Phase I trial of capecitabine in combination with interferon alpha in patients with metastatic renal cancer: toxicity and pharmacokinetics

Abstract Purpose: The present study was designed to determine the toxicity and maximum tolerated doses of oral intermittent oral capecitabine and subcutaneous (s.c.) rHuIFNz2a in patients with metastatic renal cell carcinoma (RCC). The pharmacokinetics of capecitabine and its metabolites were also investigated. Methods: A total of 27 patients were treated at four dose levels of capecitabine (825 or 1000 mg/m² twice daily orally, days 1–14, 22–36) and rHuIFNz2a (1.5 or 3.0 MU/m² s.c. three times weekly). Unchanged capecitabine and its metabolites were analyzed in plasma using liquid chromatography/mass spectrometry in ten patients. Results: The toxicity of combined capecitabine and rHuIFNz2a was moderate. Patients experienced mild nausea/vomiting (70%) and diarrhea (63%). The hand-foot syndrome was seen in 67% of patients and was generally mild, as was hematologic toxicity. Dose-limiting toxicity included diarrhea, mucositis, neutropenia and the hand-foot syndrome. The dose level recommended for further trials included capecitabine 1000 mg/m² twice daily and rHuIFNz2a 3.0 MU/m² three times weekly. One patient had a partial response of a liver lesion (duration >200 days). Pharmacokinetic parameters of capecitabine and its metabolites (5’-deoxy-5-fluorouridine, 5-fluorouracil and z-fluoro-beta-alanine) were similar to those reported by other authors. There was rapid conversion to 5’-deoxyuridine. The peak plasma concentrations of capecitabine occurred between 0.5 and 3.0 h. Conclusions: The combination of capecitabine and rHuIFNz2a was well tolerated. The recommended dose levels for phase II trials are: rHuIFNz2a 3.0 MU/m² s.c. three times weekly and oral capecitabine 1000 mg/m² twice daily for 2 weeks. No evidence of an effect of rHuIFNz2a on the pharmacokinetics of capecitabine or its metabolites was apparent. A phase II trial in untreated patients with metastatic RCC is planned.

Keywords Capecitabine · Interferon · Renal cancer · Pharmacokinetics

Introduction

Renal cell carcinoma (RCC) is the seventh leading cause of cancer death in the United States [7], and accounts for 2–3% of all cancers in adults [13]. In patients with metastatic disease, therapy remains inadequate. This neoplasm is unresponsive to conventional cytotoxic chemotherapy regimens [17]. Previous reports have suggested, however, that 5-fluorouracil (5-FU) or fluorodeoxyuridine (FUDR) when administered as a continuous intravenous infusion, do produce tumor regressions in 8–10% of patients with metastatic disease. Cytokines, such as interleukin-2 (IL-2) and/or interferon alpha (IFNz) produce responses in 10–15% of patients, with occasional complete remissions reported [3]. Despite significant advances in understanding the biology of RCC during the past decade, metastatic disease remains a therapeutic challenge, and patients have a median survival of approximately 12.0 months. Development of novel approaches and investigation of new agents is required.

Capecitabine (Xeloda), a carbamate derivative of 5’-deoxy-5-fluorouridine (5’-DFUR), is a rationally designed orally administered fluoropyrimidine. This prodrug is efficiently absorbed from the gastrointestinal tract, and is preferentially converted to 5-FU in tumor tissue by thymidine phosphorylase (dTthDPase). It is one of a series of 5’-deoxy-5-fluorocytidine (5’-DFCR) derivatives which were synthesized with the objective of having orally active drugs formed under the action of
liver carboxylesterase, and then cytidine deaminase present in the liver or tumor tissue, preventing direct release of 5-FU by gastrointestinal dThdPase [1]. In murine xenograft models, capecitabine has proved to be more active than 5-FU and has demonstrated activity in a variety of solid human tumors, including those that are 5-FU-resistant [10, 11, 12].

Previous studies have demonstrated that either continuous or intermittent therapy with capecitabine is active and well tolerated. Budman et al. [2] have reported that capecitabine when administered in a continuous twice-daily schedule has a maximum tolerated dose (MTD) of 828 mg/m² twice daily. Dose-limiting toxicities are palmar/plantar erythrodysesthesia, nausea, vomiting, abdominal pain, diarrhea and thrombocytopenia. These are reversible upon drug discontinuation.

In a second trial [14], capecitabine was administered in an intermittent schedule for 2 of 3 weeks. The MTD was 1500 mg/m² twice daily, with the dose-limiting toxicities being diarrhea, hypotension, abdominal pain and leukopenia. In view of the novel mechanisms of action of capecitabine and the activity of 5-FU and IFNα in metastatic RCC [3, 17], the toxicity of this combination was examined in a phase I trial. The intermittent schedule for capecitabine was utilized, with IFNα administered subcutaneously (s.c.) three times weekly.

The clinical and preclinical data available suggested that the combination of IFNα and capecitabine should be studied clinically. We hypothesized that concurrent administration of both agents was possible with acceptable toxicity. The objectives of the current trial were to determine the MTDs and safety profile of combined capecitabine and IFNα, and in a preliminary fashion investigate the antitumor activity in patients with metastatic RCC. Additionally, the pharmacokinetics of capecitabine during IFNα therapy were investigated in view of previous studies indicating pharmacologic interactions between IFNα and 5-FU [9] including a decrease in clearance, changes in catabolism, and increased area under the curve (AUC) for 5-FU.

Patients and methods

The current trial was an open-label, single-institution, phase I study conducted at The Cleveland Clinic Foundation, Cleveland, Ohio, USA. Patient entry was initiated in March 1997 and completed in January 1999.

Patient selection

Patients with advanced and/or metastatic RCC were eligible. All patients were ≥18 years of age, gave informed written consent, had measurable and/or evaluable histologically confirmed RCC, a Karnofsky performance status (KPS) of ≥70%, and a life expectancy of ≥3 months. Patients were required to have the following baseline hematologic values: hemoglobin > 9.0 g/dl, white blood cells > 3×10⁹/l, granulocytes > 1.5×10⁹/l, and platelets > 100×10⁹/l. Additional biochemical requirements included: total bilirubin ≤ 1.5 mg/dl, ASAT no more than 2.5 times normal, serum creatinine ≤ 1.5 mg/dl (in patients with prior nephrectomy ≤ 2.0 mg/dl), and serum calcium ≤ 11.5 mg/dl. Exclusion criteria included any of the following: prior history of another malignancy within 3 years (except for basal cell carcinoma of the skin and carcinoma in situ of the cervix); major surgery within 4 weeks; clinical or CT evidence of CNS metastases; history of clinically significant psychiatric disabilities, seizures or central nervous system disorders; clinically significant cardiovascular abnormalities and/or New York Heart Association Functional classification III or IV; poor medical risk because of non-malignant organ or systemic disease; prior history of systemic liver disease; systemic bacterial or fungal infections; major organ grafts, seropositive for HIV, and/or HBV, and/or HCV; more than one previous chemotherapy regimen, or two previous immunotherapy regimens including biologic response modifiers, cytokines, monoclonal antibodies or antitumor vaccines.

Treatment

Capecitabine was administered orally twice daily within 30 min of the end of a meal. It was given intermittently for 2 weeks, followed by 1 week rest. rHuIFNα2a (Roferon-A) was administered s.c. three times weekly continuously. One cycle of therapy consisted of 6 weeks of capecitabine and rHuIFNα2a. Capecitabine was administered orally on days 1–14 and 22–36, and rHuIFNα2a on Monday–Wednesday–Friday of each week. Tumor response was assessed after 6 weeks of therapy utilizing World Health Organization (WHO) criteria. Individuals with a complete response, partial response or stable disease received additional cycles of therapy until evidence of progressive disease was seen, or an unacceptable toxicity developed.

The dose escalation schema utilized is outlined in Table 1. The first cohort of patients received rHuIFNα2a 1.5 MU/m² s.c. three times weekly and capecitabine 825 mg/m² twice daily. Subsequent patient cohorts were treated with 1.5 to 3.0 MU/m² of rHuIFNα2a with capecitabine escalated from 825 to 1000 mg/m² twice daily. Patients were seen once weekly, and toxicity assessed using the National Cancer Institute of Canada Common Toxicity Criteria (NCI-C-TC). Hand-foot syndrome, a toxicity not listed in the NCIC-CTC system, was graded as mild (grade 1), moderate (grade 2), or severe (grade 3) as previously described [11].

The MTD was defined as the dose level of capecitabine and rHuIFNα2a that caused drug-related grade 3/4 toxicity in one-third or more of patients treated. Five additional patients were then treated at this dose level to further characterize the toxicity profile of the combination.

Dose modifications

In the presence of grade 1 toxicity, treatment was continued. If a patient experienced grade 2 drug-related toxicity that did not resolve despite symptomatic treatment drug administration was withheld until it resolved to grade 0 or 1. If the same NCIC-CTC grade 2 toxicity occurred, treatment was withheld until recovery, and restarted at the preceding dose level. For grade 3 toxicity, drug administration was withheld until the toxicity recovered to grade 1 or less. Subsequent therapy was continued at 75% of the original doses, and at 50% if this was the second appearance of the same

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**Table 1** Treatment scheme and dose levels of capecitabine and rHuIFNα2a: phase I trial

<table>
<thead>
<tr>
<th>Dose level</th>
<th>Capecitabine (mg/m² twice daily, days 1–14, 22–36*)</th>
<th>rHuIFNα2a (MU/m², s.c. three times weekly)</th>
<th>Number of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>825</td>
<td>1.5</td>
<td>4</td>
</tr>
<tr>
<td>B</td>
<td>825</td>
<td>3.0</td>
<td>6</td>
</tr>
<tr>
<td>C</td>
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<td>6</td>
</tr>
<tr>
<td>D</td>
<td>1000</td>
<td>3.0</td>
<td>11</td>
</tr>
</tbody>
</table>

*cycles repeated every 6 weeks