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Letter to the Editor

Serious haematological toxicity of cyclophosphamide in relation to CYP2B6, GSTA1 and GSTP1 polymorphisms

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Cyclophosphamide (CPA) is widely used as an anticancer and immunosuppressive agent in various indications, and the dosage given may vary considerably depending on the disease treated. A recent review [1] has described the pharmacokinetics of CPA, a prodrug of which 70–80% of the administered dose is activated by cytochrome P450 (CYP) to the active alkylating species 4-hydroxycyclophosphamide (4OH-CPA). Several CYPs are responsible for CPA activation, mainly CYP2B6 and, secondarily, CYP2C9, CYP2C19 and CYP3A4/5 (Figure 1) [2]. Systemic exposure to cyclophosphamide metabolites after fixed doses of cyclophosphamide may vary by up to 10-fold between patients [1]. Genetic variants of CYPs involved in CPA metabolism may contribute to its pharmacokinetic variability and genetic polymorphisms of glutathione S-transferases may influence its toxicity.

We report a case of a patient who experienced severe toxicity (pancytopenia) with small dosages of CPA (1.60 mg kg^{-1} day^{-1}). A 25-year-old female patient presenting with extramembranous glomerulonephritis (with tubulointerstitial lesions) began treatment with cyclophosphamide in association with prednisone (40 mg day^{-1}). She also received the following treatments: an angiotensin-converting enzyme inhibitor, an oral anticoagulant, a statin and recombinant erythropoietin. When cyclophosphamide treatment was initiated, creatinine clearance was 32 ml min^{-1}, leucocytes 6500 μl^{-1}, absolute neutrophil count (ANC) 4550 μl^{-1}, platelet count 345 000 μl^{-1} and haemoglobin 11.6 g dl^{-1}. After 14 days of treatment (day 14), the patient was admitted to hospital because of an intense asthenia accompanied by fever (38.8–39.5°C) which had appeared 78 h previously. The patient had ulcerative pharyngitis with dysphagia, about 20 pyodermitis lesions infected by *Staphylococcus epidermidis*, total body hair loss and painful diarrhoea. Severe neutropenia (ANC < 100 μl^{-1}) and anaemia (haemoglobin 8.8 g dl^{-1}) were observed, leucocyte and platelet absolute counts were 6000 μl^{-1} and 178 000 μl^{-1}, respectively. Hepatic enzymes were within normal range. All the treatments were stopped and antibiotherapy was initiated in association with an erythropoiesis-stimulating agent and recombinant granulocyte colony-stimulating factor. At day 20 the platelet count was 34 000 μl^{-1} and haemoglobin 5.8 g dl^{-1}. At day 21, the patient was apyretic. Aplasia ceased on day 22. Pharyngitis and pyodermitis were cured on day 23 and hairiness was normal 3 months after cyclophosphamide discontinuation. As all the drugs previously used were recommenced without any side-effect and as the clinical symptoms observed caused a CPA overdosage, we therefore suspected an alteration of CPA metabolism or detoxification pathways. Genetic variants of enzymes involved in these pathways were explored. Results were the following: CYP2B6516TT, CYP2C9*1/*3, CYP2C19*1/*1, CYP3A4*1 A/*1 A, CYP3A5*3/*3, GSTA1*A/*B, GSTM1+ (presence of gene), GSTT1+, GSTM3*B/*B and GSTP1*A/*B.

The major side-effects observed were aplasia and total body hair loss. They are more likely to be observed when cyclophosphamide is used as a cancer treatment (500–4000 mg m^{-2} day^{-1}) than for nonmalignant kidney disorders (glomerulonephritis) (100–200 mg m^{-2} day^{-1}). As leukopenia, thrombocytopenia and anaemia are dose-related, we hypothesized that the aplasia observed in the present patient, despite the low dose of CPA, could be explained by enhanced 4OH-CPA exposure because of increased activation pathway of CPA into 4OH-CPA and less active detoxification pathways of 4OH-CPA and phosphoramide mustard. This was specially as the CLCr was 32 ml min^{-1} and hepatic function was normal. Indeed, Xie *et al.* [3] have demonstrated *in vivo* (patients with haematological malignancies) that the CYP2B6516T variant allele contribution to CPA elimination clearance was about twice that from wild-type gene. Moreover GSTA1*B/*B

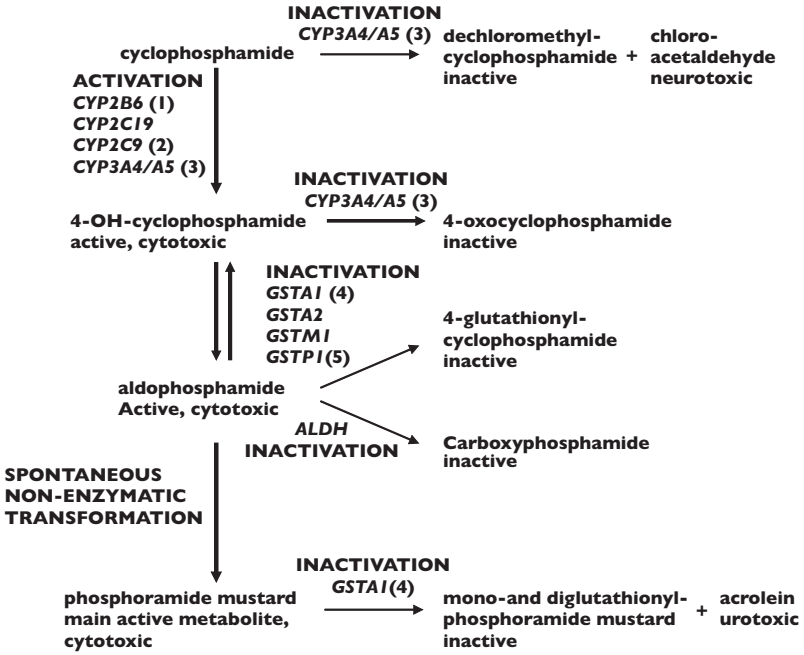

Figure 1

Cyclophosphamide metabolic pathways (adapted from Timm *et al.* [2]). The mutations **(1)** CYP2B6516TT, **(2)** CYP2C9*1/*3, **(3)** CYP3A5*3/*3, **(4)** GSTA1*A/*B, and **(5)** GSTP1*A/*B were identified in the presented case

polymorphism, corresponding to lower detoxification, was correlated with greater survival than GSTA1*A/*B or GSTA1*A/*A in breast cancer therapy with CPA [4]. The detoxification pathway of anticancer drugs was decreased in carriers of GSTP1 variant alleles [5]. Nakajima *et al.* [6] have demonstrated *in vitro* that inhibition of GSTP1 enhances the antitumour activity of CPA.

The genetic polymorphisms observed in our patient might contribute to decreased detoxification pathways and to increased exposure to 4OH-CPA and could explain the reported adverse effects. Further studies are needed to confirm these results.

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