Letter to the Editors

Failure of liver function tests in predicting drug clearance of chemotherapeutic agents in a patient who had recovered from hepatic congestion

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Vincristine and doxorubicin are frequently used for the treatment of haematologic malignancies. Myelosuppression and mucosal damage are common adverse effects of these agents and rigorous dose adjustment is required. Since vincristine and doxorubicin are mainly metabolized by the liver [1, 2], dosage adjustment in patients with liver dysfunction is essential to avoid excessive accumulation of the drugs.

Several quantitative liver tests have been used to adjust dosage regimens for drugs in patients with hepatic dysfunction. However, little information is available on whether full doses of anticancer agents can be safely given to patients who have recovered from liver damage.

An 85-year-old man was admitted to our hospital due to progressive exertional dyspnoea. A computed tomography scan revealed a mass measuring 68 × 32 mm attached to the anterior wall of the right ventricle, and bilateral pleural effusions. The diagnosis of lymphoma with cardiac infiltration was established based on flow cytometric and pathological examination of the pleural liquid.

At admission, the patient presented with acute respiratory failure and hypotension. An echocardiogram showed massive pericardial effusions, leading to the diagnosis of cardiac tamponade. Blood examination revealed abnormalities in liver function: total bilirubin (T-Bil) 5.6 mg dL⁻¹ (normal range 0.3–1.2 mg dL⁻¹), direct bilirubin (D-Bil) 3.4 mg dL⁻¹ (normal range 0.0–0.4 mg dL⁻¹), aspartate aminotransferase (AST) 458 U L⁻¹ (normal range 10–40 U L⁻¹) and alanine aminotransferase (ALT) 600 U L⁻¹ (normal range 5–40 U L⁻¹). After emergent pericardiocentesis, respiratory and hepatic functions improved, and serum concen-

trations of T-Bil, D-Bil, AST and ALT normalized (Figure 1). On day 20, liver function tests were as follows: T-Bil 1.1 mg dL⁻¹, AST 39 U L⁻¹ and ALT 32 U L⁻¹. Repeated echocardiography failed to show any evidence of the residual pericardial fluid.

On day 20 after admission, the patient was treated with cyclophosphamide 525 mg m⁻², doxorubicin 35 mg m⁻², vincristine 2 mg infusion and prednisolone 100 mg. His clinical course was uneventful until day 23, when the patient presented with massive haematochezia and mild liver dysfunction. Intestinal peristalsis was arrested and a diagnosis of gastroparesis was made. The patient also developed a neutropenic fever on the same day. Microbiological examination of the blood and stool was negative. Despite broad-spectrum antibiotics, the fever persisted and his conditions deteriorated rapidly. The patient finally died of hypovolaemic shock which was unresponsive to fluid replacement on day 25. Serum concentrations of vincristine and doxorubicin were not determined during the treatment.

At postmortem examination, the lymphoma was in complete remission. Extensive mucosal damage was documented in the duodenum and the jejunum, and erosion was mild in the oesophagus and the stomach. Gross appearance of the liver was normal, while microscopic examination detected persistent hepatic congestion with degenerated hepatocytes. Bone marrow was hypoplastic.

This case suggested that serum concentrations of AST, ALT and bilirubin do not reflect the capacity of drug clearance in patients who have recovered from hepatic congestion. We suspected that severe mucosal damage of the

Figure 1

Clinical course, laboratory data and treatment of the patient. Chemotherapy included cyclophosphamide 525 mg m⁻² doxorubicin 35 mg m⁻², and vincristine 2 mg infusion

duodenum and jejunum, hepatic failure and myelosuppression were attributable to the toxicity of vincristine and doxorubicin, since they are common adverse effects of these agents, and thorough examination failed to show any evidence of infectious complications. The presence of neurological damage also supported this diagnosis. His clinical course suggests that 35 mg m⁻² of doxorubicin and 2 mg of vincristine caused fatal complications to the patient who had recovered from liver dysfunction due to right ventricular failure. Doses of vincristine and doxorubicin are usually reduced in patients with liver dysfunction, since these agents are mainly metabolized in the liver. However, it should be noted that his liver function remained within normal limits when he received these agents.

It remains unknown why serum concentrations of bilirubin were not useful as aids to prevent drug toxicities. We can postulate some possibilities. There might be a significant difference in metabolism between total bilirubin and the anticancer agents used in this patient. In general, exogenous products are hepatically metabolized mainly via two mechanisms: phase I and phase II reactions [3]. Phase I reactions are catalyzed predominantly by the cytochrome P450 superfamily of mixed function oxidases (CYP). In phase II reactions, the drug or its metabolite is conjugated to a large water-soluble polar group, such as glucuronic acid. While phase II enzyme activity is maintained in most liver diseases, CYP activity is frequently impaired in patients with liver dysfunction [4]. Both phase

I and phase II reactions are involved in the metabolism of vincristine and doxorubicin. Meanwhile, metabolism and elimination of bilirubin is mainly mediated by the phase II reaction (enzyme-catalyzed glucuronidation). It is reasonable to assume that phase I enzyme activity might not have fully recovered at the time of administration of the anticancer agents, and that their clearance might have been delayed. Thus, impaired metabolism of these agents might have resulted in an increased excretion of unchanged drugs and/or active metabolites into the bile acid, leading to the direct mucosal damage in the intestine. This hypothesis was compatible with the fact that the gastrointestinal necrosis was confined to the duodenum and jejunum in this case.

We cannot deny the possibilities of age-related liver dysfunction or idiosyncratic reactions and further studies are warranted.

Clinicians should recognize that dose adjustment of chemotherapeutic agents according to liver function tests might lead to fatal complications in patients who have recovered from hepatic congestion.

Competing interests

There are no competing interests to declare.

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