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Observed benefit and safety of aflibercept in elderly patients with metastatic colorectal cancer: An age-based analysis from the randomized placebo-controlled phase III VELOUR trial

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ABSTRACT

Objectives: Aflibercept (ziv-aflibercept) significantly improves progression-free (PFS) and overall survival (OS) when added to 5-fluorouracil, leucovorin and irinotecan (FOLFIRI), compared with FOLFIRI alone, in patients with metastatic colorectal cancer previously treated with oxaliplatin-based therapy. This subset analysis of the VELOUR study investigates aflibercept plus FOLFIRI versus placebo plus FOLFIRI according to age.
Methods: Efficacy and safety were analyzed by treatment arm and age (≥ or <65 years).
Results: Overall, 443 patients were ≥65 years old (205 in aflibercept arm; 238 in placebo arm) and 783 were <65 years old (407 in aflibercept arm; 376 in placebo arm). Median OS was 12.6 versus 11.3 months (hazard ratio [HR]: 0.85; 95.34% CI 0.68–1.07) in patients ≥65 years old and 14.5 versus 12.5 months (HR: 0.80; 95.34% CI 0.67–0.95) in those patients <65 years old, for patients receiving FOLFIRI plus aflibercept or placebo, respectively. There was no interaction between treatment and age. Treatment-emergent adverse events (AEs) were comparable for patients <65 years and ≥65 years old. The incidence of grade 3/4 AEs was higher for patients ≥65 years old than for those <65 years old in both the aflibercept (89.3% versus 80.5%) and placebo (67.4% versus 59.4%) arms. Interaction tests for grade 3/4 antiangiogenic agent-related AEs suggested no heterogeneity between the older and younger patient populations ($p > 0.1$).
Conclusion: A limited but consistent benefit on both OS and PFS was associated with the addition of aflibercept to FOLFIRI compared with placebo in patients <65 and ≥65 years old, with a marked but manageable increase in the toxicity profile in older patients.
Trial Registration: clinicaltrials.gov NCT00561470

1. Introduction

Colorectal cancer (CRC) is the third most common cancer diagnosed worldwide after lung cancer and breast cancer and the second most common cause of cancer death after lung cancer [1,2]. CRC principally affects individuals aged 65 years and older, with the incidence doubling every 7 years in patients aged over 50 years [1–3]. Almost half of newly diagnosed cases occur in patients aged over 75 years [3,4]. As a result, the medical and social burdens of CRC can be expected to increase over the coming decades as the number of individuals living beyond 70 years of age steadily increases.

There is a scarcity of evidence to support guidelines for the treatment of older patients (≥65 years) with CRC due to the fact that older patients with CRC are generally underrepresented in clinical trials [5]. Also, the so called 'fit' older patients who are recruited into

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chemotherapy trials (i.e. those with lower Eastern Cooperative Oncology Group performance status [ECOG PS 0, 1], greater life expectancy, and fewer co-morbidities) are not representative of most older individuals in the general population [6,7].

When feasible, surgery is the most successful treatment option for eradicating the primary lesion, and also where possible eradicating limited metastases, particularly those in the liver. Increasingly, however, combination chemotherapy regimens plus a targeted agent such as the vascular endothelial growth factor (VEGF)-A-targeting monoclonal antibody (mAb) bevacizumab or the epidermal growth factor receptor (EGFR)-targeting mAbs cetuximab and panitumumab are being used to treat patients with metastatic CRC (mCRC) either as stand-alone systemic therapy or as an adjunct to surgery and locally ablative techniques [8,9]. Unfortunately, in older patients with CRC, the use of combination chemotherapy has been debated, due to concerns over the physical and mental frailty of the patients and the fact that older patients are more likely to have co-morbidities and age-specific deterioration in their general organ function, especially kidney and bone marrow [6].

As a consequence, older patients (≥65 years) with mCRC are less likely to be offered optimized systemic therapy, due to the conservative treatment approaches employed by many health care professionals in the management of their disease, which are often based on patient age. This is despite the fact that the efficacy of 5-fluorouracil (5-FU)-, irinotecan- and oxaliplatin-based chemotherapy has been clearly demonstrated in selected older patients [10–14]. Furthermore, the availability of more data on the efficacy and safety of chemotherapy in combination with the targeted agents bevacizumab and cetuximab in older patients has led the International Society of Geriatric Oncology (SIOG) to suggest in their recent guidelines [6,7] that age alone should not be an exclusion criterion for the use of systemic cytotoxic combination therapy plus or minus the newer targeted agents in the treatment of patients with mCRC [7]. This comes with the obvious caveat that careful monitoring of toxicities, and early intervention if required, is essential in the management of elderly patients with mCRC undergoing systemic therapy, and the recognition based on the data from two randomized studies of chemotherapy in the first-line setting [15,16] that it is important to evaluate risk factors for toxicity in older patients with cancer [17].

Disruption of tumor angiogenesis using the VEGF-A-targeting mAb bevacizumab has been shown to be a clinically effective strategy in both the first- and second-line treatment of patients with mCRC in combination with standard chemotherapy regimens [18–20]. However, antiangiogenic agents in particular have a side-effect profile that requires careful monitoring in older patients, who are likely to have a small or moderately increased risk of thromboembolic events, hypertension, and impaired renal function.

Evidence from two pooled analyses showed the benefit conferred by bevacizumab to be maintained in patients aged ≥65 years and ≥70 years enrolled in clinical trials [21,22]. In the first of these analyses of data from four randomized trials, three in the first-line setting and one in the second-line setting, involving 1864 patients with mCRC aged <65 years and 1142 patients aged ≥65 years, the addition of bevacizumab to fluoropyrimidine-based chemotherapy was shown to significantly prolong progression-free survival (PFS) and overall survival (OS) [21]. The PFS and OS benefits were similar in both older (≥65 years and ≥70 years) and younger patients (<65 years). Increases in arterial thromboembolic events (ATEs) in the bevacizumab group versus the control group in patients aged 65 years and 70 years of age or older were reported, but no other 'substantial' increases in grade 3–5 adverse events (AEs) were reported. In the second of these analyses, data for bevacizumab from seven randomized trials, involving 3763 patients with mCRC, of whom 1492 patients were aged ≥65 years and 426 patients were aged ≥75 years, confimed that the statistically significant benefits in OS and PFS conferred by bevacizumab reported for the individual trial populations were maintained across all age groups (<65 or ≥65 years; ≥75 years) [22]. No data were presented for safety (incidence of AEs) according to the <65 years and ≥65 years age groups in this pooled analysis.

More recently, the multinational, randomized, double-blind, phase III VELOUR study (clinicaltrials.gov NCT00561470) [23] demonstrated that the addition of the antiangiogenic recombinant fusion protein aflibercept (also known as VEGF-Trap or ziv-aflibercept), that binds VEGF-A and VEGF-B, as well as placental growth factor, to infusional 5-FU, leucovorin and irinotecan (FOLFIRI), significantly improved OS (hazard ratio [HR] 0.82, 95.34% confidence interval [CI] 0.71–0.94; $p = 0.0032$), PFS (HR 0.76, 95% CI 0.66–0.87; $p < 0.0001$) and response (19.8% [95% CI 16.4–23.2%] versus 11.1% [95% CI 8.5–13.8%]) compared with FOLFIRI plus placebo in patients with mCRC who had failed prior oxaliplatin-containing therapy [23]. This benefit was also apparent in patients pretreated with bevacizumab (with HRs for OS and PFS of 0.86 and 0.66 respectively) [24], and the results of other prespecified subgroup analyses of OS and PFS suggested that the benefit of combining aflibercept with FOLFIRI was achieved across a range of subgroups defined by key baseline characteristics [24].

The present analysis assesses the efficacy and safety of aflibercept plus FOLFIRI and placebo plus FOLFIRI according to age (≥65 versus <65 years) of patients with mCRC treated in the VELOUR study.

2. Materials and Methods

2.1. Study Design

The design of the multinational, randomized, double-blind, phase III VELOUR study has been described in detail previously [23,24].

Briefly, patients with an unresectable adenocarcinoma of the colon or rectum who had progressed during or following the administration of one prior oxaliplatin-containing regimen were randomized 1:1 to receive either aflibercept, at a dose of 4 mg/kg administered intravenously every 2 weeks, in combination with FOLFIRI, or FOLFIRI plus placebo [23,25]. Randomization was stratified according to ECOG PS 0, 1, or 2 and whether patients had received prior therapy with bevacizumab (yes versus no) [23,25]. Treatment was to be continued until disease progression, the occurrence of unacceptable toxicity, or patient refusal [23,25]. The VELOUR study was approved by the local institutional review boards/ethics committees at each trial center and was conducted in accordance with the Declaration of Helsinki. Prior to participation, all patients provided written informed consent [23,25].

In the present analysis, the efficacy and safety of the two treatment arms were investigated in patients from the VELOUR study intention to treat (ITT) population who were aged ≥65 years and <65 years [24]. The endpoints investigated were PFS, OS, and incidence of grade 3/4 AEs.

2.2. Assessments

At each cycle, a clinical examination and laboratory assessments were carried out and AEs (according to National Cancer Institute [NCI]-Common Terminology Criteria for Adverse Events [CTCAE] v3.0) and concomitant medications were recorded. Disease assessments took place every 6 weeks until progression and every 8 weeks following progression (or every 6 weeks if treatment was discontinued prior to progression). Response was measured according to RECIST (Response Evaluation Criteria in Solid Tumors, version 1.0) and assessed by an independent review committee (IRC) blinded to study treatment allocation.

2.3. Statistical Considerations

Median OS and PFS times were calculated as estimates, using the Kaplan–Meier product limit method [23,25,26]. OS was defined as the time interval between randomization and death from any cause. PFS was defined as the time interval from randomization to first observation

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