Population Analysis of Myelosuppression Profiles Using Routine Clinical Data after the ICE (Ifosfamide/Carboplatin/Etoposide) Regimen for Malignant Gliomas

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Received 11 September 2008; accepted 28 January 2009

Published online 10 July 2009 in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/jps.21731

ABSTRACT: We propose a simple and practical modeling approach for analysis of the data for myelosuppression after cancer chemotherapy, which can be applied when pharmacokinetic data are not available and several anticancer drugs were simultaneously administered. The model equation is based on the probability density function for the Erlang distribution. The data for cell counts of leukocytes (white blood cell, WBC), platelets (PLT), and reticulocytes (RET) obtained in routine clinical laboratory tests after the ICE (ifosfamide/carboplatin/etoposide) regimen for cancer chemotherapy were retrospectively collected from 28 patients, and a population analysis was applied. The time course profiles could be well explained by the proposed model. The individual values of the time to reach the nadir were obtained by the Bayesian method, and their medians (days) were 16.8 for WBC, 12.8 for PLT, and 8.2 for RET. Such information would be useful to determine the day of visit for outpatients especially for additional treatment to prevent side effects such as infections. The model is simple and applicable to explain the time course profiles for myelosuppression irrespective of cell types, and also practical because it requires only the data from routine clinical laboratory tests without any additional burden to patients. © 2009 Wiley-Liss, Inc. and the American Pharmacists Association J Pharm Sci 98:4402–4412, 2009

Keywords: erlang distribution; pharmacodynamics; population analysis; myelosuppresion; cancer chemotherapy; ICE; modeling and simulation

INTRODUCTION

In the treatment of cancer with chemotherapy, hematological toxicity is often a dose-limiting factor and medical staff need to know the possible lowest counts (nadir) of blood cells such as leukocytes and the time to the nadir (T_{nadir}) after the administration of anticancer drugs. Understanding such time course profiles and the variability of myelosuppresion is useful for determining the day of visit for outpatients and for planning additional treatments to prevent side effects such as infections.[1]

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Journal of Pharmaceutical Sciences, Vol. 98, 4402–4412 (2009)

For this purpose, mathematical modeling techniques based on empirical pharmacodynamic models[2,3] and mechanistic models relating to the plasma concentration or area under the plasma concentration curve (AUC) of anticancer drugs[4–9] have been proposed. Other approaches using sophisticated mechanistic models, including a "transit compartment model" for explaining the time course profile of cell counts in terms of cell proliferation and serial transition compartments, have also been proposed.[10–20] Most of those reports show the results of pharmacokinetic/pharmacodynamic modeling combined with a population analysis in well-designed clinical studies, some of which were phase 1 studies in drug development. A typical scheme for semi-physiologic population pharmacokinetic/pharmacodynamic modeling is given by Hing et al.[19] where a pharmacokinetic model was connected with a serial compartment pharmacodynamic model via an effect compartment model. A recent approach to this type of pharmacodynamic modeling is to estimate the "system-related" parameters and the "drug-related" parameters separately,[10,18] a concept which makes it possible to analyze data after combination chemotherapy by setting a weighting factor for the plasma concentration of each drug.

For routine chemotherapy in hospitals, the degree of myelosuppression should be monitored for each patient, however while the clinical studies are well-designed, the data obtained from routine therapy are usually limited, for example, plasma drug concentrations are rarely measured except for therapeutic drug monitoring, and the observed data for hematological toxicity such as leukocyte counts are usually sparse. As a result, it is usually difficult to predict the degree of side effects, that is, myelosuppression and related infections. Given these limitations, a simple and practical model would be useful so that we can explain the time course of the cell counts obtained in routine clinical therapy. The purpose of the present study was to propose a modeling strategy for analyzing and simulating myelosuppression profiles in such limited conditions where application of complicated pharmacokinetic/pharmacodynamic model analysis is difficult. In this study, we focused on the ICE regimen, a combination of ifosfamide (IFM), carboplatin (CBDCA), and etoposide (VP-16), for treatment of malignant gliomas,[21–24] and analyzed the data regarding myelosuppression such as leukocyte counts obtained from routine clinical laboratory tests with a simple and practical model, which we developed.

METHODS

Patients and Data Collection

Data from 28 patients who received ICE chemotherapy for the treatment of malignant glioma in the Department of Neurosurgery in Kyoto University Hospital from April 2003 to September 2006 were retrospectively collected. The time course data for routine clinical laboratory tests such as leukocyte (white blood cell, WBC), platelet (PLT), and reticulocyte (RET) counts, and patients' background data such as age, body weight, gender, serum creatinine (Scr), and total bilirubin (T-Bil) levels at the beginning of the chemotherapy, and the dose of anticancer drugs were collected from electronic medical charts. In the ICE treatment, the anticancer drugs (IFM, CBDCA, and VP-16) were administered via intravenous infusion once daily for 3 days in a cycle, and the doses of these drugs were determined according to the body surface area (BSA, m^2) of each patient. The standard dose and infusion period were; IFM—0.75 g/m^2 for 0.5 h, CBDCA—75 mg/m^2 for 2 h, and VP-16—75 mg/m^2 for 2 h. The doses were reduced appropriately (80% of the standard dose) in some patients and actual doses recorded in the electronic medical charts were used for the data analysis. The treatment cycle was repeated every month if necessary. This is a retrospective study using only the data available for routine cancer chemotherapy. No plasma concentrations of these drugs were measured, that is, no pharmacokinetic information was available.

This study was conducted in accordance with the Declaration of Helsinki and its amendments, and the Ethics Committee of Kyoto University Graduate School and Faculty of Medicine approved conducting this retrospective study.

Pharmacodynamic Model

In this study, there were some limitations to the pharmacodynamic modeling processes. First, no plasma concentrations of the drugs were measured during the treatment courses, and pharmacokinetic profiles could not be modeled using actually observed data. Second, the pharmacodynamic response (hematological toxicity) data after