Thrombocytopenia following high-dose chemotherapy with carboplatin, etoposide and thiotepa in patients with testicular germ cell cancer

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Introduction

Thrombocytopenia is one of the major dose-limiting toxicities in chemotherapeutic regimens containing carboplatin. In a clinical study 17 patients received high-dose chemotherapy with carboplatin, etoposide and thiotepa (CET), subsequent autologous stem cell rescue as well as additional administration of thrombocyte concentrates. The objective of the present work was to perform pharmaco-kinetic/pharmacodynamic (PK/PD) modeling to characterize the time-course of thrombocytopenia in this therapy regimen and the contribution of each chemotherapeutic agent to the observed hematological toxicity.

Patients and methods

Study population

Drug and thrombocyte data were recorded in a clinical study enrolling 29 patients with germ cell tumors who had not benefited from cisplatin-based conventional chemotherapy [1]. Of these, 17 patients receiving subsequent 1-h i.v. infusions of carboplatin (500 mg/m²/day, 3 consecutive days), etoposide (up to 600 mg/m²/day, 4 consecutive days) and thiotepa (up to 250 mg/m²/day, 3 consecutive days), respectively, were eligible for PK/PD analysis. The therapy protocol further consisted of an autologous stem cell rescue three days after the last administration of etoposide as well as additional thrombocyte concentrates as individually required. Routine hematological assessments were performed daily, resulting in a total of 450 thrombocyte concentrations (median: 24 counts per patient).

Population PK/PD data analysis

Statistical and additional graphical analyses were performed in R 2.13; population PK/PD modeling and simulation activities were performed using NONMEM® 7.2. Individual PK parameter estimates [2] were used as input variables for two PD models, an empirical turnover model (indirect response model, [3]) and a semi-mechanistic model, which were compared in terms of goodness-of-fit, precision of parameter estimates and their ability to assess the thrombocytopenic potency of the three drugs. In the empirical turnover model, the cytotoxic drug effect was exerted by the inhibition of a thrombocyte production rate constant. The introduction of an effect compartment as a link between PK profiles and the PD model accounted for the time delay between drug administration and the observed decrease in thrombocyte counts. In the semi-mechanistic model, first proposed for neutrophils and leukocytes by Friberg et al. [4], a compartment of proliferative cells in the bone marrow was linked to a compartment of circulating thrombocytes via three transit compartments mimicking thrombocyte maturation and the above-mentioned time delay. In both models, the inhibitory effect of the drugs on thrombocyte proliferation was assumed to be additive and modeled as a linear function (Effect = Slope × Concdrug). Residual variability was estimated using an additive error model.
Results and discussion

Patient population

Patient characteristics were as follows (median (5th/95th percentile P₀.05/P₀.95)): age 34.9 (22.1/46.7) years; height 178 (168/190) cm; weight 80.0 (66.2/101.8) kg. Thrombocyte concentration before therapy was $185 \times 10^9 (47/448 \times 10^9)$ cells/l. Nadir counts of $7.0 \times 10^9 (3.8/15.8 \times 10^9)$ cells/l were reached after 1.71 (1.43/2.63) weeks, reflecting a Grade 4 thrombocytopenia. During the analyzed period of time, recovery to grade 1 thrombocytopenia ($> 75 \times 10^9$ cells/l) was observed after a median time of 7.0 (4.1/11.8) weeks, though only in 65% of the patients, resulting in two apparent subgroups within the study population.

Population PK/PD data analysis

Both the empirical turnover model and the semi-mechanistic model succeeded in describing the time-course of thrombocytopenia in high-dose chemotherapy. Parameters of the semi-mechanistic model were estimated with reasonable precision applying the first-order conditional estimation method with interaction. Contrary, the turnover model only successfully converged using the less accurate first-order estimation method and when excluding six patients predominantly with incomplete thrombocyte recovery from analysis. Residual variability was estimated to be $0.42 \times 10^9$ cells/l (relative standard error (RSE) 6.30%) for the turnover model and $0.36 \times 10^9$ cells/l (RSE: 5.70%) for the semi-mechanistic model, respectively. Clinical observations of thrombocyte concentrations before therapy ($185 \times 10^9$ cells/l) were reflected more accurately by the semi-mechanistic model than by the turnover model ($181 \times 10^9$ cells/l, RSE: 14.6% vs. $199 \times 10^9$ cells/l, RSE: 10.1%). Regarding the turnover model, the estimated thrombocyte production rate constant ($0.34 \times 10^9$ cells/l/h, RSE: 20.0%) showed good agreement with the rate reported for healthy individuals ($0.29 \times 10^9$ cells/l/h assuming a blood volume of 5 l, [5]). Furthermore, the estimate of the effect compartment rate constant ($0.01/h$, RSE: 20.5%) was plausible, insofar as drug-induced thrombocyte nadir was reached after 230 – 350 hours. In the semi-mechanistic model, mean transit time through the transit compartments (MTT) was estimated to be 112 hours (RSE: 4.0%). Interestingly, there seems to be a remarkable variability of MTT for thrombocytes across different anticancer treatment protocols ranging from 103 hours to 195 hours [6], whereas MTT values for leukocytes and neutrophils were shown to be consistent across drugs [4]. Both models concurrently elucidated carboplatin to be the compound with predominant thrombocytopenic potency in the CET therapy regimen. The deviating estimates of the drug-specific parameter $SLOPE_{CARBOPLATIN}$ (turnover model: 0.51 l/µmol, RSE: 15.6% vs. semi-mechanistic model: 0.08 l/µmol, RSE: 9.80%) might be due to lower drug concentrations in the effect compartment of the turnover model, while in the semi-mechanistic model SLOPE was linked to drug concentrations directly, without any effect compartment. The impact of etoposide and thiotepa on thrombocytopenia was estimated to be 0.05 l/µmol (RSE: 26.4%) and 0.21 l/µmol (RSE: 17.4%), respectively, in the turnover model, though found to be negligible in the semi-mechanistic model (proved by systematic investigation of these parameters).
Goodness-of-fit plots of the semi-mechanistic model yielded an adequate prediction of individual PD profiles (Figure 1) as the observed concentrations showed a random and uniform spread along the line of identity. In contrast, plots indicated a tendency for nadir concentrations to be underestimated by the turnover model, further supporting the superiority of the semi-mechanistic model.

Conclusion

The time-course of thrombocytopenia and relevant physiological parameters (thrombocyte concentration before therapy, thrombocyte production rate constant, mean transit time) in germ cell tumor patients undergoing high-dose chemotherapy with carboplatin, etoposide and thiotepa could successfully be described by the two models examined. However, the semi-mechanistic PK/PD model, which also takes into account physiological details of thrombopoiesis, was shown to be superior in terms of goodness-of-fit, model stability and residual variability estimates. Hence, the applicability of this model, originally developed for leukopenia and neutropenia in conventional dose settings, could be demonstrated also for the description of thrombocytopenia in a high-dose chemotherapy setting. Of the three drugs administered, carboplatin was identified as having the highest impact on thrombocytopenia. Further steps will include model refinement by accounting for the two patient subgroups and integrating thrombocyte retransfusion into the model. This might help to optimize supportive treatment during chemotherapy and to circumvent the dose-limiting adverse event of thrombocytopenia.

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References


