Use of a topoisomerase I inhibitor (irinotecan, CPT-11) in metastatic adrenocortical carcinoma

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Background: Complete responses are rare after medical treatment of adrenocortical tumors. We performed a single center prospective study of the antitumor effect of irinotecan (CPT-11) in patients with metastatic adrenocortical cancer.

Patients and methods: Since 1999, all patients with advanced progressive adrenocortical carcinoma, referred to the Institut Gustave-Roussy, have been enrolled prospectively in this study. CPT-11 (250 mg/m²) was administered intravenously on day 1 in a 2-h infusion, every 14 days. World Health Organization (WHO) criteria were used to evaluate tumor response and toxicity.

Results: During treatment, no dose or schedule modifications were made. A median of three courses were given (range 1–8), and all but two patients received at least three complete chemotherapy courses. No objective or complete responses were observed. The best response achieved was stabilization in three patients, lasting from 1.5 to 4 months. Significant toxicity occurred in two patients.

Conclusions: Our results do not support a major role of CPT-11 in adrenocortical carcinoma.

Key words: adrenocortical carcinoma, chemotherapy, CPT-11, irinotecan

Introduction

Adrenocortical carcinoma (ACC) is a rare tumor with a 10–60% overall survival rate at 5 years [1–10]. Stage at initial diagnosis is the main prognostic parameter in ACC patient overall survival. In patients presenting with localized ACC, surgery remains the only curative therapeutic option; however, in 21–36% of ACC patients [6–9], distant metastases are present at the time of initial diagnosis, and are associated with an overall 5-year survival rate of 0–10%. In metastatic ACC patients, objective tumor responses have been reported with 1,1-dichlorodiphenildichloroethane (o,p’DDD) and/or cisplatinum-based chemotherapy, but few complete responses have been achieved and the impact on survival remains in question [11–17]. Until now, o,p’DDD was considered the most efficacious agent in treating ACC patients especially when its plasma levels exceeded 14 mg/l [16–19]. Recently, we confirmed in a prospective study the prognostic impact of plasma o,p’DDD monitoring with an objective response rate attaining 66% when o,p’DDD levels exceeded the cut-off level of 14 mg/l, and no response when they were below this level [19]. However, all patients who experienced a tumor response relapsed, underlying the need to develop new alternative therapies.

Efforts to test new cytotoxic agents in ACC are limited due to the rarity of the disease, and, to our knowledge, investigational studies on new agents such as taxanes and topoisomerase I inhibitors have not been reported in these patients. In order to rationalize our therapeutic approach we screened a large panel of cytotoxins in a human tumor cell line, H295, derived from an invasive secreting primary adrenocortical carcinoma [20]. Preliminary results showed that a topoisomerase I inhibitor, SN38 (the active metabolite of irinotecan; CPT-11) was able to achieve a higher IC₅₀ (IC₅₀ <1 µM) than the reference drug, cisplatin.

This result prompted us to carry out a single center prospective study in patients with metastatic ACC referred to the Institut Gustave-Roussy in order to investigate the antitumor activity and toxicity of CPT-11.

Patients and methods

Since October 1999, 12 patients with progressive metastatic ACC, followed up at the Institut Gustave-Roussy Institute, have been enrolled in this study. There were five males and seven females with a median age of 35 years (range 24–74) and secretory activity was demonstrated in nine of them. All histopathological diagnoses were reviewed by a single pathologist (B. Caillou, Institut Gustave-Roussy, Villejuif). Patient characteristics are detailed in Table 1. In all but one patient, previous therapy...
<table>
<thead>
<tr>
<th>Age (years)/sex</th>
<th>Hormonal production</th>
<th>Surgery/local relapse</th>
<th>Time since CPT-11 initiation (months)</th>
<th>Previous therapies</th>
<th>Metastases</th>
<th>No. of courses</th>
<th>Tumor response [duration (months)]</th>
<th>Side effects (grade)</th>
<th>Survival since diagnosis (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1–28/F</td>
<td>DOC, S</td>
<td>+/yes</td>
<td>10</td>
<td>o,p’DDD</td>
<td>Lung</td>
<td>3</td>
<td>PD</td>
<td>Nausea (1), asthenia (1)</td>
<td>AWD (33)</td>
</tr>
<tr>
<td>2–30/F</td>
<td>–</td>
<td>+/yes</td>
<td>0.5</td>
<td>o,p’DDD, etoposide–cisplatinum; 2 phase 1; liver chemoembolization</td>
<td>Liver, lung</td>
<td>1</td>
<td>PD</td>
<td>Nausea, vomiting (4), diarrhea (4), asthenia (4)</td>
<td>Dead (25)</td>
</tr>
<tr>
<td>3–45/F</td>
<td>Cortisol</td>
<td>+/no</td>
<td>3</td>
<td>o,p’DDD; etoposide–cisplatinum</td>
<td>Liver, lung</td>
<td>3</td>
<td>PD</td>
<td>Diarrhea (1)</td>
<td>Dead (34)</td>
</tr>
<tr>
<td>4–35/F</td>
<td>–</td>
<td>+/yes</td>
<td>4</td>
<td>o,p’DDD</td>
<td>Abdomen lymph nodes, peritoneum</td>
<td>3</td>
<td>PD</td>
<td>Nausea, vomiting (1), anemia (1)</td>
<td>Dead (8)</td>
</tr>
<tr>
<td>5–30/M</td>
<td>Cortisol, androgens</td>
<td>–/no</td>
<td>3.5</td>
<td>etoposide–cisplatinum</td>
<td>Liver, lung, bone, abdomen-pelvic lymph nodes</td>
<td>3</td>
<td>PD</td>
<td>Nausea, vomiting (1), diarrhea (1)</td>
<td>Dead (7)</td>
</tr>
<tr>
<td>6–57/F</td>
<td>Cortisol</td>
<td>+/no</td>
<td>4</td>
<td>o,p’DDD, etoposide–cisplatinum; liver chemoembolization</td>
<td>Liver, lung</td>
<td>2</td>
<td>PD</td>
<td>Diarrhea (1)</td>
<td>Dead (42)</td>
</tr>
<tr>
<td>7–24/F</td>
<td>–</td>
<td>+/yes</td>
<td>10</td>
<td>o,p’DDD; etoposide–cisplatinum</td>
<td>Liver, lung, peritoneum, bone</td>
<td>4</td>
<td>PD</td>
<td>Nausea, vomiting (1), asthenia (1), anemia (1)</td>
<td>AWD (39)</td>
</tr>
<tr>
<td>8–42/M</td>
<td>Cortisol</td>
<td>+/no</td>
<td>10</td>
<td>o,p’DDD, etoposide–cisplatinum; liver and bone chemoembolization; 5 fluorouracil–navelbine</td>
<td>Liver, lung, bone</td>
<td>8</td>
<td>S (4)</td>
<td>Nausea (1), asthenia (3), anemia (1)</td>
<td>Dead (54)</td>
</tr>
<tr>
<td>9–74/F</td>
<td>Cortisol, androgens</td>
<td>+/yes</td>
<td>7</td>
<td>o,p’DDD</td>
<td>No</td>
<td>3</td>
<td>PD</td>
<td>Diarrhea (1)</td>
<td>AWD (25)</td>
</tr>
<tr>
<td>10–40/M</td>
<td>DOC</td>
<td>+/no</td>
<td>3</td>
<td>o,p’DDD, doxorubicin-cyclophosphamid–cisplatinum</td>
<td>Liver, lung, pleura</td>
<td>3</td>
<td>PD</td>
<td>–</td>
<td>AWD (23)</td>
</tr>
<tr>
<td>11–34/M</td>
<td>DOC</td>
<td>–</td>
<td>9</td>
<td>o,p’DDD, etoposide-cisplatinum</td>
<td>Lung, abdomen lymph nodes</td>
<td>5</td>
<td>S (1.5)</td>
<td>Diarrhea (1)</td>
<td>AWD (40)</td>
</tr>
<tr>
<td>12–28/M</td>
<td>Androgens</td>
<td>–</td>
<td>12</td>
<td>o,p’DDD, etoposide-cisplatinum</td>
<td>Lung</td>
<td>6</td>
<td>S (1.5)</td>
<td>Asthenia (2)</td>
<td>Dead (59)</td>
</tr>
</tbody>
</table>

CPT-11, irinotecan; DOC, deoxycorticosterone; o,p’DDD, 1,1-dichlordiphenildichloroethane; S, stabilization; PD, progressive disease; AWD, alive with disease.
CPT-11 treatment was 5.5 months (range 0.5–12). The median follow-up since diagnosis was 34 months (range 7–59). At the end of study seven patients had died.

CPT-11 (250 mg/m²) was administered intravenously on day 1 in a 2-h infusion, every 14 days, as recommended [21]. In case of severe neutropenia (<1500/mm³) or thrombocytopenia (<100 000/mm³) or any other grade 3–4 side effects, except asthenia, treatment was delayed for 1 week and doses reduced by 30%. Therapy was continued until tumor progression or unresolved grade 3–4 toxicity. Appropriate anti-emetics were given.

As previously described [19], complete clinical, biological and morphological evaluations, including abdominal ultrasound and computerized tomography (CT), chest CT and bone scintigraphy, were performed every three courses or when clinical symptoms deteriorated or in case of unresolved grade 3–4 toxicity. Tumor response and toxicity were assessed according to WHO criteria. Complete response was evaluated from the date it was first documented to the date disease progression was first documented. Partial response and stabilization were evaluated from the first day of therapy to the date of disease progression.

All patients signed an informed consent form.

**Results**

All patients were evaluable for response. During treatment neither dose nor schedule was modified. A median number of three courses were administered (range 1–8) and all but two patients (patients 2 and 6) received at least three complete courses of chemotherapy.

No objective or complete responses were observed. The best response achieved was stabilization in three patients, lasting from 1.5 to 4 months. Progression was therefore observed at the first evaluation in nine patients. No clinical or biological responses were observed.

Treatment toxicities are given in Table 1. All but one patient experienced toxicity, which was usually mild. Significant toxicity consisting of digestive intolerance and asthenia occurred in two patients; the drug was discontinued in one patient, who then received CPT-11 as fifth-line chemotherapy and whose performance status was 3 at the initiation of the study (patient 2).

**Discussion**

Given that ACC is a very rare neoplasm, our results obtained in 12 patients treated consecutively with a new single drug are significant enough to be reported. The topoisomerase-I inhibitor CPT-11 is a new synthetic drug that is active in a variety of tumors including lung, gynecological and colorectal malignancies. In metastatic colorectal cancer, CPT-11 has been approved as first-line therapy [22]. These results, together with our experimental results on the H295 adrenocortical carcinoma cell line, prompted us to investigate its activity in ACC patients. Although less commonly used, the once-every-two-weekly CPT-11 regimen has been validated as an active alternative method of CPT-11 administration. A starting dose of CPT-11 250 mg/m² has been recommended [21].

No objective response was observed and only three short-lived stabilizations were achieved. One severe toxicity was observed in one ACC patient whose condition was poor at CPT-11 treatment initiation. These disappointing results do not support a major role for this new class of drug in ACC, even if CPT-11 was administered as at least a second-line chemotherapy in patients with aggressive ACC.

We conclude that CPT-11 does not exhibit significant activity in ACC, which signifies that other new therapeutic agents will have to be screened.

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**References**


