Evolving Role of Oral Chemotherapy for the Treatment of Patients With Neoplasms

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In the past 20 years, there has been an increasing trend toward the use of oral chemotherapy for the treatment of patients with a variety of malignancies. There are several advantages of oral chemotherapy. The cost of treatment is usually far lower than that of intravenous administration, which also requires the presence of a physician and/or nurse in an office or hospital setting. Oral administration is more convenient for patients, permitting them to remain at home while taking their medications and eliminating the need for venous access.

The acceptance of oral chemotherapy has been limited by several actual or perceived problems. Some drugs have shown erratic gastrointestinal absorption when administered orally, leading to concern about adequate dosing. Poor patient compliance with a multiday oral regimen has been a potential problem. There has also been a perception by some physicians and patients that intravenous treatments are “stronger” and more effective than oral treatments.

The use of oral therapy for severe chronic disease is not new. For example, digitalis preparations and diuretics are commonly used to treat congestive heart failure, as are oral antiarrhythmic agents for cardiac arrhythmias, oral cytotoxic agents for severe rheumatologic disorders, and oral antibiotics for serious infections. Furthermore, hormonal agents, such as tamoxifen (Nolvadex), flutamide (Eulexin), and megestrol acetate (Megace), and antimetabolites such as hydroxyurea (Hydrea), which are available only in oral formulation, have proven both safe and efficacious therapy for cancer patients. Several other oral drugs have been proven useful and often equivalent to their intravenous formulations, and more data are now available concerning the bioavailability of these agents. Physicians are beginning to feel more confident about using oral therapy.

Several oral drugs are now routinely used in the treatment of cancer patients, and others are being investigated. This brief review will illustrate the variety of oral medications now used in clinical practice, provide a few specific examples of recent clinical results, and discuss some of the promising agents being developed.

Tables 1 and 2 show the classes of selected oral agents and examples of their use against several neoplasms. Some of these are considered standard therapy, such as procarbazine (Matulane) and prednisone as part of the MOPP regimen (mechlorethamine/vincristine/procarbazine/prednisone) for advanced Hodgkin’s disease, and melphalan (Alkeran) with prednisone for multiple myeloma.

**Etoposide**

Etoposide (VePesid) has proven useful for a broad spectrum of malignancies, including small-cell lung cancer, germ cell neoplasms, non-Hodgkin’s lymphoma, Hodgkin’s disease, and acute leukemia. Etoposide inhibits the activity of topoisomerase II, which regulates the replication of DNA.[1] Intracellular levels of topoisomerase II are substantially higher in proliferating cells, particularly during the G2 phase of the cell cycle, [2] making these cells more sensitive to the cytotoxic effects of etoposide. In addition, the binding of etoposide to topoisomerase II is reversible, suggesting that prolonged etoposide exposure enhances cytotoxicity.

The schedule dependency of etoposide has been demonstrated by several investigators. Preclinical studies with several animal tumors showed that frequent small doses or divided daily doses were superior to higher, less frequent doses.[3,4] Cavalli et al were the first to suggest the greater efficacy of etoposide in the treatment of small-cell lung cancer when the drug was ad- ministered orally for 3 days weekly compared with a 1-day intravenous schedule.[5] Slevin et al unequivocally demonstrated the importance of etoposide scheduling in a comparison of a
24-hour continuous infusion schedule (500 mg/m$^2$/d) versus daily infusion for 5 days (100 mg/m$^2$/d) in patients with extensive stage small-cell lung cancer.[6] Response rates were 10% and 89%, respectively ($P < .001$). Survival of patients receiving the 5-day schedule was also significantly improved. Pharmacokinetic data from this study demonstrated that duration of exposure, rather than peak serum level or total exposure (as measured by plasma area under the curve [AUC]), was the most important determinant of the cytotoxicity of etoposide.[6] The authors speculated that a serum etoposide level of about 1 mg/µL was sufficient to achieve therapeutic efficacy.

**Extended Schedules of Oral Etoposide**

When Slevin’s scheduling studies were initiated, etoposide was available only as an intravenous agent. Prolonged administration schedules were therefore cumbersome and impractical. The introduction of an oral etoposide formulation facilitated further exploration of etoposide scheduling. In addition to the usual benefits of an oral agent (ie, greater ease of administration, reduced cost), the prolonged administration of etoposide offered the possibility of increased efficacy and/or reduced toxicity.

In 1989, my colleagues and I began a series of trials using extended schedules of oral etoposide. We empirically chose a 21-day schedule and demonstrated in a phase I study that a daily dose of 50 mg/m$^2$ was the maximum tolerated dose when given for 21 consecutive days.[7] Using this dose and schedule, etoposide serum levels > 1 mg/µL are maintained from 10 to 12 hours on each day of treatment.[8] Phase II trials using this 21-day schedule, as well as other prolonged oral schedules, have been reported in patients with several types of cancer.

In our initial phase II trial, 22 patients with recurrent or refractory small-cell lung cancer were treated with oral etoposide (50 mg/m$^2$/d × 21).[9] All patients had been previously treated with combination chemotherapy, and 18 of 22 had previously received intravenous etoposide given on 3- or 5-day divided dose schedules. The overall response rate with oral etoposide was 45%, and median duration of response was 4 months (range, 1.5 to 9.5 months). Patients were more likely to respond to oral etoposide if they had responded to initial induction therapy and had not received chemotherapy for more than 90 days prior to disease progression. Myelosuppression was the most common toxicity but was severe in only 19% of courses. The overall response rate observed with oral etoposide in this setting is higher than that reported with intravenous etoposide in recurrent small-cell lung cancer (10% to 15%), and is similar to results obtained with various combination chemotherapy regimens in this setting.

Extended-schedule oral etoposide has also been used as initial therapy for small-cell lung cancer. Clark and associates attempted to reduce toxicity by shortening the duration of administration, and demonstrated similar response rates (55% to 65%) using schedules of 10, 14, or 21 days’ duration.[10] Myelosuppression was reduced with the shorter schedules. This approach was particularly beneficial for small-cell lung cancer patients considered too elderly or medically unfit to receive intensive combination chemotherapy. Clark et al treated these patients with single-agent oral etoposide, 50 mg bid for 14 consecutive days, followed by a 1-week rest. The response rate was high, and median survival was similar to that reported in some trials using combination regimens. Thus, extended-schedule oral etoposide, alone or in combination with other drugs, offers a viable and well-tolerated treatment option for elderly, unfit patients who have traditionally fared poorly when given treatment with intensive combination chemotherapy.

Based on the promising results achieved in the phase II study of small-cell lung cancer, we evaluated the efficacy and toxicity of the same 21-day regimen in 25 patients with previously untreated stage IIB or IV non-small-cell lung cancer.[11] Of 22 evaluable patients, 5 (23%) had partial responses and 6 had stabilization of disease. The median response duration was 5 months, and median survival of the entire group was 5 months (range, 1 to 19+ months). Severe myelosuppression occurred in only 6% of cycles. Two other phase II studies using identical schedules of oral etoposide in patients with previously untreated non-small-cell lung cancer have been reported; response rates were 7% and 46%, respectively.[12,13]

Etoposide is highly active for the treatment of lymphoma, and has demonstrated marked activity as a component of several salvage regimens. We investigated the same 21-day oral etoposide regimen as therapy for 25 patients with refractory lymphoma.[14] Patients had either non-Hodgkin’s lymphoma (indolent or aggressive histology) or Hodgkin’s disease, and were considered incurable, having failed previous standard multidrug treatment. Eighty-four percent of patients had received two or more previous chemotherapy regimens, and 36% of patients had previously received etoposide. Patient characteristics are shown in Table 3.

Overall, 15 patients (60%; 95% confidence interval, 41% to 77%) had partial responses, including 5 of 9 patients who had previously received intravenous etoposide. Median response duration was 8
months in patients with low-grade non-Hodgkin’s lymphoma and 3 months in those with intermediate or high-grade lymphoma (Table 4). One patient with large-cell lymphoma, included as a partial responder in our initial report eventually achieved a complete response after seven courses of oral etoposide and remains free of disease 5 years later. Myelosuppression was again the major treatment-related toxicity; however, most patients who developed severe myelosuppression were able to continue with subsequent courses when the etoposide dose was reduced by 25%. Other side effects were rare, with the exception of total alopecia.

Interestingly, two patients who had experienced disease progression during or immediately following treatment with combination regimens containing intravenous etoposide had clinically significant, immediate responses to oral etoposide. This finding provides direct evidence that the increased cytotoxicity produced by extending the duration of etoposide exposure can be clinically important in some patients.

Table 5 summarizes results of phase II published studies of extended-schedule oral etoposide in several types of cancer. These results demonstrate the activity of extended-schedule oral etoposide in a variety of refractory malignancies. [9-24] Of particular interest are the results in breast and ovarian cancer, where consistent activity was seen in refractory patients.[15-19] Intravenous etoposide given according to the standard schedule has been considered relatively inactive in both of these malignancies.

A novel and potentially important use of extended-schedule etoposide was recently reported by Cooper and Einhorn.[25] Patients with refractory germ cell tumors completing salvage therapy, either with high-dose or standard-dose regimens, received daily oral etoposide, 50 mg/m² for 21 days every 4 weeks for three courses. Of 23 patients (74%) who began oral etoposide therapy while in complete remission, 17 (74%) remain disease-free with a median follow-up of 36 months. Maintenance therapy with oral etoposide decreased relapse rates as compared with previous Indiana University data, which indicated that approximately 50% of patients relapsed after achieving a complete remission following various salvage regimens without maintenance therapy.

As is evident in Table 5, most phase II trials of extended-schedule oral etoposide have used the originally defined 21-day regimen with the “maximally tolerated dose” of 50 mg/m²/d. Although this regimen has proven to be generally tolerable, myelosuppression has been the major toxicity in all of the trials and is severe in 10% to 20% of patients. Patients who have poor performance status, coexistent medical illnesses, or have received extensive previous chemotherapy are more susceptible to this toxicity. Myelosuppression can be substantially reduced by either lowering the daily etoposide dose or shortening the administration schedule. Limited data suggest that cytotoxicity is preserved with either approach, although the relative efficacy of the various schedules is unclear.

**Combination Regimens Containing Extended-Schedule Etoposide**

Recently, increased emphasis has been placed on incorporating extended schedules of etoposide into combination chemotherapy regimens. Most reported phase II trials have involved lung cancer patients, and have evaluated oral etoposide combined with either cisplatin (Platinol) or carboplatin (Paraplatin).[26-28] In all of these trials, oral etoposide was well tolerated and efficacy results were comparable to those achieved with similar combinations using a standard schedule of intravenous etoposide. The Hoosier Oncology Group reported results of a phase II study using oral etoposide (37.5 mg/m²/d for 21 days) in combination with ifosfamide (1.2 g/m²/d for 4 days) and cisplatin (20 mg/m²/d for 4 days) in patients with recurrent small-cell lung cancer.[29] Although this regimen was highly active, producing a 55% response rate and a 7-month median survival, myelosuppression was severe in these previously treated patients.

To date, only one randomized study has specifically addressed whether an extended schedule of etoposide is superior to that of the standard schedule when used in a combination regimen. The Cancer and Leukemia Group B (CALGB) randomized 319 patients with extensive stage small-cell lung cancer to receive cisplatin and intravenous etoposide for 3 days versus cisplatin and oral etoposide, the latter administered for 21 days.[28] No differences in response rates or median survival were demonstrated. Myelosuppression was more severe with the 21-day schedule of oral etoposide than with the standard intravenous schedule. Based on data now available from single-agent trials, it seems likely that a shorter (eg, 10- to 14-day) etoposide schedule would have produced less myelosuppression without compromising efficacy.

**Extended-Schedule Oral Etoposide Regimens for Elderly Patients**

Extended-schedule oral etoposide has been incorporated into several regimens designed specifically for elderly patients. The Southwest Oncology Group used a combination of oral etoposide (50 mg/m²/d for 14 days) and oral cyclophosphamide (50 mg/m²/d for 14 days) every 28 days in patients...
with stage IV non-small-cell lung cancer.[30] Although the overall objective response rate was only 12%, the median survival was 6 months, and the 1-year survival rate was 26%, comparable to that achieved with more intensive cisplatin-based combination regimens. This regimen is also being investigated in elderly patients with small-cell lung cancer.

Another “all-oral” regimen using oral etoposide (50 mg/m²/day for 21 days) and estramustine (Emcyt; 15 mg/kg/d for 21 days) has recently been reported in patients with hormone-refractory prostate cancer.[31] Nine of 18 men with measurable disease had an objective response to therapy, and 19 of 24 patients with bone only involvement had prostate-specific antigen decreases of more than 50%. Severe myelosuppression was surprisingly infrequent with this regimen; however, most patients had good performance status and had not previously received chemotherapy. Our group recently reported results of a combination first-line regimen for elderly (median age, 71 years) patients with aggressive non-Hodgkin’s lymphoma.[32] Patients received oral etoposide 50 mg/m²/d for 21 days in combination with other agents, as outlined in Table 6. Among 31 large-cell lymphoma patients, the complete response rate was 64%, and the progression-free survival of the entire group was 47% after a median of 28 months’ follow-up. Treatment was well tolerated, with no treatment-related deaths. These results compare favorably with those of other regimens for elderly lymphoma patients, and toxicity was substantially decreased, as compared with previous reports of standard regimens.

**Summary and Practical Guidelines for Use of Extended-Schedule Oral Etoposide**

A large amount of clinical data now indicate that extended-schedule oral etoposide has equivalent or superior efficacy compared with standard intravenous etoposide regimens. Other than alopecia, the major toxicity is myelosuppression, the extent of which is markedly influenced by patient performance status and extent of previous treatment. Myelosuppression with our original regimen (50 mg/m²/d for 21 days) seems similar to that produced by standard intravenous etoposide schedules; however, reducing the daily dose or the number of days of treatment clearly reduces myelosuppression. The etoposide dose and treatment duration required to produce maximum cytotoxic effect is undefined but probably requires less than the “maximally tolerated dose” of 50 mg/m² for 21 days.

When extended-schedule oral etoposide is used, several guidelines should be followed to minimize problems resulting from myelosuppression. First, weekly blood counts should be monitored. Because the nadir blood counts always occur several days after administration of the last dose, oral etoposide should be discontinued if the neutrophil count falls below 2,000/µL. Oral etoposide should not be resumed until the neutrophil count recovers to greater than 4,000/µL. If severe neutropenia occurs, or if treatment must be discontinued before completion of the desired number of days, a 25% dose reduction during subsequent courses usually avoids further problems. Treatment of extremely poor performance status patients should probably be avoided, because severe myelosuppression is common in this group.

Clinical indications for extended schedule etoposide are listed in Table 7. It is likely that additional uses will be defined once results from ongoing trials are available. In some situations (eg, indolent non-Hodgkin’s lymphoma), oral etoposide provides an additional treatment option. In others (eg, elderly patients with small-cell lung cancer) it is the best tolerated treatment option, and may be the only feasible effective therapy in some patients. In still other situations (eg, maintenance therapy following salvage treatment for germ cell tumors), treatment with oral etoposide may actually improve the cure rate. Its use in combination regimens is less well defined; however, if initial results are confirmed, regimens containing oral etoposide may provide valuable alternatives in elderly patients with lymphoma, lung cancer, and prostate cancer.

**Cyclophosphamide**

Cyclophosphamide (Cytoxan, Neosar) has demonstrated activity against a broad spectrum of malignancies, including Hodgkin’s disease, non-Hodgkin’s lymphoma, chronic lymphocytic leukemia, and breast, ovarian, lung, endometrial, cervical, and prostate cancers. Cyclophosphamide is currently used almost exclusively as a constituent of combination chemotherapy, primarily via parenteral administration. However, the oral formulation is highly bioavailable, with doses approximately equivalent to the intravenous formulation. Some of the clinical settings in which oral cyclophosphamide is used are described below. Perhaps the most notable use of oral cyclophosphamide has been as adjuvant treatment for node-positive patients with primary breast cancer. Cyclophosphamide/methotrexate/5-fluouracil, or CMF, continues to be used widely. Cyclophosphamide (100 mg/m²/d) is given orally for 14
consecutive days of each 28-day cycle. A 15-year analysis of data from the first randomized trial comparing adjuvant CMF to observation demonstrated significant benefits in both disease-free and overall survival in premenopausal, node-positive women.[33] To date, no other chemotherapy regimen has provided better survival rates than CMF, which many oncologists prefer for first-line treatment.

Another popular combination chemotherapy program using oral cyclophosphamide is the “Cooper” regimen.[34] This therapy was originally developed for patients with metastatic disease but has also been evaluated in the adjuvant setting. Although modified over the years, the original regimen is still used, and contains oral cyclophosphamide given on a chronic daily schedule with oral intermittent prednisone and intravenous methotrexate, vincristine (Oncovin), and 5-fluorouracil (CMFVP). There is no definitive answer as to the comparative merits of CMF versus CMFVP, although the five-drug program appears to compare favorably with CMF.[34]

Oral cyclophosphamide has for many years been standard treatment used alone or in combination regimens for patients with low-grade non-Hodgkin’s lymphoma. Single-agent oral cyclophosphamide (1.5 to 2.5mg/kg/d) is commonly used. The dose is tailored to maintain a white blood cell count of greater than 3,000/µL and a platelet count greater than 100,000/µL. The classic CVP regimen utilizes a combination of oral cyclophosphamide and prednisone daily for 5 days with intravenous vincristine on day 1, with cycles repeated every 21 days for several courses.

The Cancer and Leukemia Group B (CALGB) recently conducted a phase II pilot study of the combination of recombinant interferon-alfa-2b (Intron A) and oral cyclophosphamide in the treatment of patients with stage III/IV follicular lymphoma.[35] The overall response rate was 86% for patients who had not received previous chemotherapy and 62% for those who had. Survival at 5 years is estimated to be 63% and 39%, respectively, for the two patient groups. The primary toxicity was myelosuppression, with severe thrombocytopenia and anemia seen in 6% and 31% of patients, respectively. Although it had been hoped that the addition of interferon-alfa to oral cyclophosphamide would produce synergistic antitumor activity, the response rates were similar to those achieved in a previous CALGB trial of single-agent oral cyclophosphamide. Randomized comparative studies of this combination and single-agent cyclophosphamide are under way. As discussed earlier, oral cyclophosphamide has been combined with oral etoposide for the treatment of lung cancer, with good tolerability and survival results similar to those achieved with more intensive regimens.

Several other oral agents have been used in different malignancies (see Table 1); notable examples include tamoxifen (Nolvadex), megestrol acetate (Megace), flutamide (Eulexin), melphalan (Alkeran), and hydroxyurea (Hydrea).

### New Agents

The economic and practical aspects of oral chemotherapy have spurred development of several new oral equivalents of intravenous formulations, as well as new oral compounds (see Table 1). An example of a new oral platinum compound undergoing clinical study is J-M-216. Oral taxanes have been developed and will soon be studied in patients. Vinorelbine (Navelbine), topotecan (Hycamtin), and CPT-11 (irinotecan [Camptosar]) have oral equivalents and plans are under way for clinical investigations.

An area of active investigation includes oral fluorinated pyrimidines and other drugs, which modify their metabolism when used together. Uracil plus flotarafur (UFT) has been combined with oral leucovorin and compared with intravenous 5-fluorouracil plus leucovorin. Results of previous phase II trials suggest equivalence, and phase III results are awaited. Capecitabine (Xeloda), a new oral agent, and prodrug of 5-fluorouracil, is also under active study. Another approach has been to modify the metabolism of 5-fluorouracil, as typified by the dihydropyrimidine dehydrogenase inactivator GW776C85. Initial clinical data with the combination of 5-fluorouracil and GW776C85 indicate that antitumor activity is increased in some neoplasms, compared with results using 5-fluorouracil alone. Several phase II trials are complete, and phase III studies will begin soon. It is likely that one of these oral approaches using 5-fluorouracil with a biochemical modulator will be at least as effective as, or more effective than, standard 5-fluorouracil plus leucovorin, and with better tolerability.

### Conclusions

Various forms of oral chemotherapy are now available, and many of these agents are integral components of standard therapy for patients with a variety of neoplasms. The advantages of oral
therapy favor the continued study of these agents. In addition, several new and promising oral agents are likely to be introduced into clinical practice in the next few years. In the future, it is likely that oral combination chemotherapy will be an accepted and standard approach for the treatment of patients with many cancers.

**Discussion**

**Dr. Weeks:** Because oncologists realize that their patients derive substantial benefits from intravenous chemotherapy, do you think that physicians will be reluctant to replace intravenous with oral therapies?

**Dr. Greco:** Over the short term, that may be true. This is probably not a major issue in most of the socialized countries in the world, where medicine is under direct government control. But in the United States and other countries where oncologists control the use of the majority of chemotherapy, this is an issue. Once physicians realize, however, that oral medications are as effective as their intravenous counterparts, many will want to prescribe them because they genuinely want the best therapy for their patients. It is not strictly an economic issue.

**Dr. Weeks:** Has the efficacy of intravenous versus oral drugs been compared in clinical trials, and if so, what have those studies shown?

**Dr. Greco:** Several such studies have been conducted. An oral regimen consisting of the fluorinated pyrimidine compound UFT and leucovorin was compared directly with 5-fluorouracil and leucovorin in patients with metastatic colorectal cancer. A large phase III trial is now being completed, and final results are awaited. Oral etoposide has been compared with the intravenous preparation in several studies involving small-cell lung cancer patients, and efficacy was comparable with the two formulations. These are only two examples of the several studies that have been done.

**References:**


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