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ORIGINAL ARTICLE

Final results of a prematurely discontinued Phase 1/2 study of eniluracil with escalating doses of 5-fluorouracil administered orally in patients with advanced hepatocellular carcinoma

Gilberto de Lima Lopes Jr · Jennifer S. Dicksey · William P. Peters · Melvin Palalay · Alex Y. Chang

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Abstract
Purpose Eniluracil (EU) is a potent dihydropyrimidine (DPD) inhibitor, which improves the oral bio-availability of 5-fluorouracil (5-FU) and may overcome fluoropyrimidine (FP) resistance in hepatocellular carcinoma (HCC). Based on preclinical evidence, we aimed at studying a new dosing schedule for the combination with sequential administration, a lower dose of EU and higher doses of 5-FU than previously investigated.
Methods Patients with a diagnosis of hepatocellular carcinoma were eligible for this Phase 1/2 study. The primary endpoint for the Phase 1 was the determination of dose-limiting toxicity (DLT) and the maximum tolerated dose (MTD) of oral 5-FU when given 14 h after oral EU 5 mg, weekly for 3 out of 4 weeks. The starting dose of 5-FU was 20 mg, followed by 30 mg and 80 mg. Secondary endpoints were anti-tumor activity, pharmacokinetics, and DPD activity in peripheral blood mononuclear cells. RECIST was used for assessment of efficacy and NCI CTC-AE version 3.0 for describing toxicity.
Results Nine patients enrolled in the trial. Median age was 53 years. All patients were Asian (one from Hawaii, 8 from Singapore). Prior treatment was as follows: liver surgery, 2 patients; chemo-embolization, 2 patients; thalidomide, 3 patients; adriamycin, 3 patients. Patients received a median of 2 cycles (range, 1–14) of therapy. No DLTs were seen up to the 80-mg 5-FU cohort. Out of 3 patients in the 80-mg cohort, one had pancytopenia. One patient at the 20-mg cohort had stable disease that lasted for 14 months.
Conclusion EU, at a 5.0-mg weekly dose, was well tolerated. There was no evidence of dose-related safety effects. This trial did not define the MTD for oral 5-FU. No objective responses by RECIST were noted but one patient had stable disease and a decrease of 28% in the sum of the largest diameters of her target lesions. The study was terminated early because of CNS-related toxicities noted in the single higher dose levels in a companion study, AHX-03-104.

Keywords Hepatocellular carcinoma · Chemotherapy · Fluoropyrimidine · Eniluracil · Fluorouracil

G. de Lima Lopes Jr (✉) · A. Y. Chang
Department of Oncology, Johns Hopkins Singapore International Medical Centre, 11 Jalan Tan Tock Seng, Level 1, Singapore 308433, Singapore
e-mail: glopes@imc.jhmi.edu

G. de Lima Lopes Jr · A. Y. Chang
The Johns Hopkins University School of Medicine, Baltimore, MD, USA

J. S. Dicksey · W. P. Peters
Adherex, Inc., Durham, NC, USA

M. Palalay
University of Hawaii, Honolulu, HI, USA

Introduction

Eniluracil (EU) is a potent dihydropyrimidine (DPD) inhibitor, which improves the oral bio-availability of 5-fluorouracil (5-FU) and may overcome fluoropyrimidine (FP) resistance in hepatocellular carcinoma (HCC), a disease in which high levels of DPD are expressed and 5-FU has demonstrated stabilization of disease in two Phase II clinical trials [1–5].

GlaxoSmithKline (GSK, Brentford, Middlesex, United Kingdom) initially developed EU as an orally bio-available

combination therapeutic with 5-FU, but development was discontinued when a pivotal Phase 3 trial failed to show non-inferiority to intravenous 5-FU plus leucovorin [6]. On the evidence of preclinical research demonstrating that high doses of EU that are present when 5-FU is administered may inhibit anabolic activation of 5-FU, Adherex (Adherex Technology Inc., Chapel Hill, NC, USA) and the authors initiated clinical development utilizing a weekly dosing schedule [7], employing a lower dose of EU that precedes the 5-FU dose by 14 h.

Adherex planned two studies with EU in combination with 5-FU using this new schedule: AHX-03-103 and AHX-03-104. AHX-03-103 was initiated in Singapore, Hawaii, Taiwan, and Korea as a Phase 1/2 study in subjects with locally advanced, recurrent, or metastatic HCC. Adherex Study AHX-03-104 was initiated as a single site (United States) Phase 1 study evaluating the safety, pharmacokinetics, and anti-tumor activity of EU administered with 5-FU in patients with refractory solid tumors.

This manuscript describes the methods and results of the AHX-03-103 trial and discusses the reasons for its early termination and the company's plans for the future development of EU as an anti-cancer agent in combination with 5-FU.

Methods

The institutional review boards of all centers participating in the study approved the protocol, and all patients provided written informed consent.

Endpoints

The primary endpoint for the Phase 1 portion of the study was the determination of dose-limiting toxicity (DLT) and the maximum tolerated dose (MTD) of escalating doses of oral 5-FU when given 14 h after oral EU 5.0 mg, weekly for 3 out of 4 weeks.

Secondary endpoints were to assess anti-tumor activity of EU and 5-FU in Asian subjects administered in this regimen, to characterize the pharmacokinetics (PK) of EU and 5-FU in Asian subjects administered in this regimen in Cycle 1, and to characterize the activity of dihydropyrimidine dehydrogenase (DPD) in peripheral blood mononuclear cells (PBMCs) from Asian subjects at baseline and on Days 2, 3, and 6 in Cycle 1.

The primary endpoint for the Phase 2 portion of the study was to estimate the objective tumor response rate of EU at a recommended dose (RD) of 5-FU from Phase 1, administered orally once weekly for 3 weeks out of every 4 in subjects with locally advanced, recurrent, or metastatic HCC.

Other secondary endpoints for both portions of the study included as follows: characterization of the safety and tolerability of EU and 5-FU administered orally in a novel regimen (i.e., 5-FU administered 14 h after EU, orally once weekly for 3 weeks out of every 4), characterization of the duration of response, progression-free survival and overall survival of subjects receiving EU and 5-FU administered in this regimen, and characterization of changes in the Alpha-fetoprotein (AFP) level in subjects receiving EU and 5-FU administered in this regimen.

Study design

The authors designed a multicenter, open-label Phase 1/2 study to assess the safety, tolerability, PK, and anti-tumor activity of EU and 5-FU administered orally once weekly for 3 weeks out of every 4 to subjects with locally advanced, recurrent, or metastatic HCC.

A cycle was defined as doses of EU administered on Days 1, 8, and 15 and doses of 5-FU administered on Days 2, 9, and 16 in 28-day cycles.

Phase 1

All subjects were to receive weekly doses of EU (5.0 mg administered orally at 6 PM) before receiving a dose of 5-FU (administered orally at 8 AM the next morning; an interval of 12–20 h between doses was allowed).

Groups of 3 subjects were assigned sequentially to escalating dose levels of 5-FU. Based upon the incidence of DLTs, it was anticipated that up to 5 dose levels would be tested.

Phase 2

All subjects were to receive weekly doses of EU (5.0 mg administered orally at 6 PM) before receiving a dose of 5-FU (administered orally at 8 AM the next morning; an interval of 12–20 h between doses was allowed). The dose of 5-FU in Phase 2 was planned to be chosen based upon results from the Phase 1 portion of the study.

Definition of DLT/MTD

The toxicity of EU and 5-FU administrated orally was assessed by the investigator(s) using National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 3.0 [8].

DLTs were drug-related toxicities defined as follows: absolute neutrophil count $<0.5 \times 109/L$ for ≥ 7 days; $\geq$Grade 3 neutropenic infection/febrile neutropenia; platelets $<50 \times 109/L$ or thrombocytopenic bleeding; neurotoxicity $\geq$ Grade 2 severity; other non-hematological

toxicity ≥ Grade 3 severity; any drug-related toxicity that requires a >1-week delay in start of the next cycle (i.e., >Day 35 from start of the previous cycle); inability to receive 3 weekly doses of EU and 5-FU due to toxicity; ≥Grade 3 diarrhea that is uncontrolled despite; supportive care.

In Phase 1, 3 subjects were assigned to each dose level. If no DLTs occurred in any of the first 3 subjects entered at a given dose level during Cycle 1, a safety meeting was held, attended by members of the safety committee of Adherex Technologies Inc. and the participating investigators.

Enrollment of the next 3 subjects in the subsequent planned dose level commenced following review of the safety data and agreement between the sponsor and investigators regarding the next dose level. If a toxicity occurred and was considered to be dose limiting in 1 of the first 3 subjects entered at a given dose level during Cycle 1, up to 3 additional subjects would be entered at that dose level to determine whether the MTD had been reached or exceeded.

If ≥2 of the first 2–6 subjects assigned to any dose level experience a DLT during Cycle 1, then dosing at that dose level will be stopped, because the MTD would have been exceeded. The next lower dose level evaluated in the trial would then generally be declared to be the MTD and would be defined as the highest dose level where <2 of 6 subjects experienced a DLT during Cycle 1.

The MTD, or dose level immediately below the MTD, would be evaluated to determine the recommended dose (RD). Assessment of the safety and tolerability over more than 1 cycle would also be considered in defining the RD. If the incidence of DLTs in cycles beyond Cycle 1 is >30%, the RD would be modified to define a more tolerable dose.

Up to 28 subjects (including 3–6 subjects who might have received this dose level during the dose-escalation portion of the study) would receive the 5-FU RD to further characterize the safety profile and anti-tumor activity of EU and 5-FU.

Criteria for continuation

Subjects might receive weekly doses of EU and 5-FU for 3 weeks out of every 4, provided they had not experienced a DLT. If a subject experienced a DLT, the next doses of EU and 5-FU should be withheld until recovery of toxicity to ≤ Grade 2 (or to ≤ Grade 1 for neurotoxicity) or baseline, and any subsequent dose of 5-FU should be administered at 1 dose level below that at which the DLT occurred. The dose of EU should not be adjusted.

Day 29 (Day 1 of the subsequent cycle): subjects might receive the next cycle of EU and 5-FU if, on Day 29, the relevant eligibility criteria (e.g., organ function) were still met. A delay in the start of the next cycle of up to 1 week (Day 35) was permitted to allow recovery from any toxicity in order to meet the relevant eligibility criteria (e.g., organ function).

Any drug-related toxicity that required a >1-week delay in the start of the next cycle (i.e., >Day 35 from start of the previous cycle) was to be considered a DLT. The subject would be removed from study if recovery from any drug-related toxicities required a delay of >2 weeks (i.e., >Day 42 from start of dosing in any cycle) in order to meet the relevant eligibility criteria (e.g., organ function).

Inclusion criteria

Patients had to be 18 years of age or older (21 for Singapore) and had to provide signed written informed consent. Other inclusion criteria included as follows: non-resectable, locally advanced, recurrent, or metastatic HCC that was either histologically proven OR a radiologically documented liver mass with Alpha-fetoprotein (AFP) > 4,000 ng/mL, Hepatitis B surface antigen positive OR Alpha-fetoprotein (AFP) > 400 ng/mL with Hepatitis B surface antigen negative. All patients had to have radiologically documented measurable disease and an ECOG performance status of 0–1 at study entry. Adequate hepatic function, as assessed by Child–Turcotte–Pugh score of 8 or better (Class A or well compensated B) and serum or alanine aminotransferase and serum bilirubin within normal levels as well as an adequate bone marrow, renal, and other end-organ function. Women of childbearing potential had to have a negative serum pregnancy test within 7 days before study entry and had to use effective contraception throughout the course of the study (contraception was also required for male subjects). Enrolled patients also had to be willing not to receive fluoropyrimidine-containing chemotherapy for 8 weeks after the last dose of EU received in this study.

Exclusion criteria

Patients were excluded if they received chemotherapy, radiotherapy, or any other investigational drug within 28 days prior to study entry; if they had 2 or more previous treatment with systemic chemotherapy (chemotherapy administered as part of a chemo-embolization procedure was not considered systemic chemotherapy); portal hypertension with bleeding esophageal or gastric varices within the past 3 months; ascites that was refractory to conservative management; any gastrointestinal tract disease resulting in the inability to take oral medication; active peptic ulcer disease; known hypersensitivity to 5-FU or EU; history of primary brain tumors or brain metastases, unless any lesions had completely resolved following appropriate treatment and there had been no recurrence for

at least 6 months; previous or concurrent malignancy at another site within the last 5 years, other than basal or squamous cell carcinoma of the skin, or curatively treated carcinoma in situ of the uterine cervix, prostate cancer, or superficial bladder cancer; stroke, major surgery, or other major tissue injury within 30 days before study entry; history of myocardial infarction within 6 months or significant congestive heart failure, angina, arrhythmias, or ECG abnormalities; other serious chronic disease or uncontrolled metabolic disorders that, in the investigator's opinion, could render compliance or follow-up in the protocol problematic; breast-feeding or lactating; legal incapacity or limited legal capacity, unless authorization was granted by a legal guardian.

Drug administration

EU and 5-FU were provided by Adherex Technologies Inc.

Phase 1

All subjects were to receive EU (5.0 mg administered orally once weekly at 6 PM) before receiving a dose of 5-FU (administered orally the next morning 12–20 h postdose of EU). A cycle was defined as doses of EU administered on Days 1, 8, and 15 and doses of 5-FU administered on Days 2, 9, and 16 in 28-day cycles. Groups of 3 subjects were assigned sequentially to escalating dose levels of 5-FU. The starting dose of 5-FU was 20.0 mg once weekly, followed by 30.0 mg once weekly, then increased to 80.0 mg weekly, and any subsequent dose escalations for 5-FU would occur in 20-mg increments.

Phase 2

All subjects were to receive EU (5.0 mg administered orally once weekly at 6 PM) before receiving the dose of 5-FU (administered orally the next morning 12–20 h postdose of EU). The dose of 5-FU in Phase 2 was to be chosen based upon results from the Phase 1 portion of the study.

Pharmacokinetics

Blood samples for measuring EU and 5-FU plasma concentrations were collected at the following time points on the first day of administration of oral EU and 5-FU: Predose and 0.5, 1, 2, 4, 8, 12, and 24 h following the first dose of EU in Cycle 1, Day 1; and predose and 0.5, 1, 2, 4, 8, 12, and 24 h following the first dose of 5-FU in Cycle 1, Day 2. Subjects remained in the clinic overnight after the dose of EU due to the frequency of blood sample collection. Subjects might also choose to remain overnight in the clinic on the night of Day 2.

The PK parameters of EU and 5-FU were to be calculated according to standard non-compartmental and compartmental methods and presented descriptively.

Sample size

Up to 52 evaluable subjects were to be enrolled in this study, including up to 28 subjects at the 5-FU RD. A 2-stage design was to be utilized in the Phase 2 portion of the study. A response rate of 20% would have been considered of interest, and a response rate of 5% would have been considered as not of interest.

The first stage of the Phase 2 portion of the trial would have 14 subjects (including 3 or 6 patients at the RD from Phase 1). If there were no responses among these 14 subjects, then the trial would be terminated. The probability of terminating after the first stage was 0.05 if the true response rate is 20%, and it was 0.49 if the true response rate was 5%. Otherwise, the Phase 2 portion would continue until a total of 28 subjects are enrolled at the 5-FU RD level. This dose would be deemed active if there were 4 or more responses in the 28 subjects. The probability of declaring the RD active was 0.83 if its true response rate was 20%.

The primary analysis for Phase 1 was to determine the MTD, which would help define the RD for 5-FU.

Response assessment

Response was assessed according to response evaluation criteria in solid tumors (RECIST, Version 1.0) [9]. The best response reported from the time of administration of the first infusion of EU to PD or end of the study was considered (increasing order of responses is PD, stable disease [SD], partial response [PR], complete response [CR]). Subjects achieving a complete or partial response were considered responders (CR + PR). The duration of response was calculated from the time measurement criteria that were met for a CR or PR (whichever is recorded first) until the first date that PD was objectively documented. Time to tumor progression and overall survival were to be estimated using Kaplan–Meier analysis.

Results

Baseline characteristics

Nine patients enrolled in study AHX-03-103. Median age was 53 years. All individuals were Asian (1 from Hawaii, 8 from Singapore). Gender distribution: 3 patients were women and 6 were men. All subjects were pretreated for HCC including: liver surgery (2 patients), chemo-embolization (2

patients), thalidomide (3 patients), and adriamycin (3 patients).

Treatment delivery

Patients received a median of 2 cycles (range, 1–14) of EU + 5-FU and were in study for a median of 43 days (range, 9–414).

Dose-limiting toxicities

There were no DLTs at the 20- and 30-mg 5-FU cohorts. There were 3 subjects in the 20-mg cohort and 2 subjects in the 30-mg cohort. Based on data from the AHX-03-104 study, the protocol was revised (version 3.0, dated March 7, 2007) so that the next 5-FU dose level investigated after the 30-mg cohort was 80 mg. One of 4 patients in the 80-mg cohort had Grade 3 thrombocytopenia, classified as a DLT. The investigators reduced the dose to 70 mg, and the 80-mg cohort was expanded with the intention to reach 6 subjects at that dose level. No subsequent DLTs or drug-related Grade 3 or 4 toxicities were reported. The study was closed before the MTD was determined.

Other adverse events

The following adverse events were reported during the study: cough (4 subjects, 1 had Grade 3); nausea and vomiting (5 subjects, 2 had Grade 3), fatigue (5 subjects, 2 with Grade 3), hypokalemia (5 subjects, 3 had Grade 3, and 2 had Grade 4), fever (pyrexia) (5 subjects, all Grade 1 or 2), diarrhea (4 subjects, 1 had Grade 3), pain (4 subjects, all Grade 1 or 2), thrombocytopenia (2 subjects, 2 occurrences in 1 subject, Grades 1 and 2 and 1-Grade 3), seizure (1 subject, Grade 2) and anorexia (2 subjects, Grade 2).

The events of fatigue, vomiting, thrombocytopenia, and diarrhea were reported as possibly or probably related to study medication. The Grade 3 thrombocytopenia was considered to be an SAE, and the dose was reduced for that subject. No other adverse events resulted in discontinuation or reduction in dose of study medication. Three subjects died within 30 days of last dose as a result of disease progression.

Response assessment

One patient had stable disease (with a 28% decrease in the sum of the largest diameters of her target lesions) and was on therapy for 15 cycles in the 20-mg cohort. There were no clinically relevant response trends in AFP levels.

Pharmacokinetics

Six patients agreed to participate in the pharmacokinetics sub-study. Table 1 summarizes the results. The mean half-life for 5-FU in this study was 2.07 h (Median was 1.875 h).

Discussion

The investigators stopped the study (Adherex AHX-03-103) after 9 patients enrolled, without determining the maximum tolerated dose or the recommended dose for treatment with 5-FU following EU 5 mg in patients with hepatocellular carcinoma. This section will discuss the reasons for trial discontinuation and the company's plans for further development of EU in combination with 5-FU as a therapeutic option.

A second trial, Adherex Study AHX-03-104, a single site (United States) Phase 1 study, aimed at evaluating the safety, pharmacokinetics, and anti-tumor activity of EU administered with 5-FU in patients with refractory solid tumors [10]. In that study, patients with refractory solid tumors received EU 5.0 mg with escalating single doses of 5-FU administered orally 3 weeks out of 4 (identical to the AHX-03-103 study drug dosing regimen). The trial was discontinued due to dose-limiting toxicity, manifested as nervous system symptoms for the cohorts that received 5-Fu at doses of 100 and 160 mg.

The cytotoxicity of 5-FU derives from its conversion into active metabolites (FdUMP, 5-FUTP, and 5-FdUTP) that inhibit thymidylate synthase, RNA synthesis, and DNA replication [11, 12]. Pharmacokinetic studies have demonstrated however that 85% of 5-FU administered is inactivated and eliminated through the catabolic pathway, of which DPD is the rate-limiting step and alpha-fluoro-beta-alanine (F-BAL) is the main catabolite. F-BAL is responsible for the neurotoxicity and for the occurrence of hand and foot syndrome associated with fluoropyrimidines [13, 14]. The neurotoxicity seen in study AHX-03-104 was likely the result of the low doses of EU partially and selectively inactivating DPD in non-nervous tissues and not in nervous tissues [15].

Supportive evidence to the hypothesis that EU at a dose of 5 mg only partly inhibits DPD comes from a half-life of only 3 h in study AHX-03-104 and 2 (0.8–3.77) hours in the present study compared with a half-life of 5.8 (4.5–6.5) hours in another study that used the same weekly schedule and an EU dose of 20 mg [7, 16]. In addition, in the same trial, investigators determined the MTD of 5-FU to be 29 mg/m2 compared with a dose of greater than 120 mg in the Adherex trial. Finally, as suggested by Spector and Cao [15], further evidence that the 5-mg eniluracil dose was too

Table 1 Pharmacokinetics of fluorouracil after pretreatment with eniluracil in 6 patients who agreed to participate in the pharmacokinetics sub-study

Dose level (mg)	Subject	C_{max} (ng/mL)	T_{max} (hr)	Half-life (hr)	AUCinf (hr ng/mL)	CL/F (L/hr)	Vz/F (L)
20	101	737.6	0.50	0.85	1,020	19.6	24.1
20	102	773.2	0.50	3.25	3,510	5.7	26.7
20	103	892.3	0.50	1.78	2,773	7.2	18.6
30	104	467.0	2.00	0.80	1,064	28.2	32.7
30	105	623.1	1.00	3.77	4,776	6.3	34.1
80	106	2,706.6	1.00	1.97	9,030	8.9	25.2

low to inhibit DPD in nervous tissues is found in studies in rats where the required eniluracil dose to inhibit DPD in the brain is sixfold higher than the dose required to inhibit the enzyme in non-nervous tissue [17].

Based on the DLT neurotoxicity, Adherex has decided not to continue with any studies utilizing EU at a dose of 5 mg, hence the closure of AHX-03-103. As described on the company Web site, (http://www.adherex.com), further development of EU will continue in a Phase II trial in patients with breast cancer, evaluating EU at a dose of 40 mg, given in the evening on Day 1, 11–16 h before 5-FU (30 mg/m^2) on day 2 plus leucovorin (30 mg) on Days 2 and 3 on a weekly basis for 3 out of 4 weeks. This schedule is hoped to optimize the pharmacokinetics, efficacy, and safety of 5-FU while minimizing F-BAL formation and the occurrence of neurotoxicity and hand and foot syndrome. The company and investigators may consider advancing a new study in HCC in due course using a similar strategy.

In conclusion, eniluracil, at a 5.0-mg weekly dose, was well tolerated. There was no evidence of dose-related safety effects. This trial did not establish the MTD for oral 5-FU when given after EU. No objective responses by RECIST were noted, but one patient had stable disease and a decrease of 28% in the sum of the largest diameters of her target lesions. The study was terminated early because of the neurotoxicities noted in Study AHX-03-104. Further development of EU in combination with 5-FU plus leucovorin will proceed with a different dosage and schedule.

Conflicts of interest JSD and WPP were formerly employees of Adherex, Inc. GLL, AYC and MP received research funding from Adherex, Inc.

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