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Oral Etoposide in Germ Cell Tumours

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Abstract

Patients with germ cell tumours who relapse or fail to achieve disease-free status after first-line chemotherapy have a poor prognosis. When administered orally, etoposide produces responses in approximately 25% of patients whose disease is refractory to therapy and is a reasonable choice for palliative treatment in patients who are otherwise incurable. Oral etoposide has also been studied as maintenance therapy in patients who have been treated with salvage chemotherapy or surgery, with results that compare favourably with historical data. We recommend 3 months of maintenance oral etoposide for patients who achieve a complete response to any type of salvage therapy.

Testicular cancer is a rare disease, accounting for less than 1% of all cancers in males in the US.[1] However, testicular cancer is an important disease in oncology for several reasons. First, testicular cancer is the most common solid tumour in males aged 15 to 35 years, so the potential for years of life lost greatly exceeds that of malignancies occurring in elderly populations. Secondly, therapy of testicular cancer has demonstrated the importance of a multidisciplinary approach to patients with cancer. Depending on cancer stage and histology, the surgeon, medical oncologist, and radiation oncologist all have critical roles in the care of these patients. Lastly, testicular cancer has become a model for a curable neoplasm. Cisplatin-based chemotherapy can cure approximately 80% of patients with disseminated testicular cancer, and nearly 100% of patients with early-stage disease. This achievement is particularly remarkable when compared with the pre-cisplatin era, in which fewer than 10% of patients with disseminated disease had long term disease-free survival.[2]

Patients with germ cell tumours who relapse or fail to achieve disease-free status after first-line chemotherapy have a poor prognosis. Cisplatin-based salvage therapies or high dose chemotherapy with either autologous bone marrow transplantation (ABMT) or peripheral stem cell rescue result in an overall long term survival of approximately 30%.[3,4] Patients who are not cured after salvage therapy have an extremely poor prognosis and become eligible for investigational studies with novel phase I or II agents.

Etoposide (VP-16) is an inhibitor of topoisomerase II with demonstrated single agent activity in a variety of tumour types, including lymphoma and small cell lung cancer. In 1977, etoposide was reported to be the first drug with single agent activity in patients with testicular cancer refractory to standard cisplatin-based chemotherapy.[5] In preclinical and clinical studies, etoposide has been shown to be a schedule-dependent drug. Slevin et al. reported a trial in which 40 patients with extensive small cell lung cancer were randomly assigned to receive either etoposide 500 mg/m^2 as an intravenous 24-hour infusion every 3 weeks or 100 mg/m^2 intravenously for 5 consecutive days every 3 weeks.[6] The daily administration schedule produced a higher response rate (78 *vs* 10%,

$p < 0.0001$) as well as a longer median survival time (10 *vs* 6 months, $p = 0.03$).

Because of etoposide's mechanism of action as an enzyme inhibitor and the clinical data demonstrating its schedule dependency, it is thought that prolonged tumour exposure may enhance tumour cell kill. The availability of oral etoposide offers the opportunity to test this hypothesis. Use of daily oral etoposide has been tested in 2 populations of patients with germ cell tumours. The purpose of this article is to review the activity of oral etoposide in refractory germ cell tumours and to discuss the role of maintenance daily oral etoposide following salvage therapy.

1. Oral Etoposide in Refractory Germ Cell Tumours

In 1981, the European Organization for Research and Treatment of Cancer published the results of a phase II trial that included 30 evaluable patients with advanced, refractory non-seminomatous testicular cancer.[7] All but one of the patients had received 2 or more combination chemotherapy regimens, and two-thirds of the patients had also received prior radiotherapy. Oral etoposide was given as a liquid (diluted in orange juice) at a dosage of 175 mg/m^2 daily for 3 consecutive days in weekly courses for at least 6 weeks, or until disease progression. Six of the patients (20%) achieved a partial remission, all but one within 4 weeks of starting therapy. The median duration of response was 3.5 months (range: 2.0 to 4.5 months). Leucopenia was the major toxicity, requiring postponement or reduction of 55% of the scheduled courses. Other haematological toxicities were less common, with only 3 patients having grade 3 or 4 thrombocytopenia.

In 1990, investigators at Indiana University reported the results of a phase II trial of daily oral etoposide in 22 patients with refractory germ cell tumours.[8] All patients had received at least one prior treatment with cisplatin-based combination chemotherapy, which included intravenous etoposide. In 36% of the patients, disease had progressed during cisplatin-based chemotherapy, and in 30% the tumours were refractory to intravenous etoposide given according to the standard schedule. Six patients had been previously treated with high dose carboplatin and etoposide with ABMT. Patients were given oral etoposide (in capsule form) at a daily dose of 50 mg/m^2, rounded to the nearest 25mg. Blood counts were checked weekly during the first 6 weeks and every 3 weeks thereafter. Etoposide was continued until tumour progression or for a maximum of 6 months of therapy.

Of the 21 patients evaluable for response, 3 (14%) had a partial response and 3 additional patients had radiographically stable disease with a reduction in their serum markers of more than 90%. An additional 8 patients had stable disease for a minimum of 3 months. The overall median time until disease progression was 13.8 weeks (range: 5 to 38 weeks) and median survival time was 20.5 weeks (range: 8 to 48 weeks).

The primary toxicity observed was leucopenia. 52% of the patients required at least a 1-week delay in therapy and subsequent dose reduction because of grade 4 granulocytopenia. Overall, 7 patients developed febrile neutropenia, and 2 of these patients died of *Pneumocystis carinii* pneumonia. Anaemia was also common, with 9 patients requiring transfusion. Thrombocytopenia was mild: no patients developed grade 4 thrombocytopenia, and only 3 patients had platelet counts <50 000/μl. Nonhaematological toxicity was uncommon and included alopecia (29%), nausea (19%), and mucositis (14%).

2. Maintenance Chemotherapy with Oral Etoposide After Salvage Therapy

Because of the demonstrated activity of daily oral etoposide in patients with refractory germ cell tumours, investigators at Indiana University conducted a trial to evaluate the role of oral etoposide as maintenance therapy in patients who had attained either a complete response (CR) or a partial response (PR) to salvage therapy.[9] The purpose of this trial was to determine whether daily oral etoposide, given after salvage therapy, could lower

the relapse rate, prolong the duration of remission, and possibly convert patients from a PR to a CR. 34 evaluable patients were included in this study. All had been heavily pretreated, receiving a median of 2 prior salvage regimens. The salvage regimen that immediately preceded the administration of oral etoposide was ABMT in 14 patients (41%), standard-dose salvage chemotherapy in 10 patients (29%), and surgery in 10 patients (29%). Because of the significant myelosuppression seen in the previous phase II study, oral etoposide was given at a dose of 50 mg/m^2/day for 21 consecutive days, followed by a 7-day rest period; this regimen was repeated for a total of 3 cycles.

At the start of oral etoposide, 11 patients had achieved a PR and 23 patients were in CR. At the time of the report, 17 of the 23 patients (74%) in CR were still without evidence of recurrence, with a median follow-up time of 36 months (range: 26 to 49 months). Of the 11 patients in PR, 3 achieved a CR during etoposide therapy; however, all 3 have subsequently relapsed, at 4, 7, and 18 months from initiation of maintenance therapy.

These results compare favourably with historical data from the same institution. When a combination of vinblastine, ifosfamide, and cisplatin was given as initial salvage chemotherapy, 67 of 135 patients achieved no evidence of disease (NED) status; however, 33 of these 67 patients (49%) subsequently relapsed.[4] When a combination of cisplatin, ifosfamide, and either vinblastine or etoposide was used as third-line therapy, 20 of 56 patients (36%) achieved NED status, but 11 of the 20 patients (55%) subsequently relapsed.[10] Likewise, only 50% of patients who achieve NED status after ABMT and 33% of patients who achieve NED status after salvage surgery will remain continuously disease-free.[3,11]

The toxicity of this regimen was less than that observed with continuous administration. 25 of 34 patients (76%) completed all 3 cycles of therapy, with only 4 patients having to discontinue therapy because of toxicity (3 for prolonged neutropenia and 1 for mucositis). The remaining 5 patients did not complete 3 cycles because of progressive disease. Five patients had grade 3 or 4 leucopenia with 2 patients developing febrile neutropenia, including one who was found to have *P. carinii* pneumonia. Nonhaematological toxicities were also mild, with 2 patients having grade 3 mucositis.

3. Conclusions

When administered orally, etoposide can result in responses in patients whose disease is refractory to therapy. This makes it a reasonable choice for palliative treatment in patients who are otherwise incurable. Because of the toxicity seen with continuous administration, the preferred schedule is 50 mg/m^2/day for 3 weeks, followed by a week of rest to allow blood counts to recover. Determining the value of maintenance oral etoposide following salvage therapy will require a randomised trial. However, the results from Indiana University trials are encouraging and this therapy is well tolerated. We continue to recommend 3 months of maintenance oral etoposide for patients who have achieved a CR to any type of salvage therapy. It is interesting to speculate on the potential value of this method of etoposide administration as part of first-line therapy for patients with high risk disease. However, at this time no trials have been carried out, and it remains unknown whether this regimen would be superior to the standard 5-day administration schedule.

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