Single agent oral etoposide in recurrent or advanced solid tumors

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ABSTRACT

Prolonged oral etoposide has antitumor activity in a variety of solid tumors including small cell and non-small-cell lung cancer. A total of 53 patients have been treated with prolonged oral etoposide at a dosage of 50-100 mg/day for 5, 7, 10 or 14 days in a 21 days interval. The results of these patients were retrospectively evaluated. Twelve patients had small cell lung carcinoma (SCLC), 11 patients had non-small cell lung carcinoma (NSCLC) and 30 patients had different solid tumors including gastric, breast, ovarian and prostate carcinoma. Fifty-two patients were evaluated for response analysis. Objective response rate was found to be 19,2% (1,9% complete response (CR), 17,3% partial response (PR)). Stable disease was achieved in 30,8% of the patients. Grade 3 and 4 neutropenia occurred in 9,3% of the patients. We demonstrated a modest activity of single agent oral etoposide in our heterogenous group of patients with advanced and refractory disease. Oral etoposide may be a treatment choice for patients with refractory disease which there was no other alternative without supportive care. [Turk J Cancer 2003;33(4):187-190]

KEY WORDS:
Oral etoposide, solid tumors

INTRODUCTION

Etoposide is a semisynthetic epipodophyllotoxin that causes cytotoxic effects by the inhibition of topoisomerase II activity (1). Etoposide has been reported to have antitumor activity in a variety of tumor types including small cell and non-small cell lung carcinoma, ovarian, breast and germ cell tumors and squamous cell carcinoma of head and neck (2-7). Pharmacological studies indicated that oral administration of low dose etoposide for a prolonged period of time may be more effective than higher dose administration with periodic intravenous infusion (8). In clinical practice, prolonged oral etoposide has been reported to show antitumor response in traditionally etoposide-insensitive malignancies and in traditionally etoposide-sensitive malignancies which have already failed to prior bolus etoposide (3, 9-15). Oral etoposide has been tested in many solid and hematological tumors and found to have an activity in small cell carcinoma of the lung (SCLC), non-small cell carcinoma of the lung (NSCLC), ovarian, prostate, germ cell and breast tumors and lymphoma (3, 9-14). Beside its efficacy, it has also several advantages in clinical practice of physicians such as its ease administration, comparatively lower cost and more favourable toxicity profile (16).

In this retrospective study, we analysed the results of patients with different solid tumors treated with single agent oral etoposide.
MATERIALS AND METHODS

From June 1999 to February 2003, a total of 53 patients have been treated with prolonged oral etoposide in our center. The results were retrospectively evaluated. Twelve patients had SCLC, 11 patients had NSCLC and 30 patients had other malignancies including ovarian, gastric, breast and prostate carcinoma. Characteristics of patients are shown in tables 1 and 2. Oral etoposide was given as a single agent in 51 patients and combined with estramustine in 2 patients with prostate cancer. The schedule of therapy was not standard in these patients. According to performance status of the patients, oral etoposide was given at a dosage of 50-100 mg/day for 5, 7, 10 or 14 days in a 21 days interval. Dosage modification was based on Day 21 granulocyte count of preceding cycle. Dose escalation for subsequent courses was prescribed for patients experiencing no toxicity. Therapy was continued unless interrupted by tumor progression or unacceptable toxicity. Response to therapy was evaluated every cycle. Responders were defined as complete response (CR, disappearance of assessable disease) or partial response (PR, reduction of more than 50% of the lesion of the two largest tumor diameter). Stable disease (SD) meant less than 25% increase in tumor size. Progressive disease (PD) was defined by an increase of more than 25% in tumor size. Response duration in responding patients was measured from the first day of the chemotherapy to the first documentation of recurrence or progression.

RESULTS

Fifty-two patients were evaluated for response. Chemotherapy was stopped in one patient before completing the first cycle because of neutropenia. The mean number of etoposide course was 3.2 cycles (range: 1-20). Twenty-eight (52.8%) patients received one, 10 (18.9%) patients received two and 7 (13.2%) patients received three types of chemotherapy prior to oral etoposide. Eight (15.1%) patients had not been treated with any chemotherapy prior to oral etoposide. Eighteen (35.8%) patients received etoposide-containing regimens before oral etoposide (Table 1). At the time of oral etoposide treatment, 47 (88.6%) patients had metastatic, 2 (3.8%) had refractory disease and 4 (7.6%) had local recurrence (Table 2). Among 52 patients, there was one complete and 9 partial responses, for an overall response rate of 19.2%. Stable disease was the best response in 16 patients (30.8%). The remaining 26 (50%) patients had progressive disease. Details of these results are given in table 1. The mean response duration was 4.4 months (range: 2-10 months) in patients who had CR and PR. The mean duration of stable disease was 3.9 months (range: 1.5-18 months) in patients who had stable disease.

Severe neutropenia (WHO Grade 3 and 4) occurred in 5 (9.3%) patients. Two had neutropenic fever and one of them died of sepsis. Grade 1 and 2 neutropenia occurred in 5 (9.3%) patients. Three patients required blood transfusion during the treatment because of anemia. Only one patient had severe nausea. Total or partial alopecia was observed in 48 (90.5%) patients.

DISCUSSION

Etoposide is an agent with a wide spectrum of antitumor activity in many solid tumors. It has been reported to have an activity in SCLC and germ cell tumors as first line therapy and in NSCLC, ovarian, breast and gastric tumors as second line or salvage treatment (2-6, 17). Etoposide exerts its cytotoxic activity by stabilizing the formation of the DNA-topoisomerase-II complex that results in inhibition of rejoining and increased DNA scission (1). It causes double-strand DNA cleavage in cells that were entering mitosis and is less cytotoxic for resting cells (18,19). It has been reported that the antitumor effects of etoposide are highly related to schedule of etoposide and the duration of its exposure (20,21). It has been suggested that an extended tumor exposure to pharmacologically active etoposide levels and increased pharmacokinetic profile can be provided by prolonged etoposide (8,15). Previous studies have demonstrated an antitumor activity of oral etoposide both in etoposide insensitive and sensitive tumors (3, 9-15). These studies showed that prior treatment with intravenous etoposide did not affect the likelihood of response to prolonged oral etoposide.

In our center, single agent oral etoposide has been used for the palliative treatment of patients with solid tumors who failed to conventional treatment or could not tolerate aggressive chemotherapy because of their poor performance status. In different studies with single agent oral etoposide, response rate was found 45.5% in small cell carcinoma of the lung (SCLC), 23% in non-small cell carcinoma of the lung (NSCLC), 6% in ovary, 9% in prostate, 18.8% in germ
Our study included patients with various solid tumors. The objective response rate was 19.2% (1.9% CR, 17.3% PR). One patient achieved a CR after therapy, and his disease was a mediastinal germ cell tumor. The ratio of stable disease was 30.8%. In patients with SCLC (n=12), only one patient achieved a PR response. No response was observed in patients with NSCLC (n=11). This relatively lower response rates observed in our heterogenous group of solid tumors may be related with the dosage of oral etoposide used in this study. The maximum tolerated dose of oral etoposide was determined to be 50 mg/m$^2$/day for 21 days in a 28 day cycle in a variety of neoplasms and this schedule remains popular in clinical trials. The dosage of oral etoposide used in our study was generally lower compared with other studies. Adequate dose escalation could not be carried out, because of the poor performance status of the patients. Actually, in our clinic, we have usually selected oral etoposide for patients with refractory disease which there was no other alternative treatment without supportive care and this approach did not give us any possibility for dose escalation in many patients. Among the patients, 45 (84.9%) had received prior chemotherapy and 19 (35.8%) had received prior etoposide containing regimen. These may have also reduced response rate of our study.

Adverse effects were generally mild in our study. Most common toxicity was alopecia and observed in 90.5% of patients. Hematologic toxicity was not higher in our study when compared to the other studies. In previous reports,

### Table 1
Patient details and diagnosis

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>n</th>
<th>Number of prior chemotherapy</th>
<th>Prior etoposide</th>
<th>Responses (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>No 1 2 3</td>
<td>Yes No</td>
<td>CR PR SD PD OR</td>
</tr>
<tr>
<td>SCLC</td>
<td>12</td>
<td>2 7 2 1</td>
<td>10 2</td>
<td>0 (0) 1 (8.3) 3 (25) 8 (66.7) 1 (8.3)</td>
</tr>
<tr>
<td>NSCLC*</td>
<td>11</td>
<td>1 8 1 1</td>
<td>1 10</td>
<td>0 (0) 0 (0) 4 (36.3) 6 (63.7) 0 (0)</td>
</tr>
<tr>
<td>Others**</td>
<td>30</td>
<td>5 13 7 5</td>
<td>8 22</td>
<td>1 (3.3) 8 (26.7) 9 (30) 12 (40) 9 (30)</td>
</tr>
<tr>
<td>TOTAL*</td>
<td>53</td>
<td>8 28 10 7</td>
<td>19 34</td>
<td>1 (1.9) 9 (27.3) 16 (50.8) 26 (50) 10 (19.2)</td>
</tr>
</tbody>
</table>

OR: Overall response (CR+PR)

*One patient was not evaluable for response

**Ovarian (n=4), Sarcoma (n=4), Gastric (n=3), Breast (n=3), Prostate (n=3), Endometrium (n=2), Pancreas (n=2), Cervix (n=1), Nasopharynx (n=1), Melanoma (n=1), Bladder (n=1), Testicular (n=1), Germ cell (n=1), Medulloblastoma (n=1), Colon (n=1), Colon (n=1) and Thyroid (n=1) carcinoma

### Table 2
Characteristics of patients

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>n</th>
<th>Median age (yr) (range)</th>
<th>Gender (F/M)</th>
<th>Disease status (%)</th>
<th>Metastatic</th>
<th>Local relapse</th>
<th>Refractory</th>
</tr>
</thead>
<tbody>
<tr>
<td>SCLC</td>
<td>12</td>
<td>58.5 (35-72)</td>
<td>2/10</td>
<td>9 (75)</td>
<td>2 (16.6)</td>
<td>1 (8.4)</td>
<td></td>
</tr>
<tr>
<td>NSCLC</td>
<td>11</td>
<td>64.0 (43-71)</td>
<td>4/7</td>
<td>9 (81.8)</td>
<td>1 (9.1)</td>
<td>1 (9.1)</td>
<td></td>
</tr>
<tr>
<td>Other patients</td>
<td>30</td>
<td>51.0 (21-67)</td>
<td>18/12</td>
<td>29 (96.6)</td>
<td>1 (3.4)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>53</td>
<td>55.0 (21-72)</td>
<td>24/29</td>
<td>47 (88.6)</td>
<td>4 (7.6)</td>
<td>2 (3.8)</td>
<td></td>
</tr>
</tbody>
</table>
the ratio of grade 4 leucopenia has been reported to occur between 16-28% (9,11,13). In our study, severe neutropenia occurred in 5 patients (9.3%) patients. Two had neutropenic fever and one of them died of sepsis.

An association between acute myeloid leukemias and etoposide therapy has been reported in many studies (22,23). These leukemias are generally found to be related with cumulative dose of etoposide. However, leukemia was not diagnosed in our patients. This isn’t surprising because survival was very short in these patients and only few of them could receive ten or more cycles of etoposide.

In conclusion, we observed that single agent etoposide has modest activity and relatively mild toxicity in our patients. As the patients included in this study had very short survival expectancy and therefore were not considered to tolerate aggressive chemotherapy, this response rate should not be regarded as too little. Together with the importance of its lower cost especially for the countries with limited resources, we suggest that it can be used as an alternative of more aggressive chemotherapy or supportive care in selected patients with advanced and refractory cancer.

References