Cellular pharmacokinetics of doxorubicin in patients with chronic lymphocytic leukemia: comparison of bolus administration and continuous infusion

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Abstract. The purpose of this study was to determine whether administration of doxorubicin (DOX) as a continuous infusion or a bolus injection resulted in similar leukemic cell drug concentration in patients with refractory chronic lymphocytic leukemia (CLL). This study was carried out on five patients with refractory CLL, with DOX administered either as a bolus injection (35 mg/m²; CHOP protocol) or as a constant-rate infusion for a period of 96 h (9 mg/m² per day; VAD protocol). The two types of drug administration were used alternatively with the same patient. Plasma and cellular DOX concentration were determined using high-performance liquid chromatography. Peak plasma DOX levels were higher after the bolus injection than after continuous administration (1509 ± 80 ng/ml vs 11.6 ± 1.8 ng/ml, respectively), whereas the plasma area under the curve (AUC) levels were similar. Maximum DOX cellular concentrations were 8629 ± 2902 ng/10⁹ cells (bolus injection) and 2745 ± 673 ng/10⁹ cells (96 h infusion). The cellular AUC after the bolus injection was 2.85 times greater than that observed after continuous administration. This difference was due to a higher cellular peak level followed by a relatively prolonged retention of the drug, with a loss of only 25% in the first 24 h following. These findings demonstrated that in CLL the cellular DOX exposure can be notably modified by the method of drug administration, with higher drug intracellular concentrations being achieved after bolus administration than with the infusion schedule.

Introduction

Doxorubicin (DOX) is widely used in the treatment of lymphoid neoplasias. In non-Hodgkin malignant lymphomas (NHML), DOX-based regimens significantly improved both response and survival rate as compared to first-generation COP (cyclophosphamide, vincristine, prednisone) or COP-derived protocols (see [4] for review). In advanced chronic lymphocytic leukemia (CLL), DOX remains a potentially useful drug even if it is now challenged by new drugs such as fludarabine [11] and 2-chlorodeoxyadenosine (2DCA, [16]). DOX is usually administered as a bolus injection over a 1–5 min period in doses ranging from 25–75 mg/m², in association with vincristine, cyclophosphamide, and prednisone, according to CHOP or CHOP-derived regimens [6, 7, 13].

It has been argued, however, that some DOX-related side effects (including cardiotoxicity) could be related to the peak plasma concentrations [9, 12]. Therefore, some investigators have suggested that DOX be preferentially administered as a continuous infusion [12]. Subsequently, a number of protocols based on DOX continuous infusion have been developed. Among these protocols, VAD (vincristine-doxorubicin-dexamethasone) or VAD-derived regimens have been used in multiple myeloma [2] as well as in refractory CLL and NHML [14, 21].

Despite the clinical evidence that VAD represents an efficient protocol, it remains uncertain whether continuous infusion represents the most appropriate method of DOX administration in terms of DOX-induced anti-tumor cytotoxicity. Indeed, previously reported in vitro studies emphasized that both the magnitude of drug cellular exposure and peak concentration are essential for DOX cytotoxicity [1, 8, 15]. These findings strongly suggest that, in vivo, the modality of drug administration may not only profoundly influence the cellular pharmacokinetic parameters but could also modify its anti-tumor activity.

The purpose of this study was to determine whether continuous infusion (VAD) and bolus injection (CHOP) resulted in similar leukemic cell DOX exposure in refractory CLL patients with DOX being administered in the same total dose.
Table 1. Patient characteristics

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age</th>
<th>Hb (g/dl)</th>
<th>Lymphocytes (× 10⁹/l)</th>
<th>Platelets (× 10⁹/l)</th>
<th>Generalized lymphadenopathy</th>
<th>Previous treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>62</td>
<td>12</td>
<td>140 100</td>
<td>146 000</td>
<td>+</td>
<td>CLB, COAP</td>
</tr>
<tr>
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<td>9.5</td>
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<td>102 000</td>
<td>+</td>
<td>CLB, COAP</td>
</tr>
<tr>
<td>3</td>
<td>66</td>
<td>11.6</td>
<td>95 000</td>
<td>112 000</td>
<td>+</td>
<td>CLB+PDN, COAP</td>
</tr>
<tr>
<td>4</td>
<td>50</td>
<td>11.2</td>
<td>96 700</td>
<td>160 000</td>
<td>+</td>
<td>CLB, COAP</td>
</tr>
<tr>
<td>5</td>
<td>67</td>
<td>10.2</td>
<td>140 000</td>
<td>104 000</td>
<td>+</td>
<td>CLB+PDN, COAP</td>
</tr>
</tbody>
</table>

CLB, Chlorambucil; PDN, prednisone; COAP, cyclophosphamide, vincristine, aracytain, prednisone

* At time of the initiation of therapy

Patients, materials and methods

Patients. This study was carried out on five patients with B-CLL (Table 1). Patients were in advanced stages of the disease, corresponding to group B or C according to the Workshop classification [3]. They were refractory to prior therapy with chlorambucil, COP (cyclophosphamide, vincristine, and prednisone), or COAP (COP + cytosine-arabinosine) protocols. None of the patients had received DOX prior to the study.

Exclusion criteria were: age above 70 years, performance status (WHO grading) above 2, isotopic ventricular ejection fraction less than 60%, leucocytes <20000 mm², and platelets <100000 mm². Informed consent was obtained from each patient in accordance with institutional policy.

Drugs and drug administration. For the VAD protocol, DOX (9 mg/m² per day) was administered over 96 h by means of an indwelling central venous catheter connected to an external pumping device. Additional treatment consisted of vincristine (0.4 mg/m² per day) and 40 mg dexamethasone orally, both administered from day 1 to day 4.

For the CHOP protocol, DOX (36 mg/m²) was administered on day 1 over a 5-min period using an indwelling central venous catheter connected to an electric syringe. Additional therapy consisted of cyclophosphamide (750 mg/m²); vincristine (2 mg/m² on day 1), and prednisone (40 mg/m² from day 1 to day 5).

The treatment always began with a CHOP course and courses were repeated at 40-day intervals. Each patient underwent at least two courses of treatment, and treatment was interrupted if there was no response or if major toxic effects were observed. A total of 14 cycles (7 CHOP, 7 VAD) were performed.

Blood sampling. Venous blood was drawn at regular intervals from 5 min up to 216 h in ethylenediaminetetraacetate – containing tubes and placed on ice immediately to prevent further DOX loss. After centrifugation, plasma was collected and frozen at −20 °C until analysis. Mononuclear cells were obtained by separation on Ficoll-Hypaque, and the pellet of mononuclear cells was diluted in 1.1 ml 0.9% saline solution. The number of cells was determined and the sample was frozen at −20 °C until analysis. The entire procedure was carried out at 4 °C. After Ficoll separation, the mononuclear cells of CLL patients consisted of B lymphocytes (more than 95%) with a restricted CD5/CD19 membrane.

After continuous infusion, steady-state DOX concentrations were reached between 24 and 48 h and averaged 11.6±1.8 ng/ml, which corresponds to 0.7% of the peak plasma value obtained after bolus injection. After the end of the infusion, the plasma disappearance of DOX was biexponential with a terminal half-life of 44.6±8.5 h.

As shown in Table 2, except for the peak plasma concentrations the plasma pharmacokinetic parameters showed no significant differences (P <0.05) as a function of the duration of infusion. Similarly, the plasma pharmacokinetic parameters of doxorubicinol (including plasma AUC values) were not influenced by the modality of DOX administration (data not shown).