ASCO 2008
47A

5,10-Methylenetetrahydrofolic Acid with 5-Fluorouracil as Treatment for Advanced Breast Cancer in Patients who Failed Prior Treatment with Anthracyclines and Taxanes: a Phase 2 Study.

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Abstract:

Background: 5-Fluorouracil (FU) has response rates in metastatic breast cancer in the range of 17-23%. Although leucovorin (LV) modestly enhances FU activity, it has not been typically combined with FU in this setting. While LV must undergo metabolic activation, 5,10-methylenetetrahydrofolic acid (CoFactor, CF) directly modulates FU inhibition of thymidylate synthase without the need for metabolic conversion. CF + FU demonstrated enhanced efficacy and reduced hematologic toxicity compared to LV + FU in rodent models. We evaluated CF + FU in advanced metastatic breast cancer (mBC) patients.

Methods: Patients had HER2/neu-negative, taxane and anthracycline refractory mBC, fewer than 3 prior therapies for advanced disease, and performance status ECOG 0-2. Prior FU or capecitabine-based palliative chemotherapy was not allowed. Thirty-two (32) patients were enrolled, and 31 received at least one dose of drug. A treatment cycle was 60 mg/m^2 CF and 500 mg/m^2 FU, weekly iv bolus for 6 weeks, repeated every 8 weeks. The primary endpoint of response rate was measured every 8 weeks using RECIST criteria.

Results: As of May 7, 2008 data are available on 31 patients. Treatment is ongoing in 1 patient. The median age is 54 years (range 31-76). The most common adverse events were asthenia (52%), nausea (33%), diarrhoea (29%), vomiting (26%), anorexia (23%), dyspnoea (23%), and neutropenia (23%). Five patients reported 12 serious adverse events (pneumonia, abdominal pain, diarrhoea (2), general physical health deterioration (3), pancytopenia, breast pain, dyspnoea, asthenia, and hypersensitivity). None were considered Suspected Unexpected Serious Adverse Reactions (SUSARs). The objective response rate (CR + PR) based on investigator assessment is 23% (1 CR, 6 PR, 14 SD, 10 PD).

Conclusion: CF + FU is a safe, well tolerated, and active treatment in mBC. With the use of anthracycline and taxane-based regimens in the adjuvant setting, more treatment options are needed for advanced disease. The high level of activity and low toxicity of CF + FU suggests that this combination may be a good treatment option for mBC.

Objectives:

Primary Objective:

To assess the efficacy (ORR) of CoFactor in combination with 5-FU in anthracycline and taxane pretreated advanced breast cancer patients.

Secondary Objectives:

To assess the safety profile of the combination.

To estimate the efficacy parameters: duration of response, PFS, and overall survival.

Patients and Methods:

Eligibility:

Adult women with advanced breast cancer who failed prior treatment with anthracyclines and taxanes were eligible if they had measurable disease; a life expectancy of at least 3 months; had adequate performance status; and had adequate hematology and serum chemistry parameters.

Patients were not eligible if they were HER2/neu-positive; had received prior 5-FU and/or capecitabine-based palliative chemotherapy; had previous unexpected reaction to fluoropyrimidines; or had completed anticancer therapy or participated in another experimental drug study within 4 weeks prior to the first day of study treatment.

Treatment:

CoFactor was administered at a dose of 60 mg/m^2 as an iv bolus infusion over 2-3 minutes. Administration of CoFactor was followed 20 minutes later by 500 mg/m^2 5-FU as an iv bolus over 2-3 minutes. Treatment was administered weekly for 6 weeks every 8 weeks. Each treatment cycle is 8 weeks.

Patient Demographics:

Patients were enrolled in 7 sites in 5 countries: Russia, Spain, Peru, Argentina, and Mexico. The median age range was 54 years (range 31-76).

Table 1: Patient Demographics

Characteristic	N (%)
Age	
<50	13 (42%)
50-64	12 (39%)
≥65	6 (19%)
Race/Ethnicity	
Hispanic or Latino	16 (52%)
White	15 (48%)
ECOG Performance Status	
0	15 (48%)
1	15 (48%)
Unknown	1 (3%)
Karnofsky Status	
100	8 (26%)
90	7 (23%)
80	8 (26%)
Unknown	8 (26%)

Table 2: Oncology History

Characteristic	N (%)
Stage	
Stage II	13 (42%)
Stage III	11 (35%)
Stage IV	4 (13%)
Stage Unknown	3 (10%)
Sites of Disease	
Lymph Node	17 (55%)
Liver	11 (35%)
Lung	10 (32%)
Mediastinum	10 (32%)
Bone	9 (29%)
Soft Tissue	6 (19%)
Pleura	5 (16%)
Skin	4 (13%)
Breast	2 (6%)
Other	4 (13%)

Safety Results:

Table 3: Most Common Adverse Events (≥ 10%) by System Organ Class Regardless of Relationship to Treatment (N=31)

System Organ Class / Preferred Term	Grade 1-2	Grade 3-4	Total
Blood and lymphatic system disorder			
Anaemia	4 (13%)	0	4 (13%)
Leukopenia	4 (13%)	1 (3%)	5 (16%)
Neutropenia	2 (6%)	5 (16%)	7 (23%)
Cardiac disorders			
Tachycardia	3 (10%)	0	3 (10%)
Gastrointestinal disorders			
Abdominal pain	3 (10%)	1 (3%)	4 (13%)
Diarrhoea	6 (19%)	3 (10%)	9 (29%)
Nausea	10 (33%)	0	10 (33%)
Vomiting	8 (26%)	0	8 (26%)
General disorders and administration site conditions			
Asthenia	15 (48%)	1 (3%)	16 (52%)
Chest pain	3 (10%)	0	3 (10%)
General physical health deterioration	0	3 (10%)	3 (10%)
Oedema peripheral	2 (6%)	1 (3%)	3 (10%)
Pain	1 (3%)	1 (3%)	3 (10%)
Pyrexia	3 (10%)	0	3 (10%)
Infections and infestations			
Nasopharyngitis	4 (13%)	0	4 (13%)
Metabolism and nutrition disorders			
Anorexia	7 (23%)	0	7 (23%)
Hypocalcaemia	3 (10%)	0	3 (10%)
Hyponatraemia	1 (3%)	2 (6%)	3 (10%)
Musculoskeletal and connective tissue disorders			
Bone pain	2 (6%)	1 (3%)	3 (10%)
Pain in extremity	3 (10%)	1 (3%)	4 (13%)
Nervous system disorders			
Headache	3 (10%)	0	3 (10%)
Paraesthesia	4 (13%)	0	4 (13%)
Respiratory, thoracic and mediastinal disorders			
Cough	5 (16%)	0	5 (16%)
Dyspnoea	5 (16%)	2 (6%)	7 (23%)
Skin and subcutaneous tissue disorders			
Palmar-plantar erythrodysaesthesia syndrome	6 (19%)	0	6 (19%)
Vascular disorders			
Hypertension	3 (10%)	0	3 (10%)

Efficacy Results:

Table 4: Overall Response (N=31)

Response	N (%)
Objective response (complete response + partial response)	**7 (23%)**
Complete response	1 (3%)
Partial response	6 (19%)
Stable disease	14 (45%)
Progressive disease	10 (32%)

Extent of Exposure:

As of May 7, 2008, a total of 71 cycles were administered to 31 patients on study. The median number of cycles per patient was 2, ranging from 1-5.

Table 5: Study Drug Exposure

Number of cycles per patient	N (%)
1	10 (32%)
2	8 (26%)
3	8 (26%)
4	4 (13%)
5	1 (3%)

Conclusions:

Weekly iv bolus injections of CoFactor and 5-FU show acceptable response rates in a metastatic breast cancer population with refractory disease. The observed overall response rate of 23% is in a comparable range with other drugs approved in the 3rd line setting[1, 2]. Cycles of 60 mg/m^2 CoFactor and 500 mg/m^2 5-FU, weekly iv bolus for 6 weeks is a well-tolerated regimen with an acceptable safety profile. Final data on progression free survival and duration of response will be available by end of 2008.

References:

1) Blum J., Jones S., Buzdar A. et al. Multicenter phase II study of capecitabine in paclitaxel-refractory metastatic cancer. *J Clin Onc 17:485-93, 1999*.

2) Vanda L., Thomas E., Li R. et al. Phase III trial of ixabepilone plus capecitabine compared to capecitabine alone in patients with metastatic breast cancer (MBC) previously treated or resistant to an anthracycline and resistant to taxanes. ASCO 2007 Annual Meetings Summaries: Breast Cancer-Related Abstracts: No 1006 pp 18.