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Extended-Schedule Oral Etoposide in Selected Neoplasms and Overview of Administration and Scheduling Issues

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Abstract

Extended schedules of oral etoposide have been evaluated in many types of advanced cancer. In addition to their use in the common solid tumours, extended schedules have been employed in Kaposi's sarcoma (both AIDS-related and endemic types), medulloblastoma, glioma, and hepatocellular carcinoma. Single agent activity was demonstrated in all of these tumour subtypes. For patients with carcinoma of unknown primary site, we have recently incorporated a 10-day oral etoposide schedule into a combination regimen that also includes paclitaxel and carboplatin. With this regimen we achieved a 47% response rate in a group of 53 evaluable patients, with a median survival of 13.4 months. Patients with adenocarcinoma and poorly differentiated carcinoma of unknown primary site had comparable response rates and survival. According to a large number of clinical trials and pharmacokinetic data, a daily oral etoposide dose of 50 mg/m^2 consistently produces serum concentrations >1 mg/L for several hours each day. Lower doses fail to consistently produce this serum concentration, which is considered necessary for optimum tumoricidal activity. Optimal dose duration is 10 to 14 days, particularly when combination regimens are being employed. Oral etoposide has an established role as a single agent in patients with low grade non-Hodgkin's lymphoma, Kaposi's sarcoma, and testicular cancer (if residual carcinoma is resected after first-line treatment). The optimal use of extended-schedule etoposide in combination regimens is not defined but is being evaluated in a number of etoposide-sensitive malignancies.

Extended schedules of oral etoposide have now been evaluated in many types of advanced cancer and incorporated into combination chemotherapy regimens. Extensive evaluation of single agent oral etoposide in the treatment of lung, ovarian, and breast cancer has been reported, and these results are summarised elsewhere in this supplement. In addition, clinical experience in haematological malignancies, gastric cancer, germ cell tumours, and prostate cancer is reviewed.

Small phase II studies using extended-schedule etoposide in several other cancer types have been reported, and these data are reviewed in this paper. A summary and synthesis of current

knowledge regarding oral etoposide administration and scheduling are also presented, together with recommendations for clinical use and further investigation of this agent.

1. Extended-Schedule Etoposide in Selected Neoplasms

1.1 Kaposi's Sarcoma, AIDS-Related

Schwartsmann et al.[1] administered oral etoposide 25 mg/m^2 twice daily to patients with AIDS-related Kaposi's sarcoma for 7 consecutive days followed by 7 days without treatment (table I). 28 chemotherapy-naïve patients were treated with a median of 6 courses (range, 4 to 27 courses). Eight patients (32%) responded, with 2 complete responses. Response duration was only 8 weeks, with a range of 4 to 27 weeks. Treatment was well tolerated in most patients, with grade 3/4 leucopenia (36%) and thrombocytopenia (20%). Two patients had to discontinue treatment because of prolonged cytopenia.

Pharmacokinetic evaluations were performed as part of this trial. After a 25 mg/m^2 etoposide dose, the mean maximum serum concentration (C_{max}) was 2.1 mg/L, and serum concentrations remained above 1 mg/L for approximately 5 hours after each dose. These serum concentrations are somewhat higher than those reported by other investigators, and are possibly related to the oral administration of liquid etoposide (intravenous preparation) rather than etoposide capsules in this trial.

1.2 Kaposi's Sarcoma, Endemic (Mediterranean) Type

Oral etoposide was administered to 34 patients with Mediterranean Kaposi's sarcoma as part of a randomised trial that compared etoposide and vinblastine (table I).[2] Patients were previously untreated, and had a median age of 73 years. Depending on patient tolerance, etoposide was given for an increasing number of days with each course of treatment: 60 mg/m^2, days 1 to 3, course 1; 60 mg/m^2, days 1 to 4, course 2; and 60 mg/m^2, days 1 to 5, all subsequent courses. Treatment was repeated every 3 weeks.

Etoposide was highly active in this patient group, producing a 74% response rate, with 8 complete responses. Maximum response required several months of therapy. Although the median response duration had not been reached, at the time of the report it exceeded 12 months. This treatment regimen was well tolerated, with no grade 3/4 myelosuppression. Similar efficacy was seen with single agent vinblastine.

1.3 Medulloblastoma

Results have recently been reported of a study involving a small number of patients with refractory medulloblastoma who were treated with extended-schedule etoposide (table I).[3] The ages of the 7 patients in this study ranged from 5 to 16 years. Patients had received 1 to 4 previous chemotherapy regimens plus radiation therapy, and all had received prior intravenous etoposide. Oral etoposide 50 mg/m^2 was administered for 21 consecutive days, and repeated after a 1-week rest.

Table I. Single agent extended-schedule etoposide: results in selected cancers

Investigator	Tumour type	No. of patients	Previous chemotherapy	Etoposide dose/schedule	Response rate (%)
Schwartsmann et al.[1]	Kaposi's, AIDS-related	28	No	25 mg/m^2 twice daily × 7 days, repeated every 14 days	32
Brambilla et al.[2]	Kaposi's, Mediterranean	34	No	60 mg/m^2 for 3-5 days	74
Ashley et al.[3]	Medulloblastoma	7	Yes	50 mg/m^2 × 21 days	86
Chamberlain & Grafe[4]	Chiasmatic glioma	14	Yes	50 mg/m^2 × 21 days	36
Wierzbicki et al.[5]	Hepatoma	18	No	50 mg/m^2 × 21 days	0
Cheng et al.[6]	Hepatoma	33	No	50 mg/m^2 × 21 days	24

Table II. Summary of results with paclitaxel, carboplatin and extended-schedule etoposide in the treatment of carcinoma of unknown primary site

	Adenocarcinoma (n = 29)	Other histologies[a] (n = 24)	Entire group (n = 53)
Responses			
complete	3 (10%)	4 (17%)	7 (13%)
partial	10 (35%)	8 (33%)	18 (34%)
overall response rate	13 (45%)	12 (50%)	25 (47%)
Median survival (months)	13.5	13.2	13.4

a Poorly differentiated adenocarcinoma/poorly differentiated carcinoma.

Six of 7 patients had partial responses to treatment, with 2 having a duration of response >8 months. Myelosuppression was severe but tolerable in these heavily pretreated patients. Two patients received granulocyte colony-stimulating factor (G-CSF).

1.4 Chiasmatic-Hypothalamic Glioma

14 paediatric patients (2 to 15 years of age) with refractory chiasmatic-hypothalamic gliomas were treated with oral etoposide 50 mg/m^2 for 21 consecutive days followed by a 2-week rest period (table I).[4] 13 patients had received previous radiation therapy, and 12 had received previous chemotherapy, but not with etoposide. Five of 14 patients (36%) had objective responses (1 complete, 4 partial) for a median duration of 8 months.

1.5 Hepatocellular Carcinoma

Two groups have evaluated extended-schedule etoposide in patients with advanced hepatomas, with conflicting results (table I). Wierzbicki et al. saw no responses in 18 patients treated with etoposide 50 mg/m^2 daily for 21 days.[5] Cheng et al. used the same etoposide dose and schedule in combination with tamoxifen 40 mg/day, days 1 to 21, repeated every 5 weeks.[6] Eight of 33 patients (24%) had partial responses, for a median duration of 6 months. Responding patients experienced palliative benefit.

1.6 Carcinoma of Unknown Primary Site

Single agent data with extended-schedule etoposide in patients with carcinoma of unknown primary site have not been published. We recently evaluated a combination regimen containing paclitaxel 200 mg/m^2 by 1-hour infusion, carboplatin [area under the concentration-time curve (AUC) 6.0], and extended-schedule oral etoposide.[7] In this combination, etoposide was administered for 10 consecutive days at a dose of 50mg alternating with 100mg (approximately a 50 mg/m^2 dose in most patients). The regimen was repeated every 21 days for 4 courses. Cytokines were not used.

Results of this trial involving 55 patients are summarised in table II. Most patients had adenocarcinomas, and none could be categorised into any previously recognised treatable subgroup. The overall response rate was 47%, the complete response rate was 13%, and the median survival time was 13.4 months. Response rates and median survival were identical when patients with adenocarcinoma or other histologies were compared. The regimen was well tolerated: leucopenia was common, febrile episodes were uncommon, and no treatment-related deaths occurred.

In our experience, this regimen is more active and better tolerated than previously evaluated regimens for unknown primary cancer. Since the publication of the results of this phase II study, we have further documented the activity of this regimen in advanced poorly differentiated neuroendocrine carcinomas, with or without a known primary site. The 10-day schedule of oral etoposide is well tolerated, and does not appear to add much toxicity to the paclitaxel-carboplatin combination.

2. Overview of Extended-Schedule Etoposide: Optimal Dose, Schedule, and Clinical Utility

The efficacy of extended-schedule etoposide has now been demonstrated in a wide variety of cancer types. Although the doses and schedules used in various phase II trials have varied to some extent, the oral dose of 50 mg/m^2 given for 21 consecutive days has been the most commonly employed method of administration. The efficacy of single agent extended-schedule etoposide has not been compared with that of standard 3- or 5-day intravenous schedules in randomised trials. However, several observations suggest increased efficacy. First, the activity of extended-schedule (usually 21-day) etoposide has been demonstrated in several refractory neoplasms in which standard-schedule etoposide has been ineffective. These tumour types include non-small cell lung cancer, ovarian cancer, and breast cancer.[8-10] Second, responses have been observed with extended-schedule etoposide in patients who are refractory to standard-schedule etoposide. Such responses have been seen in patients with lymphoma, medulloblastoma, and testicular cancer.[3,11,12] In no tumour type has extended-schedule etoposide appeared to be less active than standard intravenous schedules. The weight of these rather considerable data has led to continued interest in optimising the dose and schedule of etoposide, and in incorporating such schedules into combination regimens.

2.1 Optimal Daily Dose

The efficacy of continued exposure to low doses of etoposide was first demonstrated in preclinical studies performed in the 1970s. Divided-dose schedules were consistently more effective than single doses, and multiple daily doses were more effective than single daily doses.[13-15] Even more pertinent was the observation that exposure of Lewis lung carcinoma to etoposide *in vitro* for 24 hours resulted in cytotoxicity at concentrations of 1 and 10 mg/L, with minimal activity at 0.01 and 0.1 mg/L. However, marked cytotoxicity was seen at these 2 lower concentrations when the cells were exposed for 72 hours.[16] In choriocarcinoma cell lines, identical cytotoxicities were achieved with a 3-hour exposure to 5 mg/L of etoposide or with a 24-hour exposure to 0.5 mg/L.[17]

In the first definitive demonstration of etoposide schedule dependency in clinical oncology, Slevin et al. documented markedly increased efficacy in patients with small cell lung cancer when an identical total dose of etoposide was administered by a 5-day divided-dose schedule rather than a 24-hour infusion.[18] Pharmacokinetic analysis in that study showed that both schedules produced very similar overall drug exposure (as measured by AUC), but that the divided-dose schedule produced twice the duration of exposure to a plasma concentration of >1 mg/L of etoposide. This observation was consistent with the preclinical data, and the authors speculated that exposure to a serum concentration of at least 1 mg/L was important in achieving clinical efficacy, while exposure to higher serum concentrations augmented drug toxicity.

The selection of a serum concentration of 1 mg/L as the critical serum concentration necessary to achieve antitumour efficacy was largely empirical, but has provided a convenient benchmark in the pharmacokinetic analysis of extended oral etoposide regimens. In actuality, the threshold serum concentration required for antitumour efficacy is probably different for each tumour type, and may also vary with the length of tumour exposure to etoposide, as observed in preclinical trials. When an extended schedule of etoposide is used, a 100mg daily dose produces maximum serum concentrations of 2 to 7 mg/L, and an exposure to serum concentrations of >1 mg/L for approximately 6 to 10 hours.[19] Therefore, patients receiving daily doses of 50 mg/m^2 generally achieve effective serum concentrations of etoposide for a substantial portion of the duration of treatment. Daily doses of 50mg do not consistently produce serum concentrations of 1.0 mg/L. In small cell lung cancer, tumour responses have been achieved with schedules using only 50mg daily, but the time to achieve

response, the response duration, and the response rate have been decreased compared with regimens using 50 mg/m^2 daily.[20] Therefore, the empirically determined serum etoposide concentration of 1 mg/L seems clinically useful, and etoposide regimens providing some daily exposure to this concentration are probably optimal. On this basis, the 50 mg/m^2 dose seems a reasonable daily dose for long term oral administration. Since oral etoposide is available in 50mg capsules, the actual dose administered to most patients receiving 50 mg/m^2 is either 100mg daily, or 50mg alternating with 100mg daily.

2.2 Optimal Duration of Administration

The duration of administration of extended-schedule oral etoposide has varied more widely than has the dose administered. Schedules of 5, 10, 14, and 21 consecutive days have been investigated. In addition, results from continuous low dose oral or intravenous administration have been reported.[21] In our initial studies with extended-schedule oral etoposide, we arbitrarily chose a 21-day schedule of administration and escalated doses to a maximum tolerated dose.[22] Although a 50 mg/m^2 dose was tolerable as a single agent given for 21 days, myelosuppression was somewhat unpredictable with this regimen, and was severe in 20 to 50% of patients. In retrospect, pushing the dose to this level of toxicity was probably not the best strategy with this drug, since efficacy can be achieved with low serum concentrations. While the 21-day schedule using 50 mg/m^2/day remains popular in clinical trials, schedules of 7, 10, and 14 days have also been used successfully, with substantially less myelosuppression.[1,20]

Although definitive data regarding the comparative efficacy of these various schedules are lacking, the extent of myelosuppression with the 21-day schedule makes its use less desirable. Certainly, when developing combination regimens, the 21-day schedule cannot be combined effectively with other myelosuppressive agents. Our recent experience of combining full doses of paclitaxel and carboplatin with a 10-day schedule of oral etoposide demonstrates the feasibility of using a shorter, yet extended, schedule of etoposide with other myelosuppressive agents.[7,23] Recent evaluation of oral etoposide phosphate, in an attempt to reduce interpatient variability in absorption, showed no advantage when compared with oral etoposide.[24]

2.3 Current Clinical Use of Extended-Schedule Oral Etoposide

Although the role of extended-schedule etoposide in clinical oncology practice continues to evolve, several conclusions can be made on the basis of existing data. As a single agent, oral etoposide provides an additional effective and attractive option in the treatment of several indolent neoplasms, including low grade non-Hodgkin's lymphoma and Kaposi's sarcoma (both AIDS-related and endemic types).[1,2,11] In testicular cancer, results from administration of oral etoposide after surgical resection of residual carcinoma following second-line treatment suggested an improvement in relapse-free survival.[25]

In other malignancies, even though the extended schedule of etoposide has demonstrated efficacy, the impact has been relatively small because of the generally short duration of response. Only recently have tolerable combination regimens containing oral etoposide been developed. None of these regimens have used the 21-day schedule; rather, a 10- to 14-day schedule has been successfully adopted. The combination of paclitaxel, carboplatin, and oral etoposide has proven highly active in small cell lung cancer,[23] and has provided the most impressive results to date in the empirical treatment of carcinoma of unknown primary site.[7] We and others are currently evaluating this 3-drug regimen in the initial treatment of advanced ovarian cancer. Other unexplored areas where extended-schedule etoposide may add activity to combination regimens include lymphoma, leukaemia, breast cancer, several paediatric neoplasms, and a variety of neuroendocrine tumours. Continued clinical research is important in all of these tumour types.

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