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Vincristine pharmacokinetics and response to vincristine monotherapy in an up-front window study of the Dutch Childhood Leukaemia Study Group (DCLSG)☆

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Abstract

The relationship between vincristine pharmacokinetics and its antileukaemic effect in children is unknown. Since vincristine plays a key role in the treatment of childhood acute lymphoblastic leukaemia (ALL), it is worthwhile to explore if efficacy can be improved by individual dose adjustment. Therefore, we studied the relationship between vincristine antileukaemic effect and pharmacokinetics in children newly diagnosed with ALL before the start of standard induction chemotherapy. Vincristine plasma concentration was measured by high-pressure liquid chromatography analysis with electrochemical detection. Primary pharmacokinetic parameters were estimated by maximum *a posteriori* parameter estimation with a Bayesian algorithm using the ADAPT II software package. Secondary pharmacokinetic parameters were calculated from the model. Response to a single dose of vincristine was determined on bone marrow (BM) and peripheral blood (PB) smears after 3 days. Variability of vincristine pharmacokinetics did not explain variability of response to vincristine monotherapy. Our results do not support the clinical application of pharmacokinetically guided adaptation of a standard body surface area-based dose of vincristine.

Keywords: Vincristine; Acute lymphoblastic leukaemia; Pharmacokinetics; Pharmacodynamics; Childhood; Response

1. Introduction

Vincristine has played a key role in the treatment of childhood acute lymphoblastic leukaemia (ALL) for several decades [1]. Two factors potentially affect the antileukaemic effect of vincristine *in vivo*: cellular drug resistance and pharmacokinetics. *In vitro* cellular drug resistance and its prognostic significance in childhood ALL have been well studied [2–5], but the relationship between vincristine pharmacokinetics and antileukaemic effects *in vivo* is unknown.

A reduced dose intensity of remission induction therapy including vincristine is associated with a decreased chance of a favourable clinical response in ALL [6,7] suggesting a correlation between drug effect and systemic exposure to drugs. In a group of 27 patients with

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various haematological disorders, a correlation between vincristine toxicity and systemic exposure was indeed reported [8]. In children with ALL or Wilms' tumour, vincristine neurotoxicity and peak plasma concentrations were correlated [9]. However, it is not known whether a correlation exists between the vincristine antileukaemic effect and systemic exposure.

A relationship between the vincristine antileukaemic effect and systemic exposure would provide a rationale for pharmacokinetically guided, individualised dosing of vincristine, with the aim to achieve a target systemic exposure in each patient [7,10]. This strategy of individualizing chemotherapy is successfully applied for methotrexate during post-remission treatment of childhood ALL [11]. Therefore, we studied the relationship between the antileukaemic effect of vincristine and its pharmacokinetics in children newly diagnosed with ALL before the start of standard induction chemotherapy. In an up-front window study of 3 days, children received a single dose of vincristine without other chemotherapeutic drugs or corticosteroids. Vincristine pharmacokinetics was determined in the study. Cellular resistance to vincristine was determined *in vitro* in blast cells collected at diagnosis. Reduction of blast cells in bone marrow (BM) and peripheral blood (PB) during the time of the 3-day window study was determined.

2. Methods

2.1. Patients

Children newly diagnosed with ALL were asked to participate in an up-front window study of vincristine pharmacokinetics and dynamics before the start of standard induction chemotherapy according to the Dutch Childhood Leukaemia Study Group (DCLSG) protocol, ALL-9. The diagnosis was confirmed by the central laboratory of the DCLSG, using conventional cytological and immunological criteria [6,12,13]. Cytogenetic studies were done in all patients. Exclusion criteria for the ALL-9 protocol were the following: age older than 18 years, treatment with corticosteroids or cytotoxic drugs in a period of four weeks before diagnosis, ALL as a second malignancy or mature B-cell leukaemia. Children with meningeal involvement at diagnosis were eligible for the ALL-9 protocol, but did not participate in the window study. Patients were enrolled between June 1997 and January 2000 in ten participating hospitals, cooperating in the DCLSG. Demographic and prognostic parameters of all patients were registered at the DCLSG central office. The study protocol was approved by the Medical Ethics Review Board of the participating hospitals and written informed consent was obtained from all patients and/or parents.

2.2. Study protocol

At the start of the study, 1.5 mg/m^2 vincristine was administered as an intravenous (i.v.) bolus injection. Blood sampling was scheduled before and 10, 30, 180 and 1440 min after vincristine administration. This schedule was designed with the optimal sampling design module of the ADAPT II software package [14,15]. Heparinised blood samples (4 ml) were drawn from a distant site from the vincristine injection and immediately placed on ice. The actual time of the vincristine injection and blood sampling was registered. Plasma was separated within 3 h after sampling by centrifugation of the blood at 4 °C and 560*g* for 10 min and plasma was stored at −80 °C until analysis.

After 3 days, the response to a single dose of vincristine was evaluated locally and at the central laboratory of the DCLSG. The percentage of lymphoblasts was determined on BM and PB smears. In addition, the white blood cell count (WBC) was determined, which allowed evaluation of three response parameters: a decrease of the percentage of lymphoblasts in BM and PB, and a decrease of the absolute number of lymphoblasts in PB. Corticosteroids or other cytotoxic drugs were not administered during the time of the study.

2.3. High-pressure liquid chromatography analysis and pharmacokinetic analysis

The vincristine plasma concentration was measured by high-pressure liquid chromatography analysis (HPLC) with electrochemical detection [16,17]. A two-compartment, first-order pharmacokinetic model was fitted to the vincristine concentration data. Primary pharmacokinetic parameters were estimated by maximum *a posteriori* parameter estimation with a Bayesian algorithm using the ADAPT II software package [14,15,18–20]. Secondary pharmacokinetic parameters were calculated from the model. Peak plasma concentrations of vincristine after 1 and 5 min were calculated with the simulation module of the ADAPT software package.

2.4. Assessment of in vitro cellular resistance to vincristine

The vincristine dose lethal to 50% of the patients BM lymphoblasts (LD50) was determined *in vitro* by using the MTT-assay, an assay based on the reduction of 3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyl tetrazolium bromide (MTT) to a formazan by living cells [2–4]. The MTT-assay was performed at the DCLSG laboratory on BM lymphoblasts collected at diagnosis.

2.5. Statistical analysis

Because the distribution of pharmacokinetic parameters and response parameters did not appear to be