RESEARCH ARTICLE

Abiraterone for Treatment of Metastatic Castration-resistant Prostate Cancer: a Systematic Review and Meta-analysis

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Abstract

Introduction: Although most prostate cancers initially respond to castration with luteinizing hormone-releasing analogues or bilateral orchiectomy, progression eventually occurs. Based on the exciting results of several randomized controlled trials (RCTs), it seems that patients with metastatic castration-resistant prostate cancer (mCRPC) might benefit more from treatment withabiraterone. Therefore we conducted a systematic review to evaluate the efficacy and toxicity of abiraterone in the treatment of mCRPC. Methods: Literature was searched from Embase, PubMed, Web of Science, and Cochrane Library up to July, 2013. Quality of the study was evaluated according to the Cochrane's risk of bias of randomized controlled trial (RCT) tool, then the Grading of Recommendations Assessment, Development and Evaluation (GRADE) System was used to rate the level of evidence. Stata 12.0 was used for statistical analysis. Summary data from RCTs comparing abiraterone plus prednisone versus placebo plus prednisone for mCRPC were meta-analyzed. Pooled hazard ratios (HRs) for overall survival (OS), radiographic progression-free survival (RPFS) and time to PSA progression (TTPP); Pooled risk ratios (RR) for PSA response rate, objective response rate and adverse event were calculated. Results: Ten trials were included in the systematic review; Data of 2,283 patients (1,343 abiraterone; 940 placebo) from two phase 3 trials: COU-AA-301 and COU-AA-302 were meta-analyzed. Compared with placebo, abiraterone significantly prolonged OS (HR, 0.74; 95% confidence interval [CI], 0.66 to 0.84), RPFS (HR, 0.59; 95% CI, 0.48 to 0.74) and time to PSA progression (HR, 0.55; 95% CI, 0.43 to 0.70); it also significantly increased PSA response rate (RR, 3.63; 95% CI, 1.72 to 7.65) and objective response rate (RR, 3.05; 95% CI, 1.51 to 6.15). This meta-analysis suggested that the adverse events caused by abiraterone are acceptable and can be controlled. Conclutios: Abiraterone significantly prolonged OS, RPFS and time to progression patients with mCRPC, regardless of prior chemotherapy or whether chemotherapy-naïve, and no unexpected toxicity was evident. Abiraterone can serve as a new standard therapy for mCRPC.

Keywords: Abiraterone - prostate cancer - castration-resistant - meta-analysis - efficacy - safety

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Introduction

Prostate cancer is the most common malignant neoplasm and a leading cause of cancer mortality in men in the Western world. The American Cancer Society estimated that 241, 740 men will be diagnosed with prostate cancer in 2012, accounting for 29% of newly diagnosed cancers. Approximately 28, 170 men will die from this disease in 2012. At diagnosis, approximately 4% of patients have advanced disease (Siegel et al., 2012). Over the past 20 years the incidence of prostate cancer has risen, and the corresponding mortality has increased in Asia (Moore et al., 2010; Kang et al., 2013). Beyond that, according to a recent study from Korea, Korean prostate cancer patients have worse disease characteristics than their American counterparts (Kang et al., 2013). Androgen deprivation therapy is the most common initial treatment for men with advanced prostate cancer (Ding et al., 2013; Zhou et al., 2013). Although most men initially respond to castration with treatment of luteinizing hormone-releasing analogues or bilateral orchiectomy, progression eventually occurs, and the median overall survival after chemotherapy is consistently less than 2 years in patients with metastatic castration-resistant prostate cancer (mCRPC) (Crawford et al., 1989). Docetaxel was the first systemic therapy to show an improvement in overall survival in patients with mCRPC, but patients invariably die of progressive disease (Petrylak et al., 2004). Recently, several promising agents with widely varied mechanisms of action and therapeutic targets have demonstrated efficacy, and four new drugs (cabazitaxel, sipuleucel-T, denosumab, and abiraterone acetate) were FDA approved for the treatment of patients with mCRPC (Beltran et al., 2011; Cersosimo, 2012; Di Lorenzo et al., 2012), treated

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before and after chemotherapy on the basis several phase 3 trials.

Abiraterone acetate is an inhibitor of the androgen biosynthesis enzyme CYP17 (17-a-hydroxylase and C17, 20-lyase) and is more potent and selective and less toxic than ketoconazole (Attard et al., 2009; Yang, 2011; Nandha, 2012). Several phase 2 trials have been conducted on abiraterone in combination with prednisone, with a prostate-specific antigen (PSA) response rate of 51–85% and durable radiologic responses in both chemotherapy-naive and docetaxel-pretreated mCRPC patients (Attard et al., 2009; Danila et al., 2010; Reid et al., 2010; Ryan et al., 2011). A phase 3 trial was conducted in 1195 patients with mCRPC, who previously received docetaxel, with the treatment of abiraterone plus prednisone versus placebo plus prednisone Based on a 4.6 months improvement in overall survival (OS) found at final analysis (15.8 months versus 11.2 months), significant improvements in median radiologic progression-free survival (RPFS) (5.6 months versus 3.6 moths) and a dramatically higher proportion of patients who had a PSA response (29.5% versus 5.5%) (Fizazi et al., 2012), abiraterone was approved by the FDA in April 2011 for mCRPC post-docetaxel. A phase 3 trial on abiraterone acetate plus prednisone versus placebo plus prednisone in men with mCRPC who have not received prior chemotherapy has been completed, the results showed that the median radiographic progression-free survival was 16.5 months with abiraterone-prednisone and 8.3 months with prednisone alone, and overall survival was significantly improved with abiraterone-prednisone too (Ryan et al., 2012).

Based on the above exciting results, it seems that patients with mCRPC might benefit more from treatment of abiraterone. Therefore, this systematic review and meta-analysis was designed, with the aim to fully evaluate the efficacy and toxicity of abiraterone for metastatic castration-resistant prostate cancer, and we also comprehensively appraised the quality of evidence and recommended the evidence with GRADE to facilitate clinical decision-making.

Materials and Methods

Inclusion criteria

Studies meeting the following criteria were included: (1) Participants: men with histologically or cytologically confirmed metastatic castration-resistant prostate cancer were eligible. (2) Interventions or comparisons: abiraterone for mCRPC; abiraterone plus prednisone versus placebo plus prednisone for mCRPC, regardless of prior chemotherapy or chemotherapy-naive. (4) Outcomes: overall survival (OS), radiographic progression-free survival (RPFS), time to PSA progression (TTPP), PSA response rate, objective response rate by RECIST and adverse events. (5) Study design: RCT, phase 1 trial, Phase 2 trial, and phase 3 trial.

Exclusion criteria

We excluded the following publications: (1) The important information was unavailable to extract the data; (2) For repeated published articles or the same study with multiple publication at different follow-time, the article with the most strictest methodology and most complete data was chosen; (3) non-original research, such as review, letter etc.

Eligibility assessment was performed independently in an unblinded standardized manner by 2 reviewers. Disagreements between reviewers were resolved by consensus. Although phase I and Phase II clinical trial were included, that were just descriptively review.

Literature search

We identified articles by searching EMBASE, PubMed, Web of Science, Cochrane Library (CENTRAL, Issue 7 of 12, July 2013) up to July, 2013. We used MeSH terms combined free terms in all the search strategies that were correctly adjusted in different database. The search strategy of PubMed is following: ((prostate cancer) OR (prostatic cancer) OR (prostate carcinoma) OR (prostatic carcinoma) OR (prostate neoplasm) OR (prostate neoplasms) OR (prostatic neoplasm) OR ("Prostatic Neoplasms"[Mesh])) AND (("abiraterone"[Supplementary Concept]) OR (abiraterone)) AND (("Randomized Controlled Trial"[Publication Type]) OR ("Randomized Controlled Trials as Topic"[Mesh]) OR (random*) OR "phase 1" OR "phase 2" OR "phase 3" OR "phase I" OR "phase II" OR "Phase III"). In addition to electronic search original papers, we also reviewed the references of included studies to look for potentially eligible articles. Furthermore, we checked abstracts that were published in major academic conferences (American Society of Clinical Oncology, European Society for Medical Oncology and American Society for Therapeutic Radiology and Oncology). No language restrictions were applied. We also contact the corresponding author to obtain information if the research results were unclear or more information was needed.

Assessing risk of bias in included studies

The methodological quality of RCTs was evaluated according to the Cochrane Collaboration's tool for assessing risk of bias (5.1.0) (Higgins et al., 2011). Evaluation index included: sequence generation; allocation concealment; blinding of participants, personnel and outcome assessors; incomplete outcome data; elective outcome reporting; other sources of bias. For each study, we made judgments about risk of bias from each of the six domains in the tool. In all cases, an answer 'Yes' indicated a low risk of bias, and an answer 'No' indicated high risk of bias, if insufficient detail was reported of what happened in the study, the judgment would usually be 'Unclear' risk of bias. Quality of phase I and Phase II clinical trial was not assessed due to the Cochrane Collaboration's tool was not suitable.

Quality of evidence

The Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach is a method of grading the quality of evidence and strength of recommendations in health, which is based on the risk of bias, limitations, the indirectness, the consistency of the results across studies, the precision of the overall estimate across studies, and other considerations. For each

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Table 1. Characteristics of Trials Included in Systematic Review

Study	Study design	Interventions and comparisons (Pts.)	No. of patients	Outcomes	Age (years)	Gleason score	PSA level (ng/ml)	Extent of disease (Pts.)	ECOG performance status	Drug and dosage	Results
Attard et al. 2008	Phase 1, open-label, dose-escalation trial	Abiraterone acetate; chemotherapy naïve; Ketoconazole naïve	21	Safety and Tolerability	Median age: 69	Range: 3 to 5	Median PSA: 46	Bone:17 soft tissue disease: 8	Range: 0 to 1	Abiraterone 250 to 2000 mg per day after fasting 5 dose escalations	Abiraterone acetate was well tolerated, antitumor activity was observed at all doses; Declines in PSA 30%, 50%, and 90% were observed in 14,12, and 6 patients, respectively, and lasted between 69 to 578 days.
Ryan et al. 2010	Phase 1, dose-escalation trial	Abiraterone acetate; chemotherapy naïve; Ketoconazole naïve:14 Pts. Ketoconazole treated:19 Pts.	33	Safety and Tolerability	Median age: 72	< 7: 3 Pts.; 7: 13 Pts.; > 7: 15 Pts.	Median PSA: 33	Elevated PSA: 33; Prostate: 14; Lymph node: 11; Bone: 23; Viscera: 6	Range: 0 to 1	Abiraterone 250 to 2000 mg per day after fasting 5 dose escalations	Adverse events were predominantly grade 1 or 2,No dose-limiting toxicities were observed;50% PSA declines at week 12 were seen in 18 of 33 patients, including nine of 19 with prior ketoconazole therapy and nine of 14 without prior ketoconazole therapy
Attard et al. 2009	Phase 1/2, open-label, single-arm study	Abiraterone acetate; chemotherapy naïve;	Phase 1/2: 54 phase 2: 42	Declines in PSA; CTC counts; TTPP	Median age of phase 2 patients: 70	Range: 6 to 10 (phase 2 patients)	Median PSA: 110 (phase 2 patients)	Increasing PSA: 4; Lymph nodes: 4; Visceral lesions: 1; Lymph nodes + visceral: 1; Bone lesions:14; Bone + lymph nodes :12; Bone + visceral + lymph nodes: 6	Range: 0 to 1	Abiraterone 42 patients were treated at 1,000 mg; 12 patients were treated at 250, 500, 750, and 2,000 mg	Decline in PSA of 50% was observed in 28 of 42 phase II patients; declines of 90% were observed in eight of 42 patients. Radiologic evaluation reported partial responses in nine of 24 phase 2 patients. Decreases in CTC counts were also documented. The median TTPP on abiraterone acetate alone for phase II patients was 225 days;
Danila et al. 2010	Multicenter, phase 2 trial	Abiraterone acetate; chemotherapy treated; Ketoconazole naïve:27 Pts. Ketoconazole treated:31 Pts.	58	Decline in PSA; Partial responses; Improved PS; TTPP; CTC counts	Median age: 69.5	Median: 7	Median PSA: 189.6	Visceral ± bone or soft tissue: 13; Bone only: 11; Soft tissue only: 8; Bone + soft tissue only: 26	Range: 0 to 2 0: 24 Pts. 1: 31 Pts. 2: 2 Pts. Unknown: 1 Pts.	Abiraterone, 58 patients were treated at 1,000 mg daily with prednisone 5 mg twice daily	50% decline in PSA was confirmed in 22 patients: including 14 of 31 ketoconazole-naïve, 7 of 27 ketoconazole-pretreated patients; Partial responses were seen in 4 of 22 patients; Median time to PSA progression was 169 days; CTC conversions from >5 to < 5 were noted in 10 of 29 patients; Main adverse events were grade 1 to 2, no grade 4 events were seen.
Reid et al. 2010 (COU-AA-303)	Multicenter, open-label, single-arm phase 2 trial	Abiraterone acetate; chemotherapy treated;	47	Decline in PSA; Responses rate; TTPP; CTC counts; Safety and Tolerability	Median age: 67	< 6: 4 Pts.; 6-7: 20 Pts.; 8-9: 17 Pts.; 10: 1 Pts.; Unknown: 5 Pts.	Median PSA: 403	Bone only: 4; Soft tissue only: 1; Bone + soft tissue: 33; Bone + visceral: 1; Soft tissue + visceral: 1; Bone + soft tissue and visceral: 7	Range: 0 to 2 0: 16Pts. 1: 27 Pts. 2: 4 Pts.	Abiraterone 1,000 mg was administered once daily	PSA declines of > 30%, >50% and >90% were seen in 68%, 51% and 15% respectively; Partial responses were reported in eight of 30 patients; Median time to PSA progression was 169 days 11 of 27 patients had a decline from at least five to less than 5 CTCs; 18 of 27 had a > 30% decline in CTCs after starting treatment; Abiraterone acetate was well tolerated.
Ryan et al. 2011	Multicenter, open-label, single-arm phase 2 trial	Abiraterone acetate + prednisone; chemotherapy naïve; Ketoconazole naïve	33	Decline in PSA; Median time on therapy; TTPP; Bone scan flare; Adverse events		Median: 8	Median PSA: 23	Visceral only: 1; Viscera + bone/soft tissue: 2; Bone only: 10; Soft tissue only: 6; Bone + soft tissue only: 14	Range: 0 to 1	Abiraterone, were treated at 1,000 mg daily with prednisone 5 mg twice daily	50% or more decline in PSA was confirmed in 22 of 33 patients; Median time on therapy and time to PSA progression were 63 weeks and 16.3 months; Bone scan flare was observed in 11 of 23evaluable patients; Adverse events were typically grade 1/2.
COU-AA-301 study	Multinational, double-blind, randomized, placebo-controlled, phase 3 trial	Abiraterone + prednisone vs. placebo + prednisone; docetaxel treated	1195 797 vs. 398 (2:1)	OS; PSA decline; TTTP; rPFS; Other Endpoints	Median age: 69 vs. 69	< or = 7: 49% vs. 46% > or =8: 51% vs. 54%	Median PSA: 128.8 vs. 137.7	Bone: 89% vs. 90%; Node: 45% vs. 41%; Liver: 11% vs. 8%	0 or 1: 90% vs. 89%; 2 10% vs.11%	Abiraterone, or placebo was given once daily as 250 mg * 4; with prednisone 5 mg twice daily	Median OS: 15.8 months vs. 11.2 months; Median TTTP: 8.5months vs. 6.6 months; Median rPFS: 5.6 months vs. 3.6 months; PSA response rate: 29.5% vs. 5.5%; Fatigue events rate: 9% vs. 10% Anaemia 8% vs. 8%; Back pain 7% vs. 10%; Bone pain 6% vs. 8%.
COU-AA-302 study	Multinational, double-blind, randomized, placebo-controlled, phase 3 trial	Abiraterone + prednisone vs. placebo + prednisone chemotherapy naïve;	1088 546 vs. 542 (1:1)	rPFS; OS; Times to opiate use, chemotherapy, decline in ECOG status and PSA progression; Other Endpoints	Median age: 71 vs. 70	< or = 7: 46% vs. 50% > or =8: 54% vs. 50%	Median PSA: 42 vs. 37.7	Bone: 51% vs. 49%; >10 bone metastases: 49% vs. 47%; Soft tissue or node: 49% vs. 50%; Other: 0.7% vs. 1.3%	Range: 0 to 1	Abiraterone, or placebo was given once daily as 250 mg * 4; with prednisone 5 mg twice daily	Median rPFS: 16.5 months vs. 8.3 months; Median OS: not reached vs. 11.2 months, HR: 0.75, 95% CI: 0.61 to 0.93, p = 0.01; Abiraterone delayed clinical decline and initiation of chemotherapy; Grade 3 or 4 mineralocorticoid-related adverse events and abnormalities on liver-function testing were more.
Persson et al. 2012	Economic evaluation of abiraterone acetate as treatment for metastatic castration resistant prostate cancer after failure of docetaxel in Sweden. Total costs per patient were $103,100 ((euro)74,400) and $104,600 ((euro)75,500) for abiraterone acetate and cabazitaxel, respectively. Quality-adjusted life years (QALYs) were 0.94 and 0.83 for abiraterone acetate and cabazitaxel, respectively. The results show that AA treatment is superior to cabazitaxel in cost per QALY gained. (This study patients come from COU-AA-301 study)										
Ostale et al. 2012	Cost-efficacy analysis of licensed drugs for the treatment of metastatic castrate resistant prostate cancer post docetaxel based on hospital drug evaluation methodology in Spain. The cost per cycle of abiraterone acetate was 3,179.26(euro) vs. 11.85(euro) for placebo+prednisone. Treatment costs for abiraterone vs. placebo+prednisone is 25,386.71(euro) (range 12,669.65(euro) - 38,103.76(euro)) In Spain, based on local hospital methodology, abiraterone would be the dominant alternative for mCRPC. (This study patients come from COU-AA-301 study)										

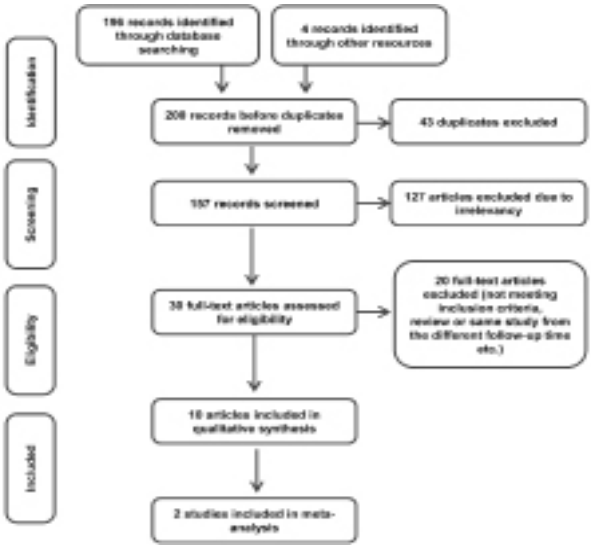

Figure 1. Flow Chart of the Study Selection Process

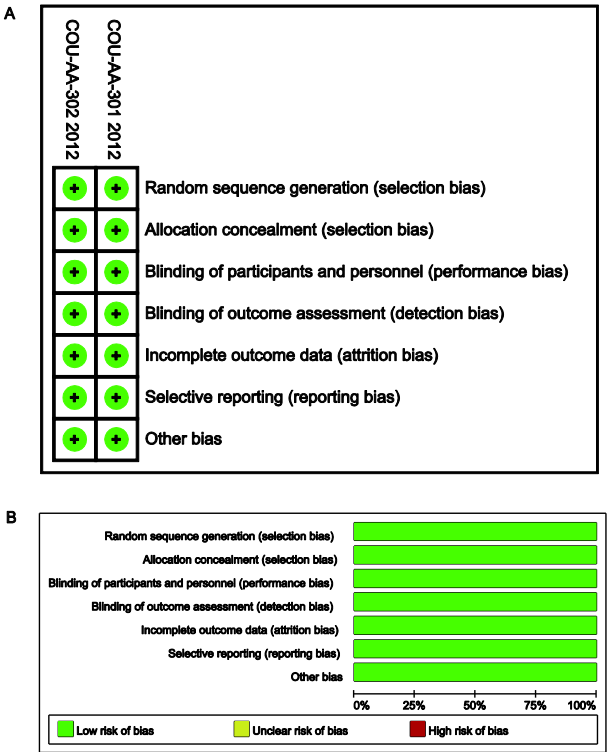

Figure 2. (A): Risk of Bias Summary: Review Authors' Judgments About Each Risk of Bias Item for Each Included Study. (B): Risk of bias graph: review authors' judgments about each risk of bias item presented as percentages across all included studies

outcome, the quality of the evidence was rated as high, moderate, low or very low using the following definitions: (1) Further research was very unlikely to change our confidence in the estimate of effect. (2) Further research was likely to have an important impact on our confidence in the estimate of effect and may change the estimate. (3) Further research was very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. (4) We were very uncertain about the estimate (Balshem et al., 2011; Guyatt et al., 2011). The methodological quality of the studies included in the meta-analysis was ascertained with GRADEpro 3.6 by two reviewers. Disagreements between the two reviewers were forward to a third author and resolved by consensus.

Data extraction

A special data extract form was used to extract relevant data from the included studies. Data extraction was performed completely independently by two reviewers. Reviewers were not blinded to authors or journals. Disagreements were resolved by discussion between the two reviewers; if no agreement could be reached, a third author would decide. The following information was sought from each article: trial design, patient eligibility, baseline patient characteristics, interventions, duration of follow-up, hazard ratio or the number of events for all the outcomes. If the trial results were reported in multiple publications, only the data from the article with the strictest methodology and the most complete data was extracted.

Data analysis

All statistical analysis was performed using Stata 12.0 software (Stata Corp, College Station, Tex). Time to event data was analyzed using hazard ratio (HR), and count data using risk ratio (RR) as effect size, and 95% confidence intervals (CI) was calculated. Chi-square test and I-square test were used for testing heterogeneity between studies. Random-effect model was adopted for analysis. In the presence of heterogeneity ($P<0.10$, $I^2>50\%$), we explored potential sources from the following three aspects: clinical, methodological and statistical. We explored heterogeneity through sensitivity analysis and by conducting subgroup analysis. In the case of excessive heterogeneity, descriptive analysis rather than meta-analysis was adopted.

Results

Study selection and baseline characteristics

Totally 200 records were collected, 43 duplicates were eliminated by the "find duplicates" function of EndNote X6 software. After reviewed the titles and abstracts of 157 records, 127 articles was excluded due to irrelevancy. The full-text versions of 30 papers were obtained to further determine eligibility. We ruled out another 20 articles: 1 review was excluded (Yang, 2011); 2 articles due to the same study from the different follow-up time (de Bono et al., 2011; Logothetis et al., 2012), 17 due to meeting or journal abstracts, which results all came from COU-AA-301 or COU-AA-302 study. Finally 10 articles were included in the systematic review (Attard et al., 2008; Attard et al., 2009; Danila et al., 2010; Reid et al., 2010; Ryan et al., 2010; Ryan et al., 2011; Fizazi et al., 2012; Ostale et al., 2012; Persson et al., 2012; Ryan et al., 2012), 2 studies were included in meta-analysis (Fizazi et al., 2012; Ryan et al., 2012). Literatures screening process was shown in Figure1. The baseline characteristics of the included studies were showed in Table 1.

Quality assessment

This systematic review included 2 RCTs: the baseline characteristics of patients were reported in all trials,

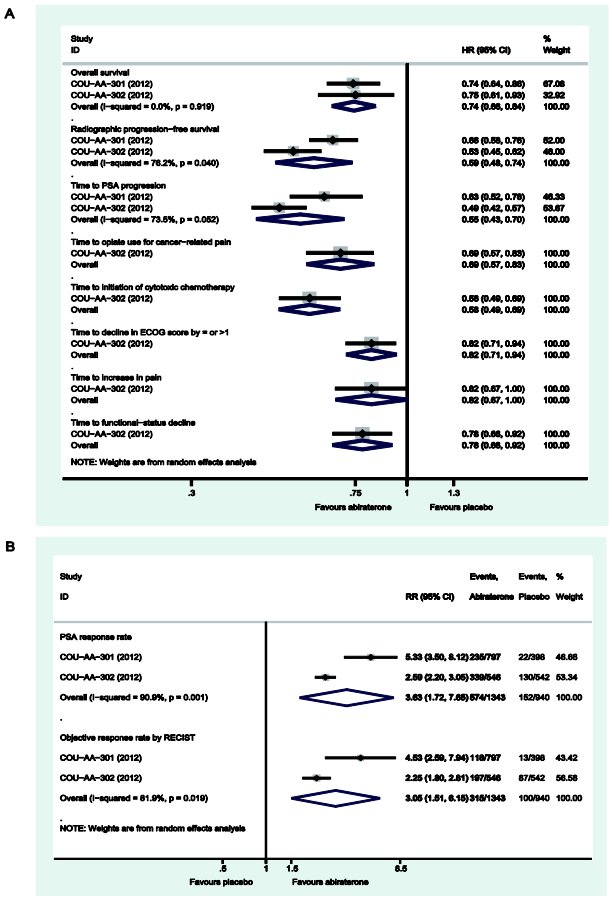

Figure 3. (A): Meta-analysis of OS, RPFS and TTPP Compared Abiraterone Plus Prednisone Versus Placebo Plus Prednisone for mCRPC. (B): Meta-analysis of PSA response rate and objective response rate by RECIST compared abiraterone plus prednisone versus placebo plus prednisone for mCRPC

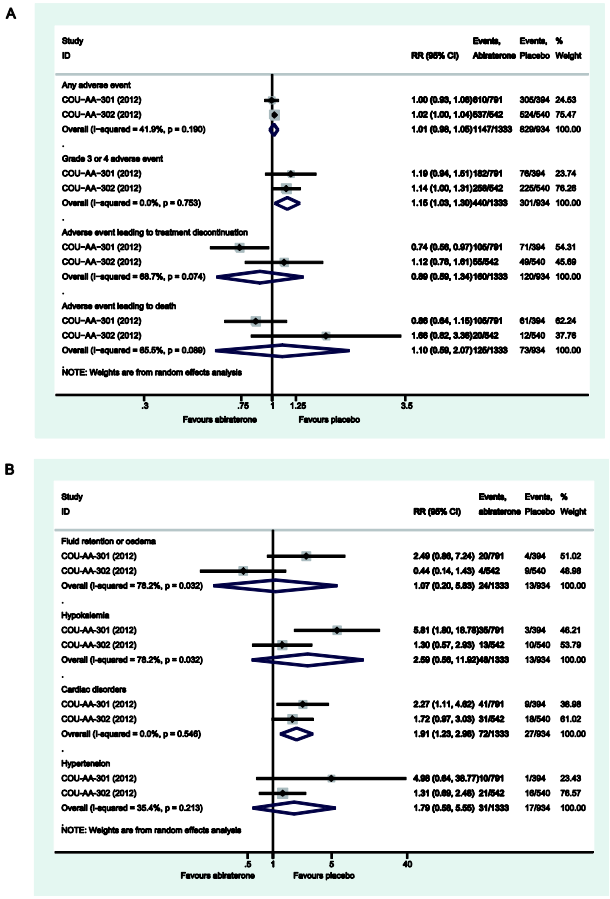

Figure 4. (A): Meta-analysis of Any Adverse Event, grade 3 or 4 adverse event, adverse event leading to treatment discontinuation and adverse event leading to death compared abiraterone plus prednisone versus placebo plus prednisone for mCRPC. (B): Meta-analysis of grade 3 or 4 adverse event

all included RCTs mentioned "random", all reported an adequate randomized sequence generation and allocation concealment; all RCTs described the reasons of incomplete outcome data; all trials mentioned whether the blind method was adopted or not (Figure 2).

Results of meta-analysis

Overall survival: Two RCTs, with a total of 2283 patients, were included in the meta-analysis to evaluate overall survival of abiraterone plus prednisone versus placebo plus prednisone. The result showed that OS was significantly improved with abiraterone plus prednisone [HR=0.74, 95% CI (0.66, 0.84)]. Heterogeneity was not detected between studies (I^2=0%, P=0.919) (Figure 3A).

Radiographic progression–free survival: Totally 2283 patients from two RCTs were included in the meta-analysis, which demonstrated that abiraterone significantly improved RPFS compared with placebo [HR=0.59, 95% CI (0.48, 0.74)]. Random effect model was used to analyze the effect size since obvious heterogeneity was observed (I^2=76.2%, p = 0.040) (Figure 3A).

Time to PSA progression: A total of 2283 patients from two RCTs were included in the meta-analysis. TTPP were significantly improved with treatment of abiraterone acetate plus prednisone compared with placebo plus prednisone [HR=0.55, 95% CI (0.43, 0.70)]; significant heterogeneity (I^2=73.5%, p = 0.052) existed, therefore, the random effect model was applicable (Figure 3A).

COU-AA-302 study showed that abiraterone plus prednisone decreased the risk of decline (by≥1 point) in ECOG performance-status score by 18%, as compared with prednisone alone (time to decline, 12.3 vs. 10.9 months; HR for decline, 0.82; 95% CI, 0.71 to 0.94). The median time to the initiation of cytotoxic chemotherapy was 25.2 months in the abiraterone plus prednisone group and 16.8 months in the prednisone alone group (HR, 0.58; 95% CI, 0.49 to 0.69). A significant delay in the time to opiate use for cancer related pain was observed with abiraterone (not reached vs. 23.7 months; HR, 0.69; 95% CI, 0.57 to 0.83). The median time to increase in pain was prolonged, with 26.7 months among patients receiving abiraterone plus prednisone and 18.4 months among those receiving prednisone alone (HR, 0.82; 95% CI, 0.67 to 1.00) (Figure 3A).

PSA response rate and Objective response assessed by RECIST: Two RCTs, totally 2283 patients, were included in the meta-analysis. The results showed that PSA response rate (a decline of 50% or more in the PSA level was based on modified Prostate Cancer Clinical Trials Working Group 2 criteria) was significantly increased in abiraterone acetate plus prednisone treatment group compared with

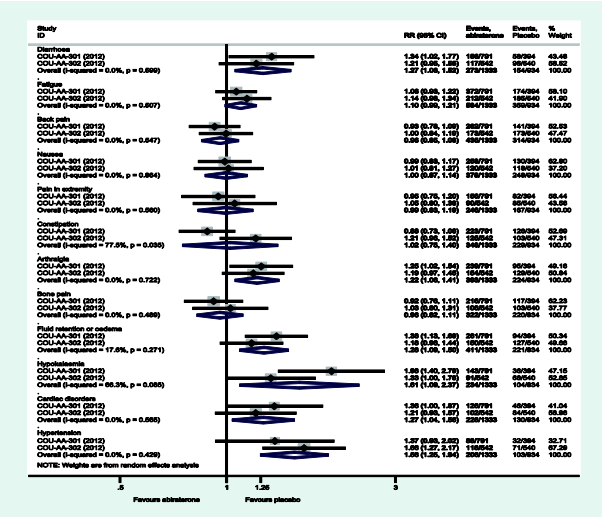

Figure 5. Meta-analysis of Grade 1 to 4 Adverse Event

placebo plus prednisone group [RR=3.63, 95% CI (1.72, 7.65)]; due to significant heterogeneity (I^2=90.9%, p = 0.001), the random effect model was used (Figure 3B). Objective response assessed by Response Evaluation Criteria in Solid Tumors (RECIST) criteria were significantly improved with treatment with abiraterone acetate plus prednisone compared with placebo plus prednisone [RR=3.05, 95% CI (1.51, 6.15)] (Figure 3B).

Adverse event

The results of phase 1 or phase 2 trials suggested that abiraterone was safe and effective (Attard et al., 2008; Attard et al., 2009; Danila et al., 2010; Reid et al., 2010; Ryan et al., 2010; Ryan et al., 2011). Two phase 3 trials were designed to further detect the safety of abiraterone (Fizazi et al., 2012; Ryan et al., 2012), all adverse events are summarized in Figure 4 and Figure 5.

Meta-analysis suggested that the incidence of treatment-related any adverse events were similar between the abiraterone group and the placebo group [RR=1.01, 95% CI (0.98, 1.05)]; Grade 3 or 4 adverse events were reported in 440 [33.0%] of 1333 in the abiraterone group vs. 301 [32.2%] of 934 in the placebo group [RR=1.15, 95% CI (1.03, 1.30)]; Meta-analysis suggested that 160 (12.0%) of 1333 patients in the abiraterone group and 120 (12.8%) of 934 patients in the placebo group had to discontinue treatment due to adverse events [RR=0.89, 95% CI (0.59, 1.34)]. Adverse events leading to death occurred in similar proportions of patients in the two groups, with 125 [9.4%] of 1333 patients in the abiraterone group vs. 73 [7.8%] of 934 patients in the placebo group [RR=1.10, 95% CI (0.59, 2.07)] (Figure 4A). Meta-analysis demonstrated that the grade 3 or 4 incidence of cardiac disorders was higher in patients taking abiraterone acetate than in those taking placebo [RR=1.91, 95% CI (1.23, 2.98)]. The incidences of such grade 3 or 4 events as fluid retention or oedema, hypokalemia, and hypertension were similar in both groups (Figure 4B). Meta-analysis suggested that diarrhoea, arthralgia, fluid retention or oedema, hypokalaemia, hypertension and Cardiac disorders were among the grade 1 to 4 adverse events more common in the abiraterone plus prednisone group than in the prednisone alone group; There was no significant difference in fatigue, back pain, nausea, pain in extremity, constipation, and bone pain among the grade 1 to 4 adverse events in the two groups (Figure 5).

Economic evaluation of abiraterone acetate for mCRPC

Ostale et al reported that, OS data from COU-AA-301 trials, the cost per cycle of abiraterone plus prednisone (AP) was 3, 179.26 (euro) vs. 11.85 (euro) for placebo plus prednisone (PP). Treatment costs for AP vs. PP is 25, 386.71 (euro) (range 12, 669.65 (euro) to 38, 103.76 (euro)) (Ostale et al., 2012). In Persson's study, a cost-effectiveness model was populated with data from COU-AA-301 trial too. Resource utilization and costs reflected Swedish treatment conditions within a broad societal perspective. Drug costs per 3-week-model-cycle were $3180 ((euro) 2300) for AP, total costs per patient were $103, 100 ((euro) 74, 400) for AP (Persson et al., 2012).

Quality of evidence

There were 5 outcomes about efficacy in this meta-analysis, OS, RPFS, and TTPP were critical results; PSA response rate and objective response rate by RECIST were both important results. Four main outcomes about safety in the meta-analysis, any adverse event, grade 3 or 4 adverse event, adverse event leading to treatment discontinuation, and adverse event leading to death were all important outcomes. Quality of OS, any adverse events and grade 3 or 4 adverse events were high. Quality of RPFS, TTPP, PSA response rate and objective response rate by RECIST were moderate. Quality of adverse event leading to treatment discontinuation and adverse event leading to death were low.

Discussion

This systematic review and meta-analysis confirmed that, compared with placebo plus prednisone, treatment with abiraterone acetate plus prednisone improved overall survival, radiographic progression–free survival and time to PSA progression, also increased PSA response rate and objective response rate by RECIST in patients with mCRPC. Both RCT studies demonstrated that the survival benefit for patients assigned to the abiraterone group compared with the placebo group, favored abiraterone acetate across most of the subgroups analyzed, providing proof of principle that mCRPC remains androgen driven. Furthermore, COU-AA-302 study showed that abiraterone decreased the risk of decline in ECOG performance-status score by 18%; the median time to the initiation of cytotoxic chemotherapy was longer in the abiraterone group than in the prednisone alone group (25.2 months vs. 16.8 months); a significant delay in the time to opiate use for cancer-related pain was observed with abiraterone treatment; the median time to increase in pain was also longer among patients receiving abiraterone than those receiving prednisone alone (26.7 months vs. 18.4 months).

The meta-analysis showed that the frequency of any adverse event, adverse event leading to treatment discontinuation, and adverse event leading to death was similar in two groups. Meta-analysis demonstrated grade

3 or 4 adverse events were reported in a little higher proportion in the abiraterone group than in the placebo group [RR=1.15, 95% CI (1.03, 1.30)]. The frequency of grade 1 to 4 diarrhoea, arthralgia, and cardiac disorders were more common in patients treated with abiraterone, and the proportion of grade 3 or 4 cardiac disorders events was higher in the abiraterone group [RR=1.91, 95% CI (1.23, 2.98)]. In COU-AA-302 study, the proportion of patients with atrial fibrillation was similar in the two groups (Ryan et al., 2012). Nevertheless we must take effective measures to prevent cardiovascular adverse events during abiraterone treatment. Although the meta-analysis suggested that grade 1 to 4 mineralocorticoid-related adverse events, hypokalaemia, hypertension, and fluid retention were more common reported in the abiraterone group than in the placebo group, there was no significant difference in prevalence of grade 3 or 4 mineralocorticoid-related adverse events in both groups. In addition, hypokalaemia was generally managed with oral potassium supplementation, and hypertension was generally amenable to increased dosage of an antihypertensive drug present at the outset of treatment, or addition of an anti-hypertensive agent. These adverse events are easily managed medically with appropriate patient monitoring and are generally less severe than the adverse events associated with cytotoxic therapies (de Bono et al., 2011; Fizazi et al., 2012). In short, this systematic review suggested the adverse event caused by abiraterone was acceptable and controlled.

According to the Cochrane Collaboration's tool for assessing risk of bias of RCT, both RCTs' qualities were high. Based on the GRADE system, critical outcomes: the quality of OS was "high", RPFS and TTPP were "moderate"; important outcomes: the quality of PSA response rate and Objective response rate by RECIST were "moderate"; the quality of any adverse event and grade 3 or 4 adverse event were "high"; and the quality of adverse event leading to treatment discontinuation and adverse event leading to death were "low". The evidence quality was degraded mainly due to the inconsistency and imprecision.

It should be noted that obvious heterogeneity existed in several pooled results. There were some possible sources of heterogeneity. Firstly, in the COU-AA-301 study, patients with histologically or cytologically confirmed mCRPC were eligible if they had been previously treated with docetaxel and a maximum of two previous chemotherapies; but in the COU-AA-302 study the patients who had not received previous chemotherapy were required. Secondly, the extent of disease and initial PSA level were not completely same in two studies, which might be an important source of heterogeneity. Last but not least, follow-up time was different in both studies, the result of COU-AA-302 study come from the second interim analyses, in this study three interim analysis and a final analysis were planned for overall survival. However, we did not detect heterogeneity in OS, any adverse event, and grade 3 or 4 adverse event, so heterogeneity may also come from statistics. In addition, the COU-AA-301 study suggested that the survival benefit of abiraterone acetate versus placebo was independent of previous docetaxel use when analyzed on the basis of timing of docetaxel administration and reason for docetaxel discontinuation. Therefore, although heterogeneity exist in several pooled results, the results of meta-analysis are still convincing.

Finally, two studies reported economic burden of abiraterone acetate, so it is not difficult to exactly evaluate the economic cost of abiraterone acetate or placebo. Abiraterone acetate certainly will increase the medical burden of patients and society compared with placebo, meanwhile significantly prolong overall survival in patients with mCRPC. In particular, according the two studies, abiraterone acetate treatment is superior to cabazitaxel in cost per Quality-adjusted life years gained (Ostale et al., 2012; Persson et al., 2012). Therefore, we must comprehensively consider the cost and benefit when making clinical decisions.

In conclusions, taking into account the current data available in this systematic review, patients with mCRPC, regardless of prior chemotherapy or chemotherapy-naïve, can benefit from abiraterone. Abiraterone can serve as a new standard therapy for mCRPC.

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