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Effectiveness and safety of first-line bevacizumab plus FOLFIRI in elderly patients with metastatic colorectal cancer: Results of the ETNA observational cohort

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ABSTRACT

Objectives: Effectiveness of bevacizumab for metastatic colorectal cancer in elderly patients has been investigated in observational studies, mainly associated with oxaliplatin-based regimens. Here, using the ETNA cohort in which the majority of patients received bevacizumab + FOLFIRI, the effectiveness of this combination in elderly patients is explored.
Materials and Methods: Patients initiating first-line therapy with bevacizumab between January 2006 and December 2007 were identified in 28 French centres and followed for 24 months. Vital status was collected over 36 months. In the present analysis those who received FOLFIRI were retained (85% of those included), and patients were stratified by age (<70/≥70 years). The Kaplan–Meier method estimated progression-free survival (PFS) and overall survival (OS), and Cox models were used to assess the independent effect of age on survival outcomes.
Results: Among the 351 patients who received bevacizumab + FOLFIRI, 33.9% were aged ≥70 years, 66.1% <70 years. Respectively 15.1% and 9.5% of patients had ECOG-PS ≥2; 49.6% and 40.1% used 'stop-and-go' treatment scheduling; and 56.3% and 44.4% experienced grade 3/4 adverse events. Overall response rate was 58.8% and 62.5%. Median [95% confidence interval, CI] OS was respectively 24.1 [20.4; 26.2] and 28.5 [25.0; 31.0] months; age ≥ 70 years and ECOG-PS ≥ 2 were significantly associated with death. Median PFS [95% CI] was respectively 10.9 [9.4; 12.6] and 9.8 [9.2; 11.2] months; hepatic metastases was associated with progression, and age ≥70 years was associated with progression after 14 months of follow-up but not before.

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Conclusions: The present study adds to the literature on the safe and beneficial effect of bevacizumab in the elderly receiving FOLFIRI regimen.

1. Introduction

Bevacizumab, an antiangiogenic agent that binds and blocks vascular endothelial growth factor A (VEGF-A),[1] received European marketing authorisation in 2005. It is approved in France as a first-line therapy for metastatic colorectal cancer (mCRC) combined with fluoropyrimidine with or without irinotecan or oxaliplatin.[2] It has demonstrated efficacy in clinical trials[3] yet a concern has been the younger age of the populations included in clinical trials[4] compared with that of real-life patients with colorectal cancer; for instance in France in 2012 the mean age at disease diagnosis was 70 years for men and 73 years for women.[5] Observational studies have since been performed,[6–11] and outcomes stratified by age have been reported.[6,12–17] In the majority of these studies bevacizumab was most frequently associated with the oxaliplatin-based regimen chemotherapy, whereas in the ETNA cohort,[11] treatment was characterised by the frequent use of bevacizumab + FOLFIRI (85%). This is in relation to the timing of the inclusion period that coincided with the original European indication for bevacizumab that was for use in combination with 5-Flurouracil with or without irinotecan (which was broadened in 2008), and provides the opportunity for the effectiveness of this combination in elderly patients to be explored. Using the ETNA study cohort data, we aimed to evaluate the effectiveness and safety of bevacizumab combined with FOLFIRI according to age.

2. Materials and Methods

2.1. Study Design

The ETNA study has been reported in detail elsewhere.[11] Briefly, this was an observational cohort study conducted in 28 public and private centres of South-West France. All patients who initiated bevacizumab between January 2006 and December 2007 were identified using hospital pharmacies. Patients treated for first-line mCRC with inoperable metastases, with at least six months between the end of adjuvant chemotherapy and the onset of first-line therapy, were included and followed for 2 years after initiation of first-line therapy. Vital status was collected over 3 years. Patients were informed of the study objectives and data collection, and could indicate their wish not to participate. The study protocol was approved by the French data protection agency. It was also submitted to the regional ethics committee, which confirmed that approval was not required according to French regulations for observational studies.

2.2. Data Collection

Data were extracted from patient medical records at baseline and during follow-up. Baseline characteristics included demographic data, history of colorectal cancer (primary tumour and metastatic disease), significant medical history, as well as clinical and biological exams before initiation of first-line therapy. During the 2 years of follow-up, patterns of bevacizumab use in first-line therapy were collected including doses, timing of administration, combined chemotherapy, as well as toxicities by cycle, treatment response, and subsequent treatment lines (with or without bevacizumab).

2.3. Clinical Outcomes

Measures of clinical outcomes were based on physician assessments documented in patient medical files. Progression-free survival (PFS) was defined as the interval between first-line therapy initiation and first disease progression, evaluated in current practise by CT-scan every 2 to 3 months based on the Response Evaluation Criteria in Solid Tumours (RECIST) criteria.[18] Overall survival (OS) was defined as the interval between start of first-line therapy and death from any cause. Follow-up was censored at progression or death (depending on the outcome studied), loss to follow-up, or the end of the study period (2 years for PFS and 3 years for OS). Adverse events documented in medical files were classified according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE), version 3.0.[19] Reported adverse events were not subsequently investigated to establish a causal relationship with bevacizumab.

2.4. Statistical Analysis

The ETNA cohort was stratified with respect to age (<70, ≥70 years). OS and PFS were estimated using the Kaplan–Meier method. Median OS and PFS estimates along with 95% confidence intervals (CI) are reported, as well as 1- and 2-year OS and PFS rates (with 95% CI), and 3-year OS rate (with 95% CI). Categorical variables were compared across the age groups using Pearson's chi-square test, or Fisher's exact chi-squared test where appropriate, and OS or PFS using the log rank test. Cox proportional hazards models were used to assess the independent effect of age on survival outcomes (OS and PFS) while adjusting for baseline covariates among patients aged <70 years and ≥70 years. All analyses were performed using SAS® (SAS Institute, v9.2, NC, USA).

3. Results

A total of 411 patients were included in the ETNA cohort, 351 (85.4%) of whom received bevacizumab combined with FOLFIRI. Among the latter, 119 (33.9%) were aged 70 years or more, and 232 patients (66.1%) less than 70 years.

Among the more elderly there was a higher proportion of male patients (70.6% vs. 53.0%, $p = 0.002$), more frequent previous medical history – notably hypertension (36.1% vs. 25.0%, $p = 0.026$), other cardiovascular diseases (23.5% vs. 12.1%, $p = 0.005$), and other cancer (13.4% vs. 5.2%, $p = 0.006$; Table 1). Non-significant differences were observed for baseline