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Does the age affect the efficacy of angiogenesis inhibitors in ovarian cancer? A meta-analysis of randomized controlled trials

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Abstract. – OBJECTIVE: There are limited data on the role of angiogenesis inhibitors (AIs) in the treatment of elderly patients with ovarian cancer. We aim to assess the overall efficacy of AIs-containing regimens in the treatment of ovarian cancer in this patients group.

MATERIALS AND METHODS: Databases and abstracts presented meetings up to November 2016 were searched to identify relevant studies. Prospective randomized controlled trials (RCTs) investigating therapies with or without AIs in elderly patients with ovarian cancer were included in the present study. Statistical analyses were conducted by using Version 2 of the Comprehensive meta-analysis program.

RESULTS: A total of 1901 elderly patients with ovarian cancer from six RCTs were identified for analysis. The pooled results demonstrated that the use of AIs-containing regimens significantly improved PFS (HR 0.70, 95% CI: 0.63-0.78, $p < 0.001$) when compared to non-AIs-containing regimens, but not for OS (HR 1.07, 95% CI: 0.86-1.34, $p = 0.54$). Subgroup analyses favored greater benefit for PFS (HR 0.60, $p < 0.001$) in second line settings compared to first-line settings (HR 0.75, $p < 0.001$). No publication bias was detected by Begg's and Egger's tests for PFS.

CONCLUSIONS: The findings of this work suggest that the use of AIs in the treatment of elderly patients with ovarian cancer offers an improved PFS, but not for OS. Further studies are needed to clearly set the role of AIs in ovarian cancer in this patients group.

Key Words:
Ovarian cancer, Elderly, Angiogenesis inhibitors, Randomized controlled trials, Meta-analysis.

Introduction

Ovarian cancer is the eighth most common cancer in women with 225,500 new cases and 140,200 deaths estimated to occur worldwide[1]. More than half of all epithelial ovarian cancers are diagnosed in women older than 65 years[2]. As the population age and life-expectancy improves, the number of older women with ovarian cancer is expected to increase in the near future[3,4]. However, there are many challenges involved in the treatment of an elderly population with ovarian cancer. In comparison with younger patients, older patients with ovarian cancer generally have more comorbidities and greater concomitant medication use, thus these patients tend to develop worse toxicity. Therefore, the optimal treatment for ovarian cancer in elderly patients remains unknown. Preclinical and clinical studies have showed that angiogenesis plays an important role in normal ovarian physiology as well as the progression of ovarian cancer. Currently, bevacizumab (Avastin®, Genentech Inc., South San Francisco, CA, USA), an antibody targeting VEGF, has been approved by the US Food and Drug Administration (FAD) for use in combination with chemotherapy in the treatment of women with platinum-resistant, recurrent ovarian cancer. The approval of bevacizumab in ovarian cancer is based on results of the phase III AURELIA study, which showed that adding bevacizumab to chemotherapy led to a statistically significant improvement in progression-free survival and objective response rate over standard chemotherapy alone, although there was no significant overall survival benefit[5,6]. Other novel angiogenesis inhibitors (AIs), such as nintedanib (BIBF 1120; Boehringer Ingelheim, Ingelheim, Germany), sorafenib (Nexavar®, Bayer HealthCare Pharmaceuticals Inc. Germany), pazopanib (GW786034; GlaxoSmithKline, Research Triangle Park, NC) and cediranib (AZD2171, Recentine, AstraZeneca, Macclesfield, UK), are currently being under investigation[7-10]. Indeeds, several previous meta-analyses have demonstrated that the use of

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AIs in ovarian cancer significantly improved progression-free survival in comparison with controls[11,12], but increased the risk of developing AIs related toxicities[13]. However, there is a significant under-representation of elderly patients in most clinical trials on ovarian cancer. Therefore, the applicability of these clinical data to the overall patient population deserves critical appraisal in the absence of trials dedicated specifically to the elderly. Currently, the concept of "elderly" has become more difficult to define. In general, the chronological age of 65 years, roughly equivalent to retirement age, is currently accepted as a threshold to define an "elderly" person. In the present study, we conduct this systematic review and meta-analysis of all available randomized controlled trials (RCTs) to determine the overall efficacy of AIs in elderly ovarian cancer patients.

Materials and Methods

Selection of Studies

All relevant trials were retrieved by searching the Pubmed, Embase and the Cochrane Library electronic databases up to December 2016. Prospective randomized controlled trials published in English language were included for analysis in the present study. We used the following key words "bevacizumab", "aflibercept", "VEGFR-TKIs", "sorafenib", "sunitinib", "vandetanib", "axitinib", "pazopanib", "regorafenib", "apatinib", "ramucirumab", "nintedanib", "thalidomide", "lenalidomide", "angiogenesis inhibitors", and "ovarian cancer" to identify relevant trials. The reference lists of the retrieved articles were hand searched to identify additional relevant articles. If more than one publication was found for the same trial, the most complete, recent, and updated report of the clinical trial was included in the meta-analysis.

Data Extraction

According to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement, two independent reviewers extracted the data[14]. Disagreements between investigators were resolved by discussion and consensus. A standardized Excel file was used for data extraction. The following data were extracted: first author, publication year, the number of enrolled patients and elderly patients, median age, hazard ratios (HRs) with 95% confidence intervals (CIs) for OS and PFS in elderly patients. Trials that met the following criteria were included: (1) prospective randomized controlled trails comparing therapies with or without AIs; (2) patients were pathologically confirmed of ovarian cancer; and (3) The study had sufficient efficacy data for extraction.

Clinical Endpoints

The outcome measures of interest were progression-free survival (PFS) and overall survival (OS). We investigated the overall efficacy of AIs in the treatment of elderly patients with ovarian cancer based on the data from the included trials. OS defined as the time from random assignment to death, and PFS defined as the time from random assignment to the first documentation of progression for disease, or death from any cause. HR and its 95% confidence intervals (CI) of OS and PFS were directly collected from each selected study. We used the 5-item Jadad scale including randomization, double-blinding, and withdrawals to assess the quality of included clinical trials[15].

Statistical Analysis

The data were analyzed using Version 2 of the Comprehensive Meta Analysis Program (Biostat, Englewood, NJ, USA). PFS and OS were considered as time-to-event variables and, therefore, were expressed as HRs with 95% CIs for each study. A statistical test with a p-value less than 0.05 was considered significant. HR > 1 reflected more deaths or progression in AIs-containing regimens group, and vice versa. Between-study heterogeneity was estimated using the χ^2-based Q statistic[16]. The I^2 statistic was also calculated to evaluate the extent of variability attributable to statistical heterogeneity between trials. If heterogeneity existed, data were analyzed using a random-effects model. In the absence of heterogeneity, a fixed-effects model was performed. We used the Begg and Egger tests to assess the presence of publication bias[17]. All p-values were two-sided. All CIs had two-sided probability coverage of 95%.

Results

Search Results

As the flowchart of the search strategy shown in Figure 1, our search yielded a total of 205 relevant citations in ovarian cancer patients. After reviewing the title or abstract, a total of 8 prospective RCTs were included, and two trials were

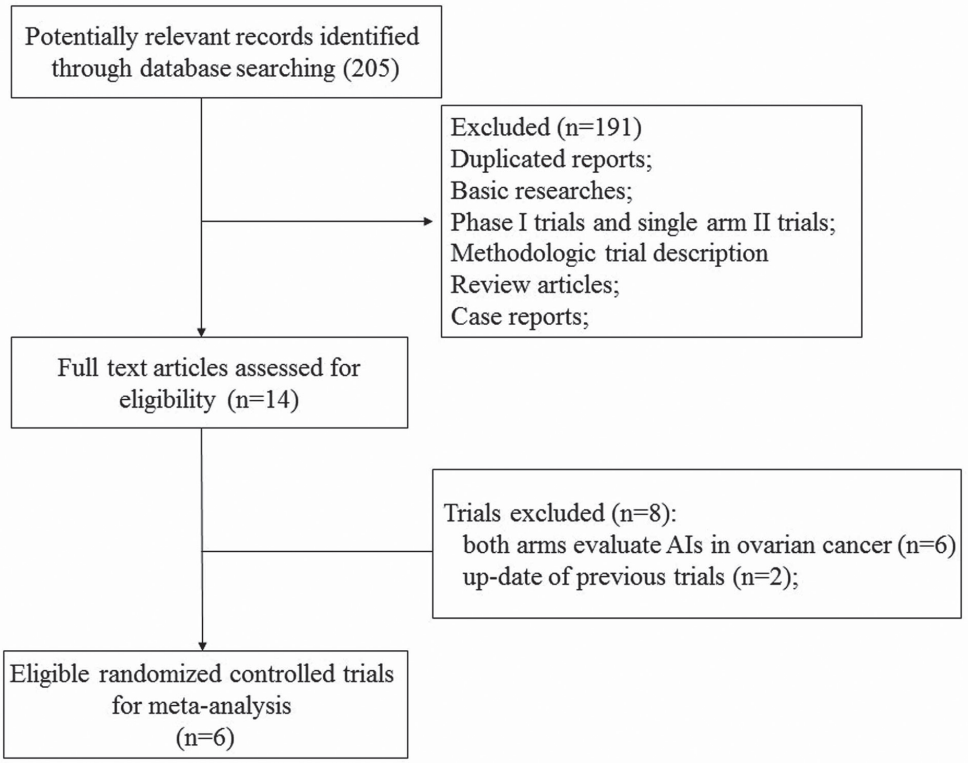

Figure 1. Studies eligible for inclusion in the meta-analysis.

up-date report of previously trials[18,19]. Finally, six published RCTs assessing the efficacy of AIs in elderly patients with ovarian carcinoma were included[5,6,20-23]. The baseline characteristics of these studies were listed in Table I. A total of 1901 patients were available for the meta-analysis. The clinical characteristics were generally balanced between the intervention and control arm. The quality of each included study was roughly assessed according to Jadad scale, and the median Jadad score of the included studies was 5 (range 3-5).

Overall Survival

Only two trials reported OS data of elderly patients. The pooled results demonstrated that AIs

Table I. Baseline characteristics of six included trials for analysis.

Authors	Year	Therapy line	Elder patients	Age	Treatment arms	Median PFS	Median OS	Jadad Score
Burger et al	2011	First-line	618	60-69 or ≥ 7 0	Bevacizumab +PTX+CBP	10.3	38.7	5
					Placebo +PTX+CBP	14.1	39.7	
Perren et al	2011	First-line	629	60-69 or ≥ 70	Bevacizumab +PTX+CBP	19	NR	3
					PTX+CBP	17.3	NR	
Aghajanian et al	2012	Second-line	178	≥ 65	Bevacizumab +chemotherapy	12.4	35.2	5
					Placebo +chemotherapy	8.4	33.3	
du Bois et al	2014	Maintenance	215	≥ 65	Pazopanib	17.9	NR	5
					Placebo	12.3	NR	
Monk et al	2014	Second-line	143	≥ 65	Trebananib 15 mg/kg +PTX	7.2	19	5
					Placebo +PTX	5.4	17.3	
Pujade-Lauraine et al	2014	Second-line	118	≥ 65	Bevacizumab +chemotherapy	6.7	16.6	3
					Chemotherapy	3.4	13.3	

Abbreviations: PFS, progression-free survival; OS, overall survival; PTX, paclitaxel; CBP, carboplatin; NR, not reported.

containing therapies did not significantly improve OS in comparison with chemotherapy alone (HR 1.07, 95% CI: 0.86-1.34, $p = 0.54$, Figure 2) using a fixed-effects model.

Progression-free Survival

All six trials with eight comparisons reported PFS data. The pooled hazard ratio for PFS demonstrated that AIs containing therapies significantly improve PFS giving HR 0.70 (95% CI: 0.63-0.78, $p < 0.0001$, Figure 3), compared with chemotherapy alone. There was no significant heterogeneity between trials ($I^2 = 11.2\%$, $p = 0.343$), and the pooled HR for PFS was performed by using fixed-effects model. Subgroup analyses favored greater benefit for PFS (HR 0.60, $p < 0.001$) in second line settings compared to first-line settings (HR 0.75, $p < 0$ .001).

Publication Bias

Begg's funnel plot and Egger's test were performed to assess the publication bias of literatures. No significant publication bias was detected for PFS by using Begg's and Egger's test ($p = 0.11$ and $p = 0.16$, respectively)

Discussion

Angiogenesis is defined as the formation of new blood vessel[24]. Normal tissues and organs rely on a balance of angiogenic and anti-angiogenic forces to control growth and development[25]. The process of angiogenesis becomes unbalanced in favor of angiogenesis in malignancy[26]. Tumor neovascularization plays a vital role in the survival and dissemination of ovarian cancer by promoting tumor growth and metastasis. The main pathway involved in tumor angiogenesis is modulated by vascular epithelial growth factor (VEGF) signaling pathway. Currently, bevacizumab has been approved for use in the treatment of advanced recurrent ovarian cancer, and other anti-angiogenesis agents have been also investigated in ovarian cancer patients, but none of these prospective trials are specially designed to assess the efficacy of AIs in the treatment of elderly patients. Preplanned and unplanned sub-group analysis of published trial data are becoming more common as a substitute method to provide valuable information to guide the use of AIs in the elderly patients with advanced cancer. As far as we known, our study is the first meta-analysis to assess the role of AIs in the treatment of this patient population group. Our study, included 1901 patients from 6 randomized controlled trials, demonstrates that AIs containing regimens significantly improves PFS (HR 0.70) in elderly patients with ovarian cancer, but it does not translate into overall survival benefits (HR 1.07). A possible explanation for this finding is that age may limit the aggressive treatment for elderly patients with ovarian cancer, and elderly patients might have a slightly worse tolerance to AIs plus chemotherapy regimen[27]. Although we could not assess the toxicities of AIs in the present study, several previous studies have demonstrated an increased risk of toxicity with bevacizumab in combination with chemotherapy in patients over 65 years old. In one study, patients who received bevacizumab were more likely to have grade 3-5 toxicity (78% *vs.* 57%), with the most common grade 3 toxicity being hypertension[28]. Similar results are also observed in elderly advanced non-small-cell lung cancer treated with bevacizumab. Although bevacizumab improves overall survival from 10.3 to 12.3 months (HR 0.79; p=0.003) in patients with advanced non-small-

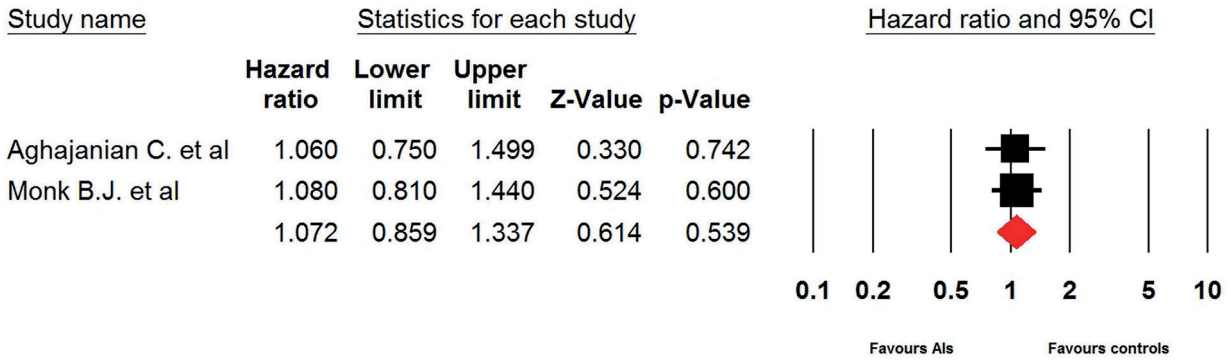

Figure 2. Fixed-effect Model of Hazard Ratio (95% CI) of OS associated with AIs-containing regimens *vs.* non-AIs-containing regimens.

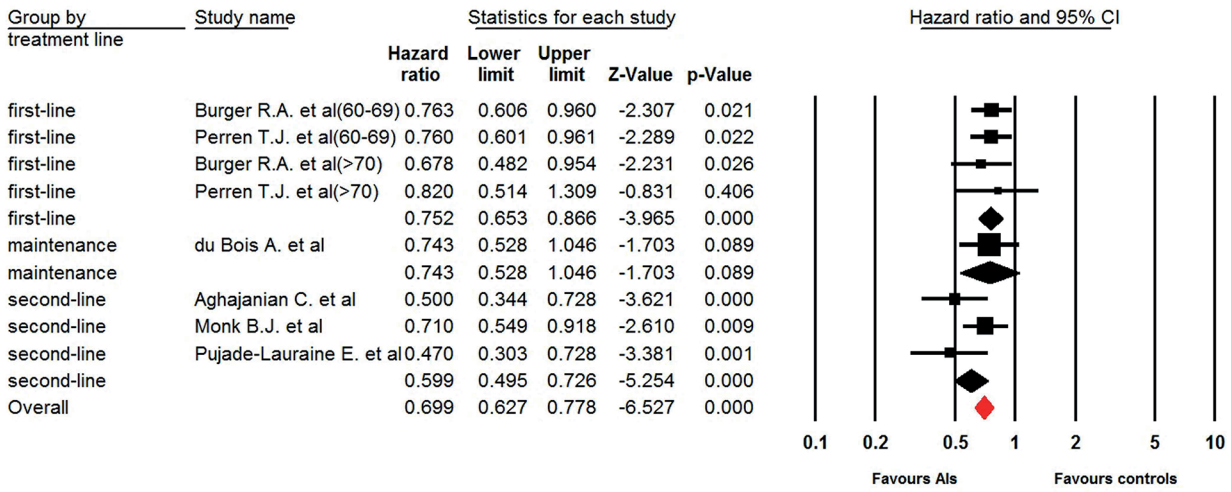

Figure 3. Fixed-effects Model of Hazard Ratio (95% CI) of PFS associated with AIs-containing regimens *vs.* non-AIs-containing regimens.

cell lung cancer when combined with paclitaxel and carboplatin[29], sub-group analyses in the elderly have been unable to conclusively attest to its benefits[30]. Ramalingam et al[31] reported that the use of bevacizumab had a trend to improve higher response rates (29% *vs.* 17%; $p = 0.067$) and improved progression-free survival (5.9 *vs.* 4.9 months; $p = 0.063$). Overall survival in elderly patients appeared to be comparable (11.3 months and 12.1 months, respectively; $p = 0.4$). However, more incidence of grade 3 or worse adverse events were observed in 87% of elderly patients treated with bevacizumab *vs.* 61% of patients not receiving bevacizumab ($p = 0.001$). Then, we perform pre-defined subgroup analysis according to treatment line and demonstrate that the most consistent and statistically significant benefit is found when AIs are used in second-line settings. This benefit has obvious implications for clinical practice. The superior efficacy of AIs in later line settings might be explained by several factors. Firstly, tumor biology might be altered by exposure to and progression after first-line chemotherapy, so that the tumors might be more sensitive to angiogenesis inhibitors targeting the VEGF pathway. Alternatively, patients who fare sufficiently well to enter a second-line trial may have tumor characteristics conferring increased sensitivity to AIs. Over the past decades, no validated biological markers have been identified to assist appropriately patient selection for anti-angiogenic therapy. In the AVAGAST of bevacizumab conducted by Van Cutsem et al[32] demonstrated that high serum VEGF-A and low tissue neuropilin-1 were both prognostic biomarkers for survival, but not necessarily predictive ones. Other studies had also been performed to investigate the associations between survival and other biomarkers, such as VEGFC, VEGFR3 or tissue VEGFR2, but the results of these studies were negative[33,34]. Several limitations exist in this analysis. Firstly, this meta-analysis only considers published literature, and a meta-analysis of individual level data might define more clearly treatment benefits in specific subgroups. For instance, elderly patients are more likely to have comorbid conditions, and we are unable to investigate whether the survival benefit is similar in elderly patients with or without comorbid conditions. Secondly, none of the included trials report the toxicities of AIs in elderly patients, thus, we could not another whether the use of AIs in this patient population would increase the toxicities in comparison with controls. Thirdly, we include patients treated with different angiogenesis inhibitors, which would increase the clinical heterogeneity among included trials, which also make the interpretation of a meta-analysis more problematic, although we pool subgroup analysis according to treatment line. In addition, two included trials define elderly patients as more than 60 years, while the other four trials define elderly patients as more than 65 years, the characteristics of these two elderly patients population might be different, which might be another source of heterogeneity. Finally, in the meta-analysis of published studies, publication bias is important because trials with positive results are more likely to be published and trials with null results tend not to be published. Our research detects no publication bias using Begg and Egger tests for PFS.

Conclusions

This is the first-meta-analysis specifically assessing the efficacy of AIs in the treatment of elderly patients with ovarian cancer. The results of our study suggest that AIs-containing regimens offer an improved PFS in elderly patients but not for OS. Further studies are recommended to investigate the efficacy of AIs in the treatment of elderly patients with ovarian cancer.

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Conflict of Interest

The Authors declare that they have no conflict of interests.

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