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Temozolomide induced liver injury

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Abstract

A 62-year female received radiotherapy over six weeks with daily 75 mg/m² Temozolomide (TMZ) for Glioblastoma (GB). At the last week of radiotherapy, her liver enzymes and serum bilirubin started deteriorating. TMZ was discontinued. The histopathology demonstrated the features of acute cholestasis and focal parenchymal inflammation. A range of investigations failed to show any other contributory cause of hepatitis. She required in-hospital care for a prolonged period for a grade three hepatic failure. The liver functions very slowly recovered over 40 weeks, but her general condition continues to deteriorate. TMZ may cause a mild temporary rise in the liver enzymes and has been reported to reactivate hepatitis B. In few other cases concomitant medications were the possible causes of hepatitis. However, searching the Medline and other bibliographic database, we have not come across any case of TMZ-induced liver injury (TMZ-DILI). Histopathology and pattern of liver enzyme elevation suggest that unlike Dacarbazine, which causes veno-occlusive type liver damage, TMZ in this patient caused mainly cholestasis type liver injury. On Naranjo Adverse Drug Reaction (ADR) probability scale, this case falls in probable grade (Scale 7).

Key words: Glioblastoma; temozolomide; DILI; hepatitis; idiosyncratic drug reaction.

Introduction

Temozolomide has now become a standard of care in patients with Glioblastoma (GB). Myelosuppression is the predominant and dose-limiting toxicity. Serious non-haematological toxicities are rare (1). We report here a patient who developed significant temozolomide drug induced liver injury (TMZ-DILI)...

Case report

A 62-year female underwent craniotomy for GB. Subsequently, she received six weeks of radiotherapy with daily 75 mg/m² of TMZ. Her weekly full blood count and biochemistry profile remained satisfactory until the last week of radiotherapy, when the liver function started deteriorating. Ultrasound of the liver and CT-scan showed no significant biliary or liver abnormality. Ultrasound-guided liver biopsy revealed acute cholestasis with canalicular bile plugs and intracytoplasmic bile pigment, predominantly in a perivenular distribution. This was associated with the formation of liver cell rosettes and with mild focal lobular inflammation. There was no evidence of alpha one- antitrypsin deficiency. Special stains for iron, copper associated protein and hepatitis B surface antigen were negative. There was no evidence of fibrosis, cirrhosis or neoplasm (Fig. 1).

Her medications included Dexamethasone 6 mg/day, Iron Sulphate 600 mg/day and Lansoprazole 30 mg/day. During her anaesthesia, she had received a single dose of Propofol 150 mg, Rocuronium 70 mg and Cefuroxime 1.5 g. She never smoked and denied any allergies. She drank one glass of wine occasionally. Her blood group was AB-ve and there was no history of blood transfusion. There was no past medical history of hepatitis or any significant family history. The range of investigations did not show any evidence to support an infective or autoimmune cause. The results of *investigations for hepatitis A, B, C, and E virus infection, Epstein-Barr Nuclear antigens and Capsid antigen bodies, Treponemal antibodies, antibodies for Rubella and Varicella Zoster were all negative. Tests for Cytomegalovirus, Legionella and H. Pylori infection were also negative. Autoimmune aetiology was excluded by negative antibody tests for antinuclear antigen and antistreptolysin*. Considering the temporal relation to TMZ and the lack of any other obvious causes of hepatitis, the diagnosis of TMZ-DILI was made. The Medical and Health Product Regulatory Agency (MHRA) was alerted through 'Yellow Card Registration', a system to alert unexpected drug reaction in the UK.

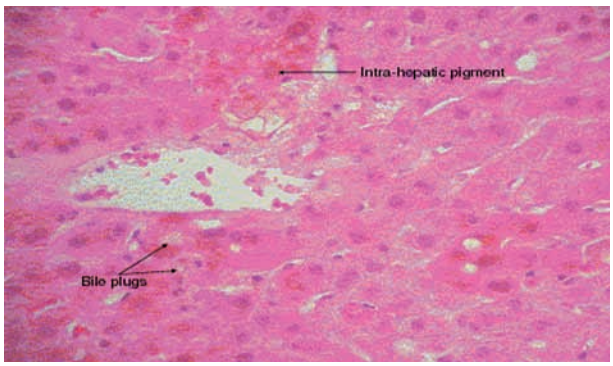

FIG. 1. — Acute cholestasis with canalicular bile plugs.

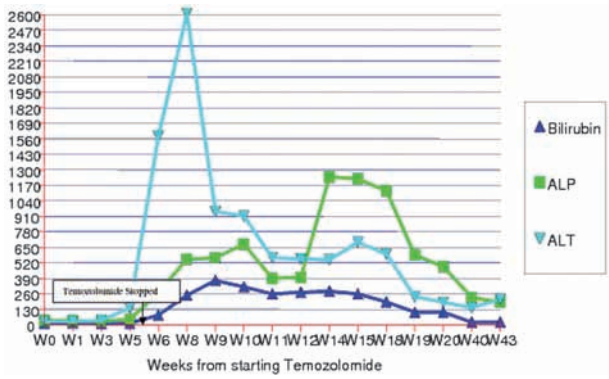

FIG. 2. — Liver Biochemistry

Table 1

Reported cases of temozolomide related hepatitis

References	Toxicity	Diagnosis/ Age/ sex	TMZ Schedule	Total cumulative dose before events	Interval between starting TMZ and toxicity	Interval between last dose and toxicity	Associated medication/ possible mechanism	Out come/ comment
Chedda MG *et al.*	Hepatitis B reactivation	GB/ 50/ M	42 days continous/ 75 mg/m2 with radiotherapy	3150 mg/m2	5 weeks	7 days	Tolterodine, Leviteracetam, Dexamethasone, Atovaqone.	Recovered following Lamivudine. Ethnicity: Chinese
Grewal J *et al.*	Hepatitis B reactivation/ Encephalopathy	GB/ 65/ F	42 days continuous 75 mg/m2 with radiotherapy then 5/28 3 cycles	6150 mg/m2	17 weeks	21 days	Valproic acid, History of hepatitis B	Died of liver injury. Ethnicity: Chinese
Herrlinger U *et al.*	Grade IV hepatitis	GB/ NA/ NA	42 days continuous 100 mg/m2 with radiotherapy and Lomustine 100 mg/m2 day 1 only	NA	NA	On TMZ	Lomustine	Recovered
Neyns B. *et al.*	Hepatitis/ Cholangitis	GB/ 48/ M	42 days continuous 75 mg/m2 and with radiotherapy and Cilengitide 500 mg/m2 IV twice weekly	3150 mg/m2	47 days	5 days	Valproic acid , cilengitide	Recovered
This case	Hepatitis. Grade IV/ Cholangitis	GB/ 62/ F	42 days continous/ 75 mg/m2 with radiotherapy	3000 mg/m2	40 days	On TMZ	Dexamethasone 6 mg/day, Iron Sulphate 600 mg/day , Lansoprazole 30 mg/day	Prolonged hospitalization with sequelae. Not completely recovered. Died of progressive GB Ethnicity: Caucasian

TMZ: Temozolomide; GB: Glioblastoma.

She remained neurologically stable, but required a prolonged admission due to protracted jaundice, gross bilateral leg oedema, and significant weight loss. The alanine-aminotransferase (ALT; normal range 5-45 iu/L) started rising at the end of week five, peaking at week eight (2610 iu/L), and then gradually reduced to 949 iu/L at week nine and 213 iu/L by week 43. Similarly alkaline phosphatase (ALP; normal range 30-125 iu/L) started increasing at week six, peaked at 1240 iu/L at week 14 then gradually reduced to 190 iu/L at week 43. Serum bilirubin (normal range 7-23 μmol/L) started rising at week six, peaked to 319 μmol/L by week 10 and gradually dropped to 23 μmol/L by week 43 (Fig. 2). Aspartate aminotransferae (AST; normal range 8-28 u/L) and Gamma-glutamyl transferase (GGT; normal range 7-33 u/L) were also increased to 762 u/L and 1638 u/L at week 8, respectively. AS per Common Terminology Criteria for Adverse Events v4.0 (CTCAE v4.0), she had grade III hepatic failure and grade IV hepatitis (2). The management with Ursodeoxycholic acid 500 mg twice a day along with high-dose prednisolone did not improve her liver functions. Though liver enzymes improved gradually, serum albumin continues to deteriorate. Subsequent treatment could not be given, and she eventually died of progressive brain tumour.

Discussion

TMZ is an oral congener of Dacarbazine. Both are the prodrugs for active moiety monomethyl triazeno-imidazole carboxamide (MTIC). Unlike Dacarbazine, TMZ does not require metabolic conversion in the liver. Other metabolites are eliminated in the urine, and hepatic clearance plays a minor role (3). Though Dacarbazine related liver toxicity has been widely reported (4). TMZ causes only mild and temporary rise in the liver enzymes. In post marketing surveillance, 1.2% patients had serious adverse events involving elevated transaminases; however, raised bilirubin has not been reported. Three other cases of non fatal liver related toxicities have been registered with MHRA.

On searching the literatures, we found four cases of TMZ associated hepatitis (Table 1). In these cases, hepatitis was observed either with the concomitant use of Valproic acid (5) or Lomustine (6) or following reactivation of Hepatitis B (7, 8). Our patient was not on antiepileptic medications. The histology and temporal relationship support the diagnosis of TMZ-DILI. The pattern of liver enzyme abnormality ($2 < ALT/ALP < 5$) indicates a combined, biliary and hepatocellular injury (9). The liver biopsy demonstrated that TMZ caused mainly cholestasis type liver injury. This is in contrast to the veno-occlusive type of liver toxicity observed with Dacarbazine (4).

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