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Case report

The role of glucocorticoids in the treatment of fulminant hepatitis induced by dacarbazine

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Dacarbazine (DTIC) is commonly used for the treatment of malignant melanoma and Hodgkin's disease. A very rare complication of this cytotoxic agent is acute vascular hepatic damage, e.g. veno-occlusive disease or Budd–Chiari syndrome. The pathophysiological mechanism involved seems to be an immune reaction. This complication is frequently fatal. We report a patient who developed severe hepatic failure following DTIC treatment who responded favorably to treatment with glucocorticosteroid. [© 2002 Lippincott Williams & Wilkins.]

Key words: Dacarbazine, fulminant hepatitis, steroids.

Introduction

Dacarbazine (DTIC) (dimethyl-triazeno-imidazole carboxamide) is commonly used for the treatment of malignant melanoma and Hodgkin's disease. Transient elevation of liver enzymes is a well-known side effect[1] and does not require modification of the treatment schedule.

Since 1979 there have been few reports on acute fatal vascular hepatotoxicity complicating treatment with DTIC[2–10] as a single chemotherapeutic agent[3–6,8–10] or in combination with other cytotoxic drugs.[2,7] The hepatotoxicity was mainly vascular, i.e. veno-occlusive disease (VOD)[3–8] or Budd–Chiari syndrome.[2,5]

The clinical manifestations appear usually during or after the second course of DTIC, and include fever, vomiting, epigastric pain, right upper quadrant tenderness and enlarged liver, followed by rapid clinical deterioration with hypotension, confusion and jaundice.[2–10] Liver enzymes are usually very high (up to 100 times normal levels) together with prolongation of the prothrombin time, hypoglycemia, metabolic acidosis and, occasionally, eosinophilia. Death often occurs within a few days of the onset of symptoms.[2–8]

At autopsy, the hepatic damage is characterized by centrilobular necrosis with extensive hemorrhage, thrombosis of small[3–8] and sometimes large[2,5] hepatic veins, and vein wall infiltration mainly with lymphocytes and eosinophils.[5–8] The same infiltrate is found in the portal tracts.[8]

We report a patient with severe hepatic failure following DTIC treatment in order to stress the importance of early recognition and immediate steroid treatment of this life-threatening situation.

Case report

A 69-year-old man with advanced ocular malignant melanoma, after enucleation of the right eye, was treated with i.v. DTIC (250 mg/m^2 daily) for 5 consecutive days. Two weeks later a second course of DTIC combined with interferon-α was administered. At the second day of this course the patient was admitted for fever of 39.3°C, profuse sweating, epigastric pain and nausea.

During the last 2 years he was treated with chlorambucil and prednisone for low-grade non-Hodgkin's lymphoma and achieved a complete remission.

On admission, the patient was hypotensive (RR 75/40 mmHg), and had a distended abdomen and right upper quadrant tenderness. No other abnormal findings were noted.

The white blood cell count was 8900/mm^3 with mild shift to the left and no eosinophilia. The

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hemoglobin level was normal and mild thrombocytopenia was found (105 000/mm^3). The Sequential Multiple Analyzer-Computer (SMA-C) profile revealed serum glutamic transaminase 7040 U/l, glutamic pyruvic transaminase 6080 U/l, lactic dehydrogenase 23 635 U/l, alkaline phosphatase 249 U/l, γ-glutamic transpeptidase 259 U/l, albumin 2.9 dl, bilirubin 1.1 mg/dl, urea 60 mg/dl and creatinine 2.1 mg/dl. Coagulation studies showed prolonged rothrombin rime (INR 1.8), normal partial thromboplastin time, normal fibrinogen level and mildly elevated di-dimers (1000–2000).

Ultrasonographic examination of the abdomen revealed a normal-sized liver, with two hyperechogenic lesions of 2.4 cm diameter, suspected to be a secondary spread, mild distention of the intrahepatic bile ducts, normal common bile duct, normal gall bladder and a moderate amount of ascitic fluid. Doppler examination of the hepatic veins and of the portal system was technically unsuccessful.

On the third day the patient developed hepatic encephalopathy, and became disoriented with flapping tremor and an elevated ammonia level (95 μmol/l). On the fourth day mild hypoglycemia occurred and on the fifth day he was stuporous.

During the first few days after the admission, the patient was vigorously treated with fluids, while lactulose and neomycin were added on the third day. On the forth day i.v. hydrocortisone 300 mg/day was initiated. Three days later a dramatic clinical improvement occurred and the patient was discharged on the 10th day. He was seen in our outpatient clinic 2 weeks after discharge, fully oriented without ascites and with marked improvement in the liver enzymes.

Discussion

Our patient developed severe hepatic failure during the second course of treatment with DTIC. Several similar cases were reported in the literature following treatment with DTIC, alone or in a combination with other chemotherapeutic drugs, for malignant melanoma[3–6,8–10] or Hodgkin's disease.[2,7] The clinical picture is that of severe, rapidly progressive liver failure. Based on autopsies of other reported cases, the hepatic damage is considered to be a result of inflammation and thrombosis of small[3–8] and sometimes large[2,5] hepatic veins, leading to massive hepatocellular necrosis. The histology of most reported cases resembles VOD.

VOD has been reported after exposure to a wide variety of antineoplastic agents and irradiation. Antimetabolites such as 6-mercaptopurine and azathioprine administered at conventional doses or alkylating agents administered at high doses as preparation for bone marrow transplantation, as well as other toxic alkaloids and herbs, have been associated with VOD.[11]

Although the pathogenesis of VOD remains obscure, DTIC hepatotoxicity is believed to be immune mediated. This assumption is based on the timing of the reaction that occurs almost always during the second course of DTIC treatment and never during the first course,[2–10] the presence of extensive lymphocytic and eosinophilic infiltration in the hepatic veins,[4–8] and occasionally the presence of eosinophilia in the peripheral blood.[4,5,8] Based on these pathogenetic features and the response to corticosteroid in two previously reported patients,[9,10] hydrocortizone was administered i.v. Within few days a dramatic clinical improvement occurred together with normalization of the liver function tests.

Although DTIC-induced hepatic damage is rare, it is extremely important to be aware of this adverse reaction, since liver failure is frequently fatal, but steroid treatment has a dramatic beneficial effect. We propose early steroid treatment in suspected cases.

References

1. Johnson RO, Metter G, Wilson W, Hill G, Krementz E. Phase I evaluation of DTIC (NSC45388) and other studies in malignant melanoma in the central oncology group. *Cancer Treat Rep* 1976; **60**: 183–7.
2. Houghton AN, Shafi N, Rickles FR. Acute hepatic vein thrombosis occurring during therapy for Hodgkin's disease: a case report. *Cancer* 1979; **44**: 2324–9.
3. Asbury RF, Rosenthal SN, Descalzi ME, Ratcliffe RL, Arseneau JC. Hepatic veno-occlusive disease due to DTIC. *Cancer* 1980; **45**: 2670–4.
4. Greenstone MA, Dowd PM, Mikhailidis DP, Scheuer PJ. Hepatic vascular lesions associated with dacarbazine treatment. *Br Med J* 1981; **282**: 1744–5.
5. Feaux de Lacroix W, Runne U, Hauk H, Doepfmer K, Groth W, Wacker D. Acute liver dystrophy with thrombosis of hepatic veins: a fatal complication of dacarbazine treatment. *Cancer Treat Rep* 1983; **67**: 779–84.
6. Erichsen C, Jonnson PE. Veno-occlusive liver disease after dacarbazine therapy (DTIC) for melanoma. *J Surg Oncol* 1984; **27**: 268–70.
7. Joensuu H, Soderstrom KO, Nikkanen V. Fatal necrosis of the liver during ABVD chemotherapy for Hodgkin's disease. A case report. *Cancer* 1986; **58**: 1437–40.

8. Ceci G, Bella M, Melissari M, Gabrielli M, Bocci P, Cocconi G. Fatal hepatic vascular toxicity of DTIC. It is really a rare event? *Cancer* 1988; **61**: 1988–91.
9. Dancygier H, Runne U, Leuschner U, Milbradt R, Classen M. Dacarbazine (DTIC)-induced human liver damage—light and electron-microscopic findings. *Hepatogastroenterology* 1983; **30**: 93–5.
10. Leroy B, Le Franc P, Thomas P, Colombel F, Scherpereel P. Hepatic veno-occlusive disease caused by Deticene: a cause of acute hypovolemic shock. *Ann Fr Anesth Reanim* 1990; **9**: 550–2.
11. Rollins BJ. Hepatic veno-occlusive disease. *Am J Med* 1986; **81**: 297–305.

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