Etoposide pathway

Jun Yang, Alessia Bogni, Erin G. Schuetz, Mark Ratain, M. Eileen Dolan, Howard McLeod, Li Gong, Caroline Thorn, Mary V. Relling, Teri E. Klein and Russ B. Altman

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*Department of Pharmaceutical Sciences, St. Jude Children's Research Hospital, Memphis, Tennessee, ‡Department of Medicine, University of Chicago, Illinois, §Department of Medicine, Washington University School of Medicine, St. Louis, Missouri, Departments of †Genetics and ‡Bioengineering, Stanford University, Stanford, California, USA

Correspondence to Dr Teri E. Klein, PhD, Department of Genetics, Stanford University Medical Center, 300 Pasteur Drive, Lane L301, Mail Code 5120, Stanford, CA 94305-5120, USA
Tel: +1 650 725 0659; fax: +1 650 725 3863; e-mail: feedback@pharmgkb.org

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Description

Etoposide is a commonly used chemotherapy agent with a broad range of antitumor activity. Etoposide and teniposide, the epipodophyllotoxins, stabilize the double-stranded DNA cleavage normally catalyzed by topoisomerase II (topo II) and inhibit faithful religation of DNA breaks [1,2]. These double-strand DNA breaks subsequently trigger the desired antitumor effects of the drugs. Metabolism of etoposide is mediated by CYP3A4 and CYP3A5 (Fig. 1) [3,4], both of which are transcriptionally regulated by NR1I2 (i.e. pregnane X receptor). Thus, xenobiotics that modulate NR1I2 activity (e.g. dexamethasone and rifampicin) have been observed to enhance etoposide clearance [5,6]. In addition to CYP3A4/5 mediated reactions, conversion of etoposide to the O-demethylated metabolites (catechol and quinone) can also be catalyzed by prostaglandin synthases or myeloperoxidase [7–9]. These metabolites have similar potency at inhibiting topoisomerase II and are more oxidatively reactive than the parent drug [10]. Glutathione [11] and glucuronide conjugation [12] seem to inactivate parent drug and metabolite, and are mediated by GSTT1/GSTP1 and UGT1A1 [13,14], respectively. Efflux of conjugated or unconjugated forms of etoposide has been associated with ABCC1, ABCC3, and ABCB1 [15,16], representing plausible mechanisms of drug resistance. Epipodophyllotoxins are highly effective anticancer agents, but can cause a delayed toxicity: treatment-related acute myeloid leukemia or myelodysplastic syndrome [17–19]. Drug-induced formation of MLL fusion genes has been associated with the development of treatment-related acute myeloid leukemia or myelodysplastic syndrome [20]. Although etoposide inhibits both topo II alpha and beta, the antitumor activity of etoposide is shown to be delivered primarily through inhibition of topo II alpha [21], whereas the carcinogenic effect has been attributed to the beta isoform [22]. Recently, 64 genetic variants that contribute to etoposide-induced cytotoxicity were identified through a whole-genome association study [23].

Fig. 1

Etoposide cellular disposition and effects.

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References


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