Original Study

Efficacy and Safety of Bevacizumab Combined With Fluoropyrimidine Monotherapy for Unfit or Older Patients With Metastatic Colorectal Cancer: A Systematic Review and Meta-Analysis

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Abstract

Whether bevacizumab represents a feasible option for the first-line treatment of unfit and elderly patients with metastatic colorectal cancer remains controversial. The present meta-analysis included data from 782 patients and provides evidence for the clinical benefit yielded in terms of progression-free survival and overall survival by the addition of bevacizumab to first-line fluoropyrimidine-based chemotherapy for these complex patients.

Background: Whether bevacizumab represents a feasible option for the first-line treatment of unfit and elderly patients with metastatic colorectal cancer (mCRC) remains controversial. The present systematic review and meta-analysis evaluated the efficacy and safety data of bevacizumab combined with first-line fluoropyrimidine monochemotherapy for these complex patients. **Patients and Methods:** A systematic search of the published data was conducted through May 31, 2016. The random-effects model was used to combine the effect estimates and the I^2 index to quantify the between-study heterogeneity unexplained by sampling error. **Results:** We included 3 randomized controlled trials, 4 single-arm phase II trials, and 1 prospective cohort study in the present meta-analysis (n = 782). The monochemotherapy administered was capecitabine in 531 patients (67.9%) and 5-fluorouracil in 251 (32.1%); 500 (63.9%) also received bevacizumab. The median age was 75 years, 441 patients (56.4%) were men, and the Eastern Cooperative Oncology Group performance status was 0 to 1 in 684 patients (87.7%). The combination with bevacizumab produced advantages in terms of both progression-free survival (hazard ratio, 0.52; 95% confidence interval, 0.43-0.64; $P < .00001$; $I^2 = 0\%$) and overall survival (HR, 0.79; 95% CI, 0.64-0.98; $P = .03$; $I^2 = 0\%$). The pooled effect estimates of the randomized controlled trials have been previously reported. As expected, all-grade hypertension (27% vs. 4.9%), bleeding (24% vs. 6.4%), thromboembolic events (10% vs. 5%), and proteinuria (25.6% vs. 8.2%) were more frequent in the bevacizumab combination group. **Conclusion:** Adding bevacizumab to first-line fluoropyrimidine monochemotherapy significantly improved progression-free and overall survival in unfit and elderly patients with mCRC, with a manageable safety profile and no unexpected toxicities.

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Introduction

With a median age of diagnosis of > 70 years and more than one third of all deaths occurring in patients aged > 80 years, colorectal cancer (CRC) is predominantly a disease of the elderly.[1] Although systemic treatment has markedly evolved in recent years, how to best approach geriatric or unfit populations remains a matter of debate, with specific guidelines lacking. A widespread use of the geriatric assessment has been advocated to improve patient selection; however, evidence of its value in the decision-making process is limited.[2] The results from 4 randomized trials (ie, Medical Research Council Fluorouracil, Oxaliplatin and Irinotecan: Use and Sequencing [MRC FOCUS], CApecitabine, IRinotecan, Oxaliplatin [CAIRO], Fédération Francophone de Cancérologie Digestive 2000-05 [FFCD 2000-05], and Australasian Gastro-Intestinal Trials Group Mitomycin, Avastin, Xeloda [AGITG MAX]) have shown that in patients with advanced or metastatic CRC (mCRC), upfront combination chemotherapy (doublet) was not superior to sequential treatment beginning with 5-fluorouracil (5-FU) alone in terms of survival.[3-6] Hence, the upfront use of single-agent fluoropyrimidine, given either intravenously or orally,[7] can still be considered a valid option for frail, highly comorbid, or very old patients. Nevertheless, the upfront use of doublet chemotherapy with 5-FU coupled with irinotecan or oxaliplatin has been shown to be as effective for older patients as for younger subjects.[8,9] However, the prescription of a combination in clinical practice has been often restrained owing to the potential for an increased risk of toxicity.[10,11]

Bevacizumab, the first recombinant humanized monoclonal antibody to vascular endothelial growth factor, is commonly used in CRC in first- and second-line therapy and between treatment lines. A more rational use of the antiangiogenic strategy in the older or unfit population has also been proposed[12] based on results of community-based registries, phase II studies, and a large, randomized phase III trial.[13] Accordingly, subgroup analyses from randomized trials have suggested a similar benefit when adding bevacizumab to chemotherapy for older or younger patients and have not recommended using age alone as a specific criterion to exclude patients from antiangiogenic treatment. Similarly, frail or unfit patients with mCRC might still benefit from doublet chemotherapy regimens.[14] Notwithstanding this large body of evidence, both chemotherapy usage and biologic prescriptions decrease for patients of advanced age.[15,16]

The aim of the present trial-level meta-analysis was to evaluate the effect of adding bevacizumab to the most frequently used cytotoxic regimens for mCRC patients who had been judged unfit to receive an intense upfront treatment (because of age or frailty) and to estimate the magnitude of this effect.

Patients and Methods

Types of Studies, Participants, Interventions, and Outcomes

We included randomized controlled trials (RCTs) or prospective cohort studies of patients with advanced or metastatic CRC. We restricted the data to patients receiving monochemotherapy plus bevacizumab because of advanced age or comorbidity. Data on the following outcome measures were studied: objective response rate (ORR), progression-free survival (PFS), and overall survival (OS).

Search Strategy and Selection Criteria

The PubMed and EMBASE databases were searched for RCTs and prospective cohort studies in May 31, 2016 with no language or publication status restrictions. The search query for PubMed was as follows: ("bevacizumab" [supplementary concept] OR "bevacizumab" [all fields]) AND ("colorectal neoplasms" [MeSH terms] OR ("colorectal" [all fields] AND "neoplasms" [all fields]) OR "colorectal neoplasms" [all fields] OR ("colorectal" [all fields] AND "cancer" [all fields]) OR "colorectal cancer" [all fields]) AND ("aged" [MeSH terms] OR "aged" [all fields] OR "elderly" [all fields] OR unfit [all fields]). For EMBASE, the query was "bevacizumab"/exp OR "bevacizumab" AND ("aged"/exp OR "aged" OR "elderly"/exp OR "elderly" OR "unfit") AND ("colorectal tumor"/exp OR "colorectal tumor" OR "colorectal carcinoma"/exp OR "colorectal carcinoma" OR "colorectal neoplasm"/exp OR "colorectal neoplasm" OR "colorectal cancer"/exp OR "colorectal cancer") AND [embase]/lim NOT [medline]/lim.

Ongoing studies and studies with < 10 patients per arm were excluded.

Data Extraction

Two investigators (V.T., L.P.) independently screened the titles and abstracts for inclusion. Full reports were retrieved for further assessment if the information in the abstract suggested that the study met all the prespecified criteria.

Two investigators (V.T., L.P.) were responsible for data assessment and extraction. Details on the study design, participants, setting, interventions, quality components, and efficacy and safety outcomes were recorded. Any inconsistency was resolved by discussion (F.P., G.M.).

For studies included in > 1 publication, the data were extracted from all the publications. However, we considered the final or updated version of each trial as the primary reference. We included trials in which patients crossed-over to the other treatment arm at progression or received other treatment off-study and were analyzed according to the arm to which they had been originally randomized. We also extracted data from patient subgroups if these answered our original question.

Statistical Analysis

The measure of association for PFS and OS was expressed as the hazard ratio (HR). The measure of association for the ORR was the odds ratio (OR). The estimation of the median time to PFS and OS was calculated using the weighted average of the hazard rate with the weights calculated by the inverse variance approach. The hazard rate and its standard error were estimated using the median time as the denominator under the assumption of exponential distribution. The I^2 index was calculated to estimate the heterogeneity among trials. The random effects model was used for estimating and testing results in all analyses.

Although the efficacy analyses included data from RCTs, the safety analysis also incorporated data from cohort studies. The determination of toxicity (all National Cancer Institute Common Terminology Criteria for Adverse Events grades and grade 3-4) focused on the main class of toxicities involving chemotherapy and bevacizumab: hematologic, cardiovascular, and renal toxicity and