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Clinical Factors impact on Pharmacokinetics of CT-P10 and Reference Rituximab in patients with Advanced-stage Follicular Lymphoma

W. Kim, B. Coiffier, C. Buske, M. Ogura, L. Kwak, S. Lee, Y. Bae, S. Kim, M. Kim, S. Lee, D. Kwak, H. Lee

Division of Hematology and Oncology, Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea, Republic of, *Department of Hematology, Hospices Civils de Lyon, Lyon, France*, *CCC Ulm, University Hospital of Ulm, Ulm, Germany*, *Department of Haematology, Tokai Central Hospital, Kakamigahara, Gifu, Japan*, *Toni Stephenson Lymphoma Center and Department of Haematology and Hematopoietic Cell Transplantation, City of Hope Duarte, Duarte, United States*, *Clinical Development Division, CELLTRION, Inc., Incheon, Korea, Republic of*

Background CT-P10 is the first biosimilar to the innovator rituximab (RTX), which was approved by the European Medicines Agency for all indications for which RTX is approved. Pharmacokinetic equivalence and comparable efficacy was demonstrated in advanced-stage follicular lymphoma patients (Kim WS et al. Lancet Haematol. 2017; S2352-3026(17)) as well as in rheumatoid arthritis (Yoo DH, et al. Arthritis Rheumatol. 2016; 68 (suppl 10)). It is known that there are several factors affecting on pharmacokinetics (PK) of rituximab. However, there are limited data on comparing PK data between a biosimilar of rituximab and RTX with different subgroups in advanced-stage follicular lymphoma (AFL) patients.

Objective This report is to investigate the PK of CT-P10 according to the several relevant clinical factors and to compare with RTX in the post-hoc analysis of randomized controlled trial to compare CT-P10 and RTX in advanced-stage follicular lymphoma (NCT02162771).

Methods A total of 121 patients of PK population were included in this analysis. Fifty nine patients in the CT-P10 group and 62 patients in the RTX group received CT-P10 or RTX (375 mg/m^2 i.v) plus CVP (cyclophosphamide, vincristine and prednisone) for every 3 weeks over 8 cycles. Area Under the Concentration-time curve at steady state (AUC_{tau}) and the maximum serum concentration at steady state (C_{maxSS}) at Cycle 4 and trough serum concentration (C_{trough}) at Cycle 4 and Cycle 8 were calculated by standard non-compartmental methods using Phoenix WinNonlin. The parameters were analysed by subgroups of Gender (male vs. female), Eastern Cooperative Oncology Group (ECOG) Performance Status (0 vs. ≥1), Follicular Lymphoma International Prognostic Index (FLIPI) Score (0-2 vs. 3-5) and its component (Age (≥60 vs. <60), Hemoglobin [Hb] (≥120g/L vs. <120g/L), Lactate dehydrogenase [LDH] (>UNL vs. ≤UNL), number of nodal sites (>4 vs. ≤4)), presence of bulky lesion at baseline (≥7cm vs. <7cm) and Complete response (CR)/Complete response unconfirmed (CRu) as best overall response assessed by International Working Group 1999 in the each and combined group of CT-P10 and RTX. Outliers which determined by robust regression outlier testing were excluded in this analysis.

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For AUC_{tau}, 7 patients (5 in the CT-P10 group and 2 in the RTX group) and among them, 4 patients (2 patients in each group) for C_{maxSS} were defined as outliers.

Result Higher AUC_{tau} and C_{maxSS} were observed in patients who are female, under 60 years old, good ECOG Performance Status, low FLIPI score, normal Hb and LDH levels, and non-bulky disease at baseline as shown in Table 1. In patients who achieved CR/CRu as their best overall response during 8 cycles showed higher AUC_{tau}, C_{maxSS} and C_{trough} than in patients who did not achieve CR/CRu response in both CT-P10 and RTX groups. At Cycle 4 and Cycle 8, mean C_{trough} in the CR/CRu responder were 72 μg/mL, 108 μg/mL, respectively, and those concentrations are 56 μg/mL, 96 μg/mL in the CR/CRu non-responder. Importantly, there was no statistically significant difference between the CT-P10 and RTX in any of subgroup analyses; confidence interval of the ratio of geometric mean of CT-P10 to RTX contains 1 using Satterthwaite approximation for each comparison.

Table 1. Summary of PK parameters by subgroup analysis

	AUC_{tau} (h*μg/mL)			C_{maxSS} (μg/mL)		
	CT-P10	**RTX**	**Total**	**CT-P10**	**RTX**	**Total**
Gender						
Female	61566	67277	64470	290	300	295
Male	57782	56250	56935	261	254	257
ECOG						
0	59970	66328	63287	274	291	283
≥1	59990	54649	57103	281	257	269
FLIPI						
0-2	59529	67899	63477	282	295	288
3-5	60546	57527	58780	270	266	268
Age						
<60	60727	63651	62258	280	290	286
≥60	58852	60014	59473	271	262	267
Hb (g/L)						
≥120	59936	63329	61858	282	281	281
<120	60081	56036	58498	265	270	267
LDH						
≤UNL	59354	63129	61310	279	281	280
>UNL	62469	58942	60475	269	273	271
Number of Nodal sites						
≤4	60143	63093	61127	272	278	274
>4	59865	61954	61130	280	279	279

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Bulky Disease						
<7cm	60515	64412	62620	277	289	283
≥7cm	57824	50385	54300	274	228	252
CR/CRu						
Responder	61997	66845	64364	271	291	281
Non-responder	58389	59345	58920	281	272	276

Conclusion Female gender, younger age (<60), better ECOG Performance Status, lower FLIPI score, LDH and Hb levels in normal range, absence of bulky disease at baseline and better response are factors associated with increased serum rituximab concentration in the combined treatment groups. No statistically significant differences were found between CT-P10 and RTX groups in PK at all subgroup analyses. Therefore, this result shows that the PK of CT-P10 is in accordance with the RTX from historical data and further supports the PK similarity between CT-P10 and RTX.