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Original article

Bevacizumab as adjuvant treatment for colon cancer: Updated results from the S-AVANT phase III study by the GERCOR Group

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ABSTRACT

BACKGROUND: The AVANT study did not meet its primary endpoint of improving disease-free survival (DFS) with the addition of bevacizumab to oxaliplatin-based chemotherapy in stage III resected colon cancer (CC). We report here long-term survival results (S-AVANT).

PATIENTS AND METHODS: Patients with curatively resected stage III CC were enrolled into the AVANT trial and were randomized to FOLFOX4, FOLFOX4-bevacizumab, or XELOX-bevacizumab.

RESULTS: A total of 2867 patients were randomized: FOLFOX4: 955, FOLFOX4-bevacizumab: 960, XELOX-bevacizumab: 952. With a median of 6.73 years median follow up (IQR 5.51-10.54), 672 patients had died, of whom 198 (20.7%) in FOLFOX4 arm, 250 (26.0%) in FOLFOX4-bevacizumab arm, and 224 (23.5%) in XELOX-bevacizumab arm. The 10-year OS rates were 74.6%, 67.2%, and 69.9%, (*P*=0.003) and 5-year DFS rates were 73.2%, 68.5%, and 71% (*P*=0.174), respectively. The OS and DFS hazard ratios (HRs) were 1.29 (95% confidence interval [CI] 1.07-1.55; *P*=0.008) and 1.16 (95% CI 0.99-1.37; *P*=0.063) for FOLFOX4-bevacizumab versus FOLFOX4 and 1.15 (95% CI 0.95-1.39; *P*=0.147) and 1.1 (95% CI 0.93-1.29; *P*=0.269) for XELOX-bevacizumab versus FOLFOX4, respectively. Colon cancer-related deaths (n=542) occurred in 157 patients receiving FOLFOX4 (79.3%), in 205 receiving FOLFOX4-bevacizuamb (82.0%), and in 180 receiving XELOX-bevacizumab (80.4%), with no difference between arms (*P*=0.764), while non-colon cancer-related deaths occurred in 41 (20.7%), 45 (18.0%), and 44 (19.6%) patients, respectively. Late cardiovascular-related and sudden deaths were reported in 13 (6.6%), 17 (6.8%), and 14 (6.3%) patients, in arm FOLFOX4, FOLFOX4-bevacizuamb, and XELOX-bevacizumab respectively (*P*=0.789). Treatment arm, gender, age, histological differentiation, performance status, T and N stages, and localization of primary CC were independent prognostic factors of OS in stage III.

CONCLUSIONS: S-AVANT shows a detrimental effect of the addition of bevacizumab to FOLFOX4 adjuvant therapy on OS in patients with stage III CC, without increase in non-colon cancer-related deaths. This finding is consistent with the initial AVANT report.

Keywords: colon cancer, adjuvant, bevacizumab, FOLFOX, XELOX

Key message (400 characters with spaces)

The AVANT study did not improve disease-free survival (DFS) with the addition of bevacizumab to oxaliplatin-based chemotherapy in stage III resected colon cancer (CC). The current finding with a median of 6.73 years median follow-up is consistent with the initial AVANT report showing a detrimental effect of bevacizumab on OS when given with adjuvant FOLFOX4 therapy in stage III CC.

Introduction

Colorectal cancer (CRC) is the fourth most common cancer in the world and the second leading cause of death [1]. Close to 25% of patients with colon cancers (CCs) are diagnosed with stage III disease in western countries [2].

Adjuvant chemotherapy with fluoropyrimidines (5-fluorouracil and leucovorin [5-FU/LV] or capecitabine) and oxaliplatin (FOLFOX or XELOX) is the current standard of care for patients with stage III CC based on findings from three large phase III trials, the Multicenter International Study of Oxaliplatin/5-FU/LV in the Adjuvant Treatment of Colon Cancer (MOSAIC), the National Surgical Adjuvant Breast and Bowel Project (NSABP) C-07, and the NO16968 [3-7].

Vascular endothelial growth factor (VEGF) inhibition with bevacizumab, a humanized anti-VEGF monoclonal antibody, has a direct anti-vascular effect in patients with metastatic CRC when given with chemotherapy reflected by improved overall survival (OS) [8]. The AVANT (Bevacizumab-Avastin® adjuVANT) phase III trial failed to demonstrate the superiority of bevacizumab added to oxaliplatin in combination with either 5-FU/LV (FOLFOX4) or capecitabine (XELOX) compared with FOLFOX4 in terms of disease-free survival (DFS) in patients who had undergone surgery with curative intent for stage III CC [9]. In line with the AVANT study results, the National Surgical Adjuvant Breast and Bowel Project (NSABP) C-08 trial that also evaluated bevacizumab with adjuvant oxaliplatin-based chemotherapy showed no efficacy (DFS) of this treatment in US patients with stages II and III CC [10, 11]. The QUick And Simple And Reliable 2 (QUASAR 2) trial showed similar results when bevacizumab was added to adjuvant capecitabine [12].

Here we report the final survival results for the AVANT study with the long-term survival follow-up of patients with stage III CC (the S-AVANT study).

METHODS AND PATIENTS

Patients

Complete eligibility criteria have been previously reported [9]. Briefly, eligible patients had histologically-confirmed stage III colon carcinoma according to the American Joint Cancer Committee/International Union Against Cancer (AJCC/UICC) staging system, were older than 18 years of age, and had their curative surgery performed 4 to 8 weeks before randomization.

The main exclusion criteria included: the presence of a remaining tumor, carcinoembryonic antigen >1.5 x the upper normal limit after surgery, prior anti-angiogenic treatment, major surgery, open biopsy or major traumatic injury <28 days before the study treatment, and abnormal hematologic, hepatic, or renal function. The S-AVANT protocol was approved by the Ethics Review Committee or Institutional Review Board at participating sites. All patients provided informed consent.

Trial design

AVANT was a prospective, multicenter, randomized, parallel, open-label, 3-arm phase III trial in patients operated for high-risk stage II and III CC. It was an event or time-driven trial only for stage III patients. The study continued until 36 months after the last patient was randomized. The 3-year DFS for stage III (the primary objective) data were mature for analysis in 2010 and were published in 2012 [9].

The S-AVANT study was designed for the final OS analysis with extended follow-up of patients randomized in the AVANT trial. The sponsor (ROCHE) followed-up on study and locked data on June 30, 2010 (a 3-year minimum follow-up period). At that time, median follow-up for the study population was 48 months. In 2012, the sponsor transferred the AVANT database to GERCOR for an additional update.

Treatment plan

Patients were randomized (stratified by geographic region and stage of disease) in a 1: 1: 1 ratio to receive one of the three treatment options: 1/ FOLFOX4 for 24 weeks followed by a 24-week observation (arm A), 2/ FOLFOX4-bevacizumab for 24 weeks followed by bevacizumab monotherapy for a further 24 weeks (arm B), or 3/ XELOX-bevacizumab for 24 weeks followed by bevacizumab monotherapy for a further 24 weeks (arm C). FOLFOX4 and XELOX were administered as previously described [9]. Bevacizumab 5 mg/kg was administered over 30 to 90 minutes as an intravenous infusion on day 1 prior to oxaliplatin 5 mg/kg every 2 weeks (FOLFOX4) or oxaliplatin 7.5 mg/kg every 3 weeks (XELOX). Bevacizumab monotherapy was administered at 7.5 mg/kg every 3 weeks. If capecitabine or 5-FU was discontinued due to toxicity, the patient could continue bevacizumab, but not oxaliplatin.

Endpoints

The primary endpoint of S-AVANT was OS of the stage III population randomized in the AVANT study. Secondary endpoints were updated DFS, prognostic factors, sub-group analysis, and late comorbidities.

OS was defined as the time between randomization and death. Patients who were still alive at the clinical cutoff date were censored at the date at which they were last confirmed to be alive. DFS was defined as time from randomization to the first relapse, second primary cancer, or death from any cause. Event-free patients at the clinical cutoff date were censored at the last date at which they were known to be disease-free. Recurrences and new occurrences were based on the investigator's tumor evaluations scheduled every 6 months after randomization up to 4 years. The centers open in S-AVANT were requested to actualize the 8 and 10 years follow-up data.

Statistical analysis

The final OS analysis included all randomized patients in the AVANT trial including those lost to follow-up in the centers not participating in the S-AVANT study. Median value (interquartile range), mean (standard deviation) and frequency (percentage) were provided for description of continuous and categorical variables, respectively. Categorical variables were compared using a chi-square test (or Fisher's exact test, if appropriate). Median value (interquartile range) for continuous variables was compared using Kruskal Wallis test. OS and DFS were estimated using the Kaplan-Meier method and described using median or rate at specific time points with 95% confidence intervals (CI). Follow-up duration was calculated using a reverse Kaplan-Meier estimation [13]. Cox proportional hazard models were performed to estimate hazard ratio (HR) and 95% CI for factors associated with OS and DFS. The association of baseline parameters with OS and DFS were first assessed using univariate Cox analyses and then parameters with *P* values of less than 0.05 were entered into the final multivariable Cox regression model with stratification for treatment arm, after consideration of collinearity among variables of the correlation matrix. The assumption of proportionality was checked by plotting log-minus-log survival curves and cumulative martingale process plots. Subgroup analysis for a treatment arm association (FOLFOX4-bevacizumab versus FOLFOX4 and XELOX-bevacizumab versus FOLFOX4) with OS and DFS were performed and summarized with forest plot. The interaction term in each subgroup was obtained by considering subgroup, treatment arm, and interaction in the Cox model. An interaction was considered as significant if $P < 0.1$. A sensitivity landmark analysis of the treatment effect in patients alive at 4 years without any recurrence event was performed. All analyses were performed using SAS version 9.4 (SAS Institute, Cary NC) and R software version 2.15.2 (R Development Core Team, Vienna, Austria; http://www.r-project.org). *P* values of <0.05 were considered statistically significant, and all tests were two-sided.

RESULTS

Patient characteristics

From 20th December 2004 to 8th June 2007, 3451 CC patients were randomised at 330 centres in 34 countries (the ITT population, Figure 1). Overall, 2867 (83.0%) patients had stage III; 955 in arm A (FOLFOX4), 960 in arm B (FOLFOX4-bevacizumab), and 952 in arm C (XELOX-bevacizumab). Patient characteristics were well balanced between groups (Table 1). The median follow-up for the whole population was 6.73 years (IQR: 5.51-10.54) with no difference among the treatment arms. Of 2322 stage III patients still alive after the AVANT study database lock (30th June 2010), 976 (42.0%) had an updated median follow-up of 11.0 years.

Survival

OS events were observed in 198 (20.7%), 250 (26.0%), and 224 (23.5%) patients in the FOLFOX4, FOLFOX4-bevacizumab, and XELOX-bevacizumab arms, respectively. The 3, 5, and 10-year OS rates are reported in Table 2. For patients receiving FOLFOX4, FOLFOX4-bevacizumab, and XELOX-bevacizumab the 10-year OS rates were 75% (95% CI 70.9-77.9), 67% (95% CI 63.1-70.9), and 70% (95% CI 65.8-73.6), respectively (Table 2 and Figure 2). The OS HR was 1.29 (95% CI 1.07-1.55; *P*=0.008) for FOLFOX4-bevacizumab versus FOLFOX4 and 1.15 (95% CI 0.95-1.39; *P*=0.147) for XELOX-bevacizumab versus FOLFOX4 (Figure 3).

DFS events were observed in 282 (29.5%), 326 (34%), and 305 (32%) patients in the FOLFOX4, FOLFOX4-bevacizumab, and XELOX-bevacizumab arms, respectively. For patients receiving FOLFOX4, FOLFOX4-bevacizumab, and XELOX-bevacizumab, the 5-year DFS rates were 73.2% (95% CI 70.2-75.9), 68.5% (95% CI 65.4-71.4), and 71% (95% CI 67.9-73.8), respectively (Table 2). The DFS HR was 1.16 (95% CI 0.99-1.37; *P*=0.063) for the

FOLFOX4-bevacizuamb arm versus FOLFOX4 arm and 1.10 (95% CI 0.93-1.29; *P*=0.269) for the XELOX-bevacizumab arm versus FOLFOX4 arm (Figure 3).

Of 1973 (68.8%) patients alive and relapse-free at 4 years, 33 (4.9%) treated with FOLFOX4, 35 (5.5%) with FOLFOX4-bevacizumab, and 33 (5.1%) with XELOX-bevacizumab experienced OS events (Table 2) and o

f these 1973 (68.8%) patients alive and relapse-free at 4 years, 47 (6.9%) treated with FOLFOX4, 45 (7.0%) with FOLFOX4-bevacizumab, and 52 (8.0%) with XELOX-bevacizumab experienced DFS (Table 2).

Prognostic factors

Univariate and multivariate analysis of prognostic factors for OS and DFS are reported in Supplementary Tables S1 and S2 (available at Annals of Oncology online).

In multivariate analysis, treatment arm, gender, age (<70 versus ≥70), differentiation (well/moderately versus poorly), ECOG PS (0 versus 1), T stage (T1-3 versus T4), N stage (N1 versus N2), and primary tumor localization (right versus left colon) were independent prognostic factors for OS (supplementary Table S2, available at Annals of Oncology online). The same factors, but differentiation and primary tumor localization remained as independent prognostic factors for DFS (supplementary Table S2, available at Annals of Oncology online). Forest plots for main OS and DFS prognostic factors are shown in Figures 3.

In patients at low-risk of recurrence (T1-T3N1), OS HR was 1.68 (95% CI 1.23-2.30; *P*=0.001) for FOLFOX4-bevacizuamb versus FOLFOX4 and 1.33 (95% CI 0.96-1.85 *P*=0.086) for XELOX-bevacizumab versus FOLFOX4. In patients at high-risk (T4 or N2), OS HR was 1.08 (95% CI 0.86-1.37; *P*=0.508) for FOFLOX4-bevacizumab versus FOLFOX4 and 1.05 (95% CI 0.83-1.33; *P*=0.689) for XELOX-bevacizumab versus FOLFOX4 (Figure 3 and supplementary Figure S2, available at Annals of Oncology online).

A statistically significant detrimental effect on OS for the addition of bevacizumab to FOLFOX4 (FOLFOX4-bevcizumab versus FOLFOX4) was observed in T1-T3N1 patients with an interaction *P* value of 0.035and a similar observation was made for DFS (Figure 3 and supplementary Figure S1, available at Annals of Oncology online).

Safety and causes of death

Early safety data for high-risk stage II and III CC patients have been previously reported [de Gramont 2012].

With a total 672 deaths for stage III included, CC-related deaths occurred in 542 patients (80.7%) with no difference between arms; FOLFOX4: 157/198 (79.3%), FOLFOX4-bevacizumab: 205/250 (82.0%), XELOX-bevacizumab: 180/224 (80.4%), (*P*=0.764). Non-colon cancer-related deaths occurred in 130 patients with stage III, in whom those related to cardiovascular diseases and sudden deaths were reported in 13 out of 41 non-colon cancer related deaths (31.7%), 17/45 (37.8%), and 14/44 (31.8%) in the FOLFOX4 , FOLFOX4-bevacizumab, and XELOX-bevacizumab arms, respectively (*P*=0.789).

DISCUSSION

The long-term follow-up results of the S-AVANT study confirm the lack of a DFS benefit for the addition of bevacizumab to either FOLFOX4 (HR=1.16) or XELOX (HR=1.11) in patients with resected stage III CC. The data actualization with a longer follow-up shows a detrimental effect on OS with bevacizumab and oxaliplatin-based adjuvant chemotherapy (FOLFOX4 [HR=1.29] or XELOX [HR=1.15]). The negative effect of bevacizumab and oxaliplatin-based chemotherapy on OS (FOLFOX4 versus FOLFOX4-bevacizumab) support that administration of bevacizumab should be avoided completely in patients with stage III CC in the adjuvant setting. Moreover, this observation also put into question the use of bevacizumab as part of adjuvant therapy after curative resection of metaseses for stage IV disease. The detrimental effect of bevacizumab in our study occurred early since the death rate was similar for patients without relapse after 4 years.

Several hypotheses could explain the failure of bevacizumab in the adjuvant setting. Arrested angiogenesis is a component of cell dormancy [14] and experimental models have shown that dormant tumor cells can be protected from chemotherapy [15]. In our sub-group analysis (FOLFOX4 versus FOLFOX4-bevacizumab), bevacizumab had a significant detrimental effect on DFS and OS in the T1-T3N1 low-risk subgroup, but not in the T4 or N2 high-risk subgroup. Our hypothesis is that negative tumor dormancy induced by bevacizumab is balanced by its antiangiogenic benefit on undetectable metastasis that is more frequent in high-risk patients. One hypothesis is lower rate of residual cells after surgery in low-risk CC (micro-metastasis with few tumoral cells aggregate without vascularization) than in those with high-risk stage III disease (with vascularized micro-metastasis) most probably reducing the negative potential of tumor dormancy.

The two other studies, with a shorter follow-up period than S-AVANT, showed a non-significant deleterious effect of bevacizumab in the adjuvant setting of CC or CRC. In

QUASAR 2 (high-risk stage II and stage III CRC), after a median follow-up of 4.92 years, the median OS was 89.4% in the capecitabine arm and 87.5% in the capecitabine plus bevacizumab arm (HR: 1.11) [12]. In NSABP C08, after 5-year median follow-up, the median OS for patients with stage III CC was 78.7% in the mFOLFOX6 arm and 77.6% in the mFOLFOX6 plus bevacizumab arm (HR: 1.00) [4, 5, 10, 11].

No new or unexpected safety signals were observed in the current study that could explain the death rates with bevacizumab in our findings. The long-term safety of bevacizumab in combination with FOLFOX4 or XELOX did not demonstrate increased cardiovascular disease-related or sudden deaths rates.

Bevacizumab is not the only drug to show efficacy in metastatic CRC, but not in the early-stages of disease. Irinotecan and cetuximab, which are both approved for metastatic disease, failed to show benefit in adjuvant trials [16-19]. The disappointing results from the recent trials of molecularly targeted agents against stage II and/or III CC highlight a need to identify new potential strategies for adjuvant treatment of CC. Given that adjuvant trials are long, expensive and large, it would be valuable to have access to preclinical models predictive of early-stage disease. The confounding outcomes of adjuvant trials suggest that the concept of an indisputable signal should be discarded and indicate the necessity of alternative developmental approaches in adjuvant CC therapy [20].

While non-inferiority of 3 months compared to 6 months of oxaliplatin-based chemotherapy was established for low-risk stage III CC patients treated with XELOX in the recent International Duration Evaluation of Adjuvant Chemotherapy (IDEA), it was not supported for FOLFOX. A highly statistically significant interaction between regimen and duration of chemotherapy (P=0.0061) was reported [21]. Unlike in IDEA, our study, which is the only to randomize patients between FOLFOX and XELOX-based regimens, does not suggest a difference between the effect of these two drugs.

In conclusion, S-AVANT, confirms that bevacizumab does not prolong DFS when added to adjuvant chemotherapy in patients with stage III CC and for OS even suggests a potential statistically significant detrimental effect with bevacizumab plus FOLFOX4-based adjuvant therapy, without increase in non-colon cancer-related deaths. Therefore, bevacizumab should not be used in adjuvant treatment of patients with curatively resected stage III CC. This difference effect of bevacizumab on survival between high-risk (T4 or N2) and low-risk stage III patients could be partly explained by a phenomenon of bevacizumab-induced tumor cell dormancy that makes these cells inaccessible to chemotherapy.

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DISCLOSURES

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