Bevacizumab plus chemotherapy versus chemotherapy for the elderly patients with ACRC: a systematic review and meta-analysis of comparative studies

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BACKGROUND: Bevacizumab combined with chemotherapy(BEV+CT) has been used as a standard regimen for metastatic colorectal cancer since ten years ago. However, the elderly are often excluded from clinical trial, so there is no consistent result till now whether the geriatric patients achieve the benefit from adding bevacizumab to the chemotherapy, and suffer more toxicities in the combination group than chemotherapy(CT) alone group. HYPOTHESIS: To access the current evidence regarding the efficacy and safety of BEV+CT compared with CT in the elderly patients with advanced colorectal cancer (ACRC). Our primary outcomes were odds ratios (ORs) of overall survival (OS), progression-free survival (PFS) and adverse events (AEs). **METHODS:** The reports studying BEV+CT vs CT in the geriatric patients with ACRC were comprehensively searched in PubMed, Embase, OVID and Web of Science without restriction of publication date. After screening all these papers, we chose satisfactory randomized control studies (RCTs) and retrospective comparative studies, which were further studied by systematic review and cumulative meta-analysis. ORs and 95 % CIs of OS, PFS and AEs were synthesized using random-effects or fixed-effects models based on the heterogeneity of the included studies. Heterogeneity was assessed using the Q statistic and I^2. RESULTS: One RCT, five subgroup analysis of RCTs and two retrospective studies were identified, including 2813 old patients of ACRC treated by CT with BEV or without BEV. In pooled analysis of efficacy, two retrospective studies were excluded since the detail about the effect data was not list. All the studies were employed when we analyzed the safety. The pooled analysis showed that the addition of BEV to CT significantly improved both the PFS (HR 0.55, 95% CI, 0.48-0.63,*P*<0.001) and OS (HR 0.83, 95% CI, 0.74-0.94, *P*=0.003). In the assessment of adverse events (AEs), the OR of total grade AEs and grade 3-5 AEs were 1.85 (95% CI, 1.12-3.04, *P*=0.02) and 2.09 (95%CI, 1.69-2.57,*P*<0.001), respectively. On the subgroup analysis of overall grade toxicities, we found that proteinuria (OR 10.89, 95%CI 1.37-86.28, P=0.02), hypertension (OR 4.44, 95%CI 1.85-10.62, P<0.05) and fistulae/abscess (OR 12.07, 95%CI 1.54-94.88, P<0.05) were significantly higher in BEV+CT arm than CT arm. However, each statistically significant adverse event had only one study provided its evidence in overall grade toxicities analysis of them respectively. Subgroup analysis of grade 3-5 adverse events exhibited statistically significantly increased risk in hypertension(OR 3.91, 95%CI 2.48-6.16,P<0.001), arterial thromboembolism (OR 3.25, 95%CI 1.70-6.19,P<0.001) and venous thromboembolism(OR 2.17, 95%CI 1.11-4.25, P=0.02) when BEV was added to

CT. Neither overall AEs analysis nor high grade AEs analysis showed that adding BEV to CT was associated with cardiac diseases, bleeding or bowel perforation. In conclusions, our meta-analysis showed that the addition of BEV to CT significantly improved both PFS and OS in the elderly patients with ACRC, and BEV was related with higher risk of developing some bevacizumab-specific AEs, including hypertension, proteinuria, fistulae/abscess, arterial thromboembolism and venous thromboembolism. The clinicians should be aware of these AEs when the elderly patients with ACRC accept BEV and treat them in time.