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Temsirolimus

Updated: December 10, 2013.

OVERVIEW

Introduction

Temsirolimus is an inhibitor of cell proliferation and anticancer agent that is used as treatment of advanced renal cell cancer. Temsirolimus therapy is frequently associated with mild serum enzyme elevations, but has yet to be linked to instances of clinically apparent liver injury with jaundice.

Background

Temsirolimus (tem" sir oh' li mus) is an ester of sirolimus, both of which bind to the same intracellular receptor as tacrolimus and cyclosporine, but which block the "mammalian target of rapamycin" (mTOR) rather than calcineurin. mTOR is a serine/threonine kinase which plays an important role in signaling pathways of several cytokines and growth factors, which are involved in carcinogenesis and cancer progression. Inhibition of mTOR causes a decrease in protein synthesis and cell cycle arrest. Temsirolimus therapy has been shown to inhibit progression and prolong survival in patients with advanced and metastatic renal cell cancer. Temsirolimus was approved for use in the United States in 2007 and current indications are limited to therapy of advanced renal cell cancer. Temsirolimus is being actively investigated as therapy of other solid tumors. Temsirolimus is available as liquid solution for injection in vials of 25 mg/mL under the brand name of Torisel. The recommended dose is 25 mg intravenously once weekly until disease progression or unacceptable toxicity. Temsirolimus has many, largely dose dependent, side effects including hypersensitivity reactions, oral ulcers, diarrhea, nausea, poor appetite, fatigue, peripheral edema, rash, anemia and interstitial pneumonitis.

Hepatotoxicity

Serum aminotransferase elevations occur in 30% to 40% and alkaline phosphatase in 60% to 70% of patients receiving temsirolimus, but the abnormalities are usually mild, asymptomatic and self-limiting, rarely requiring dose modification or discontinuation. Elevations of liver enzymes above 5 times the upper limit of normal occur in only 2% to 3% of patients. Temsirolimus, like sirolimus, is immunosuppressive and therapy is likely to be associated with episodes of reactivation of hepatitis B, which can be severe and even fatal. Reverse seroconversion (development of HBsAg in a person with preexisting antibody to hepatitis B, either anti-HBs or anti-HBc) has not been reported. Idiosyncratic, clinically apparent acute liver injury has not been linked to temsirolimus therapy, but the total number of patients treated with this drug is limited. Thus, acute liver injury with jaundice due to temsirolimus is probably quite rare, if it occurs at all. Hypersensitivity reactions to temsirolimus infusions are not uncommon (for which reason premedication with an antihistamine is recommended) and instances of Stevens Johnson syndrome have been reported.

Mechanism of Injury

Temsirolimus undergoes extensive hepatic metabolism, largely via the cytochrome P450 system (CYP 3A4). Liver injury might be due to a direct effect of temsirolimus or to a toxic intermediate of its metabolism. Temsirolimus is prone to drug-drug interactions if used with inhibitors or inducers of the cytochrome P450 drug metabolizing enzymes.

Outcome and Management

Acute, symptomatic liver injury associated with temsirolimus therapy has not been described, and the serum enzyme elevations associated with its use are usually mild and transient, resolving spontaneously or with dose modification. Because temsirolimus can lead to reactivation of chronic hepatitis B, routine screening of patients for HBsAg before starting therapy is advisable. Patients who develop reactivation should be treated with an oral nucleoside analogue with potent activity against hepatitis B (entecavir or tenofovir). Temsirolimus is an ester of and partially metabolized to sirolimus and cross sensitivity to adverse effects between these two agents is likely. Whether such cross sensitivity extends to other inhibitors of mTOR (such as everolimus) or calcineurin (cyclosporine, tacrolimus) is not known.

Drug Class: Antineoplastic Agents, Miscellaneous; Transplant Drugs

Other Drugs with Similar Intracellular Actions: Cyclosporine, Everolimus, Mycophenolate, Sirolimus, Tacrolimus, Temsirolimus

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Temsirolimus – Torisel®

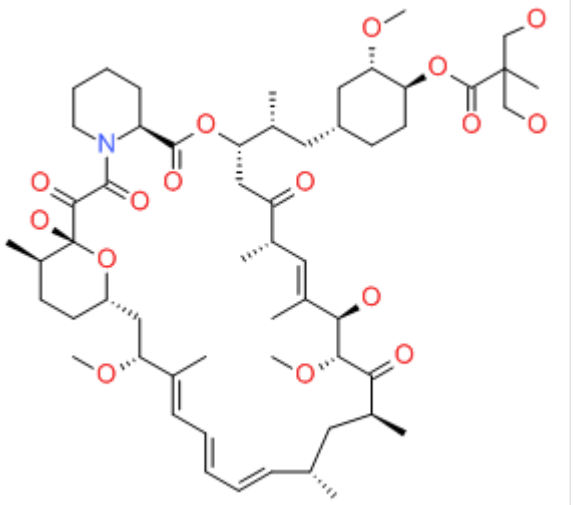
DRUG CLASS

Antineoplastic Agents; Transplant Drugs

COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

CHEMICAL FORMULA AND STRUCTURE

DRUG	CAS REGISTRY NUMBER	MOLECULAR FORMULA	STRUCTURE
Temsirolimus	162635-04-3	C56-H87-N-O16	

ANNOTATED BIBLIOGRAPHY

References updated: 10 December 2013

Zimmerman HJ. Cyclosporine. Oncotherapeutic and immunosuppressive agents. In, Zimmerman HJ. Hepatotoxicity: the adverse effects of drugs and other chemicals on the liver. 2nd ed. Philadelphia: Lippincott, 1999, pp.697-8.

(Expert review of hepatotoxicity published in 1999 before the availability of temsirolimus).

Krensky AM, Vincenti F, Bennett WM. Immunosuppressants, tolerogens, and immunostimulants. In, Brunton LL, Lazo JS, Parker KL, eds. Goodman & Gilman.s the pharmacological basis of therapeutics. 11th ed. New York: McGraw-Hill, 2006, pp. 1405-31.

(Textbook of pharmacology and therapeutics).

Hudes G, Carducci M, Tomczak P, Dutcher J, Figlin R, Kapoor A, Staroslawska E, et al. Global ARCC Trial. Temsirolimus, interferon alfa, or both for advanced renal-cell carcinoma. N Engl J Med 2007; 356: 2271-81. PubMed PMID: 17538086.

(Controlled trial of temsirolimus vs interferon alfa vs the combination in 626 patients with advanced renal cell carcinoma found prolongation of survival with temsirolimus compared to interferon [10.9 vs 7.3 months]; AST elevations occurred in 8% [>5 times ULN in 1%] of temsirolimus vs 14% of interferon [>5 times ULN in 4%] treated subjects).

Bellmunt J, Szczylik C, Feingold J, Strahs A, Berkenblit A. Temsirolimus safety profile and management of toxic effects in patients with advanced renal cell carcinoma and poor prognostic features. Ann Oncol 2008; 19: 1387-92. PubMed PMID: 18385198.

(Analysis of adverse events reported in trials of temsirolimus therapy of renal carcinoma; no discussion of hepatotoxicity or serum enzyme elevations).

Simpson D, Curran MP. Temsirolimus: in advanced renal cell carcinoma. Drugs 2008; 68: 631-8. PubMed PMID: 18370442.

(Concise review of the mechanism of action, pharmacology, efficacy and safety of temsirolimus in advanced renal cell carcinoma; no mention of serum enzyme elevations or hepatotoxicity).

Bhatia S, Thompson JA. Temsirolimus in patients with advanced renal cell carcinoma: an overview. Adv Ther 2009; 26: 55-67. PubMed PMID: 19172239.

(Review of the mechanism of action, efficacy and safety of temsirolimus mentions that therapy is associated with elevations in ALT and Alk P, but does not mention clinically apparent liver injury).

Hudes GR, Berkenblit A, Feingold J, Atkins MB, Rini BI, Dutcher J. Clinical trial experience with temsirolimus in patients with advanced renal cell carcinoma. Semin Oncol 2009; 36 Suppl 3: S26-36. PubMed PMID: 19963097.

(Review of results of clinical trials of temsirolimus in advanced renal cell carcinoma; no mention of hepatotoxicity or serum enzyme elevations).