Original Study

Eniluracil Plus 5-Fluorouracil and Leucovorin: Treatment for Metastatic Breast Cancer Patients in Whom Capecitabine Treatment Rapidly Failed

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Abstract

As part of a comparative phase II study of eniluracil plus 5-fluorouracil (5-FU) and leucovorin (Lv) vs. capecitabine, an oral 5-FU prodrug for metastatic breast cancer (MBC), 10 evaluable patients with rapid disease progression (PD) during capecitabine treatment crossed over to take eniluracil/5-FU/Lv. Of these patients, 3 had partial tumor response (PR), 6 had stable disease (SD), and 4 had > 7 months progression-free survival (PFS) with eniluracil/5-FU/Lv treatment.

Background: As part of a comparative phase II study of eniluracil/5-FU/Lv vs. capecitabine (Xeloda), an oral 5-FU prodrug for MBC, patients with rapid PD during capecitabine therapy crossed over to take eniluracil/5-FU/Lv. **Patients and Methods:** Ten evaluable patients with radiologically documented PD within 70 days of capecitabine treatment were treated with a modified oral weekly eniluracil/5-FU/Lv regimen. **Results:** After switching to eniluracil/5-FU/Lv, 3 (30%) patients had PR. Six (60%) had SD, producing a total of 90% with PR or SD. The median PFS was 140 days (vs. 42.5 days for capecitabine). Four (40%) patients had > 7months PFS. Eniluracil/5-FU/Lv was well tolerated with mild to moderate diarrhea and nausea as the most common side effects. **Conclusion:** These positive efficacy and safety results encourage a larger study in patients with rapid PD during capecitabine treatment. Eniluracil/5-FU/Lv might enable these patients to continue with oral 5-FU rather than switching to the generally less well tolerated intravenous microtubule-interfering agents. In addition, the eniluracil/5-FU/Lv regimen might also provide any overall survival contribution of 5-FU that, for pharmacokinetic reasons, was not provided by capecitabine and would not be provided if these patients progressed directly to the other approved treatments.

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Introduction

5-Fluorouracil (5-FU) is rapidly inactivated by dihydropyrimidine dehydrogenase (DPD) and then converted to α-fluoro-β-alanine (F-Bal). F-Bal is neurotoxic, might contribute to hand-foot syndrome, and might interfere with antitumor activity of 5-FU. Levels of DPD are highly variable, causing markedly variable 5-FU pharmacokinetic characteristics that significantly affect 5-FU efficacy and safety. Eniluracil irreversibly inactivates DPD, thereby eliminating the problems associated with 5-FU variability and the formation of F-Bal (Reviewed in Paff et al.[1] and Spector et al.[2]). Eniluracil confers linear, consistent pharmacokinetic characteristics, 100% oral bioavailability, and a 5-hour half-life on 5-FU.[3-9] It also markedly reduces the incidence of hand-foot syndrome.[10,11] In the year 2000, oral eniluracil/5-FU failed to achieve equivalence in overall survival vs. intravenous 5-FU/leucovorin (Lv) for colorectal cancer.[10] Subsequently, a study in laboratory animals revealed that the high eniluracil to 5-FU ratio in those phase III studies could have decreased antitumor activity.[12]

The main study (AHX-03-202) compared the efficacy and safety of eniluracil/5-FU/Lv with capecitabine (Xeloda), an oral prodrug of 5-FU, for treatment of metastatic breast cancer (MBC). It provided

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first- or second-line therapy for patients who had previous treatment with an anthracycline and a taxane. The study was encouraged by the previously reported activity of eniluracil/5-FU in this patient population.[13,14] The study used a new treatment protocol that avoided high eniluracil to 5-FU ratios. It is based on a promising phase I trial with weekly dosed oral eniluracil, 5-FU, and Lv that produced durable tumor responses in patients with advanced colorectal cancer that was refractory to intravenous 5-FU/Lv.[8] The regimen was modified to: (1) administer a high (40 mg) eniluracil dose to eliminate all DPD, including DPD in nervous tissue to minimize neurotoxicity[12]; (2) wait 11 to 16 hours for excess eniluracil to be cleared and then administer 5-FU when the eniluracil to 5-FU ratio was very low to optimize efficacy[12]; and (3) administer Lv with 5-FU and 24 hours afterward to provide extended potentiation of 5-FU efficacy.

The secondary aspect of the comparative study assessed patients with disease progression (PD) during capecitabine treatment who had crossed over to take eniluracil/5-FU/Lv. The crossover part of the study has been completed and the results are final. We report here encouraging results for patients taking eniluracil/5-FU/Lv after experiencing rapid (within 70 days) PD during capecitabine treatment. The main study was discontinued because the preliminary data indicated eniluracil/5-FU/Lv and capecitabine had produced similar clinical benefit and eniluracil/5-FU/Lv would not meet the primary end point of superior efficacy.

Patients and Methods

Patients

Adult women needing first- or second-line treatment for MBC and having previous treatment with an anthracycline and a taxane were randomized into the comparative study. To participate, patients must have had measurable disease according to Response Evaluation Criteria in Solid Tumors (RECIST) 1.1, an Eastern Cooperative Oncology Group performance status of 0 or 1, adequate renal function (creatinine clearance $\geq$ 50 mL/min), no previous capecitabine treatment, and been willing to avoid any other dose or form (intraveous, oral, or topical) of 5-FU or related derivatives during treatment and for 8 weeks after the last dose of eniluracil. Previous treatment with 5-FU, but not capecitabine was allowed. The protocol was approved by the local ethics boards. Informed consent was obtained for all participants. The study (NCT01231802) was registered on ClinicalTrials.gov.

Study Design

Up to 140 evaluable patients were randomized in a 4:3 ratio to receive eniluracil/5-FU/Lv or capecitabine (Xeloda), an oral prodrug of 5-FU.

Patients with radiologically documented PD after at least 2 cycles of capecitabine were allowed to cross over to take eniluracil/5-FU/Lv, provided that no more than 21 days had passed between their last tumor assessment in the capecitabine arm and the first dose of eniluracil/5-FU/Lv. Patients were evaluable if they had a tumor assessment after being in study for at least 6 weeks $\pm$ 1 week and had taken the scheduled eniluracil/5-FU/Lv during that time period.

The primary objective was progression-free survival (PFS) and the secondary objectives were safety, antitumor response rate, disease control rate, duration of response, and time to treatment response. The completed final results for crossover patients are reported here.

Tumors were evaluated using computed tomography or magnetic resonance imaging every 6 weeks according to RECIST 1.1. Routine safety, laboratory, and hand-foot syndrome assessments were performed at every clinic visit. The Kaplan-Meier method was used to estimate median PFS. The associated 95% confidence intervals (CIs) are presented.

Chemotherapy

All agents were self-administered as oral tablets. Patients taking eniluracil/5-FU/Lv started with 40 mg eniluracil, followed 11 to 16 hours later with 30 mg/m^2 5-FU plus 30 mg Lv. The Lv dose was repeated 24 hours later. The regimen was taken for 3 consecutive weeks followed by 1 week without treatment. Patients receiving capecitabine ingested 1000 mg/m^2 capecitabine twice a day for 2 weeks followed by 1 week without treatment. Patients received regular telephone calls to remind them to take their study drugs. Capecitabine administration compliance was verified for patients who entered the crossover arm.

Results

Antitumor Efficacy

Twenty-five patients with PD during capecitabine treatment crossed over to take eniluracil/5-FU/Lv. Twelve patients had rapid (within 70 days) PD during capecitabine treatment. Ten of the 12 were evaluable. Of those not evaluable, 1 experienced clinical PD before the scheduled tumor assessment at 6 weeks and 1 was ineligible because more than 21 days passed between the last tumor assessment in the capecitabine arm and first dose of eniluracil/5-FU/Lv. The characteristics of the 10 evaluable patients who experienced PD within 70 days of capecitabine treatment are presented in Table 1. They ranged from 39 to 70 years in age. Seventy percent had 1 or 2 previous 5-FU treatments in the adjuvant or neoadjuvant setting. Capecitabine had been administered as first-line treatment for 3 patients and as second-line for the remaining 7 patients.

These patient's clinical responses are presented in Table 2. PD was detected at the first tumor assessment, at 39 to 43 days for 8 patients during capecitabine treatment. The other 2 patients had PD at 63 and 64 days, respectively (Fig. 1). Their median PFS was 42.5 days (95% CI, 39-43) with capecitabine treatment. None of these patients had a tumor response during capecitabine treatment.

However, after switching to eniluracil/5-FU/Lv, these 10 patients had a median PFS of 140 days (95% CI, 37-268) (Fig. 1). Four patients had $>$ 7 months PFS. Three (30%) patients had partial tumor response (PR). Six (60%) had stable disease (SD), producing a total PR + SD in 9 patients (90%). Their tumor response durations were 43, 78, and 84 days. Two of the 3 responders had 63% reductions in the sum of the diameters of their target lesions and had confirmed responses at subsequent tumor evaluations. The third responder had 100% reduction in the sum of the diameters of target lesions, but a new nontarget tumor lesion was detected at the subsequent scan.

In contrast to the patients with PD within 70 days during capecitabine treatment, the 13 patients who crossed over to take eniluracil/5-FU/Lv when PD occurred after 70 days (range, 87-422

Table 1 Clinical Characteristics

Characteristic	Value
Age, Years	
Average ± standard deviation	56 ± 9
Range	39-70
39-50, n	3
>50, n	7
Hormone Receptor Status, n	
ER^+ and PR^+	2
PR^+	1
$HER2^+$	2
ER^+, PR^+, and $HER2^+$	2
ER^-, PR^-, and $HER2^-$	3
Neoadjuvant/Adjuvant 5-FU Treatments, n	
0	3
1	5
2	2
Previous Treatments for Metastatic Breast Cancer (Before Capecitabine), n	
0	3
1	7

Number of evaluable patients = 10.
Abbreviations: ER = estrogen receptor; 5-FU = 5-fluorouracil; PR = progesteron receptor.

days) with capecitabine received little benefit. Three of the 13 had SD, lasting from 66 to 93 days, but none had any tumor responses.

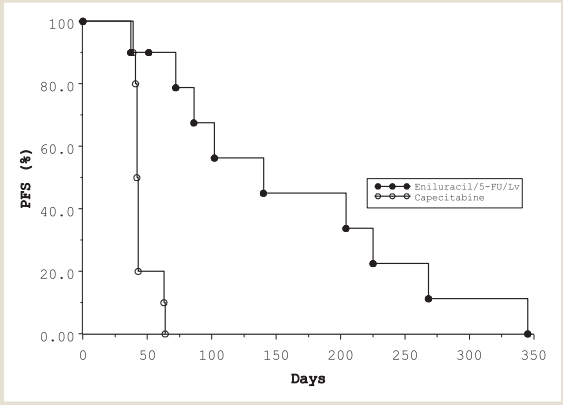
Safety

The unique eniluracil/5-FU/Lv-related adverse events (AEs) for all patients who crossed over from capecitabine treatment are presented in Table 3. The most common side effects were mild to moderate diarrhea and nausea. Two drug-related serious AEs occurred in these patients; a pulmonary embolism and 1 death due to PD.

Discussion

Ninety percent of the evaluable patients who had rapid PD during capecitabine treatment had PR or SD with eniluracil/5-FU/Lv treatment. This result is striking because 5-FU is the active agent of both oral regimens. Clearly, these patients had rapid PD on capecitabine for reasons other than inherent resistance to 5-FU. The different pharmacokinetic properties of the 2 treatments provide likely explanations for rapid capecitabine treatment failure and subsequent benefit from eniluracil/5-FU/Lv.

Figure 1 Kaplan-Meier PFS Graph. Patients With Rapid Disease Progression During Capecitabine Treatment Were Then Treated With Eniluracil/5-FU/Lv



Abbreviations: 5-FU = 5-fluorouracil; Lv = leucovorin; PFS = progression-free survival.

These patients represent an enriched population for whom capecitabine most likely fails to deliver adequate 5-FU to their tumors. Deficient exposure to 5-FU might have resulted from inadequate capecitabine absorption or metabolic conversion to 5-FU, and/or extensive catabolic degradation of 5-FU by DPD. Low or variable capecitabine absorption could decrease its efficacy. Capecitabine absorption is highly variable and could have extended lag periods.[15] After absorption, capecitabine must be converted to 5-FU by 3 enzymatic steps catalyzed sequentially by a carboxylesterase, cytidine deaminase, and thymidine phosphorylase.[16] The complexity of this 3-step process results in highly variable 5-FU pharmacokinetic properties.[17,18] Low or deficient levels of 1 or more of the 3 enzymes could decrease the generation of 5-FU. In addition, low intratumoral thymidine phosphorylase would prevent the formation of 5-FU at this critical site.

After 5-FU is formed from capecitabine, it might be subject to rapid degradation by elevated DPD. This enzyme is present in highly variable levels among individuals and has up to 85-fold fluctuations in diurnal levels within individuals.[19] Furthermore, the end product of 5-FU degradation, F-Bal, has been shown to interfere with 5-FU antitumor activity.[20,21]

Table 2 Antitumor Results for Evaluable Patients With Rapid Disease Progression During Capecitabine Treatment Followed by Eniluracil/5-FU/Lv Treatment

Result	Treatment Regimen		
	Capecitabine	➡	Eniluracil/5-FU/Lv
Median PFS, Days (95% CI)	42.5 (39-43)		140 (37-268)
PFS > 7 Months, n (%)	0		4 (40)
Response Rate (PR), n (%) (95% CI)	0		3 (30) (7-65)
Response Duration (PR), Days for Each Patient	0		43, 78, 84
Disease Control (PR + SD), n (%) (95% CI)	2 (20)		9 (90) (56-100)

Abbreviations: 5-FU = 5-fluorouracil; Lv = leucovorin; PFS = progression-free survival; PR = partial response; SD = stable disease.

Table 3 Summary of All Unique Eniluracil/5-FU/Lv-Related Adverse Events for All Crossover Patients

Adverse Event	PD Within 70 Days During Capecitabine Treatment, n = 12		PD After 70 Days of Capecitabine Treatment, n = 13	
	Grades 1 or 2	Grades 3 or 4	Grades 1 or 2	Grades 3 or 4
Thrombocytopenia	1	–	–	–
Abdominal Pain or Discomfort	2	–	–	–
Diarrhea	5	–	3	–
Entercolitis	–	–	–	1
Nausea	3	–	1	–
Vomiting	1	–	–	–
Asthenia	–	1	2	–
Fatigue	1	–	–	–
Peripheral Edema	1	–	1	–
Decreased Appetite	–	–	1	–
Myalgia	–	–	1	–
Cachexia	–	–	1	–
Alopecia	–	–	1	–
Hand-Foot Syndrome	2	–	–	–
Hypokalemia	1	–	–	–

Data are presented as n.
Abbreviations: 5-FU = 5-fluorouracil; Lv = leucovorin.

In contrast, by eliminating DPD, eniluracil circumvents all the problems associated with capecitabine absorption, conversion to 5-FU, and 5-FU degradation. By preventing 5-FU breakdown in the gastrointestinal track and in all other tissues,[22] eniluracil enables 5-FU to be administered directly with 100% oral bioavailability and consistent, linear pharmacokinetic characteristics.[3-9] All the uncertainty associated with variable rates of 5-FU degradation are also eliminated. Moreover, because F-Bal formation is negligible,[7-9] it cannot interfere with 5-FU antitumor activity.[20,21]

In addition, the predictable 5-FU blood levels enable the safe use of Lv,[3,8,23] which might contribute to enhanced 5-FU efficacy. Lv is generally not used with capecitabine[24] because it increases the incidence of hand-foot syndrome and diarrhea without adding any efficacy benefit,[24] probably due to variable plasma levels of 5-FU.[17]

Eniluracil use also avoids the severe and even fatal toxicity observed in DPD-deficient patients treated with conventional doses of 5-FU.[25-28] Because eniluracil universally creates the DPD-deficient state, all patients are subsequently treated with the appropriately low 5-FU dose.

In contrast to patients with rapid PD with capecitabine treatment, patients who crossed over to take eniluracil/5-FU/Lv when PD occurred after 70 days (range, 87-422 days) of capecitabine treatment received little benefit. Initially, these patients' tumors probably received adequate exposure to 5-FU, but then became resistant to it during capecitabine treatment. Progression by 70 days during capecitabine treatment appears to be the appropriate cutoff time for probable benefit with subsequent eniluracil/5-FU/Lv treatment. Seventy days would capture PD at the first tumor assessment in the clinical setting for future studies.

The eniluracil/5-FU/Lv antitumor efficacy in patients with rapid PD during capecitabine treatment was fairly similar to the efficacy capecitabine produced in MBC patients previously treated with an anthracycline and a taxane in several monotherapy arms of comparative studies. When capecitabine was dosed at 1250 mg/m^2 every 12 hours (2 weeks on, 1 week off) in studies of 612,[29] 377,[30] and 230[31] MBC patients, the PFS was 118, 118, and 117 days, and the tumor response rate was 29%, 14%, and 9.1%, respectively.

These promising efficacy and safety results obtained with eniluracil/5-FU/Lv encourage a larger study in MBC patients who had rapid PD with capecitabine treatment. Currently there are 2 intravenous microtubule-interfering agents that are approved by the Food and Drug Administration (FDA) for patients in whom standard lines of chemotherapy have failed. The safety database of > 1500 patients treated with eniluracil/5-FU with or without Lv plus the current study indicate that eniluracil/5-FU/Lv should be considerably better tolerated than these agents.

Intravenous ixabepilone monotherapy (Ixempra) is currently FDA-approved for MBC patients in whom an anthracycline, a taxane, and capecitabine treatment has failed. Ixabepilone produces high rates (72%) of peripheral neuropathy (15% Grades 3-4), 54% Grade 3 to 4 neutropenia, and 48% alopecia.[32]

Intravenous eribulin (Halaven) is available for MBC patients who have previously received at least 2 chemotherapeutic regimens for the treatment of metastatic disease. Their previous therapies should have included an anthracycline and a taxane in either the adjuvant or metastatic setting. The side effects are similar to those of ixabepilone, 35% peripheral neuropathy (8% Grades 3-4), 57% Grade 3 to 4 neutropenia, and 49% alopecia.[33]

In the main comparative trial (AHX-03-202), 19 of the 61 evaluable eligible patients treated with capecitabine experienced rapid PD (12 crossed over to take eniluracil/5-FU/Lv). Similar apparent proportions of rapid capecitabine treatment failures were observed in other larger studies of 136 and 377 patients in identical MBC populations.[30,34] These patients would meet the previous treatment requirements necessary to receive ixabepilone. Some would also be

eligible for eribulin treatment. Others would need a second treatment for metastatic disease before qualifying for treatment with eribulin.

However, before patients' rapid PD with capecitabine treatment, oral 5-FU (in the form of capecitabine) was their physician's drug of choice. Eniluracil/5-FU/Lv could possibly provide an advantage by enabling all of these patients to continue with oral 5-FU rather than switching to these generally less well-tolerated intravenous agents.

Conclusion

The positive efficacy and safety results of eniluracil/5-FU/Lv treatment for patients who have rapid PD during capecitabine treatment encourage a larger study in this enriched population. Eniluracil/5-FU/Lv might provide an option for the patients and physicians who prefer to continue with oral 5-FU and delay or avoid progressing to the more toxic intravenous microtubule inhibitors. In addition, the eniluracil/5-FU/Lv regimen might also provide any overall survival contribution of 5-FU that, for pharmacokinetic reasons, was not provided by capecitabine and would not be provided if these patients progressed directly to the other FDA-approved treatments.

Clinical Practice Points

- Patients with rapid PD with capecitabine treatment, for pharmacokinetic reasons, might not have had adequate 5-FU delivered to their tumors.
- Eniluracil/5-FU/Lv overcomes or avoids these pharmacokinetic issues and consistently delivers the expected levels of 5-FU.
- Preliminary data indicate that eniluracil/5-FU/Lv might provide clinical benefit to this specific patient population. Future studies are encouraged.

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Disclosure

The authors have stated that they have no conflicts of interest.

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