

Letter to the editor

Veno-occlusive disease of the liver induced by gemcitabine

We report the case of a 48-year-old female patient suffering from non-small-cell lung cancer (NSCLC) with bone metastasis who developed hepatic veno-occlusive disease (VOD) after being treated with gemcitabine (Gemzar[®], Lilly, France). Gemcitabine is a novel analogue of deoxycytidine which inhibits DNA synthesis and has been shown to produce objective tumor response in a variety of cancers, e.g., NSCLC, pancreatic cancer, ovarian cancer, bladder cancer etc. This drug appears to be well tolerated. The major dose-limiting side effect seems to be myelosuppression, other common adverse effects WHO 3 and 4 include transient elevation of hepatic enzymes (not associated with dose or treatment duration), nausea and vomiting [1].

The patient received a total of 11 applications of gemcitabine (1000 mg/m² as a 30 minute intravenous infusion once weekly for three weeks, then 1 week off) over a period of fifteen weeks. Because of bone pain additional analgetic oral medication with morphine sustained release and naproxen was administered. During gemcitabine therapy no dose-limiting toxicity was observed. At the beginning of the therapy there was no sign of liver function impairment or liver metastasis. After seven applications a partial response in the primary tumor site and in the mediastinal lymph node metastasis were noted. Unexpectedly, the patient was hospitalized one week after the last dose of gemcitabine due to nausea, vomiting, jaundice, right upper quadrant pain and confusion. She was found to have a decreased platelet count (9000/ μ l), liver tests revealed a 10-fold increase in ASAT and five-fold increase in total bilirubin. The abdominal ultrasound showed a thickening of the gallbladder and perihepatic ascites without hepatomegaly or liver metastasis. Six days after admission the patient developed progressive liver failure which resulted in hepatic coma. She died two days later. The autopsy revealed typical findings of veno-occlusive disease with occlusion of the terminal hepatic venules, sinusoidal congestion and zone 3 hepatocyte necrosis [2]. No hepatomegaly was found. Histologically rare tumor cell deposits could be detected. The presence of portal lymphoid infiltrates and the serological evidence of hepatitis C (HCV) infection at death and in serum collected six months earlier account for chronic HCV infection.

Several groups have reported various risk factors associated with development of veno-occlusive disease after high dose chemotherapy and bone marrow transplantation (BMT) [3]. One group related VOD to pre-transplant infection by HCV

[4]. In our patient, preexisting HCV infection might represent a risk factor for developing VOD, due to an increased susceptibility of hepatocytes to the toxic effect of cytoreductive therapy. In the pathogenesis, endothelial injury through chemotherapy would cause capillary leakage and activation of the coagulation cascade, resulting in VOD.

The majority of cases of VOD occur secondary to high dose chemotherapy with or without irradiation in patients undergoing BMT [5]. Additionally, a few reports have been published on VOD in patients receiving non transplant dosage of chemotherapy (e.g., low dose cyclophosphamid, actinomycin D, 6-thioguanin, etc.) or following ingestion of pyrrolizidine alkaloid-containing plants.

To our knowledge, this is the first report of hepatic veno-occlusive disease associated with gemcitabine.

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