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A phase II study for the evaluation of quinine as a modulator of multidrug resistance in non-Hodgkin's lymphoma

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1. Introduction

Reversal of P-glycoprotein-mediated multidrug resistance (MDR) has been the subject of much attention and a large variety of original compounds have been evaluated in clinics, but none of them has entered routine practice. The initial molecules that were shown to reverse MDR, such as verapamil, cyclosporine or quinidine, appeared too toxic, at the doses required for MDR reversal, to be used in this indication. It is also clear that most solid tumours display several mechanisms of resistance, among which MDR may not play the major role. Nevertheless, the proof that MDR reverters could recruit new chemotherapy responders has been brought in haematological malignancies, especially in non-Hodgkin lymphoma (NHL), with several compounds including verapamil[1] and dex-verapamil.[2] None of them could be developed as a resistance modulating agent because of its own toxicity. In the process of seeking a clinically useful MDR modulator to be associated with chemotherapy for the treatment of NHL, we selected quinine because of its low and reversible toxicity and of the validation of its MDR modulating activity in acute leukaemias in phase II studies.[3] This drug was not favourably considered after two negative phase III studies combining quinine with mitoxantrone[4] or idarubicin,[5] but these drugs are not liable for Pgp–mediated MDR, mitoxantrone because it is not a good substrate for Pgp transport, and idarubicin because of its very high lipophilicity, which overpasses Pgp–mediated efflux.[6]

2. Patients and methods

In order to validate the use of quinine as a MDR modulating agent in NHL, we performed a phase II study with a drastic selection of patients who were only included when resistance to chemotherapy was established with certainty. Patients should have been previously treated with at least 2 lines of chemotherapy, including an anthracycline-based protocol (CEOP,[7]) and a regimen containing etoposide plus ifosfamide. Patients were only included in the study: 1) after having received new courses of CEOP as third-line therapy, if they were non-responsive; and 2) directly, if they had never responded to first and second-line treatments. Resistance was defined by progression or stable disease after one or two cycles of CEOP or by complete

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absence of any objective response to previous regimens. Other inclusion criteria included: age between 18 and 70 years, performance status $\leqslant 2$, bi-dimensionally measurable disease, adequate bone marrow, renal and hepatic functions and were not at risk for cardiac toxicity. All patients were required to give written informed consent before entry. The study was approved by the Comité Consultatif de Protection des Personnes dans la Recherche Biomédicale of Bordeaux. CEOP regimen consisted of cyclophosphamide 750 $mg \times m^{-2}$ intravenous (IV) day 1, epirubicin 60 $mg \times m^{-2}$ IV day 1, vincristine 1.4 $mg \times m^{-2}$ (maximum 2 mg) IV day 1 and prednisolone 40 $mg \times m^{-2}$ per os day 1 through 5. Quinine was administered at a dosage of 30 $mg \times kg^{-1}$ per day as a 48-hour continuous infusion, starting 24 hours prior to chemotherapy.[3] Treatment was repeated every 21 days, with hospitalisation and cardiac monitoring required for each administration. Toxicity was assessed according to the World Health Organisation toxicity criteria. Response assessment had to be performed after the two first cycles and 4 weeks after the 6^{th} cycle, using NCI-sponsored international working group recommendations. A pharmacokinetic study of epirubicin and quinine was performed, using validated HPLC methods and a limited sampling strategy.[8] MDR phenotyping was done by immunohistochemistry using the monoclonal antibody JSB1.

3. Results

Between January 1997 and December 2002, a total of 62 patients with relapsed NHL were treated in our institution with CEOP regimen after having previously received at least two lines of chemotherapy, including anthracycline-based and etoposide plus ifosfamide-containing regimens. Among these patients, only 15 could be considered to have an anthracycline-refractory disease at this stage, and thus were eligible for modulation of chemotherapy by quinine. A total of 41 courses of CEOP-quinine were delivered. The mean dose of quinine was 27.2 $mg \times kg^{-1}$ per day. For epirubicin, dose intensity was 18.8 $mg \times m^{-2}$ per week (range 11.7–20.7) and relative dose intensity was 94% (range 58.3–103.7). Among 15 assessable patients, there were 2 complete responses and 2 partial responses, for an overall intent-to-treat response rate of 26.7% (95% confidence interval: 7.7–55). The first patient with complete response had a partial response after first-line treatment with CEOP; he received afterwards the ifosfamide-etoposide combination as second-line treatment and developed a novel partial response; at the second recurrence, he received once again the CEOP regimen and was progressing when quinine was added, according to the design of the study. He remains well and disease-free with a 61-month follow-up. The other complete responder had received the CEOP regimen as first-line treatment. Since he was responding neither to CEOP, nor to ifosfamide-etoposide, he received directly CEOP + quinine as third-line treatment, and developed a complete response. This patient is still alive and disease-free with a 35-month follow-up. The two patients with partial response remained progression-free for 5 and 2 months respectively and eventually died from their disease. Treatment delay because of haematological toxicity was required in 8 (19%) courses. Extra-haematological toxicity was mild. One patient had transient hearing loss and tinnitus that resolved within cycle 3, while another complained of tinnitus and vertigo on first cycle only. Two other patients had otologic signs that were transient and non-severe. Baseline cardiac evaluation was available for all 15 patients. Re-assessment of left ventricular ejection fraction after cycle 2 was performed in 7 patients, and after cycle 6 in 3 patients with no evidence of cardiac toxicity. The pharmacokinetics of epirubicin was not altered in comparison with a reference population and the mean plasma levels of quinine (3.67 to 19 $\mu g \times ml^{-1}$) fell within the range of the expected values. Four tumour samples were positive for P-glycoprotein, 3 of them originating from responders, showing a significant association between response and Pgp positivity ($P = 0.015$).

4. Conclusion

Our study outlines the importance of MDR among the mechanisms of resistance to chemotherapy in aggressive lymphomas. Furthermore, it shows that this resistance can be reversed by quinine in a limited but significant number of patients, without alteration in the pharmacokinetics of epirubicin. We consider that a phase III trial ascerting the role of quinine in the management of NHL is warranted.

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