Journal of BUON **17:** 350-356, 2012

ORIGINAL ARTICLE

Intermittent androgen blockade or continuous androgen blockade in advanced prostate cancer: a meta-analysis of efficacy, quality of life and side effects

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Summary

Purpose: *To compare the efficacy, quality of life (QoL) and side effects of intermittent androgen blockade (IAB) vs. continuous androgen blockade (CAB) as treatment of advanced prostate cancer (PCA).*

Methods: *Using the search terms "advanced prostate cancer", "prostate cancer", "intermittent androgen blockade", "continuous androgen blockade", "randomized controlled trial" (RCT), the literature in Chinese and English language was searched in several databases to see for any difference between IAB and CAB concerning the effectiveness, QoL and side effects. Then, the studies to be included were identified according to previously established inclusion criteria, and those selected were assessed by methodological quality. Finally, the data of the studies included were extracted using self-tabulate tables, and the criteria of RCTs were studied. At the same time, odds ratio (OR) and weighted mean difference (WMD) of random effects model and fixed effects model were calculated to evaluate sensitivity.*

Results: *There were 16 RCTs that compared IAB with CAB with a total of 3264 patients (1624 with IAB and 1640 with CAB). Pooled effects indicated no significant difference between IAB and CAB groups in terms of death and progression rate (OR=0.99, 95% CI 0.80-1.23, and OR=1.03, 95% CI 0.84-1.26 respectively). Calculated results indicated that QoL on sexual activity was significantly higher in the IAB group (OR=0.24, 95% Cl 0.17-0.33, p<0.00001). Moreover, IAB could effectively reduce side effects.*

Conclusion: *The therapeutic efficacy (progression and death rate) was not significantly different between the IAB and CAB groups. However, IAB can effectively preserve the QoL (sexual life) and reduce the side effects. With analysis of more RCTs with strict design stronger evidence of the superiority of IAB could be proven.*

Key words: advanced prostate cancer, continuous androgen blockade, intermittent androgen blockade, randomized controlled trial

Introduction

PCA is the most common cancer in males with approximately 210,000 new cases diagnosed during 1997 in the USA [1]. This malignancy ranks first in incidence and sixth in mortality in males.

Huggins and Hodges first speculated on the role of androgen deprivation therapy (ADT) in PCA in the early 1940s [2]. The process that reduces intracellular dihydrotestosterone to below 20% can induce apoptosis of PCA cells depending on androgens [3]. Huggins and Hodges also demonstrated in a patient with advanced PCA that surgical castration can delay tumor progression [2]. However, surgical or medical castration eliminate only about 90% of testosterone. The major cause of failure may be incomplete androgen suppression. Therefore, great efforts have been put forward to achieve maximal androgen blockade (MAB), by using drugs which can inhibit and block androgens derived from the testis and adrenals at the same time. The 5-year survival rate of patients with MAB has increased by 2-3% compared with androgen suppression (AS) alone [4]. In recent years, investigations indicated that MAB is unable to prolong the time of PCA cells to progress to androgen-independent state [5], while it can reduce the QoL (erectile dysfunction, reduced libido, reduced general activity).

Klotz et al. [6] first reported in 1986 that withdraw-

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Received 09-10-2011; Accepted 03-11-2011

al of diethylstilbestrol from patients with metastatic PCA after initial clinical response can lead to reduction of side effects without any obvious adverse outcome. However, Gleave et al. [7] and Goldenberg et al. [8] suggested that after interruption of MAB, the surviving cancer cells can enter a normal differentiation pathway if androgens are supplemented.

Hot dispute is going on whether IAB or CAB is better to deal with advanced PCA. Therefore, there is a role for meta-analysis of these studies to particularly clarify the treatment efficacy, QoL and side effects between IAB and CAB.

Methods

Search strategy and selection criteria

CNKI, EMCC, Medline, PubMed, Google Scholar, Chinese Bio-Medicine Database (CBM) were searched using the following key words: "prostate cancer" or "advanced prostate cancer"; "intermittent androgen blockade" or "intermittent androgen suppression"; and "continuous androgen blockade" without language restriction. The available data from published and unpublished articles (by contacting the authors) before July 2011 were retrieved and all eligible articles were checked for their references and rechecked for other relevant articles. The inclusion criteria were: 1: Cases with advanced PCA patients, irrespective of age and race; 2: Published and unpublished (by contacting the authors) RCT comparing IAB vs. CAB; 3: Research outcomes i.e. therapeutic effect, QoL and side effects; 4: Randomized trials using blind, double blind or open label methodology; 5: Lost to follow-up cases <15%. The exclusion criteria were: 1: nonrandomized clinical trials; 2: untreated, clinically localized PCA (T1/T2N0M0 stage); 3: articles with insufficient or unavailable data.

Data extraction

Two of the authors performed the review and extracted the data independently which were registered in a self-developed data extraction form. Studies reported in non-English language journals were translated before assessment. Where more than one publication of one trial existed, only the publication with the most complete data was included. When necessary, we sent a letter to the study authors for further information. Disagreements were resolved by majority vote, if necessary, of a third review author. One author entered data into the Review Manager software (RevMan 5.0.20), and a second author independently checked the data entry.

Assessment of risk of bias in the included studies

Two authors independently used the GRADE criteria [9] to assess the risk of bias for all included studies.

Measures of treatment efficacy

For dichotomous data, results were summarised as risk ratios (RR), with 95% confidence intervals (CI). No statistically significant difference existed if 85% CI equaled to 1. For continuous outcomes we used WMD (when measures were in the same unit), or standardized mean difference (SMD) (when different scales were used to evaluate the same outcome) with 95% CI as well. No statistically significant difference existed if 85% CI equaled to 0.

Unit of analysis issues

Cross-over trials were not included in the present study. We tried to identify cluster-randomized trials which were included and analysed in accordance with section 16.3 of the Cochrane Handbook.

Dealing with missing data

The authors of papers with missing data were contacted. We made a note of all trials that did not use intention-to-treat (ITT) analysis and made any effort to analyse the data by this principal.

Assessment of heterogeneity

Heterogeneity was detected by visual inspection and by using the chi-square test, and was quantified by calculating the I^2 statistics by the equation: $I^2 = (Q\text{-}df)/Q$, where Q us the heterogeneity statistics and df reflects the percentage of the variability between studies that can be attributed to heterogeneity rather than to sampling. $I^2 > 50\%$ was considered to show considerable heterogeneity.

Assessment of reporting biases

We assessed reporting bias by funnel plots. We searched multiple databases, contacted authors, utilized clinical practice guidelines and systematic reviews, to minimize reporting and publication bias.

Data synthesis

A fixed-effects model was used unless significant heterogeneity was detected with $I^2 > 50\%$ among studies. In that case a random-effects model was used.

Subgroup analysis and investigation of heterogeneity

Subgroup analysis was used to explore possible sources of heterogeneity. Heterogeneity among studies was estimated by I^2 statistics. Typically, values >50% are deemed to suggest significant heterogeneity. Values of 25-50% are deemed to show modest heterogeneity, and values <25% are deemed to represent low heterogeneity.

Sensitivity analysis

We performed a sensitivity analysis in case of significant heterogeneity ($I^2 > 50\%$).

Results

Characteristics of identified studies

There were 59 studies fit for inclusion criteria, of which 32 were in English language and 27 in Chinese language. After reading the title and summary, accord-

ing to the inclusion and exclusion criteria, only 22 were left. For English language articles, 11 of 12 [10-20] referred to 6 researches [10,15,16,18-20]. Furthermore, 2 articles [21,22] were excluded because of incomplete data, therefore 16 studies [10,15,16,18-20,23-32] were finally included in our meta-analysis. The publication dates were from 2001 through July 2011 (Table 1).

Methodological quality

The characteristics of the included studies and Jadad score are shown in Table 1. No study described randomized methods and allocation concealment; 3 studies adopted double-blind methodology.

Results of treatment

Progression rate

Eleven studies reported the progression rate, so these studies [10,15,16,20,24-29,31] were finally included in here having 1880 patients altogether: IAB (944) and CAB (936) (Figure 1). The meta-analysis showed no difference in therapeutic efficacy between IAB and CAB (OR=1.03, 95% CI 0.84-1.26).

Death rate

Nine studies were included assessing the death rate [9,14,18,19,23,26-29]. There were 1676 patients alto-

Table 1. Characteristics of included studies

First author	*Publishing year*	*Methodological quality*					*Outcomes*
		Study design	*Randomized method*	*Allocation concealment*	*Double blind*	*Withdraw*	*Jadad score*	
Langenhuijsen [23]	2011	RCT	Unclear	Unclear	Yes	Yes	3	QoL
De Leval [10]	2002	RCT	Unclear	B	No	Yes	2	PR, DR
Calais [14,15]	2003	RCT	Unclear	B	No	Yes	2	PR, DR
Schasfoot [16]	2001	RCT	Unclear	B	No	Yes	2	PR
Calais [18]	2008	RCT	Unclear	B	Unclear	Yes	2	QoL, SE
Jacques [19]	2008	RCT	Unclear	B	Yes	Yes	2	DR, QoL, SE
Calais [20]	2009	RCT	Unclear	B	Unclear	Yes	2	PR, DR
Chen W [32]	2008	RCT	Unclear	Unclear	Unclear	Yes	2	QoL
Lan [24]	2004	RCT	Unclear	B	No	Yes	2	PR, DR
Wu [25]	2008	RCT	Unclear	Unclear	No	Yes	3	PR
Zhu [26]	2008	RCT	Unclear	Unclear	No	Yes	2	PR, SE
Chen JH [27]	2008	RCT	Unclear	B	Unclear	Yes	2	PR, DR,
Yu [28]	2006	RCT	Unclear	Unclear	Yes	Yes	3	PR, SE
Huang [29]	2008	RCT	Unclear	B	No	Yes	2	PR, DR, SE
Wang Q [30]	2005	RCT	Unclear	B	No	Yes	2	DR, QoL
Wang JH [31]	2008	RCT	Unclear	Unclear	Unclear	Yes	2	PR, SE

RCT: randomized controlled trial, B: blind allocation, PR: progression rate, DR: death rate, QoL: quality of life, SE: side effect

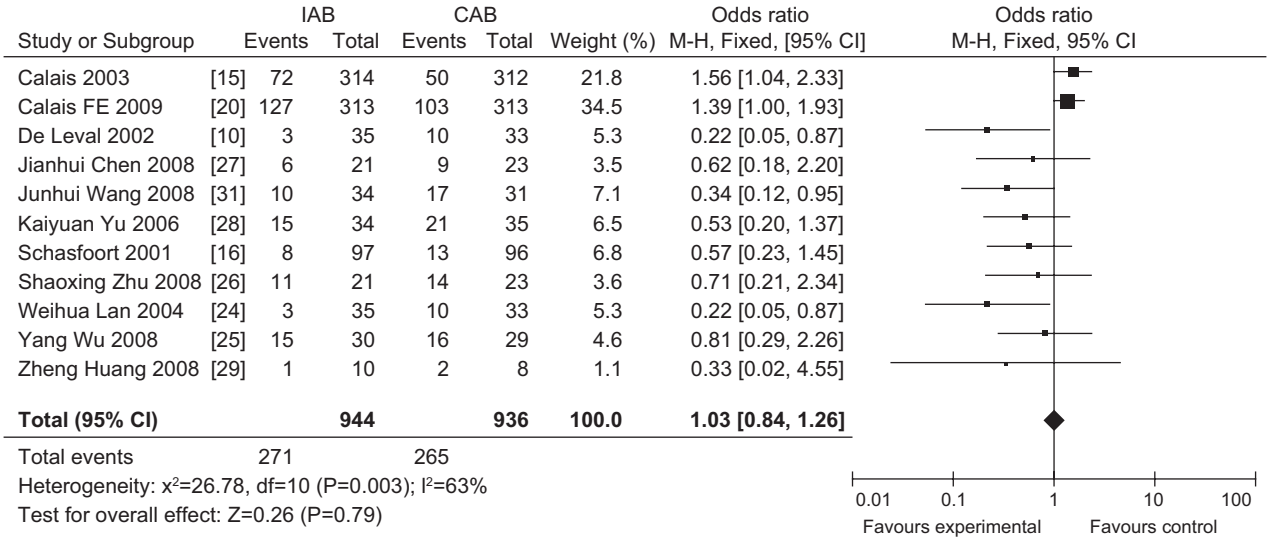

Figure 1. Meta-analysis of progression rate of prostate cancer comparing IAB vs. CAB.

gether: IAB (834) and CAB (842). Meta-analysis showed no significant differences between IAB and CAB. The OR was 0.99 and 95% CI 0.80-1.23 (Figure 2).

Quality of life

We evaluated QoL through the sexual function of advanced PCA patients. Six studies [15,18,19,23,30,32] reported QoL, however, one [19] presented the QoL by the European Organization for Research and Treatment of Cancer Core Quality of Life Questionnaire C30 (EORTC QLQ-C30) [32], so it was excluded. The remaining 5 studies [15,18,23,30,32] were included. The results suggested that IAB was better than CAB when evaluating QoL (OR= 0.24; 95% CI 0.17-0.33; Figure 3).

Side effects

Side effects of advanced PCA patients were evaluated by hot flushes and acute mastitis. Although 6 studies [18,19,23,28,29,31] reported mean hot flushes and acute mastitis, one paper [19] presented them by EORTC QLQ-C30 [33]. So, we included 5 studies [18,23,28,29,31], as previously described. There were 1259 patients altogether: IAB (635) and CAB (624) (Figure 4). Meta-analysis showed significant differences between IAB and CAB for hot flushes (OR=0.11, 95% CI 0.08-0.14, p<0.00001; Figure 4A) and acute mastitis (OR=0.31, 95% CI 0.22-0.42, p=0.78; Figure 4B).

Discussion

In recent years, many studies have shown that MAB can not prolong the time of PCA cells to progress to androgen-independent state. In the end, most PCA patients develop androgen-independent disease. IAB therapy allows androgen-sensitive cancer cells to start proliferation and androgen-independent disease will be delayed when the androgen-independent cell growth is competitively inhibited [34]. Based on randomized clinical studies between IAB and CAB as previously described, we planned a meta-analysis to present the results of these therapies.

Our research showed that there were no significant differences between IAB and CAB. However, De

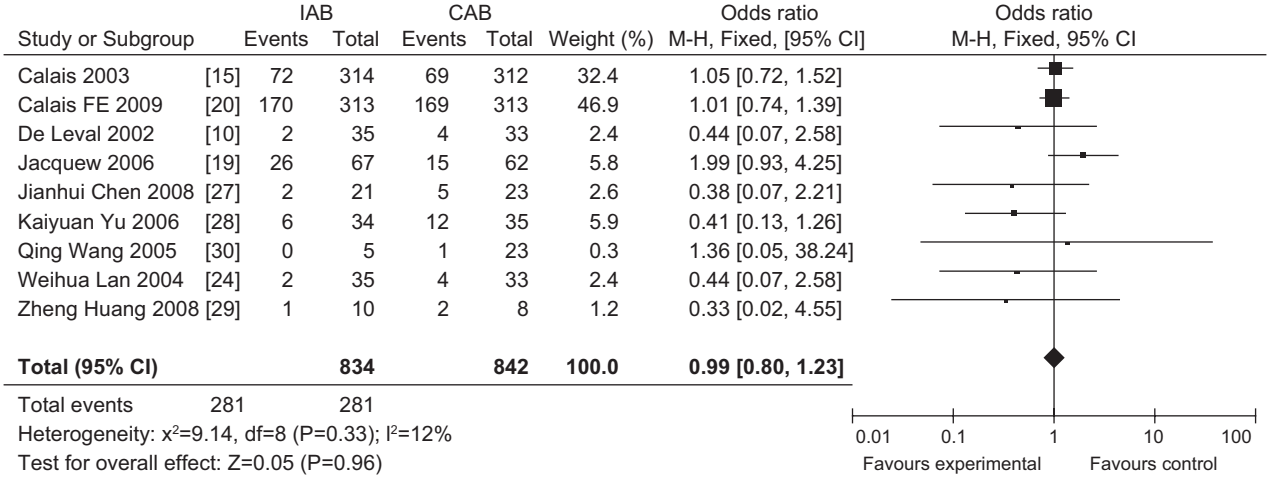

Figure 2. Meta-analysis of death rate of prostate cancer patients comparing IAB vs. CAB.

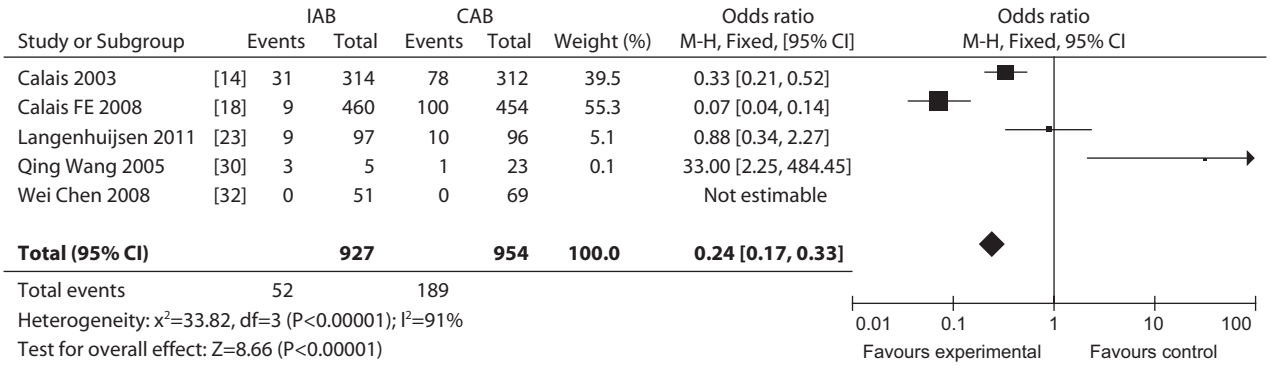

Figure 3. Meta-analysis of quality of life of prostate cancer patients comparing IAB vs. CAB.

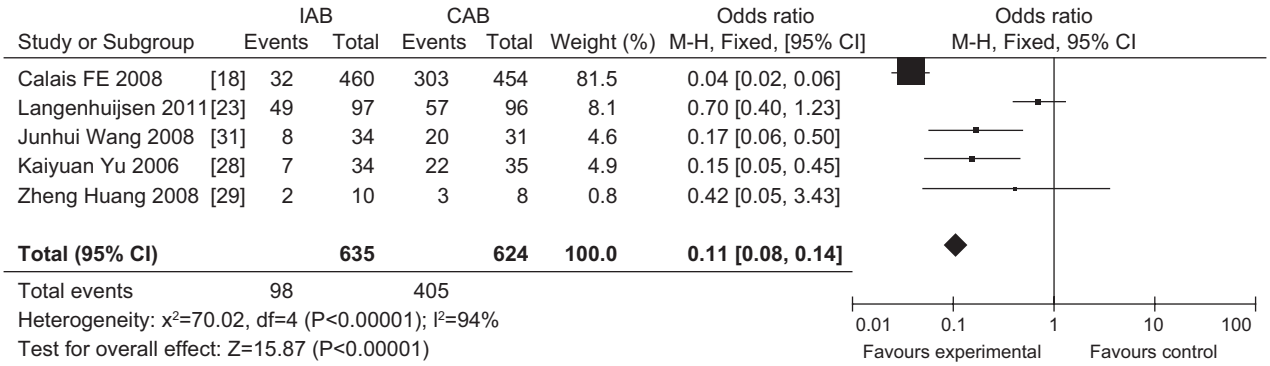

Figure 4A. Meta-analysis of hot flushes of prostate cancer patients comparing IAB vs. CAB.

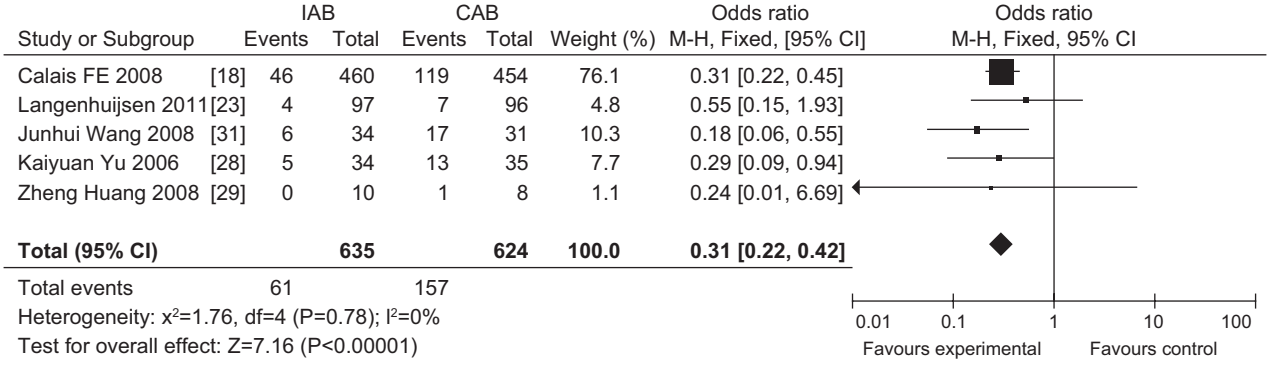

Figure 4B. Meta-analysis of acute mastitis of prostate cancer patients comparing IAB vs. CAB.

Leval et al. [10] found that the 3-year rate of progression to androgen-independent state with IAB (Gleason score >6) was significantly inferior to CAB (p=0.02); however, there was no significant difference between IAB and CAB (p=0.08) when Gleason score was lower or moderate. On the other hand, there was significant difference between IAB and CAB (p<0.001) in the 3-year progression rate of patients without bone metastases (M0). Such difference was not detected (p=0.32) in patients with bone metastases (M+) [35]. Conclusively, there was a good therapeutic effect for PCA patients with lower tumor grade with IAB rather than CAB therapy. By contrast, Kaneko et al. in a randomized study [36] reported no significant difference between IAB and CAB (58 vs. 89%; p=0.5) in the 5-year progression rate; however, IAB achieved better results in PCA patients with high tumor differentiation, and CAB had a better therapeutic effect in medium or low tumor differentiation. Conti et al. [37] found no significant difference in disease progression between IAB and CAB in any Gleason score. Up to now, the arguments still exist over the therapeutic effect of IAB and CAB, calling for more randomized clinical studies.

QoL should be assessed in studies with PCA patients [38]. Since changes in the sexual life are of major importance for most of the patients, they were included in the present study. The results of our meta-analysis showed that IAB can effectively maintain the sexual life of advanced PCA patients' compared to CAB. However, most studies did not assess the patient sexual life before drug administration, reporting only that some patients developed sexual dysfunction after therapy [18]. In addition, there is a bigger dispute about the methods of evaluating QoL [39-43]. In summary, the QoL evaluation, especially of the sexual life, is rather insufficient and should be supplied by more clinical research data.

At present, most clinical studies evaluate the side effects together with QoL. In our study, we estimated the side effects of therapy through hot flushes and acute mastitis of advanced PCA patients. As described previously, the results of this meta-analysis showed that hot flushes and acute mastitis were reduced with IAB compared to CAB. However, a need still exists for a standard model with specificity and practical applicability to evaluate more accurately whether IAB can effectively reduce the side effects.

In conclusion, our study has shown that there was no significant difference in the therapeutic effect (disease progression and survival rate) between IAB and CAB. However, IAB effectively maintained the sexual life and reduced the side effects.

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