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ORIGINAL ARTICLE

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Pharmacological considerations in high-dose chemotherapy

Abstract Recent advances in pharmacokinetic/pharmacodynamic analysis have been applied to the development of anticancer agents. In addition, there has been an increase in the interest in pharmacokinetic/pharmacodynamic analysis in relation to the field of high-dose (HD) chemotherapy. The basis for investigation of the concept of the dose-response relationship in HD should be the "exposure-response relationship"; this can be investigated in phase I and pharmacology trials of HD chemotherapy designed to define the relationship between escalation of the target drug dose and exposure. Whether pharmacokinetics are linear or nonlinear is important in the determination of optimal dosing. Nonhematological toxicities have become more important than hematological toxicities as pharmacodynamic parameters in HD chemotherapy; however, the relationship between drug exposure and the clinical outcome remains unclear. Cellular concentration and plasma exposure are important predictors of clinical effect. Wide interpatient pharmacokinetic or exposure variability is more important in HD chemotherapy than in conventional-dose chemotherapy due to the increase in the frequency and severity of nonhematological toxicities. Drug–drug interactions are also important issues in HD chemotherapy, although definitive evidence is difficult to obtain. Future investigations of HD chemotherapy are warranted on the basis of pharmacokinetic/pharmacodynamic analysis.

Key words Pharmacokinetics · Pharmacodynamics · High-dose chemotherapy

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Introduction

The use of high-dose (HD) chemotherapy with either bone marrow transplantation or autologous hematopoietic progenitor stem-cell support in the treatment of solid tumors as well as leukemia and lymphomas has recently been increasing [2, 11, 15]. Before the initiation of HD chemotherapy, information from preclinical and clinical pharmacology trials is necessary, and recent advances in pharmacokinetic/pharmacodynamic analysis have been applied to the development of anticancer agents. In addition, several approaches to the investigation of the safety of drug administration and pharmacological issues have been used in HD chemotherapy. In this review, several topics relating to clinical pharmacology in HD chemotherapy are discussed.

Dose-exposure relationship in HD chemotherapy

It is generally believed that HD chemotherapy should be effective due to the steep dose-response relationship observed in preclinical models used to test the anticancer agents in such regimens [5–7]. The dose-response relationships of several agents have also been investigated in vitro; these studies show that melphalan, thiotepa, cisplatin, and 4-hydroxycyclophosphamide have steep "dose-response" relationships in the MCF-7 breast cancer cell line [7]; however, these relationships are more accurately termed "exposure-response relationships". Recently, increasing information has become available regarding the relationship between the delivered dose and the plasma drug exposure; such information includes the area under the concentration versus time curve (AUC) and the relationship between exposure and the clinical anticancer effect. In addition, the concept of phase I and pharmacology trials of HD chemotherapy as a means of defining the relationship between escalation of the target drug dose and the AUC and that between the AUC and nonhematological toxicity

has been recognized. Such trials are similar to conventional phase I trials without stem-cell support.

Recent phase I studies have reported nonsaturable dose-exposure relationships in HD chemotherapy. Stemmer et al. [16] reported on paclitaxel dose escalation in combination with cyclophosphamide and cisplatin with autologous hematopoietic progenitor stem-cell support. A proportional increase in the AUC of paclitaxel was observed with increasing dose, although paclitaxel disposition has been reported to be predicted by a model with saturable kinetics [8, 14]. The plasma pharmacokinetics of mitoxantrone have also been reported to be linear at doses ranging between 15 and 90 mg/m^2 [3]. The pharmacokinetic nonlinearity or saturable pharmacokinetics of anticancer agents is an important issue in the selection of anticancer agents in HD chemotherapy.

An inverse relationship between the delivered thiotepa dose and steady-state clearance in patients receiving high-dose thiotepa and cyclophosphamide was reported by Henner et al. [10]. This observation, although not confirmatory, suggests that thiotepa is metabolized to tepa by a saturable enzymatic process.

Exposure-response relationship in HD chemotherapy

Myelosuppression is thought to be the most important pharmacodynamic parameter in conventional phase I trials of new agents. However, nonhematological toxicities have become more important than hematological toxicities in terms of pharmacodynamics in the HD setting. Van Warmerdam et al. [18] reported that ototoxicity was strongly related to the cumulative carboplatin AUC when HD carboplatin was given in combination with cyclophosphamide and thiotepa, although no relationship was found between other toxicities and the AUC of carboplatin; this may have been due to the influence of the overlapping toxicities of cyclophosphamide and thiotepa. Jones et al. [12] showed that 20/38 patients (53%) developed pulmonary injury following treatment with high-dose cyclophosphamide, cisplatin, and carmustine (BCNU) [12]. Analysis revealed that a BCNU AUC of >600 mg $\cdot$ ml^{-1} $\times$ min is associated with an increased risk for acute lung injury.

Hepatic veno-occlusive disease (HVOD) is known to be a frequent life-threatening toxicity in patients who receive bone marrow transplantation after administration of HD busulfan-containing chemotherapy [9]. Recent studies have shown that HVOD is associated with the plasma AUC of busulfan and that the morbidity and mortality of HVOD in adults may be reduced by pharmacokinetically guided busulfan dose adjustment. Vassal et al. [17] also reported that the mean AUC of busulfan was higher in patients with HVOD than in those without HVOD. Although nonhematological toxicities are important pharmacodynamic parameters, clinical outcomes, including disease-free survival and complete response rates, are more important end points in HD chemotherapy.

Unfortunately, few studies have shown a correlation between pharmacokinetics and clinical outcome. The pharmacological approach will become more important in evaluations of the relationship between drug exposure and the patient's prognosis not only in phase I trials but also in large-scale phase II or phase III studies of HD chemotherapy.

Cellular pharmacokinetics in HD chemotherapy

Although plasma exposure is important in predicting pharmacodynamics, cellular concentration is important in predicting the clinical effect. Canal et al. [3] reported a correlation between the plasma mitoxantrone AUC and the lymphocyte AUC as well as a correlation between the mitoxantrone dose given and the plasma AUC in patients with refractory lymphoma. Although the authors measured the cellular concentration in lymphocytes, not in lymphoma cells, this type of information is helpful in evaluating whether a drug is a good candidate for an HD chemotherapy regimen. In addition, analysis of the "dose-plasma exposure-cellular exposure-clinical outcome" relationship will be a new research area in HD chemotherapy.

Interpatient pharmacokinetic variability

Anticancer drug doses are generally close to the maximum tolerated dose; therefore, the concept of pharmacokinetic variability is important. In the case of drugs with wide interpatient pharmacokinetic or exposure variability, some patients may be treated at subtherapeutic doses, whereas others may be exposed to lethal drug levels. This concept is more important in HD chemotherapy than in conventional-dose chemotherapy because the risk of treatment-related death is increased in patients whose plasma clearance of cytotoxic drugs is low. The HVOD induced by busulfan is attributable to high plasma exposure of the drug and to the wide interpatient variability of busulfan disposition [9, 17].

Cyclophosphamide is a widely used anticancer agent that requires metabolic activation. This prodrug is initially activated in hepatic microsomes to form 4-hydroxycyclophosphamide and aldophosphamide; beta elimination removes acrolein from aldophosphamide, forming the active alkylating species phosphoramide mustard. Large differences in the rate of conversion from cyclophosphamide to 4-hydroxycyclophosphamide and aldophosphamide have been observed on incubation of cyclophosphamide with microsomal preparations [1]. This finding is in accordance with the wide interpatient pharmacokinetic variability of cyclophosphamide in HD chemotherapy [16]. Similar observations have been reported for cisplatin, carmustine (BCNU) [12], and thiotepa [10] as well as for busulfan [17]. Pharmacokinetically guided, individualized dosing in HD chemotherapy may be possible after analyzsing of population parameters relating drug clearance and population pharmacodynamics.

Drug-drug interactions in HD chemotherapy

Drug-drug interactions have been one of the most important topics in oncologic pharmacology in recent years. However, only limited data are available for HD chemotherapy.

Thiotepa is often given simultaneously with cyclophosphamide by continuous i.v. infusion. However, Anderson et al. [1] have reported that thiotepa inhibits the conversion of cyclophosphamide in vitro, although the clinical significance of alterations in exposure to 4-hydroxycyclophosphamide and aldophosphamide during coadministration with thiotepa is uncertain. Similar clinical observations have been reported by Chen et al. [4], who have concluded that an interaction between cyclophosphamide and thiotepa may explain the lower initial clearance rate observed for cyclophosphamide during the second cycle of therapy. However, it has become clear that HD paclitaxel does not alter the pharmacokinetics of cyclophosphamide or cisplatin [16].

Recent investigations have revealed that not only anticancer drugs but also other agents influence the pharmacokinetics of anticancer drugs in HD chemotherapy. Chen et al. [4] also reported that there was no change in cyclophosphamide clearance in a patient taking phenytoin but that a change was observed in a patient taking phenobarbital. However, another report showed that the disposition of cyclophosphamide and thiotepa was unaffected by the alkylating agent modulator novobiocin [13].

Lack of phase I and pharmacology trials in Japan

To date, few phase I or pharmacology trials have been conducted or reported in Japan. HD chemotherapy has been performed mainly by investigators in the field of hematology rather than oncology; such investigators are unfamiliar with the methodology for performance of phase I trials, even those of conventional-dose anticancer agents. Most of the HD regimens are similar to those used in the United States and Europe, and the drug doses are similar to or lower than those used in the West. When the dose is reduced the reduction is decided empirically and is not based on pharmacology data. Thus, unfortunately, we have no information on the racial effects of HD anticancer treatment on pharmacokinetics. The establishment of more scientific and effective clinical research systems is essential if phase I and pharmacology studies of HD chemotherapy are to be initiated in Japan.

Conclusions

Pharmacokinetic information is helpful in defining the optimal dose and rate of infusion used in HD chemotherapy. A pharmacological approach that includes phase I and pharmacokinetic/pharmacodynamic analysis should be extensively used, particularly in Japan. One of the most important problems relating to pharmacokinetics/pharmacodynamics in HD chemotherapy is that limited information is available about the relationship between drug exposure and the clinical outcome. Studies providing data to support the rationale for HD chemotherapy are necessary.

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