Published in final edited form as:

Dig Dis Sci. 2013 May ; 58(5): . doi:10.1007/s10620-012-2493-9.

Clinical and Histological Features of Idiosyncratic Acute Liver Injury Caused by Temozolomide

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Abstract

Objective—To describe the clinical, biochemical and histological features of 4 patients with apparent hepatotoxicity due to temozolomide and to summarize the available literature of hepatotoxicity associated with this agent.

Design—Case series

Setting—Patients were participants in the Drug-Induced Liver Injury Network a United States multicenter cooperative study.

Patients—Four patients (ages 47 to 70 years; 3 men, 1 woman) developed liver injury 1 to 7 months after starting temozolomide chemotherapy.

Intervention—Discontinuation of temozolomide therapy.

Results—Among the first 1000 cases of drug-induced liver injury enrolled in a prospective U.S. multicenter database, 4 cases of temozolomide hepatotoxicity were identified (0.5%). Three were jaundiced and the initial pattern of serum enzyme elevations was often hepatocellular or mixed, but usually became cholestatic with time. Immunoallergic and autoimmune features were absent. Liver biopsies showed varying degrees of cholestasis, mild inflammation, focal hepatocellular injury and prominent bile duct damage or paucity. The liver injury tended to be prolonged and 3 patients still had liver tests abnormalities (one with jaundice) when they died of brain tumor or complications of its therapy 1 to 18 months later.

Conclusion—Temozolomide hepatotoxicity although infrequent, can necessitate interruption of cancer chemotherapy and cause significant debility in already compromised patients.

Keywords

Temozolomide toxicity; Temozolomide hepatotoxicity; Drug induced liver injury; Temozolomide hepatitis

Introduction

Temozolomide (Temodar®)¹ is an orally or parenterally available alkylating drug indicated for the treatment of adult patients with primary brain tumor. Initially approved by the Food and Drug Administration (FDA) in 1999 for refractory anaplastic astrocytoma, it was subsequently approved for the primary treatment of glioblastoma multiforme with concomitant radiotherapy in 2005.¹⁻³ Temozolomide is also used off-label for selected patients with metastatic melanoma with encouraging results.^{4,5} The oral or intravenous daily dose of temozolomide is 75 to 200 mg/m² for varying duration depending on the clinical setting. The main dose limiting side effects are related to myelosuppression, with only a minority of patients experiencing reversible neutropenia, thrombocytopenia and anemia that leads to early cessation of the drug. The most commonly reported non-hematologic adverse events are nausea, vomiting, headache, fatigue and constipation that develop in 10% or more of treated patients.^{1,5-7} Reports of hepatotoxicity are uncommon and when they have been noted, the injury was mainly seen as transient elevation in serum aminotransferase levels. Details regarding response to dose reduction or continued dosing were generally not provided.⁸ Updated prescribing information indicates that there are reports of hepatotoxicity but the precise scope of this remains unknown.⁹ The Drug-Induced Liver Injury Network (DILIN) was initiated in 2004 to register patients with well-characterized liver injury presumed due to medications, herbal and dietary supplements.^{10,11} Because the presenting features, clinical course, and outcomes of temozolomide hepatotoxicity have not been well defined, the aim of this review is to describe the clinical, biochemical and histological features of 4 DILIN patients with apparent hepatotoxicity due to temozolomide and to summarize the available literature of hepatotoxicity associated with this agent.

Methods

A MEDLINE search using the key words temozolomide and toxicity, hepatotoxicity, drug-induced liver injury, liver injury and hepatitis was performed. Of the eleven citations generated, only one noted elevated transaminases solely as a result of temozolomide but the patients and clinical course were not well characterized.

The DILIN prospective study was approved by the Institutional Review Boards of all participating centers and all patients gave written, informed consent for the evaluation and blood testing. The four patients with suspected temozolomide hepatotoxicity were enrolled in DILIN between 2004 through September 2011. Patients had an initial enrollment visit where detailed laboratory, imaging and histological data were evaluated to determine eligibility and exclude other possible causes of liver injury. Surviving patients were asked to return for a 6-month follow-up visit. DILIN causality was assessed using the Roussel Uclaf Causality Assessment Method (RUCAM)¹² and by expert consensus.¹¹ For each case, 3 experienced clinicians determined likelihood using a scale of 1 (definite), 2 (highly likely), 3 (probable), 4 (possible) and 5 (unlikely) and arrived at consensus after discussion. The severity of liver injury was also characterized using a scale of mild (1: enzyme elevations only), moderate (2: jaundice), moderate-severe (3: jaundice leading to hospitalization), severe (4: jaundice and signs of hepatic or other organ failure), fatal (5: death from liver failure or liver transplantation).¹¹ Liver biopsies were reviewed by a hepatopathologist (DEK) for features of liver injury and classification of the diagnostic pattern.

Results

Among 1000 cases of suspected drug-induced liver injury enrolled in the prospective cohort of DILIN between 2004 and 2011, 4 cases (0.5%) were attributed to temozolomide. A

summary of the major features of the four cases are shown in Table 1 and individual case reports are given below.

Case 1

A 70-year-old Caucasian man developed anorexia followed by jaundice and confusion 8 weeks after starting chemotherapy for a malignant astrocytoma. Treatment consisted of oral temozolomide 150 mg daily for six weeks. Past history included hypertension, hypercholesterolemia, atrial fibrillation, dilated cardiomyopathy, steroid induced diabetes and moderate past alcohol consumption with normal pre-treatment liver biochemistries. There was no family history of liver disease. Other medications include levetiracetam, dexamethasone and simvastatin.

Physical exam at presentation revealed jaundice without rash, fever, or stigmata of chronic liver disease. Laboratory data included alanine aminotransferase (ALT) 342 U/L, aspartate aminotransferase (AST) 100 U/L, alkaline phosphatase 383 U/L, total bilirubin 8.0 mg/dL and albumin 3.4 g/dL. A complete blood count revealed white blood cell count of 6,600/ μ L without eosinophilia, hemoglobin 13.7 g/dL and platelet count of 134,000/ μ L. INR measurements were normal (peak value 1.2). Inpatient imaging studies including abdominal ultrasound, CT scan and magnetic resonance cholangiopancreatography (MRCP) were normal without evidence of biliary obstruction. Tests for acute hepatitis A, B and C, Epstein Barr virus and herpes simplex virus infections were negative. Anti-mitochondrial antibody (AMA), anti-nuclear antibody (ANA) and anti-smooth muscle antibody (ASMA) were also negative. Liver biopsy obtained 3 weeks after onset showed prominent zone 3 cholestasis, mild portal inflammation and interface hepatitis. Strikingly, there was early bile duct paucity with 7 of 16 portal tracts lacking an identifiable bile duct (Figure 1, A-C). Temozolomide, levetiracetam and simvastatin were discontinued 4 days after the initial presentation and not restarted; lactulose was given for confusion, although there was no other clinical or biochemical evidence of hepatic encephalopathy.

Six weeks after presentation, he had improved clinically but was still jaundiced, ALT was 62 U/L, alkaline phosphatase was 320 U/L and bilirubin was 6.2 mg/dL. The patient died of tumor progression before his 6 month DILIN study visit. The final causality assessment was definite (1) with a severity score of moderately severe (3).

Case 2

A 47-year-old Caucasian man with metastatic melanoma was treated with temozolomide at a daily dose of 170 mg orally combined with 5 cycles of high dose infusions of interleukin 2. Seven months after beginning treatment he noted dark urine and pruritus. Past history included hypertension, gastroesophageal reflux disease and hepatitis C, but he had no ongoing risk factors for viral hepatitis and did not drink alcohol. Pre-treatment liver biochemistries were not available.

On presentation, physical examination revealed jaundice without fever, rash, or stigmata of chronic liver disease. Laboratory values included ALT 1754 U/L, AST 852 U/L, alkaline phosphatase 151 U/L, total bilirubin 9.4 mg/dL, INR of 1.1, and albumin 3.5 g/dL. The initial white blood count was 8.7/ μ L (a differential was not done), hemoglobin was 13 g/dL, and platelets were 186,000/ μ L. Tests for acute hepatitis A and B were negative as were ANA, AMA, and ASMA. While anti-HCV was positive, HCV RNA was not tested. A CT scan revealed diffuse fatty infiltration of the liver and a large mass in the right kidney, presumed to be metastatic disease. Liver biopsy obtained 3 weeks after onset revealed changes of acute hepatitis with portal infiltrates composed of lymphocytes, plasma cells and

eosinophils, marked interface hepatitis and widespread duct injury without ductal paucity, a formal count revealing ducts in 19 of 24 portal areas (Figure 1-D). Temozolomide was immediately discontinued and liver enzymes subsequently improved. Three months after presentation, the liver tests abnormalities had resolved; ALT was 27 U/L, AST was 21 U/L, alkaline phosphatase was 86 U/L and total bilirubin was 0.8 mg/dL. The patient died of hemorrhage from a ruptured cerebral aneurysm shortly before the 6-month study visit. The DILIN causality assessment was probable (3) and severity score was moderate (2).

Case 3

A 58-year-old Caucasian woman with a history of an oligoastrocytoma since 1993 was treated in 2004 with temozolomide (200 mg to 250 mg daily) for 13 months. During that time, liver biochemical test results were normal. Three years later, the drug was re-started at a dose of 200 mg daily and continued for 21 days. Eleven days into therapy, serum alkaline phosphatase was 337 U/L. Twenty days after starting temozolomide, serum ALT levels were elevated and the drug was stopped the following day. She denied symptoms of liver disease and serum bilirubin levels were normal. Other past medical history included an acoustic neuroma and seizures for which she had taken levetiracetam for 7 years. She denied drinking alcohol during treatment.

At presentation, physical exam was unrevealing. Laboratory data revealed ALT of 127 U/L, AST of 97 U/L, alkaline phosphatase of 383 U/L, a total bilirubin of 0.2 mg/dL, and an INR of 1.2. The white blood count was 6100/ μ L hemoglobin 11.2 g/dL, and platelets 287,000/ μ L. Tests for acute hepatitis A, B, and C, ANA, AMA, and ASMA were negative as were assays for CMV and EBV DNA. An abdominal ultrasound showed no evidence of biliary obstruction. Liver biopsy obtained 4 weeks after onset showed moderate intrahepatic cholestasis mainly in zone 3 (Figure 1-E) with minimal inflammation and probable bile duct paucity; 2 of 5 portal areas present in the biopsy having identifiable ducts.

Both temozolomide and levetiracetam were stopped and not restarted. Serum ALT levels rose to a peak of 395 U/L and alkaline phosphatase to 481 U/L, but serum bilirubin remained normal and the patient denied symptoms. Over the next few months serum enzyme elevations improved, but serum alkaline phosphatase levels remained mildly elevated at the 6 month study visit (210 U/L) and again upon testing shortly before she died of tumor progression 18 months after starting therapy. DILIN causality assessment was very likely (2) and severity score was mild (1).

Case 4

A 65-year-old Caucasian man was diagnosed with glioblastoma multiforme and was treated with oral temozolomide (200 mg daily). At the same time, levetiracetam was started for seizure prophylaxis. Approximately 10 weeks later, he presented with a 3-day history of jaundice and nausea. Other medications included a 10-day course of cephalexin for cellulitis 3 weeks before presentation and a 5-day course of ciprofloxacin for the same infection 6 days before presentation. Other past medical history included hyperlipidemia, erectile dysfunction and prostate cancer. He had no history of liver disease, alcohol abuse or risk factors for viral hepatitis and pre-treatment laboratory test results were normal.

On presentation, physical examination revealed jaundice without fever, rash, or stigmata of chronic liver disease. Laboratory results were: ALT 656 U/L, AST 502 U/L, alkaline phosphatase 540 U/L, total bilirubin 16 mg/dL, and INR 1.0. Serological tests for acute hepatitis A, B, and C, and CMV IgM were negative as were ANA, ASMA, and AMA. An abdominal ultrasound showed a thickened gallbladder wall and internal echoes suggesting

debris. Endoscopic retrograde cholangiopancreatography (ERCP) showed no evidence of choledocholithiasis or biliary dilation. A CT scan showed fatty infiltration of the liver. A course of piperacillin/tazobactam was initiated to treat the recurrent cellulitis. A liver biopsy performed 12 days after presentation revealed canalicular cholestasis, mild perivenular fibrosis and mild ductopenia. Upon withdrawal of temozolomide, serum ALT levels decreased but bilirubin rose to 23 mg/dL which led to the discontinuation of levetiracetam on day 15. Serum enzyme elevations continued to improve, but the patient died suddenly of complications of a gastrointestinal bleed on day 22. The DILIN causality assessment was probable (3) and severity score was moderately severe (3).

Discussion

Temozolomide is rapidly absorbed when administered orally with a half-life of 1.8 hours and a bioavailability that approaches 100%.¹³ Once absorbed, temozolomide undergoes spontaneous conversion via hydrolysis, to its active metabolite, methyl-triazeno-imidazole-carboxamide (MTIC). It is subsequently converted to inactive 5-aminoimidazole-4-carboxamide (AIC), which methylates several DNA bases, most crucially, guanine. The guanine-methyl product creates breaks in the host tumor DNA and eventually cell death due to a disruption in DNA replication.^{14,15} Temozolomide crosses the blood-brain barrier, which makes it a preferred agent in treatment of brain tumors. Temozolomide is mostly excreted via the kidneys and, unlike other alkylating agents, such as dacarbazine (DTIC), requires no hepatic metabolic activation.^{13,16} The lack of hepatic metabolism may explain why temozolomide hepatotoxicity is an infrequent event. Dacarbazine and mitozolomide are the other two most closely related alkylating agents of the imidazotetrazine family. Dacarbazine is a well known hepatotoxin, but the pattern of injury is sinusoidal obstruction syndrome (veno-occlusive disease) rather than hepatitis or cholestasis.¹⁷ Both dacarbazine and mitozolomide, like temozolomide, cause varying degrees of bone marrow suppression. This led to the abandonment of mitozolomide after phase II clinical trials showed that it caused severe and unpredictable myelosuppression.¹⁸

Underreporting may also be a contributing factor to the absence of reports of hepatotoxicity of temozolomide. Patients receiving chemotherapy have multiple reasons for developing liver enzyme elevations, and the agents are often simply discontinued without further investigation if the enzyme resolution is complete. There have been no reports of rechallenge with temozolomide after suspected hepatotoxicity.

One large retrospective review involved 1059 patients with glioblastoma multiforme, 749 of whom received chemotherapy with temozolomide. Elevations of serum aminotransferase levels above 5 times the upper limit of normal (3+; as scored with the Common Terminology Criteria for Adverse Events v3.0 [CTCAE])¹⁹ were reported in 1.7% patients undergoing concomitant radiotherapy only and in 0.9% of those treated with temozolomide after radiation.⁶ Information on jaundice, hospitalization or liver pathology was not provided.

A synopsis of the four cases is shown in Table 1 and Figure 2. The patients ranged in age from 47 to 70 years. Duration of temozolomide therapy ranged from 1 to 7 months. The patient with the shortest latency to onset had received the agent previously without known liver injury. The long latency period, the absence of immunoallergic and autoimmune features, and the cholestatic pattern of injury in three of the four cases, suggest that the mechanism of liver injury is metabolic, perhaps due to slow accumulation of a relatively toxic intermediate with the major damage directed at biliary cells. It is noteworthy that case 2 presented with a predominantly hepatic pattern of injury compared to the cholestatic pattern of the other cases. The hepatotoxicity appears to be independent of myelotoxicity,

but might be exacerbated by other medications (levetiracetam, antibiotics) or environmental or host factors.

The histological picture was a predominantly mixed pattern of injury with significant cholestasis and evidence of bile duct loss in three cases and bile duct injury in the fourth. A striking feature was the relative paucity of symptoms, particularly pruritus and abdominal pain, despite the cholestatic pattern which was sometimes prolonged. None of the cases were fatal or had any manifestations of hepatic failure.

Formal adjudication of the 4 cases of suspected temozolomide hepatotoxicity by the DILIN investigators scored one case as definite, one as highly likely, and two as probable.²⁰ Competing diagnoses in the two probable cases included chronic hepatitis C (Case 2) and recent receipt of antibiotics capable of causing cholestatic liver injury (Case 4: cephalexin and ciprofloxacin). Interestingly, 3 of the 4 patients were also taking levetiracetam at the time of onset of liver injury. However, levetiracetam is an extremely uncommon cause of liver injury (it has little or no hepatic metabolism) and has not been linked to cholestasis. Nevertheless, levetiracetam was discontinued in all three patients and it is impossible to say that it did not at least contribute to the liver injury.

Thus, temozolomide appears to be a definite but rare cause of drug-induced liver injury, contributing to 0.5% of cases in our DILIN experience. The latency to onset is variable and adds to the challenge of diagnosis. The predominant pattern of injury is cholestatic with a distinctive histological finding of bile duct injury and paucity. However, this is not always so as one of the cases demonstrated a pattern of hepatitis. Therefore, the lack of cholestasis should not eliminate Temozolomide from consideration. The liver injury can be prolonged, but is potentially self-limiting. Importantly, temozolomide hepatotoxicity often interferes with potentially life-prolonging chemotherapy and causes significant delirium in already compromised cancer patients.

Acknowledgments

Patients were participants in the Drug-Induced Liver Injury Network which is funded as a cooperative agreement by the National Institute of Diabetes and Digestive and Kidney Disease and National Institutes of Health (NIH). This research was also supported by the Intramural Research Program of the National Cancer Institute, NIH.

We acknowledge referral to the study registry from Dr. Abdullah Mubarak of The Liver Institute at Methodist Dallas Medical Center.

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Figure 1.

Representative pathologic changes in temozolomide hepatotoxicity. Case 1 (A-C). A: Portal area with mild inflammation. No duct is seen. (H&E, 400x) B: (106-0028) Zone 3 cholestasis (arrows) with mild inflammation. (H&E, 600x) C: (106-0028) Cytokeratin 7 staining highlights periportal hepatocytes as well as the bile ducts in this portal area. (CK7, 200x). Case 2 (D only). Marked interface hepatitis with eosinophils and duct injury (arrow) (H&E, 400x). Case 3 (E only). Zone 3 cholestasis, most evident in canaliculi (arrows). Foamy macrophages (Mac) are seen in one corner. (H&E, 600x).

Figure 2. Biochemical profile over the course of liver injury and in relationship to drug administration and withdrawal. Liver biochemistries include alanine aminotransferase (ALT) and alkaline phosphatase (Alk P).

Table 1

Summary of Cases

	Case 1	Case 2	Case 3	Case 4
Age (years)	70	47	58	65
Sex	M	M	F	M
Diagnosis	Anaplastic Astrocytoma	Metastatic Melanoma	Oligoastrocytoma	Glioblastoma Multiforme
Co-morbidities	Hypertension, atrial fibrillation, cardiomyopathy, diabetes mellitus	Chronic hepatitis C, GERD	Right acoustic neuroma (surgically resected 1989)	Hyperlipidemia, prostate cancer,
Other Medications	levetiracetam, simvastatin, dexamethasone	IL-2, lansoprazole, metoprolol	levetiracetam, alendrolate, dexamethasone, donepezil, dapsone	levetiracetam, cephalexin, ciprofloxacin
Time to onset	54 days	168 days	25 days	74 days
Biochemical Pattern of injury Initial	Cholestatic (R=1.7)	Hepatocellular (R=41.3)	Cholestatic (R=0.6)	Mixed (R=2.)
Biochemical Pattern of injury Peak	Mixed (R=2.20)	Hepatocellular (R=41.3)	Mixed (R=3.31)	Cholestatic (R=0.86)
Histological Pattern of Injury	Cholestatic hepatitis; mild bile duct paucity	Acute Hepatitis with bile duct injury	Intrahepatic cholestasis; mild bile duct paucity	Canalicular cholestasis mild bile duct paucity
Peak ALT U/L	896	1754	530	656
Peak AST U/L	271	852	395	502
Peak alkaline phosphatase U/L	780	151	594	672
Peak total bilirubin mg/dL	32	9.4	0.5	23
Peak INR	1.2	1.1	1.2	1.3
DILIN Severity grade	Moderate-severe	Moderate	Mild	Moderate
Causality assessment	Definite	Probable	Very likely	Probable
Outcome of liver injury*	Not fully resolved at time of death	Resolved in 3 months	Chronic Alk P elevations at 18 months	Improving at time of death at 3 weeks
Clinical Outcome*	Died of tumor progression at 4 months	Died of tumor progression at 5 months	Died of tumor progression at 18 months	Died gastrointestinal hemorrhage at 3 weeks

* Time in relation to stopping temozolomide