Pharmacokinetic and pharmacodynamic modeling of erythropoietin and romiplostim combination therapy in rats with chemotherapy-induced anemia and thrombocytopenia

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INTRODUCTION

Chemotherapy-induced damage of hematopoietic stem and progenitor cells (HSPCs) in bone marrow is a major cause of anemia and thrombocytopenia (CIAT) in cancer patients. We have previously shown that romiplostim, a thrombopoietin receptor agonist that could stimulate the expansion of HSPCs, could synergize with recombinant human erythropoietin (rHuEPO) to promote erythropoiesis in addition to stimulating platelet production, whereas rHuEPO could influence the platelet count within the normal physiological range through stem cell competition. Therefore, we hypothesize that a combination of romiplostim with rHuEPO can alleviate CIAT simultaneously while minimizing the risk of thrombosis.

OBJECTIVES

- To investigate the pharmacokinetics (PK) and pharmacodynamics (PD) of rHuEPO and romiplostim as monotherapy and combination therapy to alleviate CIAT simultaneously.
- To develop a novel PK/PD model to quantify the effects of rHuEPO and romiplostim on megakaryopoiesis and erythropoiesis in CIAT.
- To apply this model to explain potential mechanisms of the combination therapy to alleviate CIAT.

METHODS

Study Design:

- *In vivo*: To study PK and PD of romiplostim [30 μg/kg, once weekly, subcutaneous] and rHuEPO [100, 450 or 1350 IU/kg, thrice weekly, intravenous] as monotherapy and combination therapy in a multiple dosing regimen in an orthotopic rat model with carboplatin-induced anemia and thrombocytopenia.
  - PK study: Serum concentrations of romiplostim and rHuEPO were determined by sandwich enzyme-linked immunosorbent assay (ELISA)[1]. Carboplatin was analyzed using an Agilent 1290 Ultrahigh Performance Liquid Chromatograph coupled to an Agilent 6430 Triple Quad (LC-MS/MS) with an electrospray ionization (ESI) source (Agilent Technologies Inc.).
  - PD study: The PD markers include red blood cells (RBCs), hemoglobin (Hgb), and platelet. Blood samples for PD analysis were drawn on days 0, 4, 8, 10, 12, 15, 17, 19, 22, 24, 26, 29, 31, 33, 36, 38, until day 40, on which the value of PD markers returned to baseline.

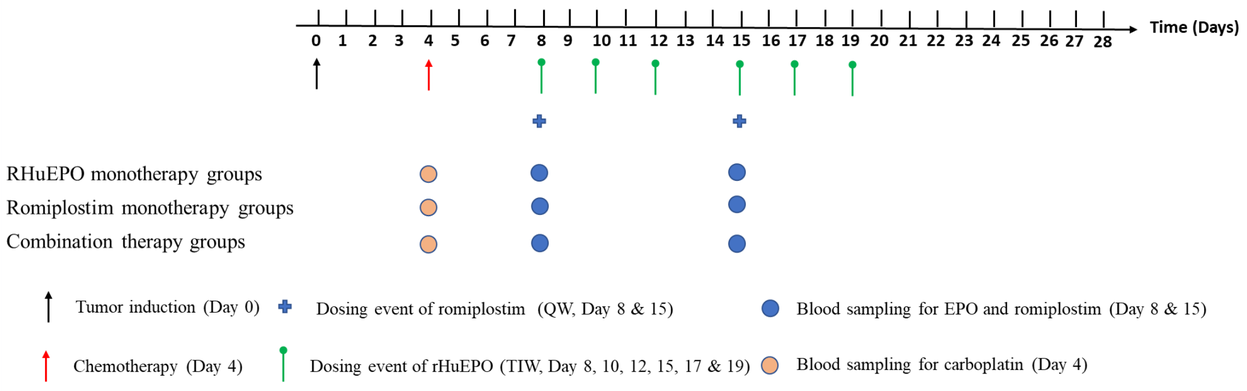

Figure 1. Schematic representation of the study design and staggered PK sampling design for all the treated groups during the first 4 weeks of the study.

- PK and PD modeling: To quantify the erythropoietic and thrombopoietic effects of rHuEPO and romiplostim in rats with CIAT.

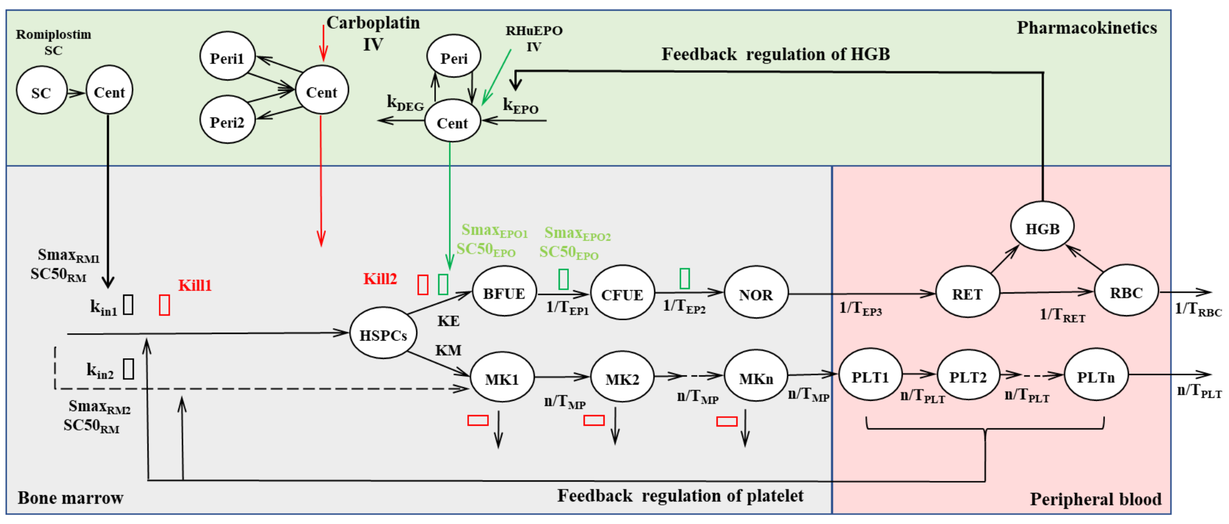

Figure 2. Schematic diagrams of the proposed PK/PD model for the effects of carboplatin, rHuEPO, and romiplostim on RBCs and platelet production. The open rectangle indicates the effects of carboplatin (red), romiplostim (black), and rHuEPO (red). Cent= central, Peri=peripheral, SC= subcutaneous, IV=intravenous. The endogenous EPO was produced through a zero-order process K_{EPO} and was degraded by a rate of K_{DEG}. T_{EP} represents the average time required for precursors to develop into the next cell population. T_{RET} and T_{RBC} represent the mean residence time for reticulocytes (RETs) and mature RBCs, respectively. Kill1 and Kill2 are the slope of the carboplatin concentration; $Smax_{EPO1}$, $Smax_{EPO2}$, $Smax_{RM1}$, and $Smax_{RM2}$ are the maximum stimulatory effect of rHuEPO and romiplostim, respectively. SC_{50} and IC_{50} = drug concentrations that induce half-maximum effect. The series of n=10 aging compartments (MKi, i=1,…,n) denotes the megakaryocyte precursor cells, with the first-order transition rates n/T_{MP}; PLTi (i=1,…,n) represents the platelet with the transition rates n/T_{PLT}. BFUE = burst forming unit-erythroid cells, CFUE = colony-forming unit-erythroid cells, NOR = normoblasts. Kin1 and Kin2 are Zero-order rate constants for producing HSPCs and MK1, respectively. HSPCs proliferate to erythroid and MK lineages according to the first-order rate constant KE and KM, respectively.

- PK modeling: The carboplatin PK data in rats following single i.v. dose (60 mg/kg) were fitted to a three-compartment model according to the literature[2], while a two-compartment disposition model and a one-compartment model were used to describe the time course of rHuEPO and romiplostim, respectively[1].
- PD modeling: Catenary indirect response model with a series of transit compartments mimicking different megakaryocytes (MK) and erythroid populations in bone marrow and peripheral blood was applied.

- Model evaluation
  - Initial visualized check: diagnostic plots, including observed value versus population predicted value and individual predicted value, conditional weighted residual (CWRES) versus population predicted value, and CWRES versus time.
  - Visual predictive checks (VPC).
- Software: NONMEM7.5 FOCEI

REFERENCES

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[2]. Woo S, Krzyzanski W, Jusko WJ. Pharmacodynamic model for chemotherapy-induced anemia in rats. Cancer Chemother Pharmacol. 2008 Jun;62(1):123-33.

RESULTS

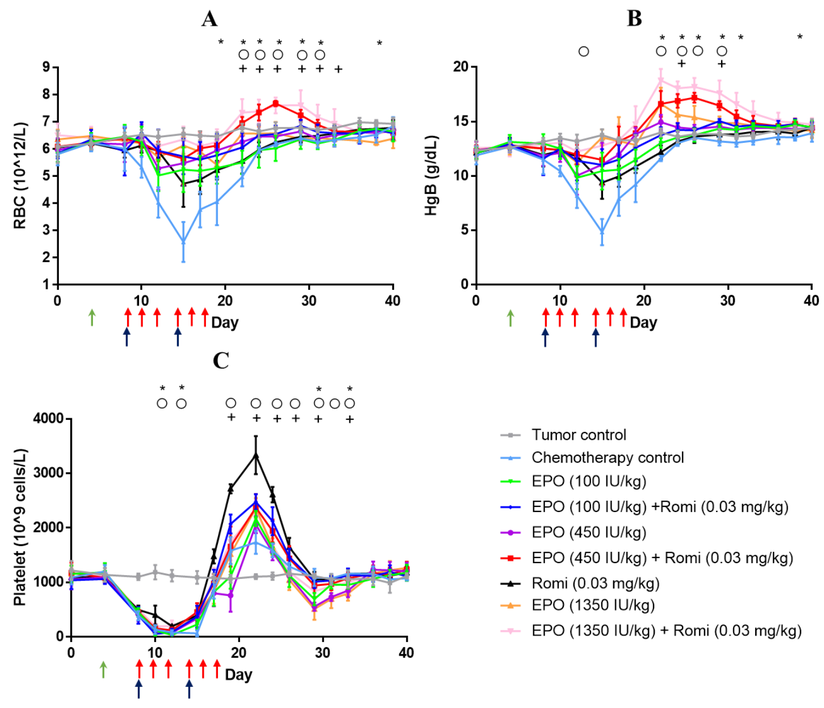

Figure 3. PD of rHuEPO and romiplostim as monotherapy and combination therapy in peripheral blood. The arrows represent the dosing event of carboplatin (green), rHuEPO (red), and romiplostim (black). Data were expressed as mean ± standard deviation (n = 6). The symbols above the lines indicate days of statistically significant differences between the following rHuEPO monotherapy groups and the corresponding rHuEPO plus romiplostim combination therapy groups: + = 100 IU/kg; o = 450 IU/kg; * = 1350 IU/kg; ($p < 0.05$, Student's unpaired t-test).

- Combination treatment promotes Hgb production synergistically and influences platelet count to a normal range.

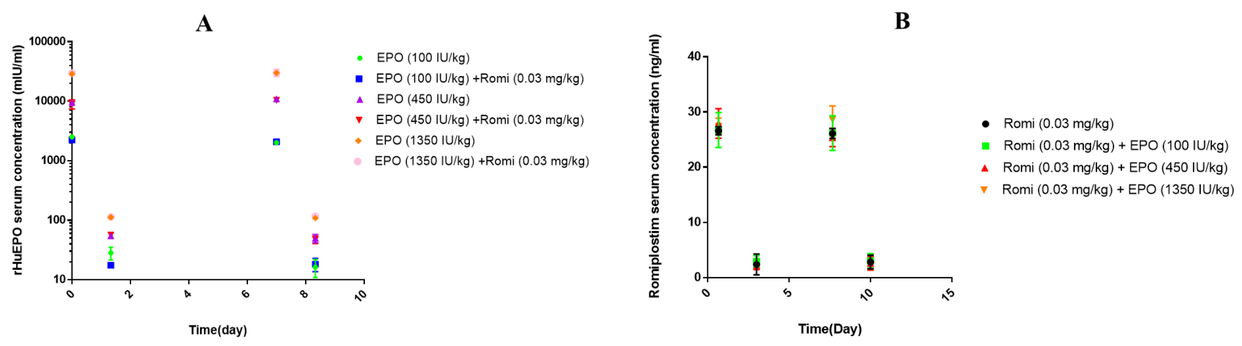

Figure 4. RHuEPO serum post-dose concentrations during multiple dosing regimens of rHuEPO in the presence or absence of romiplostim (A) and romiplostim serum post-dose concentrations during multiple dosing regimens in the presence or absence of rHuEPO (B). The symbols depict the mean profile with standard deviation (SD) error bars (n=3).

- The effect of combination therapy is due to PD interaction instead of PK interaction.

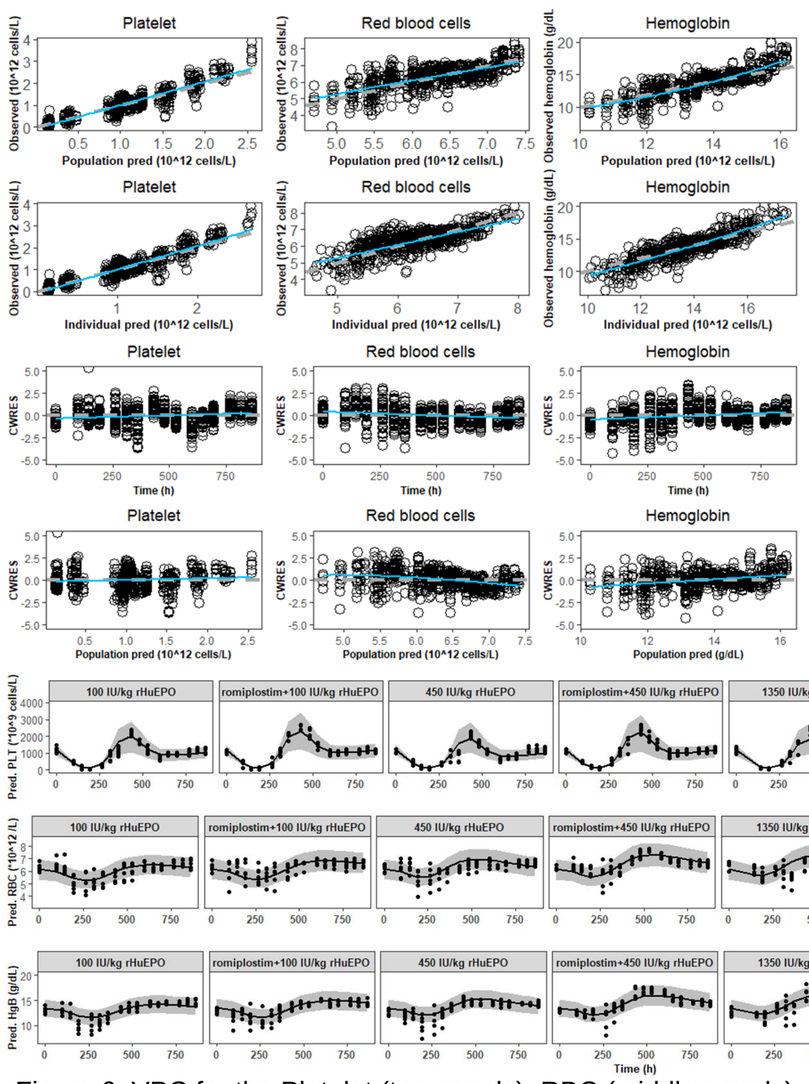

Figure 5. General goodness-of-fit of the final PD model including platelet (left panels), red blood cell counts (middle panels), and hemoglobin concentration (right panels). Following the up-to-bottom order, the panels present the observed data vs. population predictions, observed data vs. individual predictions, CWRES vs. time, and CWRES vs. population predictions, respectively. The blue lines are the loess smooth lines. The gray diagonal and horizontal lines are the identity and zero lines, respectively.

Figure 6. VPC for the Platelet (top panels), RBC (middle panels), and Hgb (bottom panels) in the monotherapy and combination therapy groups. The solid lines represent the median of the model predictions, the dots represent the observed data, and the shaded area is limited by the 5th and 95th percentile of the 200 simulated model predictions.

- The PK-PD model was capable of describing the PD response of rHuEPO and romiplostim monotherapy and combination therapy in rats with CIAT.

Table 1. Model estimates of the fixed- and random-effect PD parameters together with their relative standard errors (RSE). Note: The PK parameters were fixed at their estimated values. RSE for ω and σ are reported on the approximate standard deviation scale (standard error/variance estimate)/2. Inter-individual variability is expressed as coefficients of variation (%). σ represents the variance in the residual error. IIV means inter-individual variability. -a, fixed.

Parameters (Units)	Description	Estimate	%RSE
Kill1 (mL/μg)	Slope of carboplatin concentration for linear inhibition on the proliferation of HSPCs	3.431	11.96
Kill2 (mL/μg)	Slope of carboplatin concentration for linear inhibition on the differentiation of HSPCs into BFUE	3.695	19
RBC_0 ($\times 10^{12}$ cells/L)	Baseline RBCs concentration	6.163	1.445
T_{RET} (h)	Mean residence time for RETs	85.28	22.46
T_{RBC} (h)	Mean residence time for mature RBCs	1440	-[a]
PLT_0 ($\times 10^{12}$ cells/L)	Baseline platelets in blood	1.173	4.983
T_{MP} (h)	Mean lifespan of megakaryocyte cells	136.8	5.808
T_{PLT} (h)	Mean lifespan of platelets	139.8	5.956
KE ($\times 10^{-4}$/h)	First-order rate constant of HSPCs differentiate into BFU-E	32.66	13.67
KM ($\times 10^{-4}$/h)	First-order rate constant of HSPCs differentiate into MK1	6.678	16.95
MCH (pg/cell)	Mean corpuscular Hgb	21.82	0.8455
$Smax_{RM1}$	Maximal stimulus of romiplostim on HSPCs	1.11	661.9
$Smax_{RM2}$	Maximal stimulus of romiplostim on MK-committed pathway	0.2101	25.77
$Smax_{E1}$	Maximal stimulus of rHuEPO on HSPCs	252.6	92.91
$Smax_{E2}$	Maximal stimulus of rHuEPO on BFU-E and CFU-E	11.09	39.42
$SC50_{RM}$ (ng/mL)	The concentrations of romiplostim that induce a half-maximum effect	13.4	1069
$SC50_E$ (mIU/mL)	The concentrations of rHuEPO that induce a half-maximum effect	7477	107.2
GAM_1	Hill factor on feedback regulation of Hgb	34.12	8.442
GAM_2	Hill factor on feedback regulation of platelet on HSPCs	0.5444	14.34
GAM_3	Hill factor on feedback of platelet on MK-committed pathway	0.4859	8.909
ω_{RBC0}	IIV of RBC_0	0.1752	22.47
ω_{PLT0}	IIV of PLT_0	0.02935	72.66
σ_{PLT1}	Proportional error of platelets	0.1612	5.436
σ_{PLT2}	Additive error of platelets	0.1095	7.442
σ_{RBC}	Additive error of RBC	0.4692	5.475
σ_{HGB}	Additive error of HGB	1.029	5.704

CONCLUSIONS

- RHuEPO and romiplostim combination therapy can treat CIAT simultaneously in rats while minimizing the risk of thrombosis, indicating that combination therapy might be superior to monotherapy in the supportive therapy of cancer patients undergoing chemotherapy.
- PK-PD modeling provides mechanistic insights regarding rHuEPO and romiplostim combination therapy on CIAT and may also serve as a valuable tool to inform the clinical dosing of the combination therapy.

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