Phase II study of echinomycin in the treatment of renal cell carcinoma
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Summary

Seventeen patients were treated with echinomycin for metastatic renal cell carcinoma. Echinomycin is a bi-
functional DNA intercalating agent with broad preclinical antitumor activity. It was given at 1200 mg/m² by
intravenous infusion over 30–60 min weekly for 4 weeks. The treatment was repeated every 6 weeks. There
were no responses observed in the study. No life threatening or lethal toxicity was documented in 13 eligible
patients. The median survival of these patients was 13.7 months. We conclude that echinomycin is not active
against metastatic renal cell carcinoma at the dose and schedule tested.

Introduction

Metastatic renal cell carcinoma has been known to be notoriously refractory to chemotherapy. There
are very few chemotherapy drugs that have a response rate greater than 5% in this disease [1, 2].
Even the biological agents such as interferon or interleukin-2 have a response rate of about 20% [3,
4]. Since over 50% of the patients from the estimated 27,000 cases in 1994 will eventually end up
with metastatic disease, novel active agents are urgently needed for the treatment of this disease. The
Eastern Cooperative Oncology Group (ECOG) conducted a phase II study of echinomycin in patients
with metastatic renal cell carcinoma as part of an overall effort in identifying an active agent.

Echinomycin (NSC 526417) is a bi-functional DNA intercalating agent. It is a cyclic peptide
which is isolated from streptomyces echinatus and consists of two planar quinoxaline molecules con-
ected by an octapeptide bridge [5, 6]. It has been shown to inhibit the DNA and RNA syntheses and is
active in the preclinical screening. It is active against murine B16 melanoma, p388 leukemia, and rat hepatoma AH-130.

Materials and methods

Patient selection

In order to be eligible, patients had to have histo-
logical proof of renal cell carcinoma with disease
not amenable to cure by surgery or radiotherapy.
Patients also had to have measurable metastatic or
recurrent disease; no prior chemotherapy; ECOG
performance status 0, 1 or 2; a signed informed
consent; serum creatinine less than 2.0 mg/dl;
bilirubin less than 1.5 mg/dl; normal serum
 glutamate transaminoferase (SGOT) and normal
alkaline phosphatase. If the alkaline phosphatase
was abnormal, then the 5'-nucleotidase must have
been normal. Patients could have received prior
treatment with hormones or one biological re-

response modifier. Patients were not allowed to re-

response modifiers during treatment with echinomycin. Patients with clinical or radiographic evidence of central nervous system or hepatic metastases were ineligible as were patients with active infection. Patients were treated with echinomycin 1200 mg/m² by IV infusion over 30–60 min on days 1, 8, 15 and 22 every 42 days. The dose of echinomycin was determined based on hematological, hepatic and renal functions. Patients were treated at 100% dose if WBC > 2000/µl; platelet count > 75,000/µl; and normal SGOT, bilirubin, creatinine and BUN. Patients would receive 75% of the dose if WBC was between 1000 and 1999/µl or platelets between 50,000 and 74,999/µl. The same dose was given to patients if their SGOT was above normal but less than 2 × normal or bilirubin was between 1.6 to 2.0 mg/dl. The dose of echinomycin was reduced by 50% if the WBC was < 1000 µl, platelet count 50,000/µl, SGOT > 2 × normal, bilirubin between 2.1–2.5 mg/dl or creatinine between 1.6–2.4 mg/dl. Patients were evaluated weekly with brief histories and physical examinations, complete blood counts and serum chemistry studies. The tumor response was evaluated every 6 weeks with repeated tests of pre-treatment lesions.

Study design and statistical analysis

A two-stage sampling design was used in this study. Eighteen patients were to be entered during the first phase of the accrual. If one or more responses were observed, then an additional seventeen patients would be allowed to accrue to it. An agent was considered active if four or more responses were observed among the total 35 patients. With this design, the probability of stopping early was greater that 40% if an agent was inactive with a response rate < 5%, and less than 2% if it had significant anti-tumor activity with a response rate ≥ 20%. Similarly, the overall probability of rejecting an agent as an active drug was ≥ 0.91 if it was in fact inactive and ≤ 0.07 if it was active. Patients with liver metastases were excluded from this treatment due to concern of potential hepatic toxicities from echinomycin. Evaluation of response and toxicity were based on ECOG criteria [7]. Complete response indicates complete disappearance of all evident tumors for 4 weeks. A partial response is a decrease of at least 50% or more in the sum of all measurable tumor areas for 4 weeks. Stable disease indicates tumor response does not fit into response or progression for at least 4 weeks. Progression indicates development of any new lesion or > 25% increase in the indicator lesions.

Results

Response and survival

Seventeen patients were entered into this study. Four patients were deemed ineligible because one had elevated alkaline phosphatase; one had CNS metastatic disease; one had liver metastases and one had chronic active infection. The remaining 13 patients were evaluable for response, toxicity and survival. Their characteristics are shown in Table 1. There was no objective response in the 13 eligible patients or in the four ineligible patients. Therefore, the trial was stopped early. Survival was calculated from the date of registration to the date of death or the date last known to be alive. One patient was still alive at 48.5 months and 12 patients had died. The median survival for the 13 patients was 13.7 months.

Toxicity

There were no life-threatening or lethal toxicities encountered in any of the 13 patients. There were only two patients who experienced severe vomiting. All other toxicities were mild to moderate. Among the four ineligible patients, two patients had severe vomiting; one patient (with chronic active infection) suffered lethal respiratory toxicity and the other had no toxicity greater than grade 2.

Discussion

Echinomycin in the dose and schedule used in our study had no objective tumor response in the 13 eligible patients. The possibility that this agent might have a true response rate of 20% or greater is less than 10%. Echinomycin is well tolerated in the schedule used in our study. There were no lethal or