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Physical function and quality of life in frail and/or elderly patients with metastatic colorectal cancer treated with capecitabine and bevacizumab: An exploratory analysis

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ABSTRACT

Objectives: Optimal treatment strategies in frail and/or elderly patients with metastatic colorectal cancer have not been well defined. Using data from a prospective, phase II study of elderly patients with metastatic colorectal cancer treated with bevacizumab and capecitabine, we explored the differences in functional measure and quality of life (QoL) between patients with ECOG performance status (PS) 1 and 2.

Materials and Methods: Geriatric functional measures included patient reported limitations in ADLs and IADLs, ECOG PS, 3-item recall, hearing acuity, and the "Get up and Go" test. QoL was assessed by means of the FACT-C questionnaire and the EQ-5D questionnaire. The prognostic impact of baseline characteristics on survival was studied using univariate Cox regression analysis.

Results: The majority (62%) of the 45 patients had an ECOG PS of 2. The ECOG PS 2 group had more limitations in IADLs, lower baseline QoL, and a lower patient-rated health score. For all participants, QoL significantly improved from baseline to the start of cycle 2 (FACT-C: 99.9 vs. 105.4, $p = 0.01$) and did not deteriorate when baseline scores were compared to when participants went off study (FACT-C: 99.9 vs. 98.6, $p = 0.59$). In the Cox-regression analysis, a positive "Get up and Go" test was prognostic for improved survival (HR = 0.31, $p = 0.01$).

Conclusion: There is significant heterogeneity in functional measures and quality of life among elderly patients with metastatic colorectal cancer with ECOG PS 1 and 2. The "Get up and Go" test may be a useful prognostic indicator for survival in this population.

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1. Introduction

Colorectal cancer (CRC) is the third most common cancer in both men and women in the United States and there were 142,570 new cases and 51,370 deaths in 2010.[1] Although the majority of patients who are diagnosed with CRC are over the age of 70 years, this population is substantially underrepresented in clinical trials.[2,3] Several randomized phase III clinical trials of combination chemotherapy in mostly younger patients with metastatic colorectal cancer (mCRC) have shown improvement in progression-free and overall survival.[4,5] A pooled analysis of 9 clinical trials was performed involving 6286 patients with advanced CRC treated with first-line combination chemotherapy (excluding bevacizumab). The analysis showed that patients with an ECOG performance status (PS) of 2 experienced increased toxicity and no significant improvement in survival, while patients with ECOG PS of 0 to 1 did experience a survival advantage.[6] On the basis of these results, alternative strategies in the management of frail and elderly patients with mCRC have been explored. In a large, pivotal phase III trial, bevacizumab combined with chemotherapy, showed an improvement in overall survival (OS) in a population of mostly young patients with mCRC.[7] Although bevacizumab can exacerbate common comorbidities in the elderly such as hypertension and cerebrovascular disease, it is thought to be better tolerated than cytotoxic chemotherapy. Several observational and interventional studies have looked at the efficacy and safety of bevacizumab in the elderly. One of the earliest trials in this population was a randomized phase II trial of bevacizumab + bolus 5-flourouracil (5-FU)/leucovorin (LV) versus placebo + 5-FU/LV in patients with mCRC who were judged unfit to receive combination chemotherapy.[8] In this study, 80% of the patients were older than 65 years and almost all (93%) had an ECOG PS of ≤1. The results showed a significant increase in progression-free survival (PFS) (5.5 vs. 9.2 months) and a trend toward improved overall survival (12.9 vs. 16.6 months) in the bevacizumab arm. The treatment was well tolerated and was thought to be a safe and effective alternative to irinotecan and oxaliplatin for elderly patients. A large observational cohort study involving 896 patients with mCRC showed that first-line bevacizumab-based chemotherapy resulted in a similar PFS regardless of age; however OS decreased with increasing age.[9]

Other single arm studies have observed an older and even frailer population of patients with mCRC, but few of them have looked at the impact of chemotherapy on geriatric functional measures and changes in quality of life over time.[10] Furthermore, these trials have a fair amount of missing data, because of the inability to capture end of study outcomes. Most of these studies have been in patients treated with 5-FU/LV or combinations of these drugs with oxaliplatin.[11] Other components of comprehensive geriatric evaluations including comorbidity, depression, cognition, nutrition, and polypharmacy, have been shown to be predictors of overall survival and toxicity in older patients with cancer.[12]

We conducted a phase II, single arm, open-label, prospective clinical trial (N = 45) of capecitabine plus bevacizumab in elderly and/or frail patients with mCRC.[13] The objective of the study was to evaluate the efficacy and safety of this regimen in this population and the primary results are presented in the accompanying paper. In addition to survival and toxicity data, we collected information about geriatric function, geriatric health and quality of life throughout the trial.

2. Materials and Methods

The primary aim of this analysis was to explore the differences in geriatric function and geriatric health measures between patients with ECOG PS 1 and 2 in this phase II, single-arm, open-label, prospective clinical study of capecitabine and bevacizumab in elderly and/or frail patients. The secondary aim of the analysis was to evaluate the impact of treatment with capecitabine and bevacizumab on the quality of life of patients and the rate of the functional decline.

2.1. Patients

Patients were included in the study if they were over the age of 18 years and had an ECOG PS of 2 or if they had ECOG PS of 1 and were over the age of 70. Participants were recruited through the Translational Oncology Research International (TORI) network at UCLA and throughout California. The target population for this study was patients with metastatic colon cancer with an ECOG PS 1 or 2 who required chemotherapy but were deemed too frail by their oncologist to tolerate combination chemotherapy with either irinotecan or oxaliplatin. To enroll, patients were required to have stage IV histologically proven adenocarcinoma of the colon with at least one measurable lesion according to the Response Evaluation Criteria in Solid Tumors (RECIST) criteria. No prior chemotherapy for metastatic colorectal cancer was allowed, but prior adjuvant chemotherapy was permitted. The full inclusion and exclusion criteria are in press.[13] Comorbidity was measured by the Charlson Comorbidity Index (CCI).[14] Overall survival was measured on the basis of the intent-to-treat population and safety was evaluated in all patients who received ≥1 dose of study medication.

2.2. Treatment Protocol

Capecitabine 1000 mg/m^2 was given orally twice daily for 2 weeks followed by 1 week of rest and bevacizumab 7.5 mg/kg IV was administered every 3 weeks. Treatment was continued until disease progression, unacceptable toxicity, or withdrawal of patient consent. Tumor assessments were performed after every 3 cycles of therapy.

2.3. Assessment of Functional Status

Functional status was measured using a patient-reported 6-item activities of daily living (ADL) index,[15] a 7-item instrument activities of daily living (IADLs),[16] and the investigator-reported ECOG PS. These were recorded at baseline and every 21 days thereafter. The end of study assessment was the last evaluation before the patient went off study due to withdrawal, progression, or death. An investigator-administered brief geriatric functional examination was performed at