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Prolonged administration of low-daily-dose etoposide: a superior dosing schedule?

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Abstract. Despite the clinical use of etoposide for about 20 years, the best dose and schedule of administration remains unknown. The schedule dependency for small-cell lung cancer (SCLC) has been unequivocally demonstrated, and it is probably similar for other sensitive neoplasms (for example, lymphoma, germ cell tumors). A more extended schedule of administration (i.e., 14–21 days) may be more effective than the standard 3- to 5-day schedule. Plasma levels in reference to dose, schedule, and tumor responsiveness have been evaluated in several studies These data suggest that high peak levels (i.e., >5–10 μg/ml) are most often associated with more severe myelosuppression than are lower peak plasma levels (i.e., 1–3 μg/ml). In SCLC patients the response rates and survival observed following the administration of low daily etoposide doses for 14–21 days are similar to the results achieved with standard doses given for 3–5 days. These data as well as other studies suggest that giving low daily doses of etoposide on a prolonged schedule is superior. Randomized comparisons are necessary for an unequivocal confirmation of these observations.

Key words: Etoposide – Low dosing

Introduction

Etoposide is a very useful antineoplastic drug. Etoposide-based combination chemotherapy has become standard for a large number of patients with small-cell lung cancer, germ-cell tumors, and lymphomas. However, it has become obvious that the best dose and schedule for etoposide given either as a single agent or in combination with other drugs is not clear. Recently this issue has been further clarified and now allows for reasonable speculations regarding the best dose and schedule for etoposide. The following discussion focuses on this issue.

About 20 years ago the striking schedule-dependent activity of etoposide was demonstrated in mice with L1210 leukemia [1]. Equivalent doses divided over several days were superior to single or weekly injections. Cavalli and associates [2] treated patients with small-cell lung cancer (SCLC), and their results strongly suggested the same schedule dependency in humans. These studies formed the basis for the use of etoposide. Therefore, in clinical practice the schedule most often employed was daily doses given for 3–5 days. Nonetheless, many other schedules continue to be used, including single-day administration [3].

A randomized prospective study has definitely proven that the same dose of etoposide given daily for 5 days is dramatically superior to single-day administration in patients with SCLC [4]. An etoposide-based combination-chemotherapy comparison has also documented the schedule dependency of etoposide in SCLC [5]. Data are not available for lymphoma or germ-cell tumors, but it is likely that schedule-dependent activity of etoposide also applies to these malignancies.

The total dose of etoposide recommended (regardless of schedule) has been derived largely from early phase I studies in which myelotoxicity defined the maximum tolerated dose (usually total i.v. doses of 300–500 mg/m^2). However, total doses ranging from 300–4,200 mg/m^2 have been given to many patients. Despite this situation, dose comparisons have not established a definite dose-response relationship in human neoplasms. There is no evidence, even in sensitive tumor types, of a dose-response relationship at doses above 500 mg/m^2. The effect of dose is likely to be complicated by the schedule of administration, since the activity of etoposide is highly schedule dependent. Currently we do not know whether relatively high doses given for 1 or 2 days are comparable in efficacy with

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relatively low doses given for 3–5 days or whether very low doses given for more than 3–5 days are comparable with standard doses given for 3–5 days. Certainly higher doses are more toxic to the patient, particularly in terms of myelosuppression. In a randomized prospective study in previously treated SCLC patients, three etoposide doses (300, 600, and 900 mg/m^2) given in the same schedule (daily for 3 days) showed no advantage for any dose [6]. The response rate in all arms was $<10\%$ and the higher dose was significantly more myelotoxic.

Extended-schedule etoposide administration

The unequivocal demonstration of schedule dependency in SCLC and the availability of oral etoposide has been logically expanded to the investigation of even more extended schedules of etoposide administration. Moreover, the mechanism of etoposide cytotoxicity favors using a prolonged schedule. Etoposide inhibits topoisomerase II, causing primarily double-strand DNA breaks. The enzymatic inhibition is rapidly reversible and probably concentration-dependent. Prolonged etoposide administration produces longer periods of topoisomerase II inhibition resulting from prolonged exposure to a critical concentration. This critical concentration has not been precisely determined. The tumor cytotoxicity of etoposide appears to be more dependent on this relatively low critical concentration than on the magnitude of the peak plasma concentration. Even a very high dose given over 1 or 2 days would inhibit topoisomerase II only briefly, since etoposide is rapidly cleared from the body. With this high dose and brief schedule the effect on the bone marrow is well documented, but a superior antitumor effect is not apparent. Conversely a much lower daily dose given for a prolonged period is less myelotoxic than the high-dose brief schedule but may be at least as cytotoxic to selected sensitive tumors. A number of phase I/II studies looking at protracted etoposide administration have been done, and randomized comparisons are ongoing.

Phase II single-agent trials

Several phase II studies using either 50 mg (once or twice daily) or 50 mg/m^2 etoposide daily for 10–21 days have been done involving patients with both previously treated [7, 8] and untreated SCLC [9], previously treated germ-cell tumors [10], non-Hodgkin's lymphoma [11], soft-tissue sarcomas, ovarian cancer [12], and previously untreated melanoma and renal cell carcinoma. Responses have been seen in all tumor types, but only rarely in melanoma, sarcoma, and renal cell carcinoma. Impressive clinically useful responses have been seen in germ-cell tumors, SCLC, and non-Hodgkin's lymphoma (see Table 1). Response rates have been higher than expected as compared with historical data from similar patient populations given standard doses and schedules of etoposide. Furthermore, several patients with tumors clinically resistant (progression during therapy) to etoposide given at a standard dose and schedule have responded to the chronic use of low-dose daily etoposide [10]. These findings certainly support the notion that the protracted etoposide schedule is superior.

Slevin et al. [4, 13] and Clark et al. [9, 14–16] have used variable doses of etoposide in 8-, 10-, 14- and 21-day schedules in previously untreated patients with SCLC. These patients usually had extensive-stage disease and/or were medically unfit (i.e., poor performance status). The overall results of these studies showed good activity and very reasonable patient survival. More importantly, less myelosuppression occurred with low-dose oral etoposide given daily for 21, 14, or 10 days as compared with that reported for past studies with standard doses and schedules.

These studies and our own observations are highly suggestive that for SCLC a low steady-state plasma etoposide concentration (0.5–1 μg/ml) is associated with tumor cytotoxic activity and that higher peak levels (>3–10 μg/ml) are associated with more severe myelosuppression (but not necessarily with more tumor cytotoxicity). The critical etoposide concentration for "adequate" inhibition of topoisomerase II appears to be <1 μg/ml. We are not sure whether the prolonged schedule produces superior tumor cytotoxicity; however, lower daily doses (50 mg total) given over a prolonged period (10–21 days) produce less myelosuppression and at least as much activity as short-term, high-dose administration (standard dose and schedule) in patients with SCLC. The low daily dose given for a prolonged period has a better therapeutic ratio and is therefore superior. The optimal duration of administration is not known, nor is it clear that a "low dose" given daily for 3–5 days is inferior. A relatively low oral dose given for 5 days (1000 mg total) may be as effective as longer schedules or higher doses as suggested by the results of Carney et al. [17]. Randomized studies are required to settle these issues definitively and are under way.

To investigate further the relationship of tumor response and myelosuppression with plasma levels of etoposide we have studied chronic, continuous, low-dose i.v. etoposide infusion over many weeks in selected patients. Oral etoposide is available only in 50-mg capsules in the United States, and a single 50-mg daily dose may be too large for consistent avoidance of transiently higher plasma levels (>2 μg/ml). Furthermore, when this dose is given once daily, plasma levels are very low (<0.5 μg/ml) [8–10] for part of the day (6–12 h). If available, smaller capsules (5, 10, and 20 mg) could be given in multiple daily doses (i.e., every 4–6 h) so as to maintain chronic, very low plasma levels (0.5–1.0 μg/ml) and avoid any peak plasma level of >2 μg/ml.

Since small oral doses were not available, we conducted a phase I/II trial of continuous-infusion etoposide (18–25 mg/m^2 daily, a dose *calculated* to produce consistent plasma levels of 0.6–3 μg/ml) in selected previously treated patients with non-Hodgkin's lymphoma and germ-cell tumors and previously untreated patients with SCLC [21]. We observed activity (five responses among ten patients with lymphoma; two responses among three patients with SCLC) as well as usually minimal neutropenia and rare thrombocytopenia. Several patients were treated continuously for many months. Etoposide plasma concentrations ranged from 0.2–2.1 μg/ml (mean, 0.7 ± 0.42 μg/ml).

Table 1. Documented clinical usefulness of low-dose daily etoposide – prolonged schedule

SCLC:
Previously treated
Previously untreated (elderly, medically unfit, extensive-stage disease)
Lymphoma:
Previously treated
Previously untreated (? elderly, medically unfit)
Germ-cell tumors:
Previously treated

These results suggest that a chronic low daily dose given without associated high peak plasma levels has impressive tumor cytotoxicity and usually produces mild hematologic toxicity. The low steady-state plasma levels (usually < 1 μg/ml) were associated with effective antitumor activity. Divided, low daily oral doses may simulate the results seen in the constant i.v. infusion study, and further investigation of this issue is warranted.

Combination-chemotherapy pilot trials

Pilot studies of prolonged etoposide use as a component of combination chemotherapy for previously untreated patients have been done or are under way in several neoplasms, including SCLC [18], non-small-cell lung cancer (NSCLC) [19], and non-Hodgkin's lymphoma [20]. These studies have provided toxicity and feasibility data as well as some evidence of impressive activity. Chronic administration of oral etoposide in combination chemotherapy will likely be tested in future phase III comparative studies, particularly when the optimal dose and schedule has been clarified.

Seeking the best dose and schedule for etoposide

Several clues have emerged suggesting the best method of giving etoposide. A review of the studies providing these findings forms a compelling argument for prolonged low-daily-dose etoposide administration. Slevin et al. [4] showed that the same dose (500 mg/m^2) was superior in SCLC when given i.v. over 5 days versus 1 day. However, there was no significant difference in myelotoxicity. In a second study, the same i.v. dose (500 mg/m^2) divided over 8 days did not significantly improve the results obtained with the 5-day regimen [13]. However, the 8-day schedule produced significantly less ($P < 0.05$) myelotoxicity (absolute neutrophil count nadir, 0.8 vs 1.7×10^6/l). This provided the first clue that prolonging the schedule beyond 5 days might result in less myelosuppression (Table 2).

Clark et al. [9] studied oral etoposide given in low daily doses to two sequential series of SCLC patients. The doses used were 50 mg given twice daily for 14 days (in 21-day cycles) in the first study and 50 mg given once daily for 21 days (in 28-day cycles) in the second study. Both series showed good activity, with response rates being >50% and survival being about what one would expect to achieve with combination chemotherapy in these patients (median survival, 7–8 months). Although the time to response was longer and the response rate was a little lower in patients given the 21-day schedule as compared with those receiving the 14-day schedule, the median absolute neutrophil nadir was greater with the more prolonged treatment (3.9 vs 2.1×10^6/l, respectively). Both schedules were active yet relatively nontoxic. Patients receiving 50 mg daily frequently had peak plasma levels in the range of 1–3 μg/ml.

The results of our phase I/II study employing a continuous-infusion etoposide schedule show good activity against non-Hodgkin's lymphoma and SCLC and less myelosuppression than expected as compared with etoposide given at a standard dose/schedule. Giving 18–25 mg/m^2 etoposide daily as a prolonged i.v. infusion usually avoided peak plasma levels of >2 μg/ml and maintained plasma levels continuously at 0.2–2.1 μg/ml [21].

When the pharmacologic data from these i.v. and oral etoposide studies are compared, it appears that peak plasma levels (>3 μg/m, certainly >5 μg/ml) are associated with more severe myelosuppression yet do not produce superior tumor cytotoxicity. There is a differential sensitivity of selected neoplasms as compared with normal bone marrow when these are exposed to the "critical concentration" of etoposide. Surprisingly, lower daily doses of etoposide (30–60 mg) given chronically for 10 days or longer to maintain plasma levels in the range of 0.5–1.5 μg/ml seem to produce at least equivalent tumor cytotoxicity and less myelosuppression than do standard doses (300–500 mg/m^2) given daily for 3–5 days.

Table 2. Etoposide: clues to the most proper dose/schedule (*ANC* Absolute neutrophil count)

Investigators/tumor type	Schedule	Results
Slevin et al. [4, 13], Clark et al. [9]/SCLC	500 mg/m^2 i.v. 5 days vs 1 day	Greater efficacy (5 days); equal toxicity
	500 mg/m^2 i.v. 8 days vs 5 days	?Similar efficacy; less toxicity (8 days)
	50 mg b.i.d. p.o. 14 days vs 50 mg qd p.o. 21 days	Similar efficacy; least myelotoxic (50 mg qd 21 days; median ANC, 3.9×10^6/l)[a]
Carney et al. [17]/SCLC	200 mg qd p.o. 5 days (1,000 mg total)	Efficacy = higher-dose schedules; mild myelotoxicity (median ANC, 1.8×10^6/l)
Thompson et al. [21]/lymphoma, SCLC	18–25 mg/m^2 continuous i.v. infusion[b]	?Efficacy = higher-dose schedules; less myelotoxicity

[a] Plasma levels in patients receiving 50 mg qd ranged from 1 to 3 μg/ml

[b] Schedule given daily; several patients were treated continuously for many weeks

The study of Carney et al. [17] also suggests that a relatively low oral dose (1000 mg total dose) given in a standard 5-day schedule (approximately 100 mg/day bioequivalent dose) has good activity (probably comparable with that of higher doses) in elderly patients (≥70 years old) with previously untreated SCLC. The survival of patients given this regimen is similar to that of historical controls receiving combination chemotherapy, and myelotoxicity was very modest (median absolute neutrophil count, 1.8×10^6/l). These results also question the daily dose necessary to obtain optimal results in SCLC. It is likely that even with a standard schedule (3–5 days) the doses used in the past would be unnecessary high, and the result would be more severe myelosuppression but no greater antitumor activity.

These data taken together certainly suggest that etoposide may be more effective and/or less toxic in low, divided daily doses (30–60 mg total) given for prolonged periods (≥10–21 days). The optimal duration of therapy requires additional study. The low-daily-dose, prolonged schedule appears to provide at least comparable, perhaps improved, tumor cytotoxicity (in sensitive tumor types) and considerably less myelotoxicity than the standard dose and schedule of etoposide. This, by definition, is superior if other issues do not emerge (e.g., chronic toxicity, secondary neoplasms).

The prolonged schedule has the potential for increased leukemogenesis and other unexpected extramedullary toxicity (e.g., hepato- and cardiotoxicity). Therefore, further documentation and clarification of the apparent superiority of prolonged etoposide administration is required. Prospective randomized comparisons are nearing completion. If the prolonged low-daily-dose (single or divided) schedule is superior to the standard dose and schedule of etoposide, combination programs are likely to incorporate this new and more optimal dosing schedule of etoposide. Furthermore, if the activity of etoposide against sensitive tumor types is not lessened by the administration of low daily doses, it may be possible to improve the therapeutic index of etoposide by using a standard schedule (3–5 days) with daily doses considerably lower than those traditionally given. The treatment of patients with etoposide-sensitive neoplasms may be improved by the use of the best dose and schedule of etoposide.

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