, age, gender, liver function, renal function, interaction with other medications given concomitantly, adherence to medication regimens, and polymorphisms of enzymes or transporters related to imatinib pharmacokinetics and/or pharmacodynamics.

Reference	N	C_0 (ng/mL)		
		Mean	Minimum	Maximum
Larson et al.	351	979	153	3,910
Picard et al.	68	1,058	181	2,947
Marin et al.	84	900	400	1,600
Forrest et al.	70	1,065	203	2,910
Takahashi et al.	190	1,392	140	2,457
Ishikawa et al.	46	1,005 (median)	450	1,875

Table 4. Steady-state plasma trough concentration (C_0) range at 400 mg of imatinib daily

6. Pharmacokinetics of imatinib

Imatinib is rapidly and completely absorbed because of an oral bioavailability of 98.3% (Peng, et al. 2004a). Moreover, it is extensively metabolized, with up to 80% of the administered dose recovered in feces as metabolites or unchanged drug (Gschwind, et al. 2005). The mean plasma half-life of imatinib is 13.5–18.2 h (Gschwind, et al. 2005; le Coutre, et al. 2004; Peng, et al. 2004b; Wang, et al. 2009). The cytochrome P450 (CYP) system is involved in the oxidative metabolism of imatinib, the major reaction being catalyzed by CYP3A4/5 (O'Brien, et al. 2003b; Peng, et al. 2005; van Erp, et al. 2007). Indeed, the main metabolite of imatinib, the *N*-desmethyl derivative CGP74588, is primarily formed in the liver by cytochrome CYP3A4, whereas a number of other enzymes such as CYP1A2, CYP2D6, CYP2C9, and CYP2C19 are involved in the formation of minor metabolites (O'Brien, et al. 2003b; van Erp, et al. 2007). CGP74588 represents approximately 20% of the parent drug plasma level in patients, and it has similar biological activity but a longer terminal half-life (85–95 h) than imatinib, as measured after discontinuation of therapy

Transporter	Polymorphism	N	Effects on PK	Effects on clinical response	Reference
P-glycoprotein	3435 T	82	CL/F =	-	Gardner et al.
(ABCB1)	3435 T	90	C_0 =	MMR =	Dulucq et al.
	3435 T	34	CL/F ↓	-	Yamakawa et al.
	3435 T	67	C_0 =	MMR =	Takahashi et al.
	3435 T	22	CL/F ↑	-	Gurney et al.
	3435 T	229	-	OS ↓	Kim et al.
	3435 T	52	-	Resistance ↑	Ni et al.
	3435 T	46	-	MMR, CMR ↓	Deenik et al.
	3435 CC	65	-	Failure ↑	Maffoli et al.
	1236 T	90	C_0 =	MMR ↑	Dulucq et al.
	1236 T	34	CL/F =	-	Yamakawa et al.
	1236 T	67	C_0 =	MMR =	Takahashi et al.
	1236 T	22	CL/F ↑	-	Gurney et al.
	1236 T	229	-	CCyR, MMR =	Kim et al.
	1236 T	52	-	Resistance ↑	Ni et al.
	1236 T	46	-	MMR, CMR ↓	Deenik et al.
	2677 T/A	90	C_0 =	MMR ↑	Dulucq et al.
	2677 T/A	34	CL/F =	-	Yamakawa et al.
	2677 T/A	67	C_0 =	MMR =	Takahashi et al.
	2677 T/A	22	CL/F ↑	-	Gurney et al.
	2677 T/A	229	-	CCyR, MMR =	Kim et al.
	2677 A	52	-	CCyR ↑	Ni et al.
	2677 T	46	-	CMR ↓	Deenik et al.
	TTT haplotype	90	C_0 ↑	MMR ↑	Dulucq et al.
	TTT haplotype	22	CL/F ↑	-	Gurney et al.
BCRP	421 A	82	CL/F =	-	Gardner et al.
(ABCG2)	421 A	34	CL/F =	-	Yamakawa et al.
	421 A	67	C_0 ↑	MMR =	Takahashi et al.
	421 A	46	CL/F ↓	-	Petain et al.
	421 A	229	-	MMR, CMR ↑	Kim et al.
OCT1	480 G	229	-	Loss of response	Kim et al.
(SLC22A1)	480 G	67	C_0 =	MMR =	Takahashi et al.
	1022 T	67	C_0 =	MMR =	Takahashi et al.
	1022 T	34	CL/F =	-	Yamakawa et al.
	1222 G	67	C_0 =	MMR ↑	Takahashi et al.

Abbreviations: C_0, plasma trough concentration; CCyR, complete cytogenetic response; CL/F, clearance; CMR, complete molecular response; MMR, major molecular response; PK, pharmacokinetics

Table 5. Transporter polymorphism and effects on pharmacokinetics and the clinical response

(Gschwind, et al. 2005; le Coutre, et al. 2004). Imatinib is a substrate for P-glycoprotein, which is encoded by the *ABCB1* gene, and breast cancer-resistance protein (BCRP), which is encoded by the *ABCG2* gene (Burger and Nooter 2004; Burger, et al. 2004; Dohse, et al. 2010; Ozvegy-Laczka, et al. 2004). P-Glycoprotein is a membrane efflux transporter normally

expressed in the small intestine, biliary canalicular front of hepatocytes, and renal proximal tubules (Thiebaut, et al. 1987). BCRP is widely expressed in the small intestine, liver, and placenta (Hirano, et al. 2005; Zhang, et al. 2006). Imatinib and its metabolites are excreted predominantly via the biliary–fecal route by these ATP-binding cassette (ABC) efflux transporters, P-glycoprotein and BCRP. Imatinib is also a substrate of the uptake transporter OCT1, which is encoded by *SLC22A1* (Choi and Song 2008; White, et al. 2006). Because OCT1 is a highly expressed solute carrier in the basolateral membrane of hepatocytes, it facilitates the hepatocellular accumulation of imatinib before metabolism and biliary secretion. Further, it may play an important role in governing drug disposition and hepatotoxicity (Zhang, et al. 1998a; Zhang, et al. 1997; Zhang, et al. 1998b). One of the factors affecting interpatient variability could be polymorphism of drug transporters. However, the involvement of multiple transporters in imatinib pharmacokinetics hampers the investigation of imatinib transport mechanisms. Moreover, the level of drug transporter expression likely correlates with the intracellular imatinib concentration, because primary CML cells express the transporters on the cell surface (Burger, et al. 2005; White, et al. 2006).

7. Impact of pharmacogenetic variation of drug transporters

Pharmacogenetic research has focused on the interaction of imatinib with enzymes such as CYP3A4/5 and transporters such as P-glycoprotein, BCRP, and OCT1 (Table 5) (Deenik, et al. 2010; Dulucq and Krajinovic 2010; Gardner, et al. 2006; Kim, et al. 2009; Maffioli, et al. 2010; Ni, et al. 2011; Petain, et al. 2008; Takahashi, et al. 2010a; Yamakawa, et al. 2011).

7.1 CYP3A4/5

CYP3A4/5 expression is strongly correlated with a single-nucleotide polymorphism (SNP) in the gene (Hustert, et al. 2001; Rodriguez-Antona, et al. 2005). Nonetheless, *CYP3A4*1B* (-392A>G) and *CYP3A5*3* (6986A>G) had no significant influence on the plasma concentration of imatinib (Gardner, et al. 2006; Gurney, et al. 2007; Takahashi, et al. 2010a). A drug interaction occurs upon coadministration of imatinib and rifampicin or St. John's wort's CYP3A inducers, resulting in a decrease in the plasma concentration of imatinib (Bolton, et al. 2004; Smith, et al. 2004). In contrast, ketoconazole, a potent CYP3A4 inhibitor, significantly increased the C_{max} and AUC_{0-24} of imatinib (Dutreix, et al. 2004). However, the effects of *CYP3A4* and *CYP3A5* polymorphisms are less likely to be clinically significant in imatinib exposure.

7.2 P-Glycoprotein (*ABCB1*)

Gurney et al. (sample size = 22) reported that oral clearance of imatinib in patients receiving 600 mg of imatinib daily was significantly lower in those with the *ABCB1* 1236C/C, 2677G/G or 3435C/C genotypes than in those with the corresponding *ABCB1* 1236T/T, 2677T/T or 3435T/T genotypes (Gurney, et al. 2007). However, Gardner et al. (sample size = 82) reported that the *ABCB1* 3435C>T polymorphism had no significant effect on oral clearance of imatinib (Gardner, et al. 2006). In another study, Takahashi et al. (sample size = 62) reported that 1236C>T, 2677G>T/A, and 3435C>T polymorphisms had no significant effect on dose-adjusted imatinib C_0 (Takahashi, et al. 2010a). Although other studies have

reported the relationship between *ABCB1* polymorphisms and imatinib pharmacokinetics, or between *ABCB1* polymorphisms and clinical response, the results are still controversial (Table 5). However, the 3435T polymorphism, which is associated with low expression of P-glycoprotein, tends to correlate with poor clinical response. This finding suggests that P-glycoprotein is involved in imatinib pharmacokinetics to a greater extent than the intracellular imatinib concentration in primary CML cells.

7.3 BCRP (*ABCG2*)

Five studies have reported the *ABCG2* 421 polymorphism and imatinib pharmacokinetics or clinical response. Takahashi et al. (sample size = 62) reported that the dose-adjusted imatinib C_0 was significantly lower in Japanese patients with *ABCG2* 421C/C than in patients with C/A+A/A genotypes (Takahashi, et al. 2010a). In agreement, Petain *et al*. (sample size = 46) reported that imatinib clearance in patients carrying the *ABCG2* 421C/A genotype was significantly lower than in those with the 421C/C genotype (Petain, et al. 2008). Moreover, *ABCG2* 421A/A has a significant effect on achieving MMR/CCyR (sample size = 229) (Kim, et al. 2009). Because the 421C>A SNP of the *ABCG2* gene is associated with a higher imatinib exposure than is the wild-type genotype, CML patients with this SNP might more efficiently achieve molecular responses much more than their wild-type counterparts.

7.4 OCT1 (*SLC22A1*)

SLC22A1 (OCT1) expression levels likely correlate with the intracellular imatinib concentration, as primary CML cells expressing high levels of OCT1 have a greater drug uptake than those exhibiting more modest OCT1 expression (Thomas, et al. 2004; Wang, et al. 2008; White, et al. 2006). On the other hand, Kim et al. reported that the *SLC22A1* 480G/G genotype correlated with high rate of loss of response or treatment failure to imatinib therapy (Kim, et al. 2009). However, no association between dose-adjusted imatinib C_0 and *SLC22A1*156T>C, 480G>C, 1022C>T, or 1222A>G polymorphisms has been observed (Takahashi, et al. 2010a). The *SLC22A1* polymorphisms analyzed to date are therefore not important for imatinib exposure. OCT1 may contribute to the cellular uptake of imatinib rather than to imatinib exposure.

8. Pharmacokinetics of second-generation BCR-ABL inhibitors

Second-generation inhibitors, including nilotinib, dasatinib, and bosutinib, have been developed to counter imatinib resistances associated with BCR-ABL mutations, BCR-ABL gene amplification, increased efflux via ABC pump activation, or decreased influx via OCT1 activation. Nilotinib is a close structural analogue of imatinib with greater binding affinity and selectivity for the BCR-ABL kinase than imatinib. Dasatinib and bosutinib are dual ABL-SRC kinase inhibitors. All these second-generation inhibitors have been evaluated in clinical trials (Kantarjian, et al. 2010; Keller, et al. 2009; Saglio, et al. 2010), and nilotinib and dasatinib have already been approved in many countries for the treatment of patients with CML.

In pharmacokinetics studies with dasatinib (Christopher, et al. 2008), nilotinib (Tanaka, et al. 2010), or bosutinib (Abbas, et al. 2011), exposures (C_{max} and AUC) were shown to be linear and the dose proportional. C_{max} was observed at 0.5, 3, and 6 h after single oral

administration of each inhibitor, and a mean terminal elimination half-life ($t_{1/2}$) was <4, 17, and 32–39 h, respectively. Absorption was rapid for dasatinib and relatively slow for nilotinib and bosutinib. Similarly to imatinib, they are metabolized primarily by CYP3A4. However, unlike imatinib, nilotinib and dasatinib are not substrates for OCT1 transporter (Clark, et al. 2008; Giannoudis, et al. 2008; Hiwase, et al. 2008). Nilotinib and dasatinib are high-affinity substrates of BCRP and also interact with P-glycoprotein (Hiwase, et al. 2008). However, neither P-glycoprotein nor BCRP induce resistance to bosutinib (Hegedus, et al. 2009).

There are no published data on the relationship between drug plasma concentration and outcome or adverse events, and no clinically relevant data to suggest that dose changes are necessary based on sex, age, or pharmacokinetic differences that depend on the pharmacogenetic variation of drug transporters for second-generation inhibitors.

9. Therapeutic drug monitoring of imatinib for CML patients

Patients are more likely to achieve higher response rates with a satisfactory level of response if the 1,000 ng/mL drug plasma threshold considered as an adequate imatinib C_0 is achieved and maintained. Because the interpatient variation of imatinib levels is influenced by multiple factors, including genetic polymorphisms or coadministered drugs, a routine therapeutic drug monitoring (TDM) service for CML patients taking imatinib might be useful. According to the European Leukemia Net (ELN) recommendations (Baccarani, et al. 2009), the clinical response for CML patients receiving imatinib therapy should be evaluated at 3, 6, 12, and 18 months. In addition to *BCR–ABL* mutation analysis for CML patients, TDM could be also useful when making decisions related to imatinib therapy for patients not achieving CCyR or MMR at the above time points. If the target C_0 is not reached and no intolerance is found, dose escalation of imatinib is recommended. On the other hand, if the target is achieved but the patients lack a sufficient clinical response, imatinib could be withdrawn and replaced by a second-line tyrosine kinase inhibitor. Moreover, among the above-mentioned drug transporters, BCRP seems to most strongly influence imatinib exposure. We have reported that the daily dose of imatinib for patients with *ABCG2* 421C/C and 421C/A or 421A/A should be 400 mg and 300 mg, respectively, to attain the 1000 ng/mL drug plasma threshold (Takahashi and Miura 2011). If the ABCG2 421C>A polymorphism is detected before initiating therapy, dosing decisions may be improved to achieve optimal imatinib exposure immediately after intake. Further study is necessary to prospectively confirm the benefit of TDM of imatinib in the treatment and management of CML patients.

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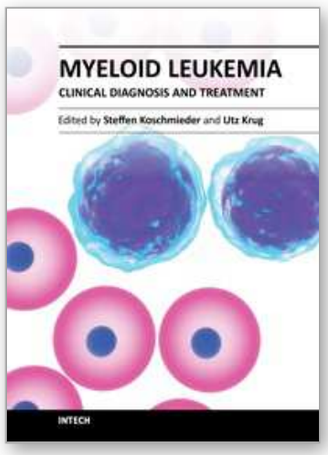

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This book comprises a series of chapters from experts in the field of diagnosis and treatment of myeloid leukemias from all over the world, including America, Europe, Africa and Asia. It contains both reviews on clinical aspects of acute (AML) and chronic myeloid leukemias (CML) and original publications covering specific clinical aspects of these important diseases. Covering the specifics of myeloid leukemia epidemiology, diagnosis, risk stratification and management by authors from different parts of the world, this book will be of interest to experienced hematologists as well as physicians in training and students from all around the globe.

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