Cancer Chemother Pharmacol (1994) 34 (Suppl): S 118–S 126

Cancer Chemotherapy and Pharmacology



# Etoposide: current status and future perspectives in the management of malignant neoplasms

**Chandra P. Belani**[1], **L. Austin Doyle**[2], **Joseph Aisner**[2]

[1] Pittsburgh Cancer Institute, Pittsburgh, Pennsylvania, USA
[2] University of Maryland Cancer Center, Baltimore, Maryland, USA

**Abstract.** Etoposide has demonstrated highly significant clinical activity against a wide variety of neoplasms, including germ-cell malignancies, small-cell lung cancer, non-Hodgkin's lymphomas, leukemias, Kaposi's sarcoma, neuroblastoma, and soft-tissue sarcomas. It is also one of the important agents in the preparatory regimens given prior to bone marrow and peripheral stem-cell rescue. Despite its high degree of efficacy in a number of malignancies, the optimal dose, schedule, and dosing form remain to be defined. It is possible that continuous or prolonged inhibition of the substrate, i. e., topoisomerase II, may be the key factor for the cytotoxic effects of etoposide. Clinical studies have shown the activity of etoposide to be schedule-dependent, with prolonged dosing, best accomplished by the oral dosing form, offering a therapeutic advantage. This benefit awaits validation by prospective randomized studies, some of which are in progress. Recent clinical investigations have focused on the use of etoposide in combination with (a) cytokines to ameliorate myelosuppression, the dose-limiting toxicity of etoposide; (b) agents such as cyclosporin A and verapamil to alter the p-glycoprotein (*mdr1*) function; and (c) topoisomerase I inhibitors to modulate the substrate upon which it acts. There is continued interest in the development of etoposide to its maximal clinical dimensions and in the examination of alternative biochemical and mechanistic approaches to further our understanding of this highly active agent.

**Key words:** Etoposide – Topoisomerase II – Malignant neoplasms

## Introduction

Etoposide, a podophyllotoxin derivative, is one of the most active antitumor agents in clinical use today. It has been commercially approved by the United States Food and Drug Administration for use in germ-cell testicular carcinoma [1, 2] and small-cell lung cancer (SCLC) [1, 3, 4], but its spectrum of activity goes beyond these relatively limited indications. Several phase II studies have shown responses in non-small-cell lung cancer (NSCLC) [5], non-Hodgkin's lymphoma [6, 7], Kaposi's sarcoma [8], soft-tissue sarcoma [9, 10], gastric carcinoma [11], and ovarian carcinoma [12]. Etoposide also is an important agent in the preparatory chemotherapeutic regimens given prior to bone marrow transplantation. Although etoposide has demonstrated proven activity in a number of human malignancies (Table 1) there continues to be increasing clinical investigation so as to widen the potential use of the agent while exploring other applications with novel approaches through alterations in the dose, schedule, and dosing form (parenteral versus oral).

**Table 1.** Role of etoposide in neoplastic diseases

| | |
|---|---|
| Front line applications | Small-cell lung cancer<br>Germ-cell tumors<br>Kaposi's sarcoma<br>Bone marrow transplantation |
| Established activity | Hodgkin's disease<br>Non-Hodgkin's lymphoma<br>Mycosis fungoides<br>Acute myeloblastic leukemia<br>Neuroblastoma<br>Ewing's sarcoma<br>Pediatric rhabdomyosarcoma<br>Ovarian carcinoma |
| Possible activity | Non-small-cell lung cancer<br>Gastric cancer<br>Hepatoma |

Paper presented at the Topoisomerase Inhibitors Conference, University of Maryland Cancer Center, 27–30 October 1993, Monterey, California, USA. Supported in part by Bristol Myers Oncology Division

*Correspondence to:* Chandra P. Belani, M.D., University of Pittsburgh Medical Center, Pittsburgh Cancer Institute, Division of Medical Oncology, 200 Lothrop Street, Pittsburgh, PA 15213, USA

## Etoposide in SCLC

Etoposide, with its schedule-dependent activity, is one of the most active agents against SCLC. Single-agent response rates range from 10% to 89% [1, 13–15], depending on the schedule of administration of the drug, the dosing form, and the characteristics of the treated population. When the 1-day schedule of 500 mg/m$^2$ i.v. etoposide given as a 24-h continuous infusion every 3 weeks was compared with the same dose given as five daily 2-h infusions of 100/m$^2$ every 3 weeks by Slevin and colleagues [13], the response rate in the multiple-day arm was 89% as compared with 10% in the 1-day arm, suggesting schedule dependency in patients with untreated SCLC. Pharmacokinetic analysis showed the same area under the curve for both treatment arms, leading to the interesting hypothesis that the drug's efficacy was related to the duration of exposure at concentrations of 1 μg/ml or greater, and this was significantly greater on the 5-day schedule.

The oral form of etoposide has in general a bioavailability of 50% (range, 15%–70%) [16]. Although the absorption may be less consistent, oral forms allow for longer-term administration of etoposide which may be critical for its optimal effect on topoisomerase II inhibition. The total cost of 5-day i.v. administration of etoposide, including i.v. fluids, tubing, preparation, overhead, and hazardous waste disposal, is probably higher than that of oral administration. Clark et al. [3] tested two prolonged schedules of single-agent oral etoposide in patients with untreated SCLC. One group received 50 mg twice daily for 14 days (every 3 weeks) and the other group received 50 mg once daily for 21 days (every 4 weeks). The response rate in the 14-day schedule was 80% as compared with 59% on the low-dose (50 mg daily) 21-day schedule, but there was no significant difference in terms of overall survival (8 months vs 7.5 months, respectively). The estimated time of serum etoposide concentrations above 1 μg/ml was almost the same in the patients treated on the two different schedules. This finding supports the earlier observation by the same group of investigators [13] that the efficacy of the drug is proportional to the duration of exposure above the 1 μg/ml threshold.

Single-agent oral etoposide given at a standard 800-mg/m$^2$ dose divided over 5 days in elderly patients (>70 years of age) with SCLC demonstrated a response rate of 76% with a median survival of 38 weeks as reported by Smit and colleagues [17]. The toxicity was acceptable on this schedule and significant myelosuppression was not observed. Thus, the efficacy of these oral regimens in previously untreated patients with extensive SCLC is comparable with that of more intensive combination regimens, especially in elderly patients, with an added advantage of its ease of administration, excellent patient compliance, and benefit in terms of quality-of-life issues [15, 17, 18].

This dosing form of etoposide (parenteral versus oral) has been the subject of numerous clinical investigations. The 3- to 5-day i.v. etoposide schedule in previously treated SCLC has shown only modest activity [19, 20]; whereas the results obtained with prolonged oral schedules (even when previous treatment has included i.v. etoposide) have been provocative, with activity ranging from 23%–50% [14, 21, 22] in previously treated patients with SCLC and from 35% to 71% in previously untreated patients with extensive SCLC [17, 23]. Thus, oral etoposide has been incorporated into front-line regimens for patients with previously untreated SCLC. The Cancer and Leukemia Group B (CALGB) has recently completed accrual on a phase III randomized trial of oral (50 mg/m$^2$×21 days, every 4 weeks) versus i.v. (130 mg/m$^2$, days 1–3, every 3 weeks) etoposide in combination with i.v. cisplatin given at the same dose intensity in extensive SCLC. The results of this study will provide a more definitive answer with respect to the best schedule and dosing form of etoposide for the management of SCLC. Because of the wide range seen in the bioavailability of the oral form [16], prolonged continuous infusions of low-dose etoposide (18–25 mg/m$^2$ daily) are also being investigated [24] in the management of SCLC. The results of these studies are preliminary in terms of both response and toxicity, and at present no definite conclusion can be made regarding the optimal use of these regimens.

Etoposide has been an essential component of combination regimens used for the management of SCLC. When etoposide was substituted for vincristine in combinations with cyclophosphamide and Adriamycin, a statistically significant survival advantage was demonstrated in a study of patients with extensive-stage disease [25]. Alternating and sequential chemotherapy studies have shown that cisplatin plus etoposide (PE) is a highly active salvage regimen for patients previously treated with cyclophosphamide, doxorubin, and vincristine (CAV) [26]. The sequence of PE following CAV regimens modestly improves the response and survival seen with CAV alone [27], whereas reverse-sequence PE followed by CAV does not produce any greater response than does etoposide plus cisplatin alone [28]. As a result, the combination of PE, which is easily integrated with chest irradiation for limited-disease patients, is considered to be a "standard treatment program" outside of a clinical trial.

At the University of Maryland Cancer Center, the PE combination was studied in a slightly different manner. Sequential studies showed that the combination of cyclophosphamide, doxorubicin, and etoposide was highly active [29]. We subsequently added cisplatin to this regimen, and the results of that program (PACE – cisplatin, doxorubicin, cyclophosphamide, and etoposide) in a limited group of patients suggested a possible prolongation of survival, but with considerable toxicity [30]. Re-evaluation of the PACE regimen with the use of colony-stimulating factors may be of interest and needs further investigation. Thus, as judged from the data available, etoposide should be an integral component of all induction regimens for the management of SCLC.

## Etoposide in NSCLC

The activity of single-agent etoposide in NSCLC ranges from 5% to 15% [31–33]. Although the agent has been used extensively in this disease, the optimal dose, dosing form, and schedule are not well established. In a study reported by Niederle et al. [32], no response was seen in

patients receiving less than 300 mg/m$^2$, whereas among those who received 330–370 mg/m$^2$ over 3 days the response rate was 23%, suggesting a possible dose-response effect. Rosso et al. [33] compared the activity of single-agent etoposide (120 mg/m$^2$×3 days) with the combination of high-dose cisplatin (60 mg/m$^2$, days 1 and 2) and the same dose of etoposide and demonstrated a significantly higher response rate for the combination (25.8% vs 7%). The combination of etoposide and cisplatin has become the leading choice of therapy for treatment of NSCLC in the community outside of a study situation. The combination of cisplatin and etoposide has also become the standard arm of phase III studies for comparison with new agents or new combinations [Eastern Cooperative Oncology Group (ECOG) study of cisplatin/etoposide versus cisplatin/taxol versus cisplatin/high-dose taxol with granulocyte colony-stimulating factor (G-CSF) support] and also a standard chemotherapeutic regimen in ongoing phase III multimodality trials for locally advanced NSCLC studies being conducted by various Cooperative Groups [Cancer and Leukemia Group B (CALGB)/Southwestern Oncology Group (SWOG)/ECOG].

Moderate activity has also been reported with prolonged oral etoposide administration (21-day regimen) in previously untreated NSCLC [5, 34, 35]. In a recently reported study by Miller et al. [36], there were 3 complete responses and 10 partial responses among 32 patients with advanced NSCLC, for an overall response rate of 41% with a 21-day oral etoposide regimen in combination with cisplatin. The investigators were able to predict the level of myelosuppression in the first course of this regimen by a pharmacodynamic model based on etoposide concentrations and pretreatment white blood cell counts. Prolonged oral schedules of etoposide in combination with cylophosphamide [37] and carboplatin [38] have also shown modest activity in NSCLC. The toxicity of etoposide is typically mild, with neutropenia being dose-limiting [1], and oral administration represents an excellent palliative option in patients with metastatic NSCLC.

## Etoposide in germ-cell tumors

Following the confirmation of durable responses in cisplatin-refractory testicular cancer [39, 40] and the demonstration of excellent activity in the salvage setting [41], etoposide was incorporated into primary treatment regimens for disseminated testicular cancer. The Southeastern Cancer Study Group (SECSG) [2] randomized 244 patients with untreated germ-cell cancer to receive either PVB [cisplatin (20 mg/m$^2$ daily ×15), bleomycin (30 u daily, days 1, 8, and 15), and vinblastine (0.3 mg/kg)] or BEP [cisplatin (20 mg/m$^2$ daily ×5), bleomycin 30 u daily, days 1, 8, and 15), and etoposide (100 mg/m$^2$ daily ×5)]. The substitution of etoposide for vinblastine in the combination resulted in increased therapeutic efficacy, especially in patients with advanced disease (63% vs 38% disease-free in the BEP and PVB groups, respectively), and there was a marked decrease in neuromuscular toxicity and weight loss in the etoposide arm. Thus, etoposide has become an essential and standard part of the primary treatment regimen (BEP) for disseminated germ-cell cancer.

In patients with good-risk features associated with minimal or moderate disease as defined by the Indiana classification system [42] for testicular germ-cell cancers, three courses of standard-dose BEP have shown efficacy equal to that of four courses of the same treatment [43], further reducing the morbidity related to treatment. Although cisplatin and etoposide are the most active single agents in the primary treatment regimen, bleomycin remains an equally important part of the combination [44], even in good-risk testicular cancer patients. On the other hand, in patients with poor-risk features associated with advanced disease, attempts to increase the cure rate by increasing the dose intensity of cisplatin in the BEP combination have not met with success [45].

In addition to cisplatin and etoposide, ifosfamide is the only other agent with greater than 20% single-agent activity in the salvage setting [46]. When combined with cisplatin and either etoposide or vinblastine [47], ifosfamide produces substantial durable responses, even when used as third- or fourth-line therapy with 30% of the patients becoming disease-free with durable remissions. A recently reported trial by the European Organization for Research and Treatment of Cancer (EORTC) Genitourinary Group [48] randomized intermediate-risk testicular cancer patients to cisplatin (20 mg/m$^2$ daily ×5) and etoposide (120 mg/m$^2$, days 1, 3, and 5) with either bleomycin (30 mg/week ×12; BEP) or ifosfamide (1200 mg/m$^2$ daily ×6; VIP). The progression-free survival of the 84 eligible patients was 88% in the BEP arm and 85% in the VIP arm, with the overall survival being 97% and 93%, respectively, and the VIP regimen was more myelotoxic than the BEP regimen. A similar trial is being performed by the ECOG in conjunction with the SWOG. In conclusion, the BEP regimen [2] continues to be the standard first-line treatment for disseminated nonseminomatous germ-cell testicular cancer, but ifosfamide-containing regimens have considerable therapeutic efficacy in the salvage setting [47].

Etoposide also plays a substantial role as a part of high-dose chemotherapy regimens with autologous bone marrow transplantation in the setting of refractory germ-cell cancers. A few patients with refractory germ-cell cancer treated with high-dose etoposide and carboplatin with autologous bone marrow transplantation have had sustained remissions [49]. Rosti et al. [50] used the combination of carboplatin/etoposide/ifosfamide in high doses in a similar group of patients prior to autologous bone marrow transplantation. Among the 21 patients treated there were 8 complete responders (duration, 2–33 months) and 3 partial responders. Regimens containing high-dose etoposide continue to be in the forefront of management in the salvage setting with bone marrow or peripheral blood stem-cell support.

## Etoposide in acute myeloblastic leukemia

Etoposide has been studied extensively in a variety of doses and schedules in acute myeloblastic leukemia (AML) and possesses an activity of approximately 17% as a single

**Table 2.** CHOPE regimen

| | | |
|---|---|---|
| Cyclophosphamide | 750 mg/m² i.v. day 1 | Every 3 weeks |
| Doxorubicin | 50 mg/m² i.v. day 1 | |
| Vincristine | 1.4 mg/m² i.v. days 1,8 (2 mg max$^{m}$ dose) | |
| Prednisone | 100 mg/day p.o. days 1–5 | |
| Etoposide | 80 mg/m² i.v. days 1–3 | |

agent [51]. This has led to the development of etoposide combinations with other active agents such as azacytidine [52, 53], amsacrine [54, 55], the anthracycline idarubicin [56], and mitoxantrone [57, 58] with complete response rates ranging from 43% to 100% in relapsed or refractory AML [2–8]. Encouraged by the single-agent activity of etoposide and its role as a part of combination chemotherapy for relapsed and refractory disease, the Australian Leukemia Study Group sought to determine the drug's role as a component of front-line AML therapy [59]. The standard induction regimen of daunorubicin/cytarabine was compared with the same drugs plus etoposide (75 mg/m² daily × 7) in a randomized trial. Among the 264 patients randomized, although the complete response rates did not significantly differ between the two treatment groups, there was a significant prolongation of remission duration in the etoposide arm (18 versus 12 months; $P = 0.01$). Subset analysis demonstrated that patients under 55 years of age had a significant improvement in survival (median, 17 versus 9 months; $P = 0.04$) in addition to the prolongation of remission duration achieved with the etoposide-containing regimen.

Other studies are examining the role of etoposide as a part of induction or intensification therapy in AML. The CALGB is conducting a randomized phase III study comparing intensification with cytarabine versus sequential cytarabine/cytoxan/etoposide and mitoxantrone/diazequone treatment in elderly AML patients in first remission. The Glasgow group in the United Kingdom is investigating induction DAT daunorubicin, cytarabine, 6-thioguanine versus ADE (cytarabine, daunorubicin, etoposide) versus DHAD-ARA-C (mitoxantrone/cytarabine), followed by short or extended consolidation with or without maintenance therapy in elderly AML patients. With very little extramedullary toxicity, etoposide is well-suited for high-dose intensity trials with or without bone marrow support in AML. Like SCLC, AML is an appropriate disease for evaluation of the importance of etoposide dose and schedule, as the drug occupies an important place in front-line induction therapy.

## Etoposide in lymphoma

Etoposide has been established as one of the most active agents in the treatment of lymphoma. It has been integrated into combination therapy for both Hodgkin's disease (HD) [60–63] and non-Hodgkin's lymphoma in front-line management as well as in the salvage setting. In addition, etoposide is an integral component of the induction-preparatory regimens used prior to autologous bone marrow and peripheral blood stem-cell transplantation for lymphoma.

**Table 3.** Etoposide-containing salvage chemotherapy combinations in Hodgkin's disease (*CCNU* Lomustine)

| | | |
|---|---|---|
| *EVA* [65]: | | |
| Etoposide | 200 mg/m² p.o. days 1–5 | |
| Vincristine | 2 mg i.v. day 1 | Every 4 weeks |
| Doxorubicin | 50 mg/m² i.v. day 1 | |
| *EVAP* [66]: | | |
| Etoposide | 120 mg/m² i.v. days 1, 8, 15 | |
| Vinblastine | 4 mg/m² i.v. days 1, 8, 15 | Every 4 weeks |
| Cytarabine | 30 mg/m² i.v. days 1, 8, 15 | |
| Cisplatin | 40 mg/m² i.v. days 1, 8, 15 | |
| *CEM* [67]: | | |
| CCNU | 100 mg/m² p.o. day 1 | |
| Etoposide | 100 mg/m² p.o. days 1–3, 21–23 | Every 6 weeks |
| Methotrexate | 30 mg/m² p.o. days 1–8, 21, 28 | |
| *CEVD* [68]: | | |
| CCNU | 80 mg/m² p.o. day 1 | |
| Etoposide | 120 mg/m² p.o. days 1–5, 22–26 | Every 6 weeks |
| Vindesine | 3 mg/m² i.v. days 1, 22 | |
| Dexamethasone | 3 mg/m² p.o. days 1–8 | |
| | 1.5 mg/m² p.o. days 9–26 | |
| *CEP* [69, 70]: | | |
| CCNU | 80 mg/m² p.o. day 1 | |
| Etoposide | 100 mg/m² p.o. days 1–5 | Every 4 weeks |
| Prednimustine | 60 mg/m² p.o. days 1–5 | |
| *MIME* [71] | | |
| Methyl-GAG | 500 mg/m² i.v. days 1–14 | |
| Ifosfamide | 1 mg/m² i.v. days 1–5 | Every 3 weeks |
| Methotrexate | 30 mg/m² i.v. day 3 | |
| Etoposide | 100 mg/m² i.v. days 1–3 | |

Although MOPP, ABVD, MOPP→ABVD, and MOPP/ABV are the most common front-line chemotherapy regimens used for the management of HD [60–63], etoposide has recently been incorporated into a combination chemotherapy regimen (CHOPE, Table 2) and is being investigated by the CALGB as first-line therapy for patients with previously untreated advanced HD.

Approximately 50% of patients with HD either fail to achieve a remission or relapse after attaining a remission [60–63]. A few of these patients benefit from the use of radiation therapy [64] or from salvage chemotherapy regimens [65–71]. A number of these salvage regimens have incorporated etoposide as an essential component [65–70] and have shown some degree of activity (Table 3). In attempts to improve these results, high dose chemotherapy regimens with autologous bone marrow transplantation have been developed for the management of patients with refractory and relapsed HD. Some of the preparatory regimens used prior to bone marrow transplantation [72, 73] have incorporated etoposide as an essential component, and the preliminary results of these studies are encouraging (Table 4). At this time it is difficult to determine the superiority of one preparatory regimen over another, as pro-

**Table 4.** Autologous bone marrow transplantation for Hodgkin's disease (*BEAM* carmustine/etoposide/cytarabine/melphalan, *CE + TLI* cyclophosphamide/etoposide/total lymphoid irradiation)

| Investigators | Regimen | Number of patients | Response | | Continued Remission |
|---|---|---|---|---|---|
| | | | Complete | Partial | |
| Gribben et al. [72] | BEAM | 44 | 39% | 44% | 45% (12–49+ months) |
| Yahalom et al. [73] | CE + TLI | 17 | 71% | 6% | 65% (4–35+ months) |

spective randomized trials will be needed to identify significant differences.

Etoposide has significant activity in the non-Hodgkin's lymphomas. Etoposide forms an integral component of the ProMACE (procarbazine/methotrexate/doxorubicin/cyclophosphamide/etoposide) regimen [74], which was developed at the National Cancer Institute (NCI). The ProMACE regimen constitutes the induction and late intensification sequence of the ProMACE-MOPP (mechlorethamine, vincristine, procarbazine, prednisone) program. The other regimen, ProMACE-CytaBOM (cytarabine/bleomycin/vincristine/methotrexate given with leucovorin rescue), consists of day-1 treatment identical to that in ProMACE-MOPP plus CytaBOM on day 8, with the second phase being largely nonmyelosuppressive [75]. In a randomized comparison of the two regimens for patients with aggressive-histology lymphoma, ProMACE-CytaBOM was superior to ProMACE-MOPP [75] in terms of complete response rate as well as long-term survival (Table 5). The provocative results obtained with the ProMACE-CytaBOM regimen led to its comparison with another third-generation regimen, MACOP-B [76]. The methotrexate in MACOP-B has also been replaced by etoposide given i.v. on day 1 and orally on days 2 and 3 to develop the VACOP-B regimen [77]. A sequential comparison of the two regimens showed complete response rates of 84% for MACOP-B versus 81% for VACOP-B, with no significant difference being found in disease-free survival, but fewer complications and life-threatening events occurred among the patients receiving VACOP-B, suggesting an advantage for the etoposide-containing regimen.

The major intergroup trial [78] of advanced intermediate- or high-grade non-Hodgkin's lymphoma failed to show any significant difference in response rate, time to treatment failure, or overall survival between CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) and the third generation regimens MACOP-B, ProMACE-CytaBOM, and m-BACOD (methotrexate/bleomycin/doxorubicin/cyclophosphamide/vincristine/dexamethasone). Attention is currently focused on the addition of other active agents such as etoposide to the CHOP program (CHOPE) to determine the contribution of the agent in the regimen.

Although combination chemotherapy results in 30%–55% long-term survivors among previously untreated patients with aggressive non-Hodgkin's lymphoma, it does not offer a chance of cure at the time of relapse or in cases of refractory disease [71]. High-dose myeloablative regimens followed by autologous or allogeneic bone marrow rescue have been tested in this group of patients, with >25%–30% of the patients achieving long-term benefit. The advantage of specific conditioning regimens remains unclear, but most have incorporated etoposide as an essential component [79–82].

Novel approaches using infusional chemotherapy (CI) with natural products in the salvage setting are being investigated in an attempt to maximize dose intensity and overcome multidrug resistance. An etoposide-containing regimen, EPOCH [etoposide (50 mg/m$^2$ daily, 72-/96-h CI), doxorubicin (10 mg/m$^2$ daily, 96-h CI), vincristine (0.4 mg/m$^2$ daily, 96-h CI), prednisone (60 mg/m$^2$ daily p.o. for 14 days), cyclophosphamide (750 mg/m$^2$ i.v. and concurrent r-verapamil (24 doses p.o.)] demonstrated a response rate of 95% complete response, (38%) at the NCI in the salvage setting [83], suggesting a possible role both as first-line therapy and as a preparatory regimen for use prior to bone marrow transplantation in patients with aggressive non-Hodgkin's lymphoma.

## Etoposide in AIDS-related Kaposi's sarcoma

Acquired immunodeficiency syndrome (AIDS)-related Kaposi's sarcoma (KS) is seen in approximately 15% of patients with AIDS [84]. Several modalities of treatment have been used successfully in the management of AIDS-related KS, but their overall use cannot be fully exploited because of the toxicity spectrum as well as the patient's

**Table 5.** Etoposide regimens in advanced intermediate- and high-grade non-Hodgkin's lymphoma (*CR* Complete response)

| Investigators | Regimen | Number of Patients | CR (%) | Survival (%) | Remarks |
|---|---|---|---|---|---|
| Longo et al [75] | ProMACE CytaBOM | 91 | 81 (86) | 69 | ProMACE-CytaBOM associated with |
| | vs | | | | |
| | ProMACE MOPP | 99 | 73 (74) | 53 | significant improvement in both response and survival |
| Frederico et al [76] | ProMACE CytaBOM | 71 | 41 (58) | 72 | MACOP-B associated with increased |
| | vs | | | | |
| | MACOP-B | 78 | 49 (63) | 71 | toxicity |

underlying immunodeficient state. Etoposide occupies a role in the palliation of patients with AIDS-related KS. Laubenstein et al. [8] used etoposide at 150 mg/m$^2$ on days 1–3 (28-day cycle) in patients with AIDS-related KS and obtained complete responses in 29% (12/41) of the patients and partial responses in 46% (19/41), with the median duration of response being approximately 9 months. When etoposide is combined with doxorubicin, bleomycin, and vincristine in alternating sequences [85], a response rate of 95% has been reported. Because of the underlying problems of AIDS patients, individualized dosing and prolonged oral administration of etoposide may offer substantial palliation with a reduction in overall toxicity, but this possibility needs further investigation.

## Etoposide in gastric cancer

The activity of etoposide in gastric carcinoma was first seen by Kelsen and colleagues [11] at Sloan-Kettering Memorial Cancer Center in a phase II study, in which 3 of 14 (21%) previously untreated patients had a partial response. This finding generated substantial interest in the drug, resulting in etoposide's incorporation into combination chemotherapy regimens for this disease. The EAP [etoposide (120 mg/m$^2$, days 4–6), Adriamycin (20 mg/m$^2$, days 1 and 7), and cisplatin (40 mg/m$^2$, days 2 and 8)] regimen developed by German investigators [86] has been shown to have an overall response rate of 64%, with 21% complete responses being observed among 67 patients with advanced gastric carcinoma. This regimen was associated with substantial myelosuppression (19% grade 4 leukopenia) and sepsis (13%). Encouraged by these provocative results in terms of tumor efficacy, the Dana Farber Cancer Center initiated a similar study [87] to confirm the results obtained with EAP. The Farber study, however, demonstrated a response rate of only 33%, with the median survival being 7.5 months for the 36 patients treated, and there was again substantial toxicity and 4 (11%) treatment-related deaths.

In a neoadjuvant setting, with the rationale of downstaging the disease to make it resectable and also to treat micrometastatic disease, the EAP regimen, retested by the same German investigators [88], again resulted in a 70% response rate, with 60% of the patients being rendered disease-free following surgery. Most of the relapses occurring in this study were locoregional, suggesting the possibility of enhancing survival with the addition of local radiotherapy after induction therapy. When the EAP regimen was compared with FAMTx (5-fluorouracil, adriamycin and methotrexate) in a phase III study [89], it was found to be inferior in terms of both response and survival, but these results need further confirmation. The ELF regimen [etoposide (100 mg/m$^2$, days 1–3), leucovorin (300 mg/m$^2$, days 1–3), and 5-fluorouracil (500 mg, days 1–3)], on the other hand, resulted in a 53% response rate (12% complete responses) with the median survival being 11 months among 51 patients treated for advanced gastric cancer [90]. The ELF regimen was well tolerated and could be safely given in the ambulatory setting.

Thus, etoposide has definite activity in gastric cancer, but because of the substantial toxicity associated with etoposide-containing combination regimens [86, 87], the dose and schedule may need modification and reevaluation. At present, the EORTC is conducting a phase III randomized study comparing the ELF regimen with FAMTx and CF (cisplatin and 5-fluorouracil) in patients with advanced gastric cancer in the hope of defining the best combination regimen for treatment of this disease. The problem of myelosuppression can be abrogated to a certain extent with growth factors, which need to be incorporated into these treatment regimens. In the interim, we should continue to search for new active agents that can be combined with etoposide to increase its therapeutic efficacy.

## Use of modulators of multidrug resistance with etoposide

The multidrug resistance (MDR) gene *mdr1* encodes P-glycoprotein (P-gp) [91–94] which acts as an efflux pump that confers cellular resistance to chemotherapeutic agents such as etoposide, vinca alkaloids, anthracyclines, and actinomycin D (MDR-related drugs). Agents such as cyclosporin A and verapamil [95–97] have been used to reverse MDR in cells by competitively inhibiting drug efflux. Marked alterations in etoposide disposition and pharmacokinetics result from the addition of cyclosporin A, demonstrated as an increase in the area under the plasma concentration-time curve (AUC) with modulation of the P-gp function [98]. These alterations in drug levels are thought to be related to the inhibition by cyclosporin A of P-gp's physiologic function in hepatobiliary excretion. The dose of etoposide should be decreased by 50% with the use of high-dose cyclosporin A. In a phase I trial of etoposide with cyclosporin, tumor regressions occurred in four patients after the addition of cyclosporin (no response was seen to initial treatment with etoposide), and biopsy specimens for three of the four patients were positive for *mdr1* expression. The recommended cyclosporin dose is 5–6 mg/kg (loading) followed by a continuous infusion of 15–18 mg/kg per day for 60 h so as to achieve serum levels of 2.5–4.0 μmol/l [99]. At present, a number of phase II and III trials of MDR modulators with chemotherapeutic agents such as etoposide and etoposide combinations are in progress.

## Future considerations

Etoposide is a highly effective and commonly used agent for both the curative and palliative treatment of a number of human malignancies. As described above, the dose-response effect, dose-schedule effect, and dosing form (oral versus parenteral)-response effect are important considerations in the use of the drug. Despite the number of clinical investigations thus far conducted in this area, the optimal dose, dosing form, and schedule of administration of etoposide in various malignant disorders remain to be determined. Whether prolonged oral dosing is superior to the standard 3-day parenteral schedule in combination with cisplatin for extensive-disease SCLC has not been established, and this issue is the primary objective of a study

currently being conducted by the CALGB. Such studies will also have to be performed in other sensitive tumor types.

Preliminary results of prolonged etoposide-infusion schedules at doses of 18–25 mg/m$^2$ per day suggest some degree of activity along with decreased toxicity [24], but these data need to be validated further. At present, it seems that the prolonged schedule may have a therapeutic advantage, and this can be best accomplished by oral use of etoposide, which has received favorable consideration to date in terms of reimbursement by third-party carriers, because its cost may in fact be lower than that of the parenteral form when costs related to preparation, administration, and office visits are considered. With the availability of colony-stimulating factors that can accelerate recovery from myelosuppression, the dose-limiting toxicity of etoposide, it may be possible to explore the drug's activity at much higher doses, especially in preparatory regimens given prior to bone marrow or peripheral stem-cell transplantation, in tumors that show a high degree of response to standard doses and, to a certain extent, in previously refractory tumors.

Another approach for further exploration of etoposide's use may rest with substances that can modulate the metabolic pathways or substrates upon which etoposide acts. For example, etoposide appears to be synergistic with topoisomerase I inhibitors, e.g., CPT-11, topotecan, 9-aminocamptothecin, and 10,11-MDA, when used sequentially. The hypothesized mechanism of this synergism is based on the in vitro observation of up-regulation of cellular topoisomerase II levels within 24–48 h after exposure to a topoisomerase I inhibitor. This observation forms the rationale of an ongoing phase I study in which topotecan is given by continuous infusion on days 1–3 and etoposide, on days 7–9 [100]. Tumor necrosis factor (TNF) [101] and retinoic acid (RA) [102] can individually increase the sensitivity of certain small-cell lung-cancer cell lines to etoposide, possibly through the induction of an apoptotic response to the drug. These preclinical observations form the rationale of the ongoing studies utilizing the combination of TNF or RA with etoposide. Etoposide has also been shown to cause a significant decrease in the number of double-minute chromosomes containing amplified oncogenes in a number of different cell lines [103]. Although the frequency and significance of double-minute chromosomes in clinical cancer specimens is not understood, this finding forms a rationale for the clinical use of etoposide in the setting in which double-minutes can be detected. The preclinical observations made both in in vitro cell lines and in animal models will continue to enhance our understanding regarding the optimal use of etoposide in various human malignancies and will also provide the foundation upon which future clinical trials will be based.

## References


1. O'Dwyer PJ, Leyland-Jones B, Alonso MT, et al (1985) Etoposide (VP-16-213): current status of an active anticancer drug. N Engl J Med 312: 692–700
2. Williams SD, Birch R, Einhorn LH, et al (1987) Treatment of disseminated germ cell tumors with cisplatin, bleomycin, and either vinblastine or etoposide. N Engl J Med 316: 1435–1441
3. Clark P, Cottier B, Joel S, et al (1991) Two prolonged schedules of single agent oral etoposide of differing duration and dose in patients with untreated small cell lung cancer (SCLC) (abstract 931). Proc Am Soc Clin Oncol 10: 268
4. Johnson DH, Hainsworth JD, Hande KR, et al (1991) Current status of etoposide in the management of small cell lung cancer. Cancer 67: 231–233
5. Waits TM, Johnson DH, Hainsworth JD, et al (1992) Prolonged administration of oral etoposide in non-small cell lung cancer: a phase II trial. J Clin Oncol 10: 292–296
6. Bender RA, Anderson T, Fisher RI, et al (1978) Activity of epipodophyllotoxin VP-16 in the treatment of combination chemotherapy-resistant non-Hodgkin's lymphoma. Am J Hematol 5: 203–209
7. Taylor RE, McElwain TJ, Barrett A, et al (1982) Etoposide as a single agent in relapsed advanced lymphoma. A phase II study. Cancer Chemother Pharmacol 7: 175–177
8. Laubenstein LJ, Krigel RL, Odejnyk CM, et al (1984) Treatment of epidemic Kaposi's sarcoma with etoposide or a combination of doxorubicin, bleomycin, and vinblastine. J Clin Oncol 2: 115–130
9. Horowitz ME (1989) Ewing's sarcoma: current status of diagnosis and treatment. Oncology 3: 101–106
10. Carli M, Perilongo G, diMontezemolo LC, et al (1987) Phase II trial of cisplatin and etoposide in children with advanced soft tissue sarcoma: a report from the Italian Cooperative Rhabdomyosarcoma Group. Cancer Treat Rep 71: 525–527
11. Kelsen DP, Magill G, Cheng E, et al (1982) Phase II trial of etoposide in the treatment of upper gastrointestinal malignancies (abstract). Proc Am Soc Clin Oncol 1: 96
12. Kuhrie H, Meerpohl HG, Lenaz L, et al (1988) Etoposide in cisplatin-refractory ovarian cancer. Proc Am Soc Clin Oncol 7: A257
13. Slevin ML, Clark PI, Joel SP, et al (1989) A randomized trial to evaluate the effect of schedule on the activity of etoposide in small cell lung cancer. J Clin Oncol 7: 1333–1340
14. Carney DN, Grogan L, Smit EF, et al (1990) Single-agent oral etoposide for elderly small cell lung cancer patients. Semin Oncol 17 [Suppl 2]: 49–53
15. Johnson DH, Greco FA, Strupp J, et al (1990) Prolonged administration of oral etoposide in patients with relapsed or refractory small-cell lung cancer: a phase II trial. J Clin Oncol 8: 1613–1617
16. Smyth RD, Pfeffer M, Scalzo A, et al (1985) Bioavailability and pharmacokinetics of etoposide (VP-16). Semin Oncol 12 [Suppl 2]: 48–51
17. Smit EF, Carney DN, Harford P, et al (1989) A phase II study of oral etoposide in elderly patients with small cell lung cancer. Thorax 44: 631–633
18. Greco F (1991) Chronic oral etoposide. Cancer 67: 303–309
19. Eagan RT, Carr DT, Fryak S, et al (1976) VP-16-213 versus polychemotherapy in patients with advanced small cell lung cancer. Cancer Treat Rep 60: 949–951
20. Tucker RD, Ferguson A, Van Wyk C, et al (1978) Chemotherapy of small cell carcinoma of the lung with VP-16-213. Cancer 141: 1710–1714
21. Matsui Y, Oshima S, Kado M, et al (1987) Phase II study of oral VP-16-213 in small cell lung cancer. Cancer 60: 2882–2885
22. Hansen M, Hirsch F, Dombernowsky P, et al (1977) Treatment of small cell anaplastic carcinoma of the lung with oral solution of VP-16-213 (NSC 141540, 4'-demethylepipodophyllotoxin 9-4-(4,6-*O*-ethylidene-β-D-glycopryanoside). Cancer 40: 633–637
23. Cavilli F, Sonntag RW, Jungi F, et al (1978) VP-16-213 monotherapy for remission induction of small cell lung cancer: a randomized trial using three dosage schedules. Cancer Treat Rep 62: 473–475
24. Greco FA, Garrow GC, Johnson DH, et al (1992) Prolonged continuous infusion of low-dose etoposide in responsive neoplasm: preliminary phase I/II results. Proc Am Soc Clin Oncol 11: 115

25. Einhorn LH, Greco A, Wampler G, et al (1987) Cytoxan, adriamycin, etoposide versus cytoxan, adriamycin and vincristine in the treatment of small cell lung cancer. Proc Am Soc Clin Oncol 6: 168
26. Evans WK, Feld R, Murray N, et al (1987) Superiority of alternating non-cross resistant chemotherapy in extensive small cell lung cancer. Ann Intern Med 107: 451–458
27. Natalir RB, Shank B, Hilaris BS, et al (1985) Combination cyclophosphamide, Adriamycin and vincristine rapidly alternating with combination cisplatin and VP-16 in treatment of small cell lung cancer. Am J Med 79: 303–308
28. Woods RL, Levi JA (1984) Chemotherapy for small cell lung cancer (SCLC2w): a randomized study of maintenance therapy with cyclophosphamide, Adriamycin and vincristine (CAV) after remission induction therapy with cisplatinum (CIS-DDP), VP-16-213 and radiotherapy. Proc Am Soc Clin Oncol 3: 214
29. Aisner J, Whitacre MY, Abrams J, et al (1986) Adriamycin, cytoxan, etoposide (ACE) and platinum, adriamycin, cytoxan, etoposide (PACE) for small cell carcinoma of the lung. Semin Oncol 13: 54–62 (suppl 3)
30. Aisner J, Whitacre MY, Budman DR, et al (1992) Cisplatin, doxorubicin, cyclosphosphamide and etoposide combination chemotherapy for small-cell lung cancer. Cancer Chemother Pharmacol 29: 435–438
31. Ruckdeschel JC (1991) Etoposide in the management of non-small cell lung cancer. Cancer 67: 250–253
32. Niederle N, Ostermann J, Achterrath W, et al (1991) Etoposide in patients with previously untreated non-small cell lung cancer: a phase I study. Cancer Chemother Pharmacol 28: 59–62
33. Rosso R, Salvati F, Ardizzoni A, et al (1991) Etoposide versus etoposide plus high-dose cisplatin in the management of advanced non-small cell lung cancer. Results of a prospective randomized FONICAP trial. Italian Lung Cancer Task Force. Cancer 66: 130–134
34. Saxman S, Logie K, Stephens D, et al (1990) Phase II trial of daily oral etoposide in patients with surgically unresectable non-small cell lung cancer (abstract). Proc Am Soc Clin Oncol 9: 238
35. Gatzcincier U, Neuhauss R, Heckmayr M (1991) Single agent oral etoposide in advanced NSCLC (chronic daily) and in elderly patients with SCLC (abstract). Lung Cancer 7[Suppl]: 102
36. Miller AA, Tolley EA, Niell HB, Griffin JP, Mauer AM (1993) Pharmacodynamics of prolonged oral etoposide in patients with advanced non-small-cell lung cancer. J Clin Oncol 11: 1179–1188
37. Grunberg SM, Crowley JJ, Livingston R, et al (1993) Treatment of stage IV non-small cell lung cancer (NSCLC) with long term administration of oral otoposide (E) and oral cyclophosphamide (C). A Southwest Oncology Group study. J Clin Oncol 11: 1598–1601
38. Walls J, Devore R, Hainsworth JD, et al (1991) Carboplatin (CBDCA) plus prolonged administration of oral etoposide (E) in the treatment of non-small cell lung cancer (NSCLC): a phase I/II trial (abstract). Proc Am Soc Clin Oncol 10: 257
39. Newlands E, Bagshawe K (1977) Epipodophyllotoxin derivative (VP16-213) in malignant teratomas and choriocarcinomas (letter). Lancet II: 87
40. Hainsworth JD, Greco FA, Williams SD, et al (1984) VP-16-213 in the treatment of refractory germinal neoplasms. In: Issel BF, Muggia FM, Carter SK (eds) Etoposide (VP-16). Current status and new developments, Academic Press (Harcourt Brace Iovanovich, Publishers) London, pp 233–243
41. Williams S, Einhorn L, Greco F, et al (1980) VP-16-213 salvage therapy for refractory germinal neoplasms. Cancer 46: 2154–2158
42. Birch R, Williams S, Cone A, et al (1986) Prognostic factors for favorable outcome in disseminated germ cell tumors. J Clin Oncol 4: 400–407
43. Einhorn LH, Williams SD, Loehrer PJ, et al (1989) Evaluation of optimal duration of chemotherapy in favorable-prognosis disseminated germ cell tumors. A Southwestern Cancer Study Group protocol. J Clin Oncol 7: 387–391
44. Loehrer PJ, Elson P, Johnson DH, et al (1991) A randomized trial of cisplatin plus etoposide with or without bleomycin in favorable prognosis disseminated germ cell tumors (abstract). Proc Am Soc Clin Oncol 10: 169
45. Nichols C, Williams S, Loehrer P, et al (1991) Randomized study of cisplatin dose intensity in advanced germ cell tumors: a Southwestern Cancer Study Group and Southwest Oncology Group protocol. J Clin Oncol 9: 1163–1172
46. Wheeler B, Loehrer P, Williams S, et al (1986) Ifosfamide in refractory male germ cell tumors. J Clin Oncol 4: 28–34
47. Loehrer PJ, Lauer R, Roth BJ, et al (1988) Salvage therapy in recurrent germ cell cancer: ifosfamide and cisplatin plus either vinblastine or etoposide. Ann Intern Med 109: 540–546
48. Stoter G, Sleijfer DT, Schornagel JH, et al (1993) BEP versus VIP in intermediate risk patients with disseminated non-seminomatous testicular cancer (NSTC). Proc Am Soc Clin Oncol 12: 232
49. Nichols CR, Tricot G, Williams SD, et al (1989) Dose-intensive chemotherapy in refractory germ cell cancer – a phase I/II trial of high dose carboplatin and etoposide with autologous bone marrow transplantation. J Clin Oncol 7: 932–939
50. Rosti G, Salvioni R, Pizzocaro G, et al (1990) High dose chemotherapy (HDC) with carboplatin (CBP) and VP-16 in germ cell tumors: the Italian experience. In: Dicke K, Armitage JO, Dicke-Evinger MJ (eds) Proceedings of the Fifth International Bone Marrow Transplant Symposium, Omaha, Nebraska, pp 186
51. Bishop JF (1992) Etoposide in the treatment of acute leukemias. Semin Oncol 19 [Suppl 13]: 33–38
52. Look AT, Dahl GV, Kalwinsky D, et al (1981) Effective remission induction of refractory childhood acute non-lymphocytic leukemia by VP-16-213 plus azacytidine. Cancer Treat Rep 65: 995–999
53. Kalwinsky DK, Dahl GV, Mirro J, et al (1986) Induction failures in childhood acute nonlymphocytic leukemia: etoposide/5-azacytidine for cases refractory to daunorubicin/cytarabine. Med Pediatr Oncol 14: 245–250
54. Letendre L, Hinemann V, Hoagland C, et al (1985) Phase I study of VP-16 (etoposide) and amsacrine (AMSA) in the treatment of refractory acute leukemia. Med Pediatr Oncol 13: 232–234
55. Tschopp L, Fliedner VE von, Saufer C, et al (1986) Efficacy and clinical cross-resistance of a new combination therapy (AMSA/VP16) in previously treated patients with acute non-lymphocytic leukemia. J Clin Oncol 4: 318–324
56. Carella AM, Santini G, Giordano D, et al (1985) Idarubicin alone or in combination with cytarabine and etoposide (3 + 3 + 5 protocol) in acute non-lymphoblastic leukemia (letter). Leuk Res 9: 631
57. Ho AD, Lipp T, Ehinger G, et al (1988) Combination of mitoxantrone and etoposide in refractory acute myelogenous leukemia – an active well tolerated regimen. J Clin Oncol 6: 213–217
58. Lazzarino M, Morra E, Alessandrino EP, et al (1989) Treatment of relapsed or refractory acute myeloid leukemia in adults. Bone Marrow Transplant [Suppl] 4: 121–123
59. Bishop JF, Joshua DE, Lowenthal RM, et al (1986) A phase I-II study of cytosine arabinoside, daunorubicin and VP16-213 in adult patients with acute non-lymphocytic leukemia. Aust NZ J Med 16: 48–51
60. DeVita VT, Serpick AA, Carbone PP (1970) Combination chemotherapy in the treatment of advanced Hodgkin's disease. Ann Intern Med 73: 891–895
61. Glick J, Tsiatis A, Schilsky R, et al (1991) A randomized phase III trial of MOPP/ABVD hybrid vs. sequential MOPP-ABVD in advanced Hodgkin's disease: preliminary results of the Intergroup Trial (abstract). Proc Am Soc Clin Oncol 10: A941
62. Bonadonna G, Zucali R, Monfardini S, et al (1975) Combination chemotherapy of Hodgkin's disease with adriamycin, bleomycin, vinblastine and imidazole carboximide versus MOPP. Cancer 36: 252–259
63. Longo DL, Young RC, Wesley M, et al (1986) Twenty years of MOPP therapy for Hodgkin's disease. J Clin Oncol 4: 1295–1306
64. Fox KA, Lippman SM, Cassady JR, et al (1987) Radiation therapy salvage of Hodgkin's disease following chemotherapy. J Clin Oncol 5: 544–549

65. Richards MA, Waxman JH, Ganesan TS, et al (1986) EVA treatment for recurrent or unresponsive Hodgkin's disease. Cancer Chemother Pharmacol 18: 51–53
66. Longo DL, Duffey PL, Young RC, et al (1992) Conventional-dose salvage combination chemotherapy in patients relapsing with Hodgkin's disease after combination chemotherapy: the low probability for cure. J Clin Oncol 10: 210–218
67. Tseng A Jr, Jacobs C, Coleman CN, et al (1987) Third line chemotherapy for resistant Hodgkin's disease with lomustine, etoposide and methotrexate. Cancer Treat Rep 71: 475–478
68. Pfreundschuh MG, Schoppe WD, Fuchss R, et al (1987) Lomustine, etoposide, vindesine and dexamethasone (CEVD) in Hodgkin's lymphoma refractory to cyclophosphamide, vincristine and decarbazine: a multicenter trial of the German Hodgkin's Study Group. Cancer Treat Rep 71: 1203–1207
69. Santoro A, Viviani SS, Valagussa P, et al (1986) CCNU, etoposide and prednimustine (CEP) in refractory Hodgkin's disease. Semin Oncol 13: 23–26
70. Cervantes F, Reverter JC, Montserrat E, et al (1986) Treatment of advanced resistant Hodgkin's disease with lomustine, etoposide and prednimustine. Cancer Treat Rep 70: 665–667
71. Hagemeister FBN, Tannir N, McLaughlin P, et al (1987) MIME chemotherapy (methyl-GAG, ifosfamide, methotrexate, etoposide) as treatment for recurrent Hodgkin's disease. J Clin Oncol 5: 556–561
72. Gribben JG, Linch DC, Singer CRJ, et al (1989) Successful treatment of refractory Hodgkin's disease by high dose combination chemotherapy and autologous bone marrow transplantation. Blood 73: 340
73. Yahalom J, Girlati S, Shank B, et al (1989) Total lymphoid irradiation, high dose chemotherapy and autologous bone marrow transplantation for chemotherapy-resistant Hodgkin's disease. Int J Radiat Oncol Biol Phys 17: 915
74. Fisher RI, Devita VT Jr, Hubbard SM, et al (1983) Diffuse aggressive lymphomas: increased survival after alternating flexible sequences of Pro MACE and MOPP chemotherapy. Ann Intern Med 98: 304–309
75. Longo DL, DeVita VT Jr, Duffy PL, et al (1991) Superiority of ProMACE-CytaBOM over ProMACE-MOPP in the treatment of advanced diffuse aggressive lymphoma: results of a prospective randomized trial. J Clin Oncol 9: 25–38
76. Frederico M, Moretti G, Gobbi PG, et al (1991) ProMACE-CytaBOM vs. MACOP-B in intermediate and high-grade NHL. Preliminary results of a prospective randomized trial. Leukemia 5: 95–101
77. O'Reilly SE, Hoskins P, Kleins P, et al (1991) MACP-B and VACOP-B in diffuse large cell lymphomas and MOPP/ABD in Hodgkin's disease. Ann Oncol 2: 17–23
78. Fisher RI, Gaynor E, Dahlberg S, et al (1993) Comparison of a standard regimen (CHOPE) with three intensive chemotherapy programmes for advanced non-Hodgkin's lymphoma N Engl J Med 328: 1002–1006
79. Herzig RH (1991) High-dose etoposide and marrow transplantation. Cancer 67: 292–298
80. Spitzer GR, Cottler-Fox M, Torrisi J, et al (1989) Escalating doses of etoposide with a cyclophosphamide and fractionated total body irradiation or busulfan as conditioning for bone marrow transplantation. Bone Marrow Transplant 4: 559–565
81. Horning SJ, Chao NJ, Negrin RS, et al (1991) The Stanford experience with high-dose etoposide cytoreductive regimens and autologous bone marrow transplantation in Hodgkin's disease and non-Hodgkin's lymphoma: preliminary data. Ann Oncol 2[Suppl 1]: 47–50
82. Freedman AS, Takvorian T, Anderson KC, et al (1990) Autologous bone marrow transplantation in B-cell non-Hodgkin's lymphoma: very low treatment related mortality in 100 patients in sensitive relapse. J Clin Oncol 8: 784–791
83. Wilson WH, Bryant G, Bates S, et al (1991) Infusional etoposide (E), vincristine (O) and Adriamycin (H) with cyclophosphamide (C), prednisone (P) (EPOCH) and r-verapamil (RV) in relapsed lymphoma (abstract). Proc Am Soc Clin Oncol 10: 276
84. Beral V, Peterman TA, Berkelman RL, et al (1990) Kaposi's sarcoma among persons with AIDS: a sexually transmitted infection? Lancet 335: 123
85. Shields P, Dawkins F, Holmlund J, et al (1989) Weekly low-dose multidrug chemotherapy (MDCT) plus pneumocystis prophylaxis for HIV-related Kaposi's sarcoma. Proc Am Soc Clin Oncol 8: 1
86. Preusser P, Wilke H, Achterrath W, et al (1989) Phase II study with the combination of etoposide, doxorubicin and cisplatin in advanced measurable gastric cancer. J Clin Oncol 7: 1310–1317
87. Lerner A, Steele GD, Mayer RJ (1990) Etoposide, doxorubicin, cisplatin (EAP) chemotherapy for advanced gastric adenocarcinoma: results of a phase II trial (abstract). Proc Am Soc Clin Oncol 9: 103
88. Wilke H, Preusser P, Fink U, et al (1989) Preoperative chemotherapy in locally advanced and nonresectable gastric cancer: a phase II study with etoposide, doxorubicin and cisplatin. J Clin Oncol 7: 1318–1326
89. Kelsen D, Atiq O, Saltz L, et al (1992) FAMTX versus etoposide, doxorubicin, and cisplatin: A random assignment trial in gastric cancer. J Clin Oncol 10: 541–548
90. Wilke H, Preusser P, Fink U, et al (1990) High dose folinic acid/etoposide/5-fluorouracil in advanced gastric cancer: a phase II study in elderly patients or patients with cardiac risk. Invest New Drugs 8: 65–70
91. Pastan I, Gottesman MM (1987) Multi-drug resistance in human cancer. N Engl J Med 316: 1388–1393
92. Goldstein LJ, Galski H, Fojo A, et al (1989) Expression of a multidrug resistance gene in human cancers. J Natl Cancer Inst 81: 116–124
93. Fojo A, Ueda K, Salmon DJ, et al (1987) Expression of a multidrug-resistant gene in human tumors and tissues. Proc Natl Acad Sci USA 84: 265–269
94. Nooter K, Herweijer H (1991) Multidrug resistance (*mdr*) genes in human cancer. Br J Cancer 63: 663–669
95. Slater L, Sweet P, Stupecky M, et al (1986) Cyclosporin A reverses vincristine and daunorubicin resistance in acute lymphatic leukemia in-vitro. J Clin Invest 77: 1405–1408
96. Willingham M, Cornwell M, Cardarelli C, et al (1986) Single cell analysis of daunomycin uptake and efflux in multidrug-resistant and sensitive KB cells: effects of verapamil and other drugs. Cancer Res 46: 591–594
97. Cornwell M, Pastan I, Gottesman M (1987) Certain calcium channel blockers bind specifically to multidrug resistant human KB carcinoma membrane vesicles and inhibit drug binding to P-glycoprotein. J Biol Chem 26: 2166–2170
98. Lum BL, Kaubisch S, Yahanda AM, et al (1992) Alteration of etoposide pharmacokinetics and pharmacodynamics by cyclosporine in a phase I trial to modulate multidrug resistance. J Clin Oncol 10: 1635–1642
99. Yahanda M, Adler KM, Fisher GA, et al (1992) Phase I trial of etoposide with cyclosporine as a modulator of multidrug resistance. J Clin Oncol 10: 1624–1634
100. Eckhardt JR, Burris HA, Rodriquez GA, Fields SM, et al (1993) A phase I study of topoisomerase I and II inhibitors topotecan (T) and etoposide (E) (abstract). Proc Am Soc Clin Oncol 12: 137
101. Doyle LA, Hamburger AW, Goldstein LH, et al (1990) Interaction of recombinant human tumor necrosis factor (TNF) and etoposide in human lung cancer cell lines. Mol Biother 2: 169–174
102. Doyle LA, Guangiulio D, Hussain A, et al (1989) Differentiation of human variant small cell lung cancer cell lines to a classic morphology by retinoic acid. Cancer Res 49: 6745–6751
103. Von Hoff DD, McGill J, Davidson K, et al (1992) Preclinical leads for innovative uses of etoposide. Semin Oncol 19 [Suppl 13]: 10–13