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The antibody-based CA125-targeted maintenance therapy for the epithelial ovarian cancer: a meta-analysis

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Summary

Objectives: To assess the effect and toxicity of CA125-targeted antibody used as maintenance therapy for advanced epithelial ovarian cancer (EOC). *Materials and Methods:* Two reviewers searched PubMed, Medline, Embase, VIP databases, and the references of selected articles for randomized controlled trials comparing maintenance CA125-targeted antibody treatment with placebo/observation. One -, two-, three-, and five-year overall survival (OS) and progression free survival (PFS) were collected. Incidence and severity of adverse events were extracted. Meta-analysis of combined risk ratio (RR) for OS , PFS, and toxicity were conducted. *Results:* Four trials including 1,259 women were identified. Meta-analysis showed the combined RR was 1.02 (95% CI, 0.85−1.22) for three-year OS and 0.98 (95% CI, 0.70−1.39) for the three-year PFS. This review found that abagovomab and oregovomab caused toxicity no more than placebo. *Conclusions:* CA125-targeted antibody used as maintenance therapy alone is not more effective than placebo but they were safe as maintenance therapy.

Key words: CA125-targeted antibody; Epithelial ovarian cancer; Maintenance therapy; Meta-analysis.

Introduction

Epithelial ovarian cancer (EOC) has the highest mortality rate of all gynecological cancers. There were an estimated 21,880 new cases resulting in 13,850 deaths in 2010 [1]. EOC accounts for approximately 90% of all cases of ovarian cancer and debulking surgery following six courses of platinum-based chemotherapy is the standard first-line treatment which results in complete clinical remission (CCR) in up to 75% of cases [2]. Despite high response rates, the recurrence and mortality rates are high [3, 4]. Proofs have shown that increasing cycles of chemotherapy is of little survival benefit but increases the adverse side effects [5, 6]. In 2003, Southwest Oncology Group (SWOG) reported a phase-III randomized trial of 12 versus three months of maintenance paclitaxel in patients with advanced ovarian cancer after complete response to platinum and paclitaxel-based chemotherapy [7]. Data showed the median progression-free survival (PFS) was 21 and 28 months in the three-cycle and 12-cycle paclitaxel arms, respectively. The p value was less than 0.005 in favor of the 12-cycle arm. The trial discontinued because of the protocol-specified early termination boundary of $p = 0.005$. As of the date of study closure, there was no difference in OS between the treatment arms. However, this result was encouraging to evoke a number of studies about maintenance therapy for EOC with different drugs and agents. Maintenance or consolidation chemotherapy for advanced EOC refers to the therapy given after the women have achieved CCR or pathological complete remission (PCR) following debulking surgery and induction chemotherapy[7, 8]. Currently the effectiveness of maintenance chemotherapy has been assessed but there is insufficient evidence to prove any drug is more beneficial than observation alone [9-12]. Maintenance radiotherapy may improve the five-year PFS [13, 14], however, because of the intolerable side effects, it is rarely recommended .

Immunotherapy is one of the novel therapeutic strategies for ovarian cancer. It aims to induce or enhance active immune responses directed towards the tumour and to consolidate anti-tumour effects of standard therapy, delay, and possibly prevent progression of disease. Within the last few years, different immunotherapies based on tumor-specific antibody, immunogenic peptides or vaccines have been developed [15]. CA125, also known as MUC16, is a large membrane-associated mucin protein which is over expressed in more than 80% of EOC. The soluble molecule secreted in patient blood is used as a marker for tumor identification and progression. Due to its poor immunogenicity, the host organism is not able to mount an adequate immune response against it alone. When the targeted antibody binds to the CA125, the complex can bind to the antigen-processing cells more readily than CA125 alone. During the past 20 years, many phase I/II clinical trials had studied the CA125-targeted antibodies like oregovomab,

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ACA125, and abagovomab in newly diagnosed or recurrent advanced ovarian cancer, which showed that they could cause specific immune response resulted in longer survival [16-21]. These trials evoked to imagine how they would act when used as the maintenance therapy. Further more, it is important for the gynecologists and women with EOC to assess the potential benefits and adverse effect of CA125-targeted antibodies, however, currently there have not been any systematic reviews published on this topic.

This systematic review aimed to evaluate the effectiveness, toxicity, and impact on the quality of life (QoL) of antibody-based CA125-targeted immunotherapy as maintenance therapy for EOC.

Materials and Methods

Eligibility criteria

Women with EOC, fallopian tube cancer (FTC) or primary peritoneal cancer (PPC) who have achieved CCR after debulking surgery and first-line chemotherapy. The patients were ≥ 18 years and have no other concurrent malignancies. The study design was a randomized controlled trial comparing maintenance CA125-targeted antibody treatment with observation, placebo or other treatment. Maintenance CA125-targeted antibody combined with the other treatment versus the other treatment alone is also included. The PFS rate, OS rate, incidence and severity of adverse events or QoL score were the primary or secondary outcomes of the original studies.

Searches

Two reviewers searched MEDLINE (from 1948 to 2014), EMBASE (from 1980 to 2014) , PubMed (up to October 2014), and VIP (1989 to October 2014) independently. It was designed to identify all published trials in English or Chinese.The aforementioned databases were searched using the keywords: immunotherapy, bioimmunotherapy, CA125, MUC16, oregovomab, abagovomab, ACA125, ovarian cancer, and maintenance/consolidation therapy . VIP was searched using the same keywords in Chinese. In addition, the authors reviewed the references of selected articles to identify studies missed through our databases searching. They also searched the relative websites for ongoing trials.

Two reviewers scanned the titles and abstracts from the initial search to exclude those articles which did not meet the eligibility criteria. Then the full text of potentially relevant studies were obtained and assessed by both review authors independently. Any disagreements were resolved through discussion with a third review author.

Data collection and analysis

The authors extracted OS and PFS after one, two, three, and five years from the included studies. The incidence and severity of adverse events such as nausea-vomiting, diarrhea, rash, back pain, myalgia, arthralgia, and flu-like syndrome were also abstracted. The published QoL scores were collected. The authors pooled the results of similar trials into a meta-analysis. Revman 5.2 was used to conduct the meta-analysis and calculate the combined RR and its 95% confidence interval (CI) for OS, PFS, and adverse events.

The authors also assessed the risk of bias of each trial in terms of randomisation process, allocation concealment, blinding, incomplete outcome data, selective outcome reporting, and other possible sources of bias and classified them as low , high or unclear risk according to the guidelines of Cochrane Handbook for Systematic Reviews of Interventions [22].

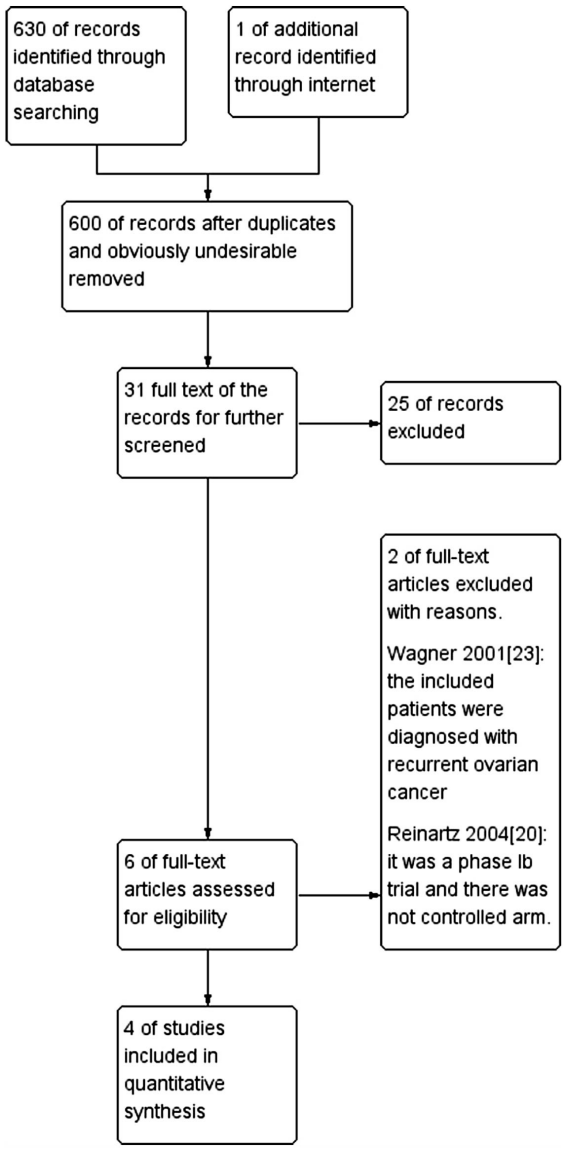

Figure 1. — Flowchart of studies screening.

Results

Data search and quality of the included studies

The search identified 631 trials and initially 600 were excluded because of duplication and obvious ineligibility after reading the titles and abstracts. Full text were obtained for the remaining 31 trials for further scrutiny and 25 ineligible trials were excluded. Two trials [20, 23] were initially identified as potentially eligible for inclusion but were subsequently found to be ineligible and therefore excluded (Figure 1). In the end, four trials (1,259 patients) were included in this review. Three trials compared oregovomab [3, 24, 25] with placebo and the other one compared abagovomab [26] with placebo. Berek *et al.* 2008 [24] is a five-year follow-up survey of Berek *et al.* 2004 [3]. Berek *et al.* 2009 [25] re-

Table 1. — *The included studies of CA125-targeted antobody as maintenance therapy for EOC.*

Study	Study Design	Patients	Outcome	Duration of follow-up	Comment
Berek *et al.*, 2004 [3]	RCT Oregovomab *vs.* placebo (1:1)	n=145 EOC of Stage III/IV achieved CCR Median age: 60 in treatment 62 in placebo group	Median TTR was 13.3 months for oregovomab and 10.3 months for placebo (p = 0.71).	Insufficient information	
Berek *et al.*, 2008 [24]	RCT Oregovomab *vs.* placebo (1:1)	n=145 EOC of Stage III/IV achieved CCR Median age: 60 in treatment 62 in placebo group	Median survival was 57.5 months for oregovomab and 48.6 months for placebo (p = 0.28)	5 years	A 5-year follow-up survey of Berek 2004
Berek *et al.*, 2009 [25]	RCT Oregovomab *vs.* placebo (2:1)	n=371 EOC of Stage III/IV achieved CCR Median age: 58.8 in treatment 59.6 in placebo group	Median TTR was 10.3 months for oregovomab and 12.9 months for placebo (p = 0.29).	5 years	The same trial of Berek 2004
Sabbatini 2013 [26]	RCT Abagovomab *vs.* placebo (2:1)	n=888 EOC/FTC/PPC of Stage III/IV achieved CCR Median age: 56.3 in treatment 56 in placebo group	HR of RFS was 1.099 (95%CI, 0.919 to 1.315) HR of OS was 1.150 (95%CI, 0.872 to 1.518).	24 months after random assignment of the last patient.	

Abbreviations: RCT: randomized controlled trial; EOC: epithelial ovarian cancer; FTC: fallopian tube cancer; PPC: primary peritoneal cancer; TTR: time to relapse; RFS: relapse free survival HR: hazard ratio; OS: overall survival.

ported the same trial but the included subjects were 226 more than Berek *et al.* 2004 and the primary end point was time to relapse. The baseline of the four studies was balanced and there was no significant heterogeneity between them (Table 1). All the four studies were randomly allocated and used blinding method. None of the trials have any attrition bias or reporting bias so the included studies had low risk of bias.

Effect of CA125-targeted antibody

Sabbatini *et al.* [26] reported the median estimated time to recurrence was 403 days in abagovomab group and 402 days in placebo group. At the end of the double-blind observation period, the hazard ratio (HR) of OS for the treatment group was 1.150 (95% CI, 0.872−1.518; p = 0.322). Berek *et al.* [3, 24, 25] reported the median survival was 57.5 months for oregovomab and 48.6 for placebo but the p-value was 0.28. The median time to relapse was 10.3 months (95% CI, 9.7− 13.0 months) for oregovomab and 12.9 months (95% CI, 10.1−17.4 months) for placebo (p = 0.29). Data from 1,033 patients was combined and the RR for three-year OS was 1.02 (95% CI, 0.85−1.22), while the combined RR for three-year PFS was 0.98 (95% CI, 0.70−1.39) (Figure 2). Therefore, there was no significant benefit of using CA125-targeted antibody alone as maintenance therapy.

Toxicity of antibody against CA125

For CA125-targeted antibodies, diarrhea was the only side effect which was recorded more in the abagovomab group (p = 0.031)[26], but the meta-analysis found that the combined RR for diarrhea was 1.36 (95% CI, 0.94−1.96) so there was no significant difference between two arms regarding diarrhea, which was the same with back pain, fatigue, and arthralgia, *et al.* (Figure 3). According to Berek *et al.*'s study [25], 13.7% of oregovomab group and 18.6% of placebo group had a serious adverse event but there was not significant difference between them (p = 0.218). Berek *et al.* [3] used European Organization for Research and Treatment of Cancer Quality of Life Questionaire C30 (EORTC QLQ-C30) to assess the overall health and overall QoL and found the QoL was similar in the oregovomab group and the control group. These results indicated that the abagovomab and oregovomab were safe and had little impact on the QoL as maintenance therapy for ovarian cancer.

Discussion

This meta-analysis is based on 1,259 women from four RCTs that used different antibodies against CA125 as maintenance therapy for advanced EOC. A number of methods were employed to identify all trials to minimize

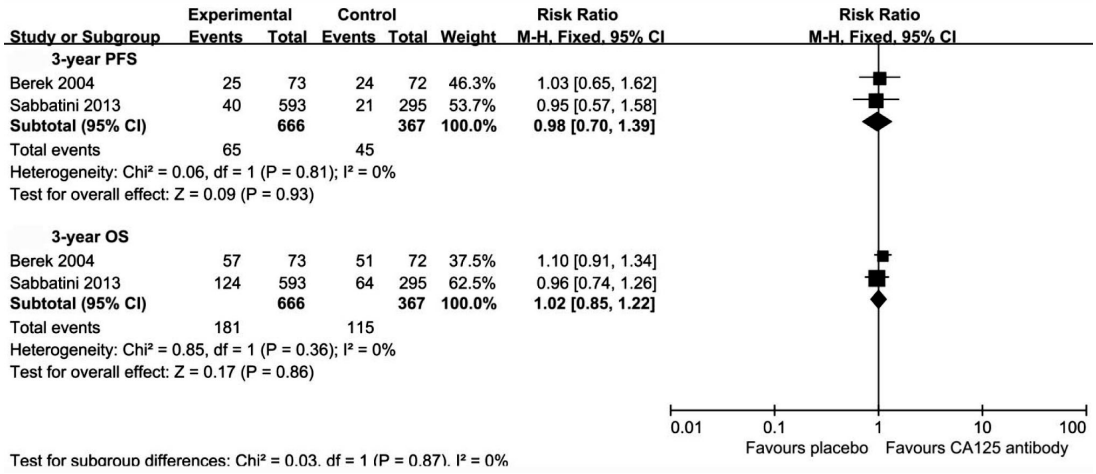

Figure 2. — Forest plot of survival analysis of CA125-targeted antibody.

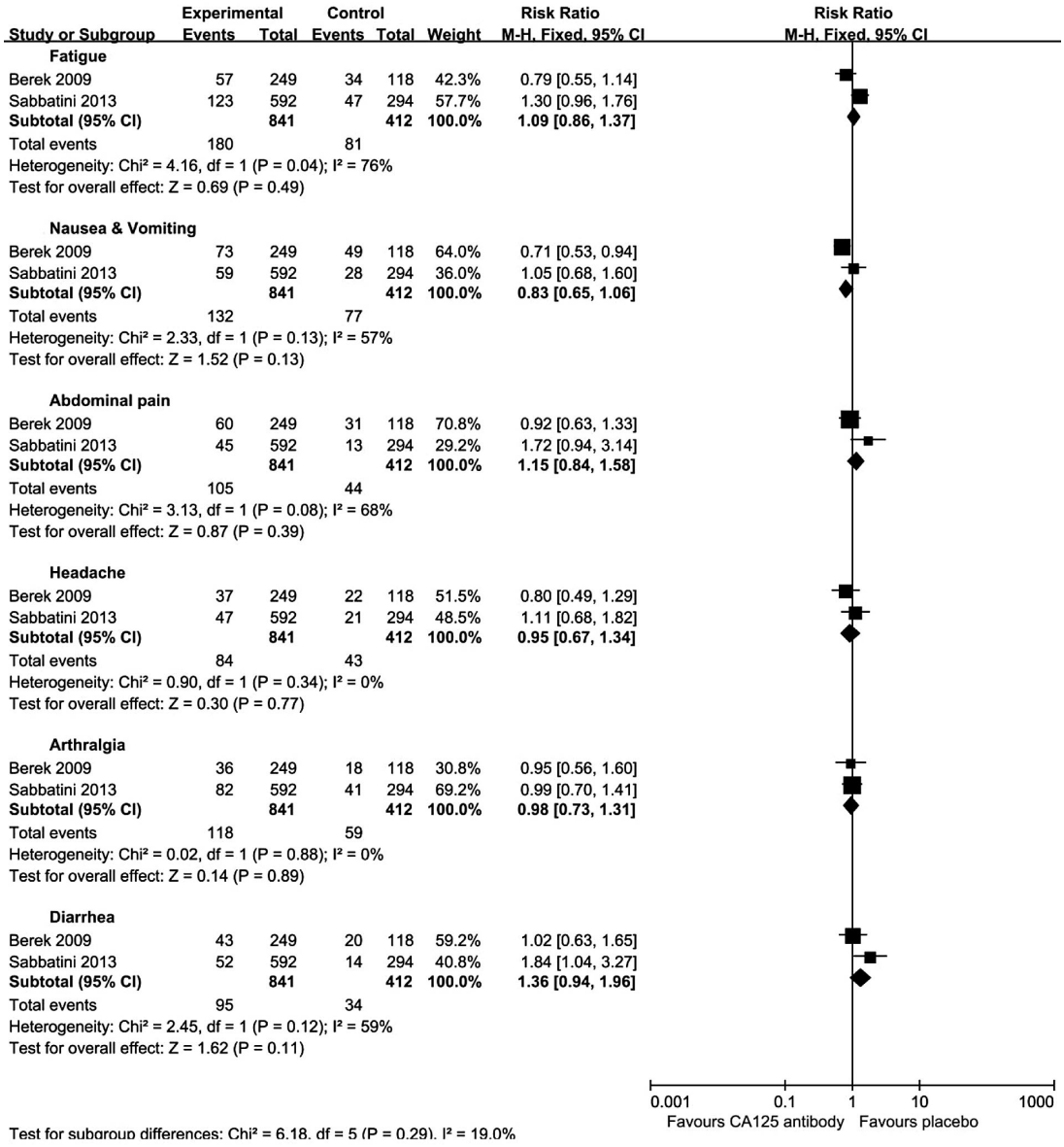

Figure 3. — Forest plot of adverse side effect of CA25-targeted antobody.

the influence of publication bias. There were no serious inconsistency, indirectness, imprecision or publication bias; this meta-analysis currently provides a reliable assessment of the average effect of CA125-targeted antibody maintenance therapy among women with advanced EOC. Overall, the quality of the evidence was moderate due to low number of studies and further researches may change the estimate.

There was no benefit of maintenance CA125-targeted monoimmunotherapy settings, the drugs, however, were well-tolerated. The adverse events were similar between treatment groups and were not life-threatening. Does it really mean maintenance CA125-targeted immunotherapy of advanced EOC is of little survival benefit? Perhaps it is too arbitrary to draw the conclusion. First of all, the included four studies had different interval between the last cycle of first-line chemotherapy and the beginning of maintenance therapy. Berek *et al.* [3, 24, 25] started oregovomab therapy within ten weeks after the last cycle of chemotherapy while Sabbatini *et al.* [26] began abagovomab therapy within 12 weeks, which was less than six months. As a consensus, the phase of CCR or PCR of platinum-sensitive cases is usually longer than six months and the prognosis and biological characteristics are totally different between platinum-sensitive and platinum-resistant cases. If maintenance therapy is initiated earlier than six months, the platinum-resistant cases would be included, which may impair the effect of the treatment.

Secondly, different studies used different criteria for judging disease relapse. Berek *et al.* [3, 24, 25] defined recurrence as identification of new intraperitoneal lesion not previously seen or a retroperitoneal lesion on CT scan greater than 2 × 2 cm. Sabbatini [26] assessed disease progression as a 20% increase in sum of longest diameters compared to baseline or appearance of any new lesions (RECIST version 1.0). Although randomization and blinding may balance the bias between the treatment and controlled arms, however the heterogeneity caused by different criteria would bring error into the meta-analysis results, especially when the weight of each study is different. As we know, second-line treatment starts usually based on an increase in serum CA125 level only, without imaging evidence for ovarian cancer because the increase of serum CA125 level occurs usually much earlier than appearance of objective disease progression. A working group of the Gynecologic Cancer Intergroup has developed definitions of CA125 progression to complement the definitions of objective disease progression in ovarian cancer [27]. It is supported that doubling in CA125 from the upper limit of normal reliably predicts objective progression. For those patients whose CA125 never fell to the normal range, a doubling from the nadir has been shown to predict progression. In an effort to address this issue in a consistent manner, the present authors suggest that the date of progression should be the date of the earlier of the two events when both the RECIT and Intergroup criteria were documented.

Braly *et al.* [17] reported a phase-II trial in which 40 patients with Stage III/IV EOC were randomized to receive a two-mg oregovomab infusion either the same day (simultaneous infusion arm) or one week after standard carboplatin-paclitaxel chemotherapy at cycles 1, 3, and 5, then quarterly for up to 11 antibody doses. Humoral immunity occurred more rapidly ($p = 0.0033$) and with greater magnitude in the simultaneous infusion arm. They came to the conclusion that the front-line chemotherapy has immune adjuvant properties when combined with oregovomab immunotherapy. Therefore combined strategies of chemotherapy with oregovomab or other CA125-targeted agents should be further studied as maintenance therapy.

Conclusions

In summary, there is insufficient evidence which adequately supports the use of antibody against CA125 as maintenance therapy alone to improve the OS or PFS for advanced EOC, however, they are safe and tolerable. The sufficient interval of CCR (> six months) before maintenance therapy and more precise unified criteria of assessing for progression may diminish the bias which would impair the results. For further study, combining the immunotherapy with the traditional chemotherapy may be a new topic.

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