2. Merino MJ, Livolsi VA. Signet ring carcinoma of the female breast: a clinicopathologic analysis of 24 cases. *Cancer* 1981, **48**, 1830–1837.
3. Perez JA, Pisano R, Cardemil B. Bilateral signet ring cell carcinoma of the breast: case report. *Rev Med Chil* 1991, **8**, 923–926.
4. Frost AR, Terahata S, Yeh IT, Siegel RS, Overmoyer B, Silverberg SG. The significance of signet ring cells in infiltrating lobular carcinoma of the breast. *Arch Pathol Lab Med* 1995, **119**, 64–68.
5. Henríquez I, Conill C, Verger E, Graus F. Is time interval between diagnosis and radiation treatment an important factor in brain metastases? *Eur J Cancer* 1996, **12**, 2183–2184.

European Journal of Cancer Vol. 33, No. 6, pp. 978–979, 1997

Printed in Great Britain
0959-8049/97 $17.00 + 0.00

PII: S0959-8049(97)00087-7

Considerable Plasma Levels of a Cytotoxic Etoposide Metabolite in Patients Undergoing High-dose Chemotherapy

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ETOPOSIDE (VP16) has been used in the treatment of various tumours for many years, but its elimination from the body, particularly its metabolism, is still not completely understood. *In vitro* studies in human liver microsomes revealed mono-*O*-demethylation, catalysed by cytochrome P450 3A4, as a metabolic pathway of etoposide in man [1]. The formed catechol metabolite has been shown to be highly cytotoxic in cellular cultures [2]. It directly interacts with DNA leading to DNA damage and inactivation [3]. Its binding to calf thymus DNA is 10 times more extensive compared to parent etoposide [2]. However, the clinical significance of the catechol is still unclear since, so far, it has never been detected and quantified in the plasma of cancer patients.

We investigated 12 patients with germ cell cancer treated with 2400 mg/m^2/4 days etoposide given as four short infusions over 1 h, 1500 mg/m^2/3 days carboplatin given as three short infusions over 1 h and 10 g/m^2/4 days ifosfamide as constant rate infusion. All patients received stem cell support 7 days after the beginning of chemotherapy. Twenty-three serial plasma samples were drawn and analysed for etoposide and etoposide catechol by two different reversed-phase HPLC assays using UV detection for the parent drug and electrochemical detection for the metabolite. Etoposide catechol was synthesised by mono-*O*-demethylation of etoposide [4]. The identity of the metabolite was verified by NMR and mass spectroscopy. Pharmacokinetic parameters were calculated using non-compartmental methods.

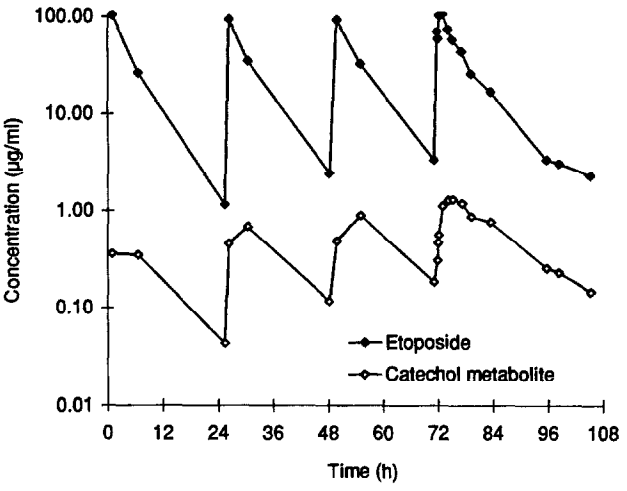

Figure 1. Plasma levels of etoposide and etoposide catechol in a representative patient receiving high-dose chemotherapy.

Etoposide catechol could be quantified in all patients up to 36 h following the last infusion of etoposide exhibiting characteristic metabolite kinetics (Figure 1). Plasma concentrations increased during therapy reaching peak values of 1.3 ± 0.5 µg/ml on the fourth day of treatment 3.4 ± 1.2 h after the start of etoposide infusion. The apparent metabolite half-life of 8.4 ± 3.0 h was only slightly longer than the corresponding half-life of the parent drug. The area under the concentration–time curve (AUC) of the metabolite reflecting its systemic exposure was calculated for the fourth day of treatment when most plasma samples were drawn. It was found to be $2.5 \pm 0.9\%$ of the AUC of etoposide.

To our knowledge, this is the first report that demonstrates that cancer patients receiving high-dose etoposide are exposed to considerable plasma levels of the cytotoxic catechol metabolite. Interindividual variability in its formation may, therefore, have clinical implications. Other anticancer agents might induce or inhibit this metabolic pathway leading to different kinetic profiles of the catechol depending on the regimen used. Future pharmacokinetic investigation should include measurements of this metabolite to reveal its contribution to tumour response as well as to treatment-induced toxicity.

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Received 31 Oct. 1996; accepted 12 Nov. 1996.

1. 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* 1993, **45**, 352–358.
2. Van Maanen JMS, De Vries J, Pappie D, *et al.* Cytochrome P-450-mediated *O*-demethylation: a route in the metabolic ac-

tivation of etoposide (VP-16-213). *Cancer Res* 1987, **47**, 4658–4662.
3. Van Maanen JMS, Lafleur MVM, Mans DRA, *et al.* Effects of the ortho-quinone and catechol of the anti-tumor drug VP-16-213 on the biological activity of single-stranded and double-stranded ϕX174 DNA. *Biochem Pharmacol* 1988, **37**, 3579–3589.
4. Fieser LS, Fieser M. *Advanced Organic Chemistry*. New York, Reinhold Publishing Co., 1961, 747.