Chinese-German J Clin Oncol
DOI 10.1007/s10330-014-0037-9
September 2014, Vol. 13, No. 9, P417–P421

Maximal androgen blockade versus castration alone in patients with metastatic prostate cancer*

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Received: 19 July 2014 / Revised: 10 August 2014 / Accepted: 28 August 2014

Abstract ***Objective:*** Maximum androgen blockade (MAB), consisting of an antiandrogen plus either a luteinizing hormone-releasing hormone agonist (LHRHA) or orchiectomy, is a standard care for patients with prostate cancer. Although, clinical trial results have been equivocal, none has shown a significant advantage in favor of MAB over castration alone in metastatic prostate cancer and MAB has been the subject of considerable controversy. The aim of this study was to compare MAB (orchiectomy or LHRHA "Goserelin") and anti-androgen "Bicalutamide" with castration alone (orchiectomy or LHRHA) in previously untreated metastatic prostate cancer patients. ***Methods:*** Hundred eligible patients with adequate performance status and adequate hematologic, hepatic and renal functions were included. MAB arm, fifty patients underwent castration either surgically by orchiectomy or medically by receiving Goserelin (3.6 mg) depot, which was injected subcutaneously every 28 days plus bicalutamide 50 mg once daily. Castration alone arm, fifty patients underwent castration alone either surgically by orchiectomy or medically by receiving Goserelin (3.6 mg) depot. ***Results:*** During the period from January 2011 to January 2013, with a median follow up of 18 months (range 6 to 24 months), there were eight deaths (16%), in MAB arm and ten deaths (20%) in castration alone arm. At three months, there were 35 patients (70%) with prostate specific antigen (PSA) normalization (≤ 4 mg/dL) in MAB arm versus 17 patients (34%) with PSA normalization in castration alone arm (P = 0.001). The median progression free survival (PFS) times were 22.18 months (95% CI, 19.7 to 24.2 months) for MAB arm versus 22 months in castration alone arm (95% CI, 18 to 25.9 months; P = 0.045). The survival rates for MAB arm were 82% at 18 months and 70.6% at 24 months versus 78.7% at 18 months and 75.1% at 24 months in castration alone arm (P > 0.05). The median overall survival (OS) was not reached in either arm. Both hematological and non-hematological toxicities were comparable in both arms. ***Conclusion:*** MAB significantly improves the PSA normalization rate at 12 weeks and PFS compared to castration alone with no significant difference in overall survival and with comparable acceptable toxicities. However further studies are needed to document such findings.

Key words castration alone; maximal androgen blockade (MAB); metastatic prostate cancer

Prostate cancer is the cause of more than 1% of all deaths in men. Its incidence is increasing by 2%–3% per year. About 50% of cases are diagnosed at a locally advanced stage, and about 30% have bone metastases at the time of diagnosis [1]. Most prostate cancer-related deaths are due to metastatic disease and the aim of treatment is not only to increase survival but also to improve quality of life [2].

The mainstay of treatment for advanced or metastatic prostate cancer is to inhibit the biosynthesis of androgens, and the hormones responsible for prostate cancer cell growth. Androgen suppression can be achieved through surgical (bilateral orchiectomy) or medical castration. Medical castration involves the long-term use of luteinizing hormone-releasing hormone (LHRH) agonists. The two methods of castration appear equally effective in removing testicular androgens [3–4].

Combination treatment, in the form of surgical or medical castration plus administration of an anti-androgen is called "maximal androgen blockade" (MAB). The use of MAB was first introduced in the early 1980s. Since then, a large number of randomized controlled trials have been conducted to evaluate the efficacy of MAB as compared with castration alone which yielded inconsistent results [5].

Patients and methods

Eligibility

This prospective randomized trial involved 100 patients with histological confirmed previously untreated metastatic prostatic adenocarcinoma. Age < 85 years;

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* This study was presented as Poster in ECCO17-ESMO38-ESTRO32 European Cancer Congress, Amsterdam, Sep. 2013.

performance status (ECOG-PS) ≤ 3; adequate bone marrow function (absolute neutrophil count ≥ 1.5×10^3/mL, platelet count ≥ 75×10^3/mL, hemoglobin ≥ 10 g/dL); adequate renal and hepatic functions [serum creatinine ≤ 1.5 mg/dL, hepatic enzymes ≤ 2.5 times upper normal limit (UNL), bilirubin ≤ 1.5 times UNL]. Baseline prostate specific antigen (PSA) level ≥ 10 ng/mL. Patients with brain metastasis, other active malignancy, history of previous hypersensitivity to LHRH agonists or its derivatives or to bicalutamide and significant cardiovascular disease were excluded.

Ethical consideration

Written informed consent was obtained from every patient before study entrance. The study was conducted in accordance with the Helsinki Declaration of the World Medical Association. The study was approved by the Ethical Review Committee at Faculty of Medicine, Ain Shams University, Egypt.

Treatment plan

MAB arm, fifty patients underwent castration either surgically by orchiectomy or medically by receiving Goserelin (3.6 mg) depot, which was injected subcutaneously every 28 days plus bicalutamide 50 mg once daily. Castration alone arm, fifty patients underwent castration alone either surgically by orchiectomy or medically by receiving Goserelin (3.6 mg) depot. All patients were scheduled to receive the previous treatment till disease progression or severe toxicity.

Evaluation of response and toxicity

Pretreatment evaluation included, complete history stressing upon symptoms of metastasis, the physical examination; ECOG-PS [6]; chest and abdominal computerized tomography scan (CT scan), bone scan; complete blood count, kidney and liver functions tests and PSA level. Tumor response was evaluated according to PSA response done every 3 months and bone scan, CT every 6 months. Toxicity was recorded according to the Common Toxicity Criteria of the National Cancer Institute (NCI-CTC, Version 4.0) [7].

Statistical analysis

The Kaplan-Meier survival analysis, log rank test, Student *T* test, Chi Square test and Fisher's exact test were used to determine the statistical analysis in this study. A $P < 0.05$ was considered significant.

Results

Patients' characteristics

From January 2011 to January 2013, a total of 100 patients were enrolled in this trial with a median follow up of 18 months (range 6 to 24 months). Patients' characteristics at baseline were listed in Table 1.

Table 1 Description and comparison of patients' characteristics in both MAB and castration alone treatment arms

Patient' characteristics	MAB arm		Castration alone arm	
	n	%	*n*	%
Age (years)				
< 75	25	50.0	23	46.0
≥ 75	25	50.0	27	54.0
Performance status				
1	19	38.0	19	38.0
2	28	56.0	26	52.0
3	3	6.0	5	10.0
Site of metastasis				
Bone	46	92.0	48	96.0
Bone and lung	4	8.0	2	4.0
Baseline PSA (ng/mL)				
< 60	20	40.0	19	38.0
≥ 60	30	60.0	31	62.0
Median value (Range)	67 (18–120)		73 (23–136)	
Gleason score				
Median value (Range)	7 (7–9)		7 (6–9)	

P value > 0.05

There was no statistical significant difference between both groups regarding patients' characteristics ($P > 0.05$).

Response and survival

Among the hundred eligible patients treated there were eight deaths (16%) in MAB arm and ten deaths (20%) in castration alone arm. Eight patients (16%) in MAB arm and sixteen (32%) patients in castration alone arm had disease progression during treatment.

At three months, there were 35 patients (70%) with PSA normalization (≤ 4 mg/dL) in MAB arm versus 17 patients (34%) with PSA normalization in castration alone arm ($P = 0.001$). There was a statistically significant difference regarding PSA normalization at 3 months in favor of the MAB arm.

PSA responses at 3 months, 6 months and 12 months were 90%, 92%, 97.6% respectively in MAB arm, while they were 82%, 86%, 89.7% respectively in castration alone arm with no statistically significant difference between the two treatment modalities.

The median progression free survival (PFS) time for MAB arm was 22.18 months (95% CI, 19.7 to 24.2 months) versus 22 months (95% CI, 18 to 25.9 months) in castration alone arm. A statistically significant difference was detected between the two treatment modalities in favor of the MAB arm regarding PFS ($P = 0.045$; Fig. 1).

The mean survival for MAB arm was 22.6 months (95% CI, 21.7 to 23.5 months). The survival rates for MAB arm were 82% at 18 months and 70.6% at 24 months. For the castration alone arm, the mean survival was 21.5 months (95% CI, 20.1 to 22.9 months). The survival rates for cas-

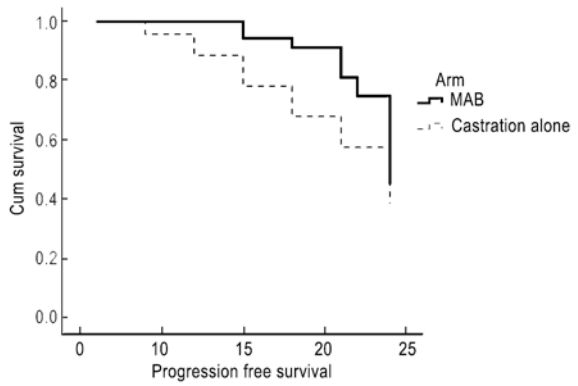

Fig. 1 Kaplan-Meier curves for progression free survival in both treatment arms

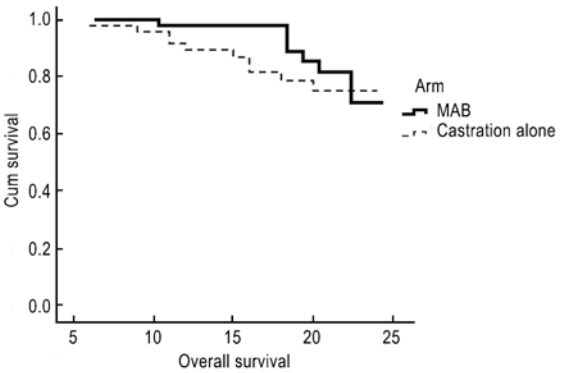

Fig. 2 Kaplan-Meier curves for overall survival in both treatment arms

tration alone arm were 78.7% at 18 months and 75.1% at 24 months.

Regarding survival rate, no statistically significant difference was detected between the two treatment modalities. The median overall survival (OS) was not reached in either group (Fig. 2).

Toxicity

In the 100 patients evaluable for toxicity, there was no significant difference regarding hematological and non hematological toxicities according to (NCI-CTC-Version 4) among both treatment groups (Table 2).

Discussion

The rationale for MAB in metastatic prostate cancer is that while castration prevents testicular androgen synthesis, androgens of adrenal origin are largely unaffected and may continue to stimulate the growth of hormone-sensitive prostate cancer cells. The addition of an antiandrogen to castration antagonizes the action of these androgens at the receptor level. Despite this clear theoretical rationale, clinical trial results have been equivocal, although none has shown a significant advantage in favor of castration alone and MAB has been the subject of considerable controversy for at least a decade [8].

Intergroup trial INT 0036 randomly assigned 603 men with metastatic disease to leuprolide plus flutamide or leuprolide alone [9]. Men treated with the combination had significantly longer progression-free and median survival compared to leuprolide alone (16.5 versus 13.9 months and 35.6 versus 28.3 months).

Intergroup trial INT 0105 randomly assigned 1387 men with metastatic disease to orchiectomy and either flutamide or placebo [10]. Although more patients treated with the combined approach achieved a serum PSA < 4 ng/mL (74% versus 62% with placebo), the differences in median and progression-free survival were not statistically significant (34 versus 30 months, and 20 versus 19 months, respectively). Withdrawal from the study due to

Table 2 Description and comparison of hematologic and non hematological toxicities between MAB and castration alone arms

Toxicities		MAB arm		Castration alone arm		*P*	Sig
		n	%	*n*	%		
Anemia	No	46	92.0	47	94.0		
	Grade 1	2	4.0	2	4.0	1.00**	NS
	Grade 2	2	4.0	1	2.0		
Hot flushes	No	44	88.0	47	94.0	0.487**	NS
	Yes	6	12.0	3	6.0		
Hepatic toxicity	No	40	80.0	41	82.0		
	Grade 1	5	10.0	7	14.0	0.162*	NS
	Grade 2	5	10.0	2	4.0		
Gynecomastia	No	48	96.0	50	100.0	0.495**	NS
	Yes	2	4.0	0	0.0		
Impotence	No	39	78.0	45	90.0		
	Grade 1	10	20.0	5	10.0	0.171*	NS
	Grade 2	1	2.0	0	0.0		

* Chi-Square test; ** Fisher exact test

toxicity was significantly more common in those assigned to flutamide (33 versus 10 patients with placebo).

The reasons for the differences in outcome between these two trials are not certain. In INT 0105, ADT utilized orchiectomy [10], while in INT 0036, ADT relied upon daily injections of leuprolide [9]. Lack of adherence to the leuprolide regimen may have led to incomplete androgen deprivation, and therefore a larger benefit when an antiandrogen was added to the treatment in the combined androgen blockade arm [10]. Castrate levels of testosterone were not systematically confirmed in INT 0036.

Several meta-analyses suggest a benefit in five-year survival but not at earlier time points for combined androgen blockade [11–14]. The largest of these, which was conducted by the Prostate Cancer Trialists' Collaborative Group, analyzed individual patient data from 27 randomized trials that included 8275 men (88 percent with metastatic disease) [13]. Combined androgen blockade was associated with a trend toward decreased five-year mortality [70.4% versus 72.4%, hazard ratio (HR) 0.96; 95% CI 0.91–1.01]. When the seven studies using the steroidal antiandrogen cyproterone acetate were excluded, the reduction in mortality with combined androgen blockade was statistically significant (72.4% versus 75.3%; HR 0.92). These data do not resolve the question of whether combined androgen blockade is preferable to medical or surgical orchiectomy alone, since toxicity and costs are higher and potential benefits limited with combined androgen blockade.

A trial carried out by Medical Research Council Prostate Cancer Working Party Investigator Group comparing early versus delayed treatment has recently been published [15]. For the first time the benefits of early treatment have been clearly demonstrated in terms of metastatic progression, complications, and deaths related to cancer.

Results of MAB in the first randomized National Cancer Institute study that took place in 1989 [14] were very encouraging, it showed an improvement in the rate of progression (13.6 versus 16.5 months) and a marked improvement in global survival (28.3 versus 35.6 months), a gain of 7.3 months ($P = 0.035$) in the MAB arm.

Since the early 1980s, there have been many randomized trials comparing MAB versus castration alone failed to show significant difference in overall survival whereas recent overviews found 3% to 5% increase in 5-year survival with MAB when non-steroidal anti-androgens (flutamide, nilutamide or cyproterone acetate) were used [16–19]. However Bicalutamide was not the drug used these trials.

Among the hundred eligible patients treated, after completing three months, 35 patients (70%) in MAB arm had PSA normalization (≤ 4 ng/dL) versus 17 patients (34%) in castration alone arm ($P = 0.001$).

PSA response after 3 months, 6 months, 12 months were 90%, 92%, 97.6% respectively in MAB arm while they were 82%, 86%, 89.7% respectively in castration alone arm ($P > 0.05$).

The mean survival time for MAB arm was 22.6 months (95% CI, 21.7 to 23.5 months). The survival rates for MAB arm were 82% at 18 months and 70.6% at 24 months. For the castration alone arm, the mean survival was 21.5 months (95% CI, 20.1 to 22.9 months). The survival rates for castration alone arm were 78.7% at 18 months and 75.1% at 24 months. Based on this result, no significant difference was detected between the two treatment modalities regarding overall survival. The median overall survival was not reached.

The mean progression free survival time for MAB arm was 22.18 months (95% CI, 19.7 to 24.2 months) versus 22 months (95% CI, 18 to 25.9 months) for castration alone arm and a significant difference was detected between the two treatment modalities in favor of MAB arm ($P < 0.05$).

The trial comparing MAB (using Biclutamide 80 mg daily in combination with castration) versus castration alone was done by Akaza *et al* [20], the result showed that MAB had a superior significant improves in the PSA normalization rate at 12 weeks and reduces the risk of treatment failure and disease progression compared with castration alone, without compromising tolerability.

In the study of Akaza and colleague, treatment failure occurred in 33 patients (32.4%) in the MAB group and 46 (45.5%) in the monotherapy group. Seventeen (16.7%) patients in the MAB group and 30 (29.7%) in the monotherapy group experienced disease progression ($P = 0.016$). These data were comparable to our current study results. However the median PFS was not reached in either group [20].

The overall survival in the comparative study before was similar in both treatment groups, where 13 (12.7%) patients in the MAB group and 18 (17.8%) in the castration only group have died. Long-term follow-up of patients is required to show if there is any correlation between the choice of treatment and a reduced risk of death. These data were comparable with our current study. Regarding toxicity evaluation in trial of Akaza *et al* [20], the most common adverse effects (AEs) were hot flushes, anemia and abnormal hepatic function and similar in the two groups [20].

The incidence of hot flushes in the MAB group was lower than in the monotherapy group (18.6% versus 31.7%). All events relating to hot flushes were mild to moderate in severity. Hepatic toxicity were reported in 13.7% in monotherapy versus 17.8% in MAB. The incidence of anemia was slightly higher in the MAB group than the monotherapy group (7.8% versus 5.9%). Gynecomastia occurred in < 2% of patients in each treatment group [20].

The most common AEs in our study population as a whole were hot flushes, abnormal hepatic function, anemia, impotence and gynecomastia. There was no significant difference in AEs between both groups. The incidence of hot flushes in the MAB arm was higher than in the castration alone arm (12% versus 6%). All events relating to hot flushes were mild to moderate in severity. Overall, AEs relating to abnormal hepatic function were reported by 20% and 18% of patients. The incidence of anemia was slightly higher in the MAB arm than the castration alone arm (8% versus 6%). Gynecomastia occurred in 4% only in MAB arm with none in castration alone arm, and all were grade 1. Impotence had higher incidence in MAB arm than castration alone arm, and 22% and 10% respectively all with Grades 1 and 2.

The incidence of toxicities in our trials were lower than the patients in trial of Akaza *et al* which may be explained due to lower dose used in our trial hence 50 mg versus 80 mg, except for hepatic toxicities which were higher in our current study but all were Grades 1 and 2.

Conclusion

MAB as first-line treatment for metastatic prostate cancer, significantly improves the PSA normalization rate at 12 weeks and improves PFS compared to castration alone with no significant difference in overall survival in both treatment groups and with comparable acceptable toxicities. However further studies and longer duration of follow up periods are needed to document such findings and to prove survival benefit if present.

Conflict of interest

The authors indicated no potential conflicts of interest.

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DOI 10.1007/s10330-014-0037-9
Cite this article as: Mahmoud AA, El-Sharawy EA, El-Bassiouny MM, *et al*. Maximal androgen blockade versus castration alone in patients with metastatic prostate cancer. Chinese-German J Clin Oncol, 2014, 13: 417–421.