

PRODUCT MONOGRAPH

VEPESID*

(etoposide)

Capsule, 50 mg

Antineoplastic Agent

Date of Preparation:
May 15, 1981

Date of Revision:
March 03, 2015

Bristol-Myers Squibb Canada
Montréal, Canada

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Control Number 179914

PRODUCT MONOGRAPH

VEPESID*
(etoposide)
Capsule, 50 mg

THERAPEUTIC CLASSIFICATION

Antineoplastic Agent

CAUTION: VEPESID (ETOPOSIDE) IS A POTENT DRUG AND SHOULD BE USED ONLY BY QUALIFIED PHYSICIANS EXPERIENCED WITH CANCER CHEMOTHERAPEUTIC DRUGS (SEE WARNINGS AND PRECAUTIONS). SEVERE MYELOSUPPRESSION WITH RESULTING INFECTION OR BLEEDING MAY OCCUR. BLOOD COUNTS AS WELL AS RENAL AND HEPATIC FUNCTION TESTS SHOULD BE TAKEN REGULARLY. DISCONTINUE THE DRUG IF ABNORMAL DEPRESSION OF BONE MARROW OR ABNORMAL RENAL OR HEPATIC FUNCTION IS SEEN.

ACTIONS AND CLINICAL PHARMACOLOGY

VEPESID (etoposide) is a semi-synthetic derivative of podophyllotoxin used in the treatment of certain neoplastic diseases.

In vitro, etoposide has cytostatic action, which prevents the cells from entering mitosis or destroys them in the premitotic phase. Etoposide interferes with the synthesis of DNA and has a secondary effect on arresting cells in resting (G_2) phase in experiments with human lymphoblastic cell lines.

Etoposide has a marked action on human hemopoietic cells causing leukopenia and thrombocytopenia. Animal experiments have shown evidence of teratogenicity.

An intravenous dose (259 mg/m^2) of tritium-labelled etoposide given over one hour in man, showed the mean volume of distribution to be 32% of body weight. The plasma decay was biphasic with a beta half-life of 11.5 hours. Urinary recovery was 44% of which 67% was unchanged drug. Recovery in feces was variable (1.5 - 16%) over a three day period.

A plasma decay with a beta half-life of 6.8 hours was observed following oral administration of etoposide. The $T_{1/2}$ for oral absorption was 0.44 hour and peak plasma concentrations were noted 0.5 to 3 hours after oral administration.

In a limited number of children, VEPESID administered in a dose of $200\text{-}250 \text{ mg/m}^2$ produced a peak serum concentration between 17 and $88 \text{ } \mu\text{g/mL}$ and showed a terminal half-life ($T_{1/2 \beta}$) of 5.7 ± 1.3 hours. Mean plasma clearance was 21.5 mL/min/m^2 and CSF concentrations 24 hours post-infusion ranged from less than 10 ng/mL to $45 \text{ } \mu\text{g/mL}$.

After either intravenous infusion or oral capsule administration of etoposide, the C_{max} and AUC values exhibit marked intra- and inter-subject variability. The overall mean value of oral capsule bioavailability is approximately 50% (range 25-75%).

Etoposide crosses the blood brain barrier in low concentrations.

Etoposide is cleared by both renal and nonrenal processes, i.e. metabolism and biliary excretion. Biliary excretion, however, appears to be a minor route of etoposide elimination.

INDICATIONS AND CLINICAL USE

VEPESID (etoposide) is indicated as follows:

For oral formulation

Small Cell Carcinoma of the Lung

- first-line therapy in combination with other established antineoplastic agents.
- second-line combination or single agent therapy in patients who have not responded or relapsed on other chemotherapeutic regimens.

Malignant Lymphoma (histiocytic type)

- first-line therapy in combination with other established antineoplastic agents.

Non-small Cell Carcinoma of the Lung

- for patients considered ineligible for surgery, etoposide has been shown effective alone or in combination with PLATINOL (cisplatin).
- for patients who require chemotherapy following surgery.

Testicular Malignancies (germ cell tumours including seminomas)

- in combination with other effective chemotherapeutic agents in patients who have already received appropriate therapy.

CONTRAINDICATIONS

VEPESID (etoposide) should not be given to individuals who have demonstrated a previous hypersensitivity to it or any component of the formulation. Also, it is contraindicated in patients having severe leukopenia, thrombocytopenia and severe hepatic and/or renal impairment.

WARNINGS

VEPESID (ETOPOSIDE) IS A POTENT DRUG AND SHOULD BE USED ONLY BY QUALIFIED PHYSICIANS EXPERIENCED WITH CANCER CHEMOTHERAPEUTIC DRUGS (SEE PRECAUTIONS). SEVERE MYELOSUPPRESSION WITH RESULTING INFECTION OR BLEEDING MAY OCCUR. BLOOD COUNTS AS WELL AS RENAL AND HEPATIC FUNCTION TESTS SHOULD BE TAKEN REGULARLY.

DISCONTINUE THE DRUG IF ABNORMAL DEPRESSION OF BONE MARROW OR ABNORMAL RENAL OR HEPATIC FUNCTION IS SEEN.

Fatal myelosuppression has been reported following etoposide administration. Patients being treated with VEPESID (etoposide) must be frequently observed for myelosuppression both during and after therapy. Dose-limiting bone marrow suppression is the most significant toxicity associated with VEPESID therapy. The following studies should be obtained at the start of therapy and prior to each subsequent dose of VEPESID: platelet count, hemoglobin, white blood cell count and differential.

The occurrence of a platelet count below 50,000/mm³ or an absolute neutrophil count below 500/mm³ is an indication to withhold further therapy until the blood counts have sufficiently recovered. A white blood cell count of between 2000 - 3000 cells/mm³ suggests that the dose of VEPESID should be reduced by 50%. Platelet counts between 75,000 - 100,000 cells /mm³ require a dosage reduction of 50%.

Bacterial infection must be brought under control before the administration of VEPESID therapy because of the risk of septicemia.

Vaccinations: Concomitant use of VEPESID with a live virus vaccine may potentiate the replication of the vaccine virus and/or may increase the adverse reaction of the vaccine virus because normal defense mechanisms may be suppressed by VEPESID. Vaccination with a live vaccine in a patient taking VEPESID may result in severe infection. Patient's antibody response to vaccines may be decreased. The use of live vaccines should be avoided and individual specialist advice sought (see DRUG INTERACTIONS, Other interactions).

Physicians should be aware of the possible occurrence of an anaphylactic reaction manifested by chills, fever, tachycardia, bronchospasm, dyspnea and/or hypotension (see ADVERSE REACTIONS). Treatment is symptomatic. The administration of VEPESID should be terminated immediately, followed by the administration of pressor agents, corticosteroids, antihistamines, or volume expanders at the discretion of the physician.

Pregnancy

VEPESID can cause fetal harm when administered to pregnant women.

VEPESID has been shown to be embryotoxic in rats and teratogenic in mice and rats. There are no adequate and well-controlled studies in pregnant women. If the drug is used during pregnancy, or if the patient becomes pregnant while receiving this drug, the patient should be apprised of the potential hazard to the fetus. Women of childbearing potential should be advised to avoid becoming pregnant.

Given the mutagenic potential of VEPESID, an effective contraception is required for both male and female patients during treatment and up to 6 months after ending treatment. Genetic consultation is recommended if the patient wishes to have children after ending the treatment. As

VEPESID may decrease male fertility, preservation of sperm may be considered for the purpose of later fatherhood.

VEPESID has caused reduced or absent spermatogenesis and reduced testes weights at autopsy in rats and dogs, as well as reduced weight of ovaries in female rats. Chronic toxicity studies in rats have shown etoposide to have an oncogenic potential (see ADVERSE REACTIONS, Hematologic Toxicity).

Nursing Mothers

There has been evidence of VEPESID being excreted in human milk.

Because of the potential for serious adverse reactions in nursing infants from etoposide, breast feeding should be discontinued.

As with any potent antineoplastic drug, the benefit to patient versus the risk of toxicity must be carefully weighed.

PRECAUTIONS

General: The physician must evaluate the need and usefulness of the drug against the risk of adverse reactions. Most such adverse reactions are reversible if detected early. If severe reactions occur, the drug should be reduced in dosage or discontinued and appropriate corrective measures should be taken according to the clinical judgement of the physician. Reinstitution of VEPESID (etoposide) therapy should be carried out with caution, and with adequate consideration of the further need for the drug and alertness to the possible recurrence of toxicity. Patients with low serum albumin may be at increased risk for etoposide-associated toxicities.

VEPESID should be administered by individuals experienced in the use of antineoplastic therapy.

Myelosuppression is dose related and dose limiting, with granulocyte nadirs occurring 7 to 14 days and platelet nadirs occurring 9 to 16 days after drug administration. Bone marrow recovery is usually complete by day 20, and no cumulative toxicity has been reported (See PRECAUTIONS).

Liver and renal function should be regularly monitored.

Professional staff administering VEPESID should exercise particular care to prevent spillage and self contact with the drug. Skin reactions, at times severe, associated with accidental exposure to VEPESID may occur. Gloves should be worn by anyone handling the drug.

Carcinogenesis

Carcinogenicity tests with VEPESID have not been conducted in laboratory animals. Given its mechanism of action, it should be considered a possible carcinogen in humans.

The occurrence of acute leukemia, which can occur with or without a preleukemic phase, has been reported rarely in patients treated with VEPESID in association with other antineoplastic drugs. Neither the cumulative risk, nor the predisposing factors related to the development of secondary leukemia are known. The roles of both administration schedules and cumulative doses of etoposide have been suggested, but have not been clearly defined.

An 11q23 chromosome abnormality has been observed in some cases of secondary leukemia in patients who have received epipodophyllotoxins. This abnormality has also been seen in patients developing secondary leukemia after being treated with chemotherapy regimens not containing epipodophyllotoxins and in leukemia occurring *de novo*. Another characteristic that has been associated with secondary leukemia in patients who have received epipodophyllotoxins appears to be a short latency period, with average median time to development of leukemia being approximately 32 months.

DRUG INTERACTIONS

Effects of other drugs on VEPESID

High dose cyclosporine, resulting in concentrations above 2000 ng/mL, administered with oral etoposide has led to an 80% increase in etoposide exposure (AUC) with a 38% decrease in total body clearance of etoposide compared to etoposide alone. Severe cases of neuropathy have been reported in 0.7% of patients possibly due to an interaction of vincristine and VEPESID.

Effects of VEPESID on other drugs

Concomitant phenytoin therapy is associated with increased VEPESID clearance and reduced efficacy. Other antiepileptic therapy may also be associated with increased VEPESID clearance and reduced efficacy.

Co-administration of antiepileptic drugs and VEPESID can lead to decreased seizure control due to pharmacokinetic interactions between the drugs.

Concomitant warfarin therapy may result in elevated international normalized ratio (INR). Close monitoring of INR is recommended.

Other interactions

Cross resistance between anthracyclines and etoposide has been reported in preclinical experiments.

There is increased risk of fatal systemic vaccine disease with the concomitant use of live vaccines. Live vaccines are not recommended in immunosuppressed patients (see WARNINGS, Vaccinations).

Pediatric Use

Safety and effectiveness in pediatric patients have not been systematically studied. Clinical experience in childhood malignancies is very limited (See WARNINGS).

ADVERSE REACTIONS

The following data on adverse events are based on both oral and intravenous administration of VEPESID (etoposide) as a single agent, using several different dose schedules for treatment of a wide variety of malignancies.

Hematologic Toxicity: Since leukopenia and thrombocytopenia have been reported in patients on VEPESID therapy, platelets and white blood cell counts should be performed prior to each cycle (see WARNINGS).

Myelosuppression with fatal outcome has been reported following etoposide administration (see WARNINGS and PRECAUTIONS).

The occurrence of acute leukemia with or without a preleukemic phase has been reported in patients treated with VEPESID in association with other antineoplastic agents.

Gastrointestinal Toxicity: Nausea and vomiting are the major gastrointestinal toxicities. The severity of such nausea and vomiting is generally mild to moderate with treatment discontinuation required in 1% of patients. Nausea and vomiting can usually be controlled with standard antiemetic therapy. Gastrointestinal toxicities are slightly more frequent after oral administration than after intravenous infusion. Mild to severe mucositis/esophagitis may occur.

Cardiovascular Toxicity: Transient hypotension following rapid intravenous administration has been reported in 1% - 2% of patients. It has not been associated with cardiac toxicity or electrocardiographic changes. No delayed hypotension has been noted. To prevent this occurrence, it is recommended that VEPESID injection be administered by slow intravenous infusion over a 30 to 60 minute period. Hypotension usually responds to cessation of the infusion and/or other supportive therapy as appropriate. When restarting the infusion, a slower administration rate should be used.

Myocardial infarction (some with a fatal outcome) and arrhythmia have been reported.

Allergic Reactions: Anaphylactic-like reactions characterized by chills, fever, tachycardia, bronchospasm, dyspnea and/or hypotension have been reported to occur in 0.7% - 2% of patients during or immediately after intravenous VEPESID administration. Higher rates of anaphylactic-like reactions have been reported in children who received VEPESID infusions at concentrations higher than those recommended. The role that concentration of infusion (or rate of infusion) plays in the development of anaphylactic-like reactions is uncertain. Reactions have occurred very rarely in patients treated with oral capsules. Anaphylactic-like reactions have usually responded promptly to the cessation of the infusion of VEPESID, and subsequent administration of pressor agents, corticosteroids, antihistamines or volume expanders as appropriate. Acute fatal reactions associated with bronchospasm have been reported. Hypertension and/or flushing and/or seizures have also been reported. Blood pressure usually normalizes within a few hours after cessation of the infusion. Anaphylactic-like reactions can occur with the initial dose of VEPESID. Apnea with spontaneous resumption of breathing following discontinuation has been described in patients receiving etoposide infusion.

Alopecia: Reversible alopecia, sometimes progressing to total baldness was observed in up to 66% of patients.

Neurologic Toxicity: Peripheral neuropathy has been reported in 0.7% of patients. The occurrence of Posterior Reversible Encephalopathy Syndrome (PRES) has been reported in patients treated with VEPESID in association with other antineoplastic agents.

Other Toxicities: Weakness (3%), mouth ulceration (2%). The following adverse events have been reported in less than 1 percent: hyperuricemia, sepsis, numbness and tingling, dizziness, depression, nail pigmentation and moniliasis. The following adverse reactions have been rarely reported: interstitial pneumonitis/pulmonary fibrosis, seizures (occasionally associated with allergic reactions), somnolence and fatigue, liver toxicity, fever, aftertaste, Stevens-Johnson syndrome, toxic epidermal necrolysis (one fatal case has been reported), rash, pigmentation, pruritus, urticaria, constipation, dysphagia, asthenia, malaise, transient cortical blindness, optic neuritis, and radiation recall dermatitis.

Occasionally following extravasation, soft tissue irritation and inflammation has occurred; ulceration is generally not seen.

Metabolic Complications: Tumor lysis syndrome (sometimes fatal) has been reported following the use of VEPESID in association with other chemotherapeutic drugs.

The incidences of adverse reactions in the table that follows are derived from multiple data bases from studies in patients when VEPESID was used either orally or by injection as a single agent.

ADVERSE DRUG EFFECT	RANGE OF REPORTED INCIDENCE (%)
<u>Hematologic toxicity</u> Leukopenia (less than 1,000 WBC/mm ³) Leukopenia (less than 4,000 WBC/mm ³) Thrombocytopenia (less than 50,000 platelets/mm ³) Thrombocytopenia (less than 100,000 platelets/mm ³) Anemia	3 - 17 60 - 91 1 - 20 22 - 41 0 - 33
<u>Gastrointestinal toxicity</u> Nausea and vomiting Abdominal pain Anorexia Diarrhea Stomatitis	31 - 43 0 - 2 10 - 13 1 - 13 1 - 6
Alopecia Peripheral neurotoxicity Hypotension Allergic reaction Hepatic	8 - 66 1 - 2 1 - 2 1 - 2 0 - 3

SYMPTOMS AND TREATMENT OF OVERDOSAGE

The anticipated acute complications would be related to VEPESID's hematotoxicity.

Total doses of 2.4 g/m² to 3.5 g/m² administered intravenously over three days resulted in severe mucositis and myelotoxicity.

Metabolic acidosis and cases of serious hepatic toxicity have been reported in patients receiving higher than recommended intravenous doses of etoposide.

There is no known antidote and therefore symptomatic measures should be taken to sustain the patient through any period of toxicity that might occur. Patients' renal and hepatic functions should be monitored for 3-4 weeks in case of delayed toxicity.

DOSAGE AND ADMINISTRATION

Oral: 100 - 200 mg/m² daily for 5 days.

The bioavailability also varies from patient to patient following any oral dose. This should be taken into consideration when prescribing this medication. In view of significant intra-patient variability, dose adjustment may be required to achieve the desired therapeutic effect. Daily doses greater than 200 mg should be given divided (BID).

Dosage should be modified to take into account the myelosuppressive effects of other drugs in the combination or the effects of prior X-ray therapy or chemotherapy which may have compromised bone marrow reserve.

Capsules should be taken on an empty stomach.

Oral

Renal Impairment: In patients with impaired renal function, the following initial dose modification should be considered based on measured creatinine clearance.

Measured Creatinine Clearance	Dose of Etoposide
> 50 mL/min	100% of dose
15 - 50 mL/min	75% of dose

Subsequent dosing should be based on patient tolerance and clinical effect. Data are not available in patients with creatinine clearance <15 mL/min and further dose reduction should be considered in those patients.

PHARMACEUTICAL INFORMATION

I. DRUG SUBSTANCE

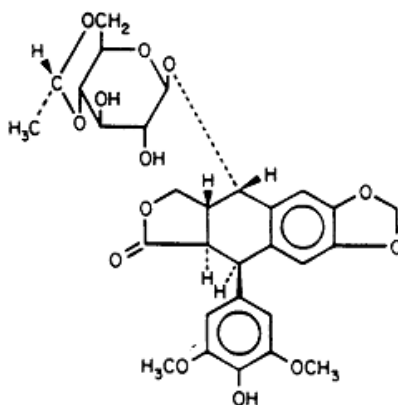
Trade Name: VEPESID

Proper Name: Etoposide

Chemical Name: (1)Furo[3',4':6,7]naphtho[2,3-d]-1,3-dioxol-6(5a*H*)-one, 9-[(4,6-*O*-ethylidene-β-D-glucopyranosyl)oxyl]5,8,8a,9-tetrahydro-5-(4-hydroxy-3,5-dimethoxyphenyl), [5*R*-[5α,5αβ,-8αα,9β(*R*^{*})]]-;(2)4'-Demethylepipodophyllotoxin 9-[4-6-*O*-(*R*)-ethylidene-β-D-glucopyranoside].

Molecular Formula: C₂₉H₃₂O₁₃

Structural Formula:



Molecular Weight: 588.58

Description: Etoposide is a white to yellowish or brown-tinged yellowish, fine, crystalline powder. Etoposide is a semi-synthetic derivative of podophyllotoxin. It is very soluble in methanol and chloroform, slightly soluble in ethanol and very slightly soluble in water and ether. It is made water soluble by means of organic solvents.

II. COMPOSITION

Capsules

Each liquid-filled, soft gelatin pink capsule contains 50 mg of etoposide in a vehicle containing citric acid, glycerol, polyethylene glycol 400 and water. The shell of the capsule contains gelatin, glycerol, parabens (ethyl and propyl), purified water, sorbitol with the following dye system: red iron oxide and titanium dioxide.

Stability and Storage Recommendations

Capsules

VEPESID capsules should be stored at room temperature (15°- 30°C).

SPECIAL INSTRUCTIONS

To minimize the risk of dermal exposure, always wear impervious gloves when handling bottles containing VEPESID capsules. This includes handling activities in clinical settings, pharmacies, storerooms, and home healthcare settings, including during unpacking and inspection, transport within a facility, and dose preparation and administration.

Procedures for proper handling and disposal of anticancer drugs should be considered. Several guidelines on this subject have been published. There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.

AVAILABILITY OF DOSAGE FORMS

VEPESID 50 mg capsules are available in bottles of 20.

HUMAN PHARMACOLOGY

Pharmacokinetics

On intravenous administration, the disposition of VEPESID (etoposide) is best described as a biphasic process with a distribution half-life of about 1.5 hours and terminal elimination half-life ranging from 4 to 11 hours. Total body clearance values range from 33 to 48 mL/min or 16 to 36 mL/min/m² and, like the terminal elimination half-life, are independent of dose over a range 100-600 mg/m². Over the same dose range, the areas under the plasma concentration vs. time curves (AUC) and the maximum plasma concentration (C_{max}) values increase linearly with dose. Etoposide does not accumulate in the plasma following daily administration of 100 mg/m² for 4 to

6 days.

The mean volumes of distribution at steady state fall in the range of 18 to 29 litres or 7 to 17 L/m². Etoposide enters the CSF poorly. Although it is detectable in CSF and intracerebral tumours, the concentrations are lower than in extracerebral tumours and in plasma. Etoposide concentrations are higher in normal lung than in lung metastases and are similar in primary tumours and normal tissues of the myometrium.

In vitro, etoposide is highly protein bound (97%) to human plasma proteins. In a study of the effects of other therapeutic agents on *in vitro* binding of ¹⁴C etoposide to human serum proteins, only phenylbutazone, sodium salicylate, and aspirin displace protein-bound etoposide at concentrations generally achieved *in vivo*.

Etoposide binding ratio correlates directly with serum albumin in cancer patients and normal volunteers. Unbound fraction of etoposide correlates significantly with bilirubin in cancer patients. There appears to be a significant inverse correlation between serum albumin concentration and free etoposide fraction (See PRECAUTIONS).

After intravenous administration of ¹⁴C-etoposide (100-124 mg/m²), mean recovery of radioactivity in the urine was 56% of the dose at 120 hours, 45% of which was excreted as etoposide; fecal recovery of radioactivity was 44% of the dose at 120 hours.

In children, approximately 55% of the dose is excreted in the urine as etoposide in 24 hours. The mean renal clearance of etoposide is 7 to 10 mL/min/m² or about 35% of the total body clearance over a dose range of 80 to 600 mg/m². An inverse relationship between plasma albumin levels and etoposide renal clearance is found in children.

Etoposide, therefore, is cleared by both renal and nonrenal processes, i.e. metabolism and biliary excretion. The effect of renal disease on plasma etoposide clearance is not known in children.

Biliary excretion of unchanged drug and/or metabolites is an important route of etoposide elimination as fecal recovery of radioactivity is 44% of the intravenous dose. The hydroxyacid metabolite [4'-dimethyl- epipodophyllic acid-9-(4,6-O-ethylidene-β-D-glucopyranoside)], formed by opening of the lactone ring, is found in the urine of adults and children. It is also present in human plasma, presumably as the trans isomer. Glucuronide and/or sulfate conjugates of etoposide are also excreted in human urine. Only 8% or less of an intravenous dose is excreted in the urine as radiolabeled metabolites of ¹⁴C-etoposide. In addition, O-demethylation of the dimethoxyphenol ring occurs through the CYP450 3A4 isoenzyme pathway to produce the corresponding catechol.

After either intravenous infusion or oral capsule administration, the C_{max} and AUC values exhibit

marked intra- and inter-subject variability. This results in variability in the estimates of the absolute oral bioavailability of etoposide oral capsules.

C_{max} and AUC values for orally administered etoposide capsules for doses up to approximately 250 mg consistently fall in the same range as the C_{max} and AUC values for an intravenous dose of one-half the size of the oral dose. The overall mean value of oral capsule bioavailability is approximately 50% (range 25-76%). A recent study concluded that the mean bioavailability of a 100 mg oral dose was 76 ± 22%. A 400 mg dose of VEPESID capsule proved to be 48 ± 18% bioavailable.

There is no evidence of a first-pass effect for etoposide. For example, no correlation exists between the absolute oral bioavailability of etoposide capsules and non-renal clearance. No evidence exists for any other differences in etoposide metabolism and excretion after administration of oral capsules as compared to intravenous infusion.

In adults, the total body clearance of etoposide is correlated with creatinine clearance, low serum albumin concentration, and nonrenal clearance. In adult cancer patients with liver dysfunction, total body clearance of etoposide is not reduced. Patients with impaired renal function receiving etoposide have exhibited reduced total body clearance, increased AUC and higher steady state volume of distribution (see DOSAGE & ADMINISTRATION). Concomitant cisplatin therapy is associated with reduced total body clearance of etoposide. In children, elevated SGPT levels are associated with reduced drug total body clearance. Prior use of cisplatin may also result in a decrease of etoposide total body clearance in children.

Although minor differences in pharmacokinetic parameters between gender and between patients ≤ 65 years and > 65 years of age have been observed, these are not considered clinically significant.

ANIMAL PHARMACOLOGY

In vitro

Etoposide interferes with the synthesis of DNA. *In vitro* experiments with radiolabelled thymidine have demonstrated that etoposide has a concentration dependent inhibition of thymidine uptake.

It has been shown that etoposide, *in vitro* tests on chick connective tissue (fibroblasts) arrested mitosis at metaphase. These effects appeared to be concentration dependent.

Etoposide will inhibit tissue culture *in vitro* as shown in studies with cell line of P-815, HeLa and L types.

Human hemopoietic cell lines treated with etoposide showed a high incidence of multiple chromosomal abnormalities.

The drug has shown activity in rodent transplantable tumors of the sarcomas 37 and 180 and the Walker carcinosarcoma, as well as leukemias P-1534 and L-1210.

Etoposide has been shown to cause metaphase arrest in chick fibroblasts. Its main effect, however, appears to be at the late S or early G₂ portion of the cell cycle in mammalian cells. Two different dose-dependent responses are seen. At high concentrations (10 µg/mL or more), lysis of cells entering mitosis is observed. At low concentrations (0.3 to 10 µg/mL), cells are inhibited from entering prophase. It does not interfere with microtubular assembly. The predominant macromolecular effect of VEPESID (etoposide) appears to be the induction of DNA strand breaks by an interaction with DNA-topoisomerase II or the formation of free radicals.

Pharmacokinetics

In rats, etoposide was distributed in highest concentrations in liver, kidney and small intestine thirty minutes after intravenous injection of radio-labelled etoposide. Etoposide accumulated to a significant degree after 24 hours in liver, kidney, bile and thyroid, and its major route of excretion was shown to be the bile.

In monkeys, following oral administration, a maximum blood level of etoposide was achieved after 45 minutes and following an intravenous bolus administration, a maximum level was seen after 15 minutes.

In monkeys, the oral half life was 1.7 hours, and the intravenous half life was 1.3 hours. Nineteen percent of the etoposide oral dose was excreted in the urine after 80 hours, and 63% of etoposide oral dose was found in the feces.

TOXICOLOGY

Acute Toxicity

The LD₅₀ was determined in mice, rats and rabbits (see following Table).

TABLE 1
LD₅₀ of etoposide I.V.

	Etoposide solution		Ampoule solvent
	mg/kg	mL/kg	mL/kg
Mouse	118 ± 9.5	5.9	6.6 ± 0.3
Rat	68 ± 3.5	3.4	4.2 ± 0.4
Rabbit	80	4.0	ca 4.0

The exact estimate of the toxicity of etoposide is limited by the toxicity of the solvent, so acute intravenous toxicity of etoposide cannot be given with certainty.

Subacute Toxicity

Etoposide was administered intraperitoneally at doses of 0.6, 1.8 and 6.0 mg/kg/day to three groups of 20 rats (10 males and 10 females) for four weeks.

A dose of 0.6 mg/kg produced no significant effects. No deaths occurred.

1.8 mg/kg/day produced anemia and transient lymphopenia with significant thymus involution and reduced splenic lymphoid tissue in some animals. No deaths occurred. 6.0 mg/kg/day had significant effects on the hemopoietic and lymphopoietic systems, characterized by fairly severe anemia and marked leukopenia with agranulocytosis in one case. Spermogenesis in the males was diminished or absent. Non-specific effects (weight loss, diarrhea, pulmonary lesions, hepatocyte degeneration) were reported. Mortality was 2/20 in this group.

0.6 mg/kg/day at necropsy showed slight evidence of thymus involution in 11/20 rats. There were marked areas of retroperitoneal hemorrhage and small petechial hemorrhages in the pleura and renal capsule.

1.8 mg/kg/day at necropsy showed moderate thymus involution in 18/20 rats. There was a small quantity of serosanguinous ascitic fluid in 7/20 rats. Also seen were small petechial hemorrhages in pleura and renal capsule as in other dosage groups.

6.0 mg/kg/day at necropsy resulted in two spontaneous deaths, one with no postmortem changes, the other with hemorrhagic peritonitis due to perforation. At necropsy significant thymus involution was seen in three, with obvious involution in the remainder. The liver appeared swollen and edematous in 10/18 rats.

Petechial hemorrhages in lungs and renal capsule were observed.

Etoposide was administered intravenously at dosage levels of 0.4, 1.2 and 3.6 mg/kg/day to three groups of four rhesus monkeys (two males and two females) for four weeks.

0.4 mg/kg/day was without any significant effect. 1.2 mg/kg/day produced non-significant anemia and leukopenia and diminished lymphoid tissue. 3.6 mg/kg/day produced progressive anemia and severe leukopenia and agranulocytosis and impaired platelet function (plasma clot retraction). There was diminished lymphoid tissue and reaction centres in the spleen and lymph nodes in all four monkeys and evidence of focal hepatocyte degeneration. Non-specific effects at this dosage included weight loss, reduced serum albumin, mild enteritis and increased hemosiderin deposition in one or two animals. Mortality was zero in all groups.

0.4 mg/kg/day at necropsy showed small grey/yellow nodules in the lungs of two monkeys. 1.2 mg/kg/day showed small grey/yellow nodules in the lungs of one monkey, and in another the liver was congested with small surface scars.

3.6 mg/kg/day at necropsy showed findings of enlarged submandibular glands, small lung abscesses, grey nodules, small hemorrhagic foci, enlarged mesenteric lymph nodes and fatty bone marrow.

The veins showed no evidence of poor local tolerance.

Chronic Toxicity

Three groups of 80 rats (40 males and 40 females) were given etoposide ampoule solution orally for 26 weeks at 3, 10 and 30 mg/kg daily. Following the completion of the 26 week study, 40 rats at the mid and high dose level received no drug orally for an additional eight weeks to detect possible reversibility of effects.

At 3 mg/kg

Females had a decrease in leukocytes. Both females and males had decreases in RBC, erythropoiesis, leukopoiesis and increased serum cholesterol.

At 10 mg/kg

Decreased total leukocytes, lymphocytes and monocytes, plasma cell increase, bone marrow changes showing moderate disturbance of erythropoiesis and leukopoiesis.

At 30 mg/kg

Females had increased platelet counts. Males had diarrhea. Both females and males had impaired food intake and weight gain, decreased leukocytes, lymphocytes, monocytes, neutrophils and anemia due to changes in the bone marrow. Serum cholesterol was increased. Urine volume was increased with enhanced electrolyte excretion.

At necropsy, the following changes were noted - reduced weight of testes, ovary and spleen; increased liver weights; thymus involution; a mammary adenocarcinoma and nephroblastoma; degenerative changes in seminal epithelium. These immunosuppressive effects on the hemopoietic and lymphatic system were reversible following treatment, however, histological lung changes were more pronounced after the recovery phase. The tumor findings can be related to the cytostatic mechanism.

Three groups of six beagle dogs (three males and three females) were given etoposide ampoule solution for 26 weeks orally at 0.5, 1.5 and 5-6 mg/kg once daily. Following the completion of the 26 week study, two dogs each of the mid and high dose level were kept for a further five weeks without drug administration to demonstrate reversibility of effects. The following toxicity was reported:

0.5 mg/kg

Changes in bone marrow, slight disturbances of erythropoiesis, sporadic occurrence of micronuclei in normoblasts and leukocytes, increased urinary excretion of potassium.

1.5 mg/kg

Increased platelet counts, disturbed erythropoiesis and leukopoiesis, ECG changes.

Three males showed decreased testicular weights and reduced spermiogenesis.

5-6 mg/kg

Reduction in body weight gain, food intake impaired, loss of weight, black pigmentation of ear skin due to melanin deposition in basal cells of epidermis. Hematological findings showed a decrease in total leukocyte counts, neutrophils, lymphocytes and monocytes and a slight decrease

in erythrocytes, hematocrit and hemoglobin. Also macrocytosis, hypochromic anemia and micronuclei in the erythrocytes and leukocytes, bone marrow changes, and increased platelet count were noted. Also a marked transient increase of SGPT values and a slight trend to increased BUN and creatinine values together with a decrease in blood protein were observed.

The immunosuppressive effects on the hematopoietic and lymphatic system were reversible following withdrawal of treatment.

In summary, the results of the two oral 26-week toxicity studies revealed clear-cut toxic effects after oral administration of high doses of the ampoule solution of etoposide in rats and dogs. The main evidence of toxicity was seen in the erythro and leukopoietic organs, thymus and testes.

Hemolysis Studies

Etoposide given in a four-week intravenous study in monkeys produced no evidence of intravascular hemolysis. Plasma protein precipitation studies *in vivo* and *in vitro* indicate that intravenous administration of etoposide ampoule solution should have no untoward effects on human blood and plasma at the doses likely to be used.

Teratology

Etoposide was subjected to a teratology study in SPF rats at doses of 0.13, 0.4, 1.2 and 3.6 mg/kg/day administered intravenously on days 6 to 15 of gestation. Etoposide caused dose-related maternal toxicity, embryotoxicity and teratogenicity at dose levels of 0.4 mg/kg/day and higher. Embryonic resorptions were 90 and 100 percent at the two highest dosages. At 0.4 and 1.2 mg/kg, fetal weights were decreased and fetal abnormalities occurred including major skeletal abnormalities, exencephaly, encephalocele and anophthalmia. At the dose of 1.2 mg/kg, a prenatal mortality of 92 percent was observed with 50 percent of the implanting fetuses abnormal. Even at the lowest dose tested, 0.13 mg/kg, a significant increase in retarded ossification was observed.

A study of Swiss-Albino mice given a single intraperitoneal injection of etoposide at dosages of 1.0, 1.5 and 2 mg/kg on days 6, 7 and 8 of gestation disclosed dose-related embryotoxicity, various cranial abnormalities, major skeletal malformations, an increased incidence of intrauterine death and significantly decreased average fetal body weights. Maternal weight gain was not affected.

Etoposide induced aberrations in chromosome number and structure in embryonic murine cells.

BIBLIOGRAPHY

1. Aisner J, Lee EJ. Etoposide: Current and future status. *Cancer* 1991; 67 (Suppl.1): 215-219.
2. Alade SL, Brown RE, Paquet A. Polysorbate 80 and E-ferol toxicity. *Pediatrics* 1986; 77(4): 593- 597.
3. Blume KG, Forman SJ, O'Donnell MR, et al. Total body irradiation and high-dose etoposide: A new preparatory regimen for bone marrow transplantation in patients with advanced hematologic malignancies. *Blood* 1987; 69: 1015-1020.
4. Dorr RT. Antidotes to vesicant chemotherapy extravasations. *Blood Reviews* 1990; 4: 41-60.
5. Fleming RA, Miller AA and Stewart CF. Etoposide: An update *Clinical Pharmacy* 1989; 8: 274-293.
6. Gaver RC, Deeb G. The effect of other drugs on the *in vitro* binding of ¹⁴C-etoposide to human serum proteins. *Proc Am Assn Cancer Res* 1989; 30: 536 (abs 2132).
7. Harvey VJ, Slevin ML, Joel SP, Johnston A and Wrigley PFM. The effect of food and concurrent chemotherapy on the bioavailability of oral etoposide. *Br J Cancer* 1985; 52: 363-7.
8. Hecker JF. Survival of intravenous chemotherapy infusion sites. *Brit J Cancer* 1990; 62: 660-662.
9. Henwood JM and Brogden RN. Etoposide. A review of its pharmacodynamic and pharmacokinetic properties, and therapeutic potential in combination chemotherapy of cancer. *Drugs* 1990; 39(3): 438-490.
10. Johnson DH, Greco FA, Wolff SN. Etoposide-induced hepatic injury: A potential complication of high-dose therapy. *Cancer Treat Rep* 1983; 67: 1023-1024.
11. Luikart SD, Propert KJ, Modeas CR, et al. High-dose etoposide therapy for extensive small cell lung cancer: A Cancer and Leukemia Group B study. *Cancer Treat Rep* 1987; 71: 533-534.
12. Pedersen-Bjergaard J, Daugaard G, Hansen SW, et al. Increased risk of myelodysplasia and leukemia after etoposide, cisplatin, and bleomycin for germ-cell tumours. *Lancet*

- 1991; 338: 359-363.
13. Piazza E, Cattaneo MT and Varini M. Pharmacokinetic studies in lung cancer in patients. *Cancer* 1984; 54: 1187-1192.
 14. Postmus PE, Mulder NH, Sleijfer DT. High-dose etoposide for refractory malignancies: A phase I study. *Cancer Treat Rep* 1984; 68: 1471-1474.
 15. Slevin ML. The clinical pharmacology of etoposide. *Cancer* 1991; 67(Suppl 1): 319-329.
 16. Stewart CF, Arbuck SG, Fleming RA, et al. Changes in the clearance of total and unbound etoposide in patients with liver dysfunction. *J Clin Oncol* 1990; 8: 1874-1879.
 17. Van Echo DA, Wiernik PH, Aisner J. High-dose VP-16-213 (NSC 141540) for the treatment of patients with previously treated acute leukemia. *Cancer Clin Trials* 1980; 3: 325-328.
 18. Van Maanen JMS, Retel J, de Vries J, et al. Mechanism of action of antitumor drug etoposide: A review. *J Natl Cancer Inst* 1988; 80: 1526-1533.
 19. Wolff SN, Fer MF, McKay CM, et al. High-dose VP-16-213 and autologous bone marrow transplantation for refractory malignancies: A phase I study. *J Clin Oncol* 1983; 1: 701-705.

Small Cell Lung Cancer

20. Banham S, Dorward A, Hutcheon A, Ahmedzai S, Cunningham D, Burnett A, Soukop M, Lucie N and Kaye S. The role of VP-16 in the treatment of small-cell lung cancer: Studies of the west of Scotland cancer group. *Seminars in Oncology* 1985; 12:2-6.
21. Cunningham D, Banham SW, Hutcheon AH, Dorward A, Ahmedzai S, Tansey P, Soukop M, Stevenson RD, Stack BR, Kaye SB, Lucie N and Burnett AK. High-dose cyclophosphamide and VP 16 as late dosage intensification therapy for small cell carcinoma of lung. *Cancer Chemother Pharmacol* 1985; 15: 303-6.
22. Evans WK, Osoba D, Feld R, Shepherd FA, Bazos MJ and DeBoer G. Etoposide (VP-16) and Cisplatin: An effective treatment for relapse in small-cell lung cancer. *J Clin Oncol* 1985; 3: 65-71.

23. Feld R, Evans WK, DeBoer G, Quirt IC, Shepherd Fa, Yeoh JL, Pringle JF, Payne DG, Herman JG, Chamberlain D, Brown TC, Baker MA, Myers R, Blackstein ME and Pritchard KI. Combined modality induction therapy without maintenance chemotherapy for small cell carcinoma of the lung. *J Clin Oncol* 1984; 2: 294-304.
24. Greco FA, Johnson DH, Hande KR, Porter LL, Hainsworth JD and Wolff SN. High dose etoposide (VP-16) in small-cell lung cancer. *Seminars in Oncology* 1985; 12: 42-4.
25. Johnson DH, Greco Fa, Strupp J, Hande K and Hainsworth D. Prolonged administration of oral etoposide in patients with relapsed or refractory small-cell lung cancer: A phase II trial. *Journal of Clinical Oncology* 1990; 8(10) October: 1613-1617.
26. Johnson DH, Hainsworth JD, Hande KR and Greco FA. Current status of etoposide in the management of small cell lung cancer. *Cancer* 1991; 67 (1 Suppl.): 231-244.
27. Johnson DH, Keller JH, Kallas GJ, DeConti RC et al. A randomized trial to compare intravenous and oral etoposide in combination with cisplatin for the treatment of small cell lung cancer. *Cancer* 1991; 67(1 Suppl.): 245-249.
28. Johnson DH, Wolff SN, Hainsworth JD, Porter LL, Grosh WW, Hande KR and Greco FA. Extensive-stage small-cell bronchogenic carcinoma: Intensive induction chemotherapy with high-dose cyclophosphamide plus high-dose etoposide. *J Clin Oncol* 1985; 3: 170-5.
29. Klastersky J, Sculier JP, Dumont JP, Becquart D, Vandermoten G, Rocmans P, Michel J, Longeval E and Dalesio O. Combination chemotherapy with adriamycin, etoposide, and cyclophosphamide for small cell carcinoma of the lung. *Cancer* 1985; 56: 71-5.
30. Littlewood TJ, Smith AP, Anderson G, Chappell AG and James KW. Cisplatin and etoposide alternating with vincristine, doxorubicin and cyclophosphamide in patients with small cell lung cancer. *Eur J Respir Dis* 1985; 67: 294-300.
31. Livingston RB, Mira JG, Chen TT, McGavran M, Costanzi JJ and Samson M. Combined modality treatment of extensive small cell lung cancer: A southwest oncology group study. *J Clin Oncol* 1984; 2: 585-90.
32. Lowenbraun S, Birch R, Buchanan R, Krauss S, Durant J, Perez C, Mill W, Vollmer R, Ogden L and the Southeastern Cancer Study Group. Combination chemotherapy in small cell lung carcinoma. *Cancer* 1984; 54: 2344-50.

33. Matelski, HW, Lokich JJ, Huberman MS, Zipoli TE, Paul S, Sonneborn H and Philips D. Adriamycin, cyclophosphamide, and etoposide (VP-16-213) in extensive-stage small cell lung cancer. *Am J Clin Oncol* 1984; 7: 729-32.
34. Murray N, Shah A, Wilson K, Goldie J, Voss N, Fryer C, Klimo P, Coy P, Hadzic E, Gudauskas G and Fowler R. Cyclic alternating chemotherapy for small cell carcinoma of the lung. *Cancer Treat Rep* 1985; 69: 1241-2.
35. Natale RB, Shank B, Hilaris BS and Wittes RE. Combination cyclophosphamide, adriamycin, and vincristine rapidly alternating with combination cisplatin and VP-16 in treatment of small cell lung cancer. *Am J Med* 1985; 78: 303-8.
36. Natale RB and Wittes RE. Alternating combination chemotherapy regimens in small-cell lung cancer. *Seminars in Oncology* 1985; 12: 7-13.
37. Reddy SK, Takita H, Lane WW, Vincent RG, Chen TY, Caracandas JE and Regal A-M. Cyclic alternating combination chemotherapy for small cell lung cancer. *Cancer Chemother Pharmacol* 1984; 12: 190-3.
38. Sculier JP, Klastersky J, Stryckmans P and the EORTC Lung Cancer Working Party (Belgium). Late intensification in small-cell lung cancer: A phase I study of high doses of cyclophosphamide and etoposide with autologous bone marrow transplantation. *J Clin Oncol* 1985; 3: 184-91.
39. Spitzer G, Farha P, Valdivieso M, Dicke K, Zander A, Vellekoop L, Murphy WK, Dhingra HM, Umsawasdi T, Chiuten D and Carr DT. High-dose intensification therapy with autologous bone marrow support for limited small-cell bronchogenic carcinoma. *J Clin Oncol* 1986; 4: 4-13.
40. Steward WP, Thatcher N, Edmundson JM, Shiu W and Wilkinson PM. Etoposide infusions for treatment of metastatic lung cancer. *Cancer Treat Rep* 1984; 68: 897-9.
41. Thatcher N, Stout R, Smith DB, Grotte G, Winson M, Bassett H and Carroll KB (From the Manchester Lung Tumour Group). Three months treatment with chemotherapy and radiotherapy for small cell lung cancer. *Br J Cancer* 1985; 52: 327-32.
42. Timothy AR, Calman FMB, Bateman NT, Farebrother M, Slevin ML, Bellamy D, Rubens RD and Costello J. Single-dose etoposide in combination with vincristine and doxorubicin in the treatment of small-cell lung cancer (SCLC). *Seminars in Oncology* 1985; 12: 45-7.

Non-Small Cell Lung Cancer

43. Albain KS, Bitran JD, Golomb HM, Hoffman PC, DeMeester TR, Skosey C, Noble S and Blough RR. Trial vindesine, etoposide and cisplatin in patients with previously treated, advanced-stage, non-small cell bronchogenic carcinoma. *Cancer Treat Rep* 1984; 68: 413-5.
44. Anderson G and Payne H. Response rate and toxicity of etoposide (VP-16) in squamous carcinoma of the lung: Report from the lung cancer treatment study group. *Seminars in Oncology* 1985; 12: 21-2.
45. Bertrand M, Multhauf P, Presant C, Rappaport D, Blayney DW, Carr BI, Cecchi G, Doroshow JH, Emont E, Goldberg D, Kogut N, Leong L and Margolin K. Phase II trial of etoposide, vincristine and high dose cisplatin in advanced non-small cell lung cancer. *Cancer Treat Rep* 1985; 69: 1335-6.
46. Bitran JD, Golomb HM, Hoffman PC, Albain K, Evans R, Little AG, Purl S and Skosey C. Protochemotherapy in non-small cell lung carcinoma. An attempt to increase surgical resectability and survival. A preliminary report. *Cancer* 1986; 57: 44-53.
47. Bonomi P. Recent advances in etoposide for non-small cell lung cancer. *Cancer* 1991; 67(1 Suppl.): 254-259.
48. Joss RA, Alberto P, Obrecht JP, Barrelet L, Hodener EE, Siegenthaler P, Goldhirsch A, Mermillod B and Cavalli F. Combination chemotherapy for non-small lung cancer with doxorubicin and mitomycin or cisplatin and etoposide. *Cancer Treat Rep* 1984; 68: 1079-84.
49. Klastersky J. VP-16 and cisplatin in the treatment of non-small-cell lung cancer. *Seminars in Oncology* 1985; 12: 17-20.
50. Mitrou PS, Graubner M, Berdel WE, Mende S, Gropp C, Diehl V and Klippstein TH. Cisplatin (DDP) and VP16-213 (etoposide) combination chemotherapy for advanced non-small cell lung cancer. A phase II clinical trial. *Eur J Cancer Clin Oncol* 1984; 20: 347-51.
51. Osaba D, Rusthoven JJ, Turnbull KA, Evans WK and Shepherd FA. Combination chemotherapy with bleomycin, etoposide and cisplatin in metastatic non-small-cell lung cancer. *J Clin Oncol* 1985; 3: 1478-85.

52. Ruckdeschel JC. Etoposide in the management of non-small cell lung cancer 1991; 67: 250-253.
53. Scagliotti GV, Lodico D, Gozzelino F, Bardesson F, Albera C, Gatti E and Pescetti G. Unresectable non-small cell lung cancer chemotherapy with high-dose cisplatin and etoposide. *Oncology* 1985; 42: 224-8.
54. Wils JA, Utama I, Naus A and Verschueren TA. Phase II randomized trial of radiotherapy alone vs the sequential use of chemotherapy and radiotherapy in stage III non-small cell lung cancer. Phase II Trial of chemotherapy alone in stage IV non-small cell lung cancer. *Eur J Cancer Clin Oncol* 1984; 20: 911-4.

Malignant Lymphoma

55. Gasser AB, Steward WP, Wagstaff J, Scarffe JH and Crowther D. Treatment of relapsed non-Hodgkin's lymphoma with a combination of hydroxyurea, ifosfamide and etoposide. *Cancer Treat Rep* 1985; 69: 225-6.
56. Hagberg H, Cavallin-Stahl E and Lind J. Ifosfamide and etoposide as salvage therapy for non-Hodgkin's lymphoma. *Scan J Haematol* 1986; 36: 61-4.
57. Hancock BW. Vindesine, etoposide (VP-16), and Prednisolone (VEP) in relapsed patients with grade II non-Hodgkin's lymphoma. *Seminars in Oncology* 1985; 12: 26-8.
58. Judson IR and Wiltshaw E. Cis-dichlorodiammineplatinum (cis-platinum) and etoposide (VP-16) in malignant lymphoma - an effective salvage regimen. *Cancer Chemother Pharmacol* 1985; 14: 258-61.
59. O'Reilly SE, Klimo P and Connors JM. The evolving role of etoposide in the management of lymphomas and Hogkin's disease. *Cancer* 1991; 67(1 Suppl.): 271-280.

Testicular Malignancies

60. Brindley CJ, Antoniow P, Newlands ES and Bagshawe KD. Pharmacokinetics and toxicity of the epipodophyllotoxin derivative etoposide (VP16-213) in patients with gestational choriocarcinoma and malignant teratoma. *Cancer Chemother Pharmacol* 1985; 15: 66-71.
61. Hainsworth JD, Williams SD, Einhorn LH, Birch R and Greco FA. Successful treatment of resistant germinal neoplasms with VP-16 and cisplatin: Results of

- a southeastern cancer study group trial. *J Clin Oncol* 1985; 3: 666-71.
62. Loehrer Sr PJ. Etoposide therapy for testicular cancer. *Cancer* 1991; 67(1 Suppl.): 220-224.
 63. Loehrer Sr PJ, Einhorn LH and Williams SD. VP-16 plus ifosfamide plus cisplatin as salvage therapy in refractory germ cell cancer. *J Clin Oncol* 1986; 4: 528-36.
 64. Pizzocaro Giorgio, Pasi M, Salvioni R, Zanoni F, Milani A and Piva L. Cisplatin and etoposide salvage therapy and resection of the residual tumor in pretreated germ cell testicular cancer. *Cancer* 1985; 56: 2399-2403.
 65. Pizzocaro G, Piva L, Salvioni R, Zanoni F and Milani A. Cisplatin, etoposide, bleomycin first-line therapy and early resection of residual tumor in far-advanced germinal testis cancer. *Cancer* 1985; 56: 2411-5.
 66. Srougi M, Simon SD and Menezes de Goes G. Vinblastine, actinomycin D, bleomycin, cyclophosphamide and cis-platinum for advanced germ cell testis tumors: Brazilian experience. *The Journal of Urology* 1985; 134: 65-9.
 67. Taylor RE, Duncan W, Davey P, Munro AJ and Cornbleet MA. Cisplatin combination chemotherapy for advanced germ-cell testicular tumours. *British Journal of Urology* 1985; 57: 567-73.
 68. Williams SD, Birch R, Einhorn LH, et al. Treatment of disseminated germ-cell tumors with cisplatin, bleomycin, and either vinblastine or etoposide. *N Engl J Med* 1987; 316: 1435-1440.