Mechanism of Action of Antitumor Drug Etoposide: A Review

J. M. S. van Maanen,* J. Retèl, J. de Vries, H. M. Pinedo

Metabolism studies of the antitumor drug etoposide show the formation of metabolites in the lactone ring, which are probably not important for the drug's mechanism of action, and oxidative transformations in the dimethoxyphenol ring (E ring), which lead to products that can cause DNA damage and may play a role in the drug's mechanism of action. The cytotoxicity of etoposide is caused by the induction of DNA damage. The occurrence of the DNA lesions can be explained by the capacity of the drug to interfere with the scission-reunion reaction of mammalian topoisomerase II by stabilizing a cleavable complex. [J Natl Cancer Inst 1988;80:1526-1533]

Etoposide (fig. 1) is an important antineoplastic agent used against several types of tumors, including testicular and small cell lung cancers, lymphoma, leukemia, and Kaposi's sarcoma (1). In combination chemotherapy, it has been used successfully with cisplatin and several other antitumor drugs including cyclophosphamide, doxorubicin, and vincristine. In the last decade, a substantial effort has been made by several investigators to elucidate the mechanism of action of this important anticancer drug. This review summarizes the research that has been performed on the metabolism of etoposide and on the most important aspects of its mechanism of action.

Metabolism

Phase I Processes

Reports by Creaven and Allen (2,3) and Allen and Creaven (4) describe the first clinical studies on the pharmacokinetics and metabolism of etoposide and teniposide using tritium-labeled drugs. These investigators based their assay of the distribution of parent drug and metabolite(s) in urine and plasma on selective chloroform extraction of unchanged drug and subsequent scintillation counting. Metabolites were assayed by counting the unextracted radioactivity. However, the authors did not take into account the possibility that chloroform-extractable metabolites were present.

After iv infusion of tritiated etoposide and teniposide, Creaven and Allen (2) found that significant portions of both drugs were excreted by the kidneys. After 72 hours, 44% of the administered doses of both drugs was recovered in the urine, 29% as unchanged drug and 15% as metabolite(s) for etoposide and 9% as unchanged drug and 35% as metabolite(s) for teniposide. The finding that the metabolite(s) of teniposide was present in the urine in larger relative amounts than the metabolite(s) of etoposide coincides with a lower renal clearance of the unchanged drug seen with teniposide. This finding could indicate that the lipid solubility of teniposide is higher than that of its ethylidene congener, etoposide (3). The slow elimination observed was not caused by exchange of tritium, retention in the body of unchanged etoposide, or excretion in the feces. The pharmacokinetic analysis showed that 66% of the etoposide was metabolized. This value agrees well with the fraction of the administered dose not recovered as unchanged drug (71%) but markedly overestimates the percentage of administered drug recovered as a metabolite (15%). This observation suggested sequestration of metabolite(s) as a possible explanation for the incomplete recovery of etoposide. This possibility was supported by study of a multicompartment pharmacokinetic model of etoposide developed for humans to account for drug plus metabolite(s) sequestered in the body (4,5).

Some chemical transformations of the 1'-lactone ring of etoposide that are analogous to known reactions of podophyllotoxin are relevant to this discussion (fig. 2). By alkaline hydrolysis, the trans lactone form of etoposide epimerizes via the enolate to the cis lactone form (picroetoposide), and the lactone ring is subsequently opened to form the cis...
hydroxy acid. Picroetoposide can be selectively produced at pH 9 and the cis hydroxy acid at pH 12. At low pH values, the cis hydroxy acid recyclizes to picroetoposide (6).

Metabolites

Hydroxy acid. The main biotransformation route for etoposide is believed to be hydrolysis of the lactone ring to the hydroxy acid derivative. Allen et al. (7) isolated the major urinary metabolite of etoposide after extraction of the unchanged drug with chloroform, lyophilization of the aqueous phase, methanol extraction of the residue, and column chromatography. The metabolite was permethylated and identified by electron impact mass spectrometry as 4'-demethyllepipodophyllic acid.

In studies with radiolabeled etoposide, Creaven and Allen (2,3) and Allen and Creaven (4) reported a metabolite in the serum and urine that was not extractable with chloroform. The metabolite may have been this hydroxy acid derivative. This metabolite has probably been isolated by other investigators. By extraction with XAD-4 resin, Strife et al. (6) isolated a metabolite from plasma of patients after administration of etoposide. From the ion-pairing properties and the similarity of retention time to that of the synthetic hydroxy acid, the investigators concluded that the metabolite is the hydroxy acid of etoposide. On the basis of the elution in the region of the synthetic hydroxy acid, Evans et al. (8) detected a hydroxy acid derivative in the plasma and urine of patients. Holthuis et al. (9,10) isolated a hydroxy acid of etoposide from urine and bile pre-extracted with 1,2-dichloroethane. Using a radioimmunoassay, Ho et al. (11) reported the presence of the hydroxy acid in urine, bile, and tissue following administration of etoposide. In a patient with a T-tube fistula who received etoposide by continuous infusion (60 mg/m² per day), 19% of the dose was excreted in the bile and 58% in the urine as this metabolite.

All of these studies lack conclusive proof that the isolated metabolite is the hydroxy acid derivative of etoposide because no identification was performed by mass spectrometry. The only conclusive identification of the hydroxy acid as a metabolite of etoposide was reported by Allen et al. (7). However, the metabolite reported in all of these studies is probably the hydroxy acid derivative of etoposide, since other metabolites are not expected to have such a high hydrophilicity and an elution profile comparable with that of the synthetic hydroxy acid. The metabolic formation of the hydroxy acid derivative should be catalyzed by an esterase, and the metabolite probably possesses the trans configuration, but this has never been unequivocally established.

In the studies described, the investigators used the synthetic cis hydroxy acid as a reference compound, and from small differences in the retention times of the metabolite and the cis hydroxy acid, they concluded that the metabolite is the trans hydroxy acid. The synthetic cis hydroxy acid was reported to have no measurable cytotoxic effect against human leukemic lymphoblasts (CCRF-CEM cells) (12). The trans hydroxy acid may possess cytotoxic activity, but unfortunately, no studies of this have been reported. One could speculate that, in addition to the formation of the hydroxy acid, the opening of the lactone ring could also produce an acylating substance capable of interacting with biomacromolecules. However, formation of the hydroxy acid by rat liver microsomes was found to be extensive (13). In this system, acylation of biomacromolecules could also have taken place in competition with hydroxy acid formation. The extensive formation of the hydroxy acid by rat liver microsomes and the fact that the hydroxy acid is more hydrophilic than
etoposide and therefore more readily excretable suggest that the opening of the lactone ring is at least partially a deactivation process. However, no firm conclusion can be drawn about the role of hydroxy acid formation in the in vivo activity of etoposide until there has been a study of the cytotoxic properties of the trans hydroxy acid and elucidation of the structure of the metabolite claimed by several investigators to be the trans hydroxy acid.

**Picroetoposide.** Another metabolite formed by conversion of the highly strained lactone ring of etoposide is picroetoposide. It is known that epimerization of podophyllotoxin and analogues at the lactone ring site to picropodophyllotoxins is a detoxification process, since the biological activity of picropodophyllotoxin as well as the other cis analogues is either much lower than that of the trans isomers or is lacking altogether (14). A similar detoxification to the picro isomer may be operative for etoposide. At elevation of the pH or the temperature, etoposide is converted into its cis isomer, indicating that the formation of the picro isomer can take place by a nonenzymatic process. This finding is supported by the observation that small amounts of picroetoposide are formed by inactivated rat liver microsomes (13). The presence of picroetoposide has been reported in plasma (8,15,16), serum (17), urine (8,15,16), cerebrospinal fluid (18), and the liver (19). The picro isomer of etoposide showed no measurable cytotoxic effect against CCRF-CEM cells (12). Jardine et al. (20), who studied the activity of the cyclic ether and ring-opened diol analogues of etoposide, reported that the lactone moiety of etoposide is not an absolute requirement for cytotoxicity but that alteration of the lactone considerably reduced the activity of the parent drug.

**AGlycone.** The aglycone of etoposide (4'-demethyllepipodophyllotoxin) is a potent cytostatic agent (8,12). In contrast to etoposide but like podophyllotoxin, the aglycone can act as an inhibitor of microtubule assembly, thus producing cell arrest in metaphase (21). The question arises whether the aglycone is formed in the metabolism of etoposide and subsequently acts as a microtubule inhibitor. The possible formation of the aglycone by β-glycosidases was suggested by Evans et al. (8). Although the production of small amounts of the aglycone by rat liver microsomes was observed (22), initial in vivo metabolism studies have produced no evidence that the glucoside moiety of etoposide is cleaved. The aglycone has not been found in the urine of patients treated with etoposide (8,17,23). However, Gouyette et al. (24) recently reported the presence of the aglycone in plasma. Evidence that the glucoside moiety is not cleaved intracellularly is provided (a) by studies from Phaire-Washington et al. (25), which suggest that etoposide does not affect the cytoplasmic organization of microtubules, and (b) by the observation that etoposide-treated cells are not arrested in metaphase (21).

In conclusion, the formation of the metabolites hydroxy acid, picroetoposide, and the aglycone of etoposide probably do play an important role in the cytotoxicity of etoposide.

**Phase II Processes**

Conjugation of etoposide with glucuronic acid has been reported by Colombo et al. (19,26), D’Incalci et al. (27), Holthuis (10), and Hande et al. (28). Colombo et al. (19,26) detected two glucuronides in the bile of etoposide-perfused rat livers; after treatment with β-glucuronidase, etoposide was liberated. These investigators suggested that the glucuronic acid is not linked to the phenolic group but that the two hydroxyl groups in the glucoside moiety are involved in glucuronide formation. D’Incalci et al. (27) reported the presence of glucuronides in the urine of patients receiving etoposide. Holthuis (10) reported that the glucuronide of etoposide isolated from patient’s urine possesses the glucuronic acid linked to the phenolic C-4' position. In contrast to the findings of Colombo et al. (19), Holthuis reported the glucuronide to be the major metabolite of etoposide instead of the hydroxy acid derivative, which was reported by other investigators to be the major metabolite. Hande et al. (28) provided mass spectrometric evidence demonstrating the formation of the glucuronide of etoposide in the rat and the rabbit.

**Mechanisms of Action**

The precise mechanism of action of etoposide is unknown. Probably, the mechanism of action of this drug differs from that of the parent compound, podophyllotoxin. Podophyllotoxin inhibits the assembly of microtubules and arrests cells in the metaphase, whereas etoposide prevents cells from entering mitosis and blocks cell-cycle progression in the late S and G2 phases (21,29). Etoposide can arrest cells in metaphase only at very high concentrations, which are probably irrelevant in vivo (29). The presence of the bulky glucoside moiety of etoposide is probably responsible for the inactivity of the drug as an inhibitor of microtubule assembly, since the nonglucoside congener of etoposide, 4-demethyllepipodophyllotoxin, is capable of inhibiting microtubule assembly. The conclusion that podophyllotoxin has a mechanism of action different from that of etoposide or teniposide is supported by the finding that podophyllotoxin-resistant Chinese hamster ovary (CHO) cells are cross-resistant to other microtubule inhibitors but not to etoposide (30–32). Conversely, it appears that cells resistant to etoposide and teniposide are not resistant to podophyllotoxin and its congeners (33).

Both etoposide and podophyllotoxin inhibit the active nucleoside transport in mastocytoma and HeLa cells, which results in inhibition of incorporation into DNA (21,34). The diffusional rate component of nucleoside transport is not inhibited, and neither is the phosphorylation of nucleosides into nucleotides. Since the concentrations of etoposide and podophyllotoxin required to inhibit nucleoside transport are much higher than those necessary for their cytotoxic effects, this inhibition process is probably irrelevant to the cytotoxic action of the drugs.

**Inhibition of DNA Topoisomerase II Activity**

Evidence is accumulating that the principal target of both etoposide and teniposide is cellular DNA. The initial suggestion that DNA is damaged by the action of etoposide came from Huang et al. (35). When these investigators treated four human hematopoietic cell lines with etoposide at a dose that inhibits cell growth, they found a high incidence of chro-
mosomal aberrations. More recently, it has been established (a) that treatment with etoposide and teniposide results in a considerable increase in the frequency of sister chromatid exchanges and (b) that these drugs are strongly mutagenic in CHO cells (36).

Loike and Horwitz (37) reported that the introduction of DNA strand breaks is a very important effect of these two drugs. These investigators studied the effect of etoposide and several other podophyllotoxin derivatives on the sedimentation behavior of DNA from HeLa cells in alkaline sucrose gradients. After brief exposure of the cells to low concentrations of etoposide, strand breaks appeared to be induced in the DNA. It was found that the presence of a hydroxyl group in the C-4' position in ring E (the dimethoxyphenol ring) was required for a podophyllotoxin derivative to induce strand breaks, since the 4'-methoxy derivatives were inactive in this respect. Incubation of purified DNA with etoposide did not lead to DNA degradation.

The observations of Loike and Horwitz were confirmed by the results of many studies in a great variety of cell lines (38-46). Using alkaline elution as the principal method, investigators (39-43) firmly established the formation of both single- and double-strand breaks as well as DNA-protein cross-links. Results of some studies (39,43,46) also suggest that, in most cell lines, there is a good relationship between cytotoxicity and production of strand breaks, double-strand breaks in particular. Another important finding is that teniposide is more potent than etoposide in the stimulation of DNA cleavage; this finding is supported by study results (42,43) showing the difference in cytotoxic effects.

An important feature in the epipodophyllotoxin-induced strand scission is that it plateaus shortly after the addition of the drugs and is rapidly repaired after their removal (43,46). Apparently, the strand scission is, for the most part, reversible. By evaluation of 14 congeners of podophyllotoxin for their ability to induce DNA breaks and to inhibit growth of A549 human lung adenocarcinoma cells, it was concluded that the following structural features were essential (42):

(a) the presence of a hydroxyl group at the C-4' atom;
(b) an epi configuration at the C-1 position; and
(c) the presence of a glucoside moiety on the hydroxyl group at the C-1 position and aldehyde condensation with the OH groups at the C-4 and C-6 positions of the hexapyranoose moiety.

An indication that some nuclear enzyme may be involved in the strand scission activity of etoposide and teniposide came from the studies of Wozniak and Ross (39), who showed that single- and double-strand breaks also occur after exposure of isolated nuclei of L1210 cells to etoposide and that this effect is temperature dependent. In subsequent studies (47-54), it became clear that the nuclear enzyme DNA topoisomerase II probably plays a predominant role in mediating epipodophyllotoxin-induced DNA strand scission. In vitro studies (47,50,51) using purified mammalian DNA topoisomerase II and pBR322 DNA showed that the epipodophyllotoxins interfere with the scission-reunion reaction of the enzyme by stabilizing a cleavable complex. Treatment of this stabilized cleavable complex with protein denaturants resulted in DNA strand breaks and the covalent attachment of a topoisomerase subunit to each of the 5' ends of the DNA fragments. Such a mechanism of action explains the protein cross-linked DNA strand breaks found in vivo (39,51) and the requirement of magnesium ions and stimulation by ATP for the production of strand breaks in isolated nuclei (47,50). Moreover, the finding that, in vitro, teniposide is more potent than etoposide in stimulating topoisomerase II-mediated DNA cleavage is consistent with the in vivo effects of these drugs (51). Besides forming a cleavable complex, the epipodophyllotoxins also inhibit the catalytic or "strand-passing" activity of DNA topoisomerase II (49,51). It is this activity that allows the enzyme to catenate DNA circles and to disentangle topologically constrained DNA.

Similar effects on the topoisomerase activities were observed for intercalative antitumor drugs such as anthracyclines, actinomycin, ellipticines, and dactinomycin (55,56). In contrast to these drugs, etoposide and teniposide show a very low level of binding to DNA (50,57). Thus, it seems likely that inhibition of the scission-reunion and strand-passing reactions is caused by the direct interaction of the epipodophyllotoxins with DNA topoisomerase II. The effect of the epipodophyllotoxins on the mammalian topoisomerase is very similar to that of nalidixic acid and oxolinic acid on Escherichia coli DNA gyrase (58-62). Oxolinic acid shares certain structural features with the epipodophyllotoxins. Since the mechanism of inhibition of DNA gyrase by oxolinic acid has been reported to be mediated by binding of the drug to DNA (63), it is possible that binding to DNA by the epipodophyllotoxins may also be relevant to their inhibition of topoisomerase action.

It is obvious that the induction of strand breaks by etoposide and teniposide can be explained by their ability to inhibit the activity of nuclear topoisomerase II. It is less clear, however, whether this effect is primarily responsible for the high frequency of sister chromatid exchange, chromosomal aberrations, and mutagenesis and also for the cytotoxicity of these two drugs. The finding that, in most cases, there is a relationship between the production of strand breaks and cytotoxicity does not demonstrate that this type of topoisomerase-linked damage is the only cause of cell death. It should be noted (a) that DNA strand breaks can be detected at concentrations of etoposide well below the level required to show effects on cell kinetics or inhibition of DNA synthesis (40) and (b) that the strand breaks can be repaired rapidly after removal of the drug, which probably reflects the reversible nature of the inhibition of type II topoisomerase reaction (43,46). These findings raise the possibility that other mechanisms of cytotoxicity are involved in combination with the topoisomerase-linked DNA degradation.

**Metabolic Activation To Form DNA-Binding Intermediates**

The results of metabolism studies have shown that etoposide and teniposide may have mechanisms of action other than the inhibition of topoisomerase. Loike and Horwitz (37) observed that the capacity of etoposide to induce DNA damage is dependent on the presence of a hydroxyl group at the C-4' of the E ring (the dimethoxyphenol ring) and that ex-

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posure of isolated purified DNA to etoposide did not lead to DNA degradation. These observations led the investigators to hypothesize that activation of one or several endonucleases or transformation into a reactive metabolite is responsible for the effect on DNA.

Special attention has been focused on metabolic alterations in the dimethoxyphenol ring of etoposide. In in vitro metabolism studies, Sinha et al. (64,65) showed that etoposide is O-demethylated by mouse liver microsomes. Cytochrome P-450-mediated covalent binding of etoposide to rat liver and HeLa cell microsomal proteins was observed by van Maanen et al. (66), who further studied O-demethylation of etoposide by rat liver microsomes and purified rat liver cytochrome P-450 and identified the product of O-demethylation as the orthohydroxy derivative or catechol of etoposide (67,68). The presence of the polycyclic skeleton (ring A,B,C,D) of etoposide was found to be a prerequisite for binding to cytochrome P-450 and O-demethylation (69). The formation of the orthohydroxy derivative by O-demethylation of etoposide was also described by Haim et al. (70).

In the presence of oxygen, the catechol of etoposide is further oxidized to a secondary metabolite, the ortho quinone (57). The conversion of the catechol to the ortho quinone most probably takes place via a semiquinone free radical (71). Haim et al. (72) also showed that the ortho quinone derivatives of etoposide and teniposide are among the products formed in vitro under the influence of horseradish peroxidase or prostaglandin E synthetase and that the phenoxy free radicals of the drugs most probably are the pivotal intermediates in the formation of the ortho quinones (72). The generation of phenoxy free radicals by horseradish peroxidase and myeloperoxidase in the presence of hydrogen peroxide has also been observed by other investigators (73–75). Both the ortho quinone and the catechol of etoposide bind strongly to purified DNA in vitro and inactivate biologically active single- and double-stranded DNA (57,67,68,76). On the other hand, investigators observed only a very low level of binding by etoposide (57) and no inactivation by etoposide or the phenoxy radical, which was prepared by electrochemical oxidation (76). These findings give strong support to the hypothesis that the antitumor activity of etoposide may also be based on the metabolic activation of the E ring of etoposide to produce metabolites that can inactivate the DNA by formation of chemical adducts.

In a recent in vitro study, Sinha et al. (77) observed that hydroxyl radicals are produced by the catechol of etoposide in the presence of iron and hydrogen peroxide, which cause nicking of SV40 DNA. However, there is no evidence showing hydroxyl radical formation in tumor cells treated with etoposide or its catechol. Because the hydroxyl group in the dimethoxyphenol ring is necessary for inactivation of DNA, it appears that this hydroxyl group may play a role in the interaction of etoposide with topoisomerase II. In studies by Long and Minocha (48) and Minocha and Long (49) on structure-activity relationships, podophyllotoxin congeners lacking a 4'-OH group showed no DNA scission activity and no inhibition of topoisomerase II. In view of the formation of the reactive metabolites catechol and the ortho quinone in the dimethoxyphenol ring of etoposide, we believe that testing of the catechol and the ortho quinone of etoposide for their ability to inhibit topoisomerase II activity is warranted.

Reports on oxidative metabolism of etoposide in the polycyclic skeleton (ring A,B,C,D) came from Broggi et al. (78) and Haim et al. (79), who described the formation of the 1,2,3,4-tetrahydro derivative of etoposide. This derivative was identified by nuclear magnetic resonance and mass spectrometry as a product of the oxidation of etoposide; it was formed by incubation of the drug with horseradish peroxidase and hydrogen peroxide. Results of the study of Haim et al. (79) suggested that etoposide-derived quinone methides are DNA-binding species formed during peroxidative activation of etoposide in the presence of DNA.

In addition to these in vitro studies, several cellular and in vivo studies indicate that oxidation-reduction processes play an important role in the cytotoxic action of the epipodophyllotoxins. Wozniak et al. (80) observed that dehydrogenase inhibitors such as disulfiram and diethyldithiocarbamate as well as free-radical scavengers such as sodium benzoate and dehydrogenase substrates prevent the etoposide-induced production of strand breaks and cytotoxicity in L1210 cells. This finding suggests that a dehydrogenase in an oxidation-reduction reaction plays a role in etoposide cytotoxicity. Teicher et al. (81) reported that etoposide cytotoxicity is greater in oxygenated EMT6 mouse mammary tumor cells than in hypoxic cells. Similarly, Teicher et al. (81,82) found that the in vivo antitumor activity of etoposide against FSa-II fibrosarcoma and Lewis lung carcinoma was increased considerably by oxygenation of the tumor tissue prior to administration of the drug. These investigators suggested that etoposide acts through an oxidation-reduction process involving the production of reactive oxygen species.

In several studies, van Maanen et al. (57,66–68) showed that the oxidation of etoposide by cytochrome P-450 to the catechol and the further oxidation to the ortho quinone is oxygen dependent. In view of these results, the findings of Teicher et al. (81) can also be interpreted to mean that these metabolites, which are involved in the oxidation-reduction process, are directly responsible for DNA damage and cytotoxicity. Yamachii et al. (83), however, reported that etoposide cytotoxicity against human sarcoma cells is diminished by severe anoxia but not by low levels of anoxia. These investigators suggested that the acute anoxia may have depleted ATP levels sufficiently to inhibit the interaction of etoposide with the highly ATP-dependent topoisomerase II. Katki et al. (84) recently reported that administration of etoposide to mice affects the thiol redox state in the liver by causing depletion of glutathione (GSH). The investigators suggested that GSH depletion may have been caused by binding of GSH to a reactive intermediate of etoposide formed by metabolic activation (e.g., the phenoxy radical or the ortho quinone of etoposide) and that the result was detoxification.

The similarities between the effects of epipodophyllotoxins and ionizing radiation are relevant to this discussion. In therapy with ionizing radiation, hydroxyl radicals are mainly responsible for the toxic effects. After studying the effect of etoposide and teniposide in a stable mutant of CHO cells
resistant to the drugs, Gupta (33) concluded that the kinetics of cell killing by these drugs were strikingly similar to those for x rays. Such a similarity was also established in clinical studies (85). Singh and Gupta (36, 86) studied the mutagenic effects of etoposide, teniposide, x rays, and other anticancer agents on five independent genetic loci in CHO cells. Etoposide, teniposide, and x rays had mutagenic effects on the hypoxanthine-guanine-phosphoribosyl transferase (HPRT) gene. Hill and Bellamy (87) reported the development of a human squamous cell carcinoma cell line, which was made resistant to etoposide by prior exposure of the cells to fractionated x rays in vitro. Finally, human ataxia telan-
giectasia (AT) fibroblasts demonstrate an increased sensitivity to etoposide (88). In addition to their increased sensitivity to ionizing radiation (89, 90), these cells are known to be sensitive to drugs like bleomycin (91), zoxatin (92, 93), and streptonigrin (94), which are thought to produce reactive oxygen species that are cytotoxic. Henner and Blazka (95) suggested that the hypersensitivity of AT cells to etoposide is caused by the production of free radicals rather than by the inhibition of topoisomerase II, since AT cells are not hyper-
sensitive to amssacrine, an inhibitor of topoisomerase II. No firm conclusions can be drawn, however, until we know the precise nature of the genetic defect that results in the hyper-
sensitivity of AT cells to etoposide and the other agents.

In conclusion, studies show that besides inhibiting DNA topoisomerase II activity, etoposide may exert its cyto-
toxic and anticancer action by metabolic activation in oxidation-reduction reactions to produce derivatives that can bind directly to the cellular DNA. Thus, the cytotoxicity of etoposide may depend on a dual mechanism of DNA inactiv-
ation. These findings illustrate the intriguing complexity of the properties of this anticancer drug.

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