Published in final edited form as:

Pharmacogenet Genomics. 2009 July ; 19(7): 552–553. doi:10.1097/FPC.0b013e32832e0e7f.

Etoposide pathway

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Keywords

etoposide; pathway; pharmacogenetics; pharmacogenomics; pharmGKB

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 *CPY3A5* (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

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Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's website (<http://www.pharmgkb.org/do/serve?objId=PA2025&objCls=Pathway>).

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].

References

1. Burden DA, Osheroff N. Mechanism of action of eukaryotic topoisomerase II and drugs targeted to the enzyme. *Biochim Biophys Acta*. 1998; 1400:139–154. [PubMed: 9748545]
2. Berger NA, Chatterjee S, Schmotzer JA, Helms SR. Etoposide (VP-16-213)-induced gene alterations: potential contribution to cell death. *Proc Natl Acad Sci U S A*. 1991; 88:8740–8743. [PubMed: 1681541]
3. Relling MV, Nemec J, Schuetz EG, Schuetz JD, Gonzalez FJ, Korzekwa KR. O-demethylation of epipodophyllotoxins is catalyzed by human cytochrome P450 3A4. *Mol Pharmacol*. 1994; 45:352–358. [PubMed: 8114683]
4. Zhuo X, Zheng N, Felix CA, Blair IA. Kinetics and regulation of cytochrome P450-mediated etoposide metabolism. *Drug Metab Dispos*. 2004; 32:993–1000. [PubMed: 15319341]
5. Luo G, Guenther T, Gan LS, Humphreys WG. CYP3A4 induction by xenobiotics: biochemistry, experimental methods and impact on drug discovery and development. *Curr Drug Metab*. 2004; 5:483–505. [PubMed: 15578943]
6. Kishi S, Yang W, Boureau B, Morand S, Das S, Chen P, et al. Effects of prednisone and genetic polymorphisms on etoposide disposition in children with acute lymphoblastic leukemia. *Blood*. 2004; 103:67–72. [PubMed: 12969965]
7. Haim N, Roman J, Nemec J, Sinha BK. Peroxidative free radical formation and O-demethylation of etoposide (VP-16) and teniposide (VM-26). *Biochem Biophys Res Commun*. 1986; 135:215–220. [PubMed: 3006680]
8. Fan Y, Schreiber EM, Giorgianni A, Yalowich JC, Day BW. Myeloperoxidase-catalyzed metabolism of etoposide to its quinone and glutathione adduct forms in HL60 cells. *Chem Res Toxicol*. 2006; 19:937–943. [PubMed: 16841962]
9. Kagan VE, Kuzmenko AI, Tyurina YY, Shvedova AA, Matsura T, Yalowich JC. Pro-oxidant and antioxidant mechanisms of etoposide in HL-60 cells: role of myeloperoxidase. *Cancer Res*. 2001; 61:7777–7784. [PubMed: 11691792]
10. Lovett BD, Strumberg D, Blair IA, Pang S, Burden DA, Megonigal MD, et al. Etoposide metabolites enhance DNA topoisomerase II cleavage near leukemia-associated *MLL* translocation breakpoints. *Biochemistry*. 2001; 40:1159–1170. [PubMed: 11170441]
11. Mans DR, Lafleur MV, Westmijze EJ, Horn IR, Bets D, Schuurhuis GJ, et al. Reactions of glutathione with the catechol, the ortho-quinone and the semiquinone free radical of etoposide. Consequences for DNA inactivation. *Biochem Pharmacol*. 1992; 43:1761–1768.
12. Hande K, Bennett R, Hamilton R, Grote T, Branch R. Metabolism and excretion of etoposide in isolated, perfused rat liver models. *Cancer Res*. 1988; 48:5692–5695. [PubMed: 3167829]
13. Wen Z, Tallman MN, Ali SY, Smith PC. UDP-glucuronosyltransferase 1A1 is the principal enzyme responsible for etoposide glucuronidation in human liver and intestinal microsomes: structural characterization of phenolic and alcoholic glucuronides of etoposide and estimation of enzyme kinetics. *Drug Metab Dispos*. 2007; 35:371–380. [PubMed: 17151191]
14. Watanabe Y, Nakajima M, Ohashi N, Kume T, Yokoi T. Glucuronidation of etoposide in human liver microsomes is specifically catalyzed by UDP-glucuronosyltransferase 1A1. *Drug Metab Dispos*. 2003; 31:589–595. [PubMed: 12695347]
15. Jedlitschky G, Leier I, Buchholz U, Barnouin K, Kurz G, Keppler D. Transport of glutathione, glucuronate, and sulfate conjugates by the MRP gene-encoded conjugate export pump. *Cancer Res*. 1996; 56:988–994. [PubMed: 8640791]

16. Zelcer N, Saeki T, Reid G, Beijnen JH, Borst P. Characterization of drug transport by the human multidrug resistance protein 3 (ABCC3). *J Biol Chem.* 2001; 276:46400–46407. [PubMed: 11581266]
17. Yang J, Bogni A, Cheng C, Bleibel WK, Cai X, Fan Y, et al. Etoposide sensitivity does not predict MLL rearrangements or risk of therapy-related acute myeloid leukemia. *Clin Pharmacol Ther.* 2008; 84:691–697. [PubMed: 18509329]
18. Pui CH, Ribeiro RC, Hancock ML, Rivera GK, Evans WE, Raimondi SC, et al. Acute myeloid leukemia in children treated with epipodophyllotoxins for acute lymphoblastic leukemia. *N Engl J Med.* 1991; 325:1682–1687. [PubMed: 1944468]
19. Ratain MJ, Kaminer LS, Bitran JD, Larson RA, Le Beau MM, Skosey C, et al. Acute nonlymphocytic leukemia following etoposide and cisplatin combination chemotherapy for advanced non-small-cell carcinoma of the lung. *Blood.* 1987; 70:1412–1417. [PubMed: 2822173]
20. Super HJ, McCabe NR, Thirman MJ, Larson RA, Le Beau MM, Pedersen-Bjergaard J, et al. Rearrangements of the MLL gene in therapy-related acute myeloid leukemia in patients previously treated with agents targeting DNA-topoisomerase II. *Blood.* 1993; 82:3705–3711. [PubMed: 8260707]
21. Zhou Z, Zwelling LA, Ganapathi R, Kleinerman ES. Enhanced etoposide sensitivity following adenovirus-mediated human topoisomerase IIalpha gene transfer is independent of topoisomerase IIbeta. *Br J Cancer.* 2001; 85:747–751. [PubMed: 11531262]
22. Azarova AM, Lyu YL, Lin CP, Tsai YC, Lau JY, Wang JC, et al. Roles of DNA topoisomerase II isozymes in chemotherapy and secondary malignancies. *Proc Natl Acad Sci U S A.* 2007; 104:11014–11019. [PubMed: 17578914]
23. Huang RS, Duan S, Bleibel WK, Kistner EO, Zhang W, Clark TA, et al. A genome-wide approach to identify genetic variants that contribute to etoposide-induced cytotoxicity. *Proc Natl Acad Sci U S A.* 2007; 104:9758–9763. [PubMed: 17537913]

Fig. 1.
Etoposide cellular disposition and effects.