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Original Article

Efficacy and toxicity between luteinising hormone releasing hormone analogue therapy and maximal androgen blockade therapy in patients with advanced prostate cancer in China

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Abstract: Objectives: The aim of this study was to examine the efficacy and toxicity between luteinising hormone releasing hormone analogue (LHRH-a) therapy and maximal androgen blockade (MAB) therapy in patients with advanced prostate cancer in China. Materials and methods: A total of 392 patients with advanced prostate cancer were included in the study. Patients who received LHRH-a therapy were included in LHRH-a group (*n*=120) and those who accepted MAB therapy were included in MAB group (*n*=272). Progression-free survival (PFS), overall survival (OS) and complication rates were compared between two groups. Results: No significant difference was found in PFS (25.4±1.0 vs. 25.3±0.6, P=0.354) and OS (34.6±1.0 vs. 36.3±0.6, P=0.215) between the two groups. LHRH-a group had significantly lower incidence of hot flush (24.2% vs. 34.9%, P=0.035), anaemia (8.3% vs. 38.2%, P<0.001), aminotransferase elevation (5.8% vs. 23.2%, P<0.001), weakness (8.3% vs. 18.8%, P=0.009) and constipation (3.3% vs. 12.9%, P=0.004) compared with MAB group. Furthermore, univariate and multivariate analysis showed that the prostate specific antigen (PSA) level was associated with PFS and OS in patients with PCa. Conclusions: LHRH-a therapy has similar efficacy but lower side effect compared with MAB therapy in patients with advanced prostate cancer.

Keywords: Prostate cancer, hormonal therapy, efficacy, survival, Chinese

Introduction

Prostate cancer (PCa) is the most common malignant tumour in European and American countries. In 2012, 241,740 cases diagnosed with PCa were reported in the United States. Of those, 28,170 patients died, making PCa the second leading cause of death for men in the United States [1]. Although prostate specific antigen (PSA) screening has gained popularity and the early diagnostic rate of PCa has increased, 35.8% of PCa patients have high risk of having locally advanced PCa at the time of diagnosis [2]. Currently, the first-line therapy scheme for patients with PCa is still endocrine therapy. Treatment methods include simple castration, antiandrogen monotherapy, maximal androgen blockade (MAB) treatment and intermittent hormonal therapy. However, the effectiveness and side effects of endocrine therapy should both be considered in the treatment of PCa.

Studies have shown that luteinising hormone releasing hormone analogue (LHRH-a) therapy and MAB therapy in hormone sensitivity exhibited similar efficacies in the treatment of PCa. No significant difference has been found in the overall survival (OS) and progression-free survival (PFS) of the two types of therapy [3]. To our knowledge, no domestic research has compared the efficacy and safeness of LHRH-a therapy and MAB therapy. Therefore, we conducted a retrospective analysis of clinical data of patients with PCa enrolled in the First Affiliated Hospital of Nanjing Medical University between January 2007 and December 2015.

Material and methods

Patient samples

This retrospective study included the clinical data of 392 patients with PCa (age: 37-83) who accepted endocrine therapy in the First Affilia-

Table 1. Patient characteristics in LHRH-a and MAB groups

variable	LHRH-a group N (%)	MAB group N (%)	t/X^2 value	*P* value
Age (year)	67.9±7.6	67.5±6.2	0.490	0.625
PSA (ng/ml)	370.0±974.3	365.7±939.2	0.041	0.967
Gleason score			0.479	0.633
6	7 (5.8)	13 (4.8)		
7	36 (30.3)	79 (29.0)		
8	31 (25.8)	69 (25.4)		
9	31 (25.8)	76 (27.9)		
10	15 (12.5)	35 (12.9)		
ECT lesions			2.290	0.130
Visible	52 (43.3)	96 (35.3)		
Invisible	68 (56.7)	176 (64.7)		

ted Hospital of Nanjing Medical University between January 2007 and December 2015. All patients with PCa confirmed by prostate biopsy pathology, patient age, PSA, Gleason score and bone metastases and other related information were recorded during the diagnosis. The patients were divided into two groups on the basis of their regimen. The LHRH-a treatment group included 120 cases and the MAB treatment group included 272 cases.

Therapeutic methods

The LHRH-a therapy group received the following treatment: leuprorelin 3.75 mg, Goserelin 3.6 mg or triptorelin acetate 3.75 mg subcutaneously, once every four weeks. The MAB therapy group received the following treatment: bicalutamide 50 mg oral once daily or 0.25 g flutamide oral thrice daily.

Observation targets

All patients attended monthly outpatient appointment and PSA review. Every 3 months, routine blood tests and liver and kidney function were reviewed. If signs of disease progression, such as elevated PSA, bone pain, and worsened micturition were found, then bone scan or Magnetic Resonance Imaging was conducted, and follow-up times of such patients were shortened. Castration-Resistant Prostate Cancer is described as follows: 1. The serum level of testosterone after castration was <50 ng/dl or <1.7 nmol/L); 2. Three consecutive PSA rises were noted within a week, and the lowest rise was more than 50%. The database was searched and patients were followed up regarding their treatment, survival, condition, breast tenderness and other side effects.

Statistical analysis

Using SPSS18.0 processing data, independent sample t test was used to compare continuous variables, and *chi*-square test was used to compare classification variables. Patient survival was evaluated using the Kaplan-Meier method. Univariate and multivariate Cox regression analyses were performed to analyze the survival data. $P<0.05$ was considered statistically significant.

Results

A total of 392 patients were included in this study, with 120 and 172 cases in the LHRH-a and MAB groups, respectively. The average age of patients was 67.6±6.6 years. The follow-up time was 8 months to 53 months, with an average of 33.1±8.3 months. The age (P=0.625), PSA (P=0.967), Gleason score (P=0.633) and Emission Computed Tomography results (P=0.130) of the LHRH-a and MAB groups showed no significant difference (**Table 1**).

Based on the follow-up results, the PFS of the LHRH-a and MAB groups exhibited no significant difference (25.4±1.0 vs. 25.3±0.6, P=0.354) and the OS between the two groups had no statistical difference (34.6±1.0 vs. 36.3±0.6, P=0.215) (**Figure 1**).

No significant differences between the two groups were found in part of side effects, such as feminine breast (69.2% vs. 66.9, P=0.660), breast tenderness (73.3% vs. 76.8, P=0.455), decreased sexual desire (76.7 vs. 74.6, P=0.667) and osteoporosis (51.7% vs. 58.8%, P=0.188). However, the number of cases that reported hot flushes (24.2% vs. 34.9%, P=0.035), anaemia (8.3% vs. 38.2%, P<0.001), abnormal liver enzymes (5.8% vs. 23.2%, P<0.001), fatigue (8.3% vs. 18.8%, P=0.009) and constipation (3.3% vs. 12.9%, P=0.004) in the LHRH-a group was significantly lower than in the MAB group (**Table 2**).

As shown in **Tables 3** and **4**, univariate and multivariate analysis showed that the PSA level was associated with PFS (P=0.013) and OS

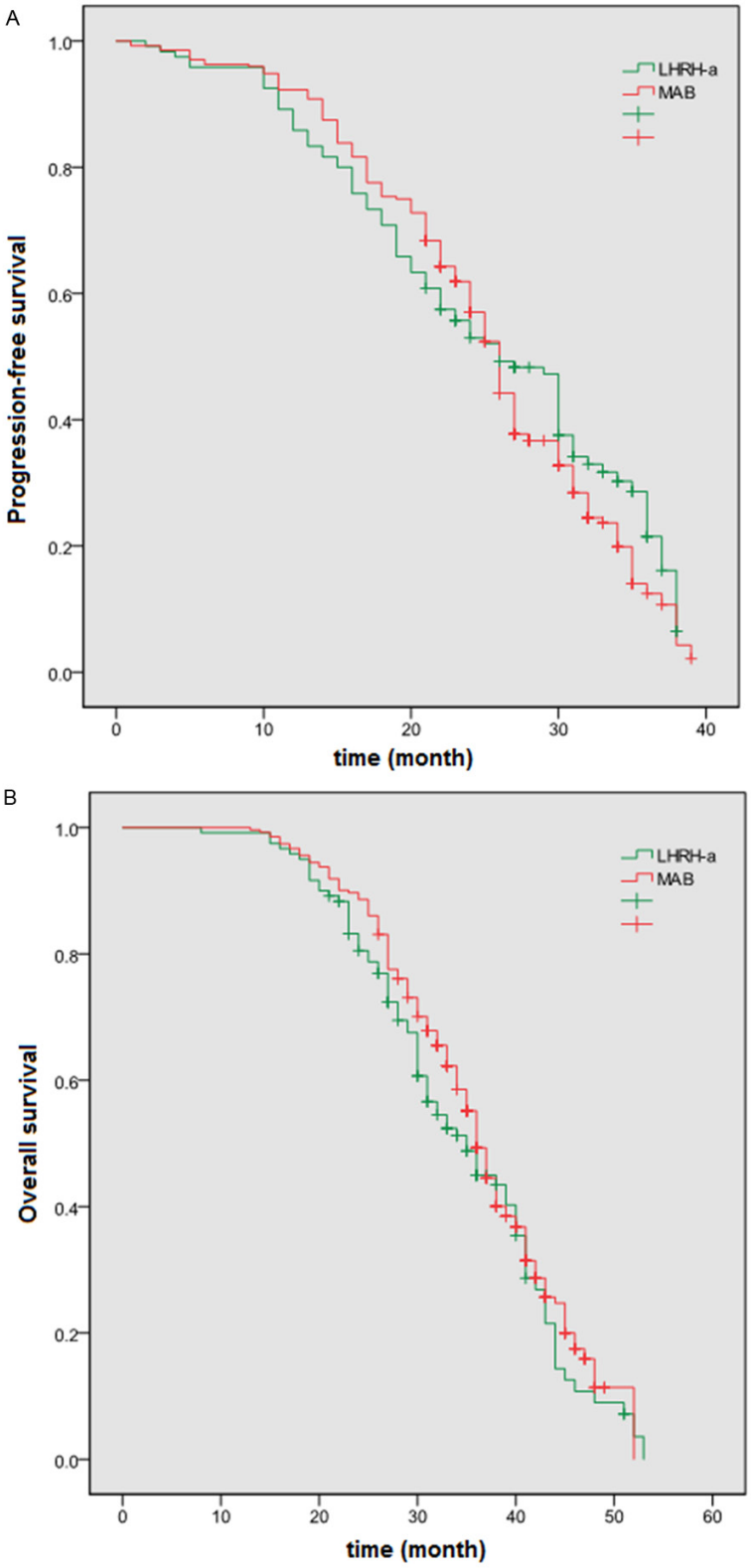

Figure 1. Kaplan-Meier survival curves of prostate cancer patients based on LHRH-a and MAB groups (A and B). The PFS of the LHRH-a and MAB groups had no significant difference (25.4±1.0 vs. 25.3±0.6, P=0.354) and the OS between the two groups had no statistical difference (34.6±1.0 vs. 36.3±0.6, P=0.215).

(P=0.003) in patients with PCa.

Discussion

The prostate is an androgen-dependent organ. In 1941, Canadian doctor Huggins first found that PCa is a type of hormone-dependent tumour. Disease progression can be inhibited to a certain extent by reducing the role of androgens. Huggins first proposed orchiectomy (castration) treatment for advanced PCa [4, 5]. Deprivation therapy aims to reduce the concentration of serum testosterone, and many scholars agree that the level of castration in the treatment effect should be more than 50 ng/dL, or below 20 ng/dL [6]. Traditional surgical castration is the gold standard treatment as it is safe, simple and relatively inexpensive. Nevertheless, given that the operation causes negative psychological effects in men, the scope of this treatment gradually narrowed in recent years.

Drug castration involves use of drugs to achieve castration levels of testosterone, and LHRH-a is currently the most widely used castration drug. The side effects of drug castration are similar to that of surgical castration, including female libido, male breast, breast tenderness, hot flushes and bone loss. If the testes are retained, the psychological impact on patients is smaller. Therefore, drug castration has become the primary mode of deprivation therapy around the world.

Androgen receptor (AR) antagonist drugs are classified into non-steroidal and sterol sub-

Table 2. Comparison of side effects between LHRH-a and MAB groups

Side effects	LHRH-a group	MAB group	X^2 value	*P* value
	N (%)	N (%)		
Feminine breast	83 (69.2)	182 (66.9)	0.193	0.660
Breast tenderness	88 (73.3)	209 (76.8)	0.557	0.455
Hot flashes	29 (24.2)	95 (34.9)	4.457	0.035
Decreased libido	92 (76.7)	203 (74.6)	0.185	0.667
Anemia	10 (8.3)	104 (38.2)	36.098	<0.001
Osteoporosis	62 (51.7)	160 (58.8)	1.737	0.188
Abnormal liver enzymes	7 (5.8)	63 (23.2)	17.045	<0.001
Fatigue	10 (8.3)	51 (18.8)	6.876	0.009
Constipation	4 (3.3)	35 (12.9)	8.448	0.004

Table 3. Univariate and multivariate analyses of progression-free survival (Cox proportional hazards regression model)

Variable	Univariate analysis		Multivariate analysis	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Age (year) ≥65 vs. <65	0.855 (0.549-1.333)	0.490		
PSA (ng/ml) ≥100 vs. <100	1.583 (1.082-2.317)	0.018	1.658 (1.111-2.475)	0.013
Gleason score ≥7 vs. <7	1.369 (0.433-4.326)	0.593		
ECT lesions Visible vs. Invisible	1.090 (0.744-1.598)	0.657		
Group LHRH-a vs. MAB	0.715 (0.471-1.086)	0.116		

Table 4. Univariate and multivariate analyses of overall survival (Cox proportional hazards regression model)

Variable	Univariate analysis		Multivariate analysis	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Age (year) ≥65 vs. <65	0.749 (0.491-1.142)	0.180		
PSA (ng/ml) ≥100 vs. <100	1.757 (1.233-2.505)	0.002	1.741 (1.206-2.513)	0.003
Gleason score ≥7 vs. <7	0.878 (0.278-2.768)	0.824		
ECT lesions Visible vs. Invisible	0.952 (0.665-1.364)	0.791		
Group LHRH-a vs. MAB	1.164 (0.789-1.718)	0.444		

types. AR antagonist drugs compete with testosterone to bind AR collection target organs, partly blocking testosterone androgen action in the nucleus. Surgical castration and drug castration both lower testicular testosterone levels. Considering that adrenal androgen can not be blocked sometimes, some scholars proposed the use of joint castration antiandrogen drug with MAB therapy [7]. In theory, MAB can maximise androgen effects on PCa and has better curative effect than LHRH-a alone. However, the curative advantage of MAB is debatable. A total of 27 randomised trials were chosen from 8275 cases enrolled at the Prostate Cancer Trialists' Collaborative Group Meta-analysis Multiple Centre. Results show that the 5-year survival rates of the MAB group and the LHRH-a group were 25.4% and 23.6%, respectively, with no significant differences [8]. Samson DJ and Schmitt have reported that the MAB plan has a slim majority in curative effect [9, 10]. The efficacies of MAB therapy and LHRH-a therapy are unknown, and no report exists on the efficacy of these therapeutic methods in the Chinese population.

This study aimed to compare the effect of MAB therapy and LHRH-a therapy on PCa patients in Jiangsu. The results indicated no significant difference in PFS (25.4±1.0 vs. 25.3±0.6, P=0.354) and OS (34.6±1.0 vs. 36.3±0.6, P=0.215) between the LHRH-a and MAB groups. In addition, univariate and multivariate analysis showed that the PSA level was associated with PFS (P=0.013) and OS (P=0.003) in patients with PCa.

Studies have showed that AR not only affects PCa, but can also be generated through the induction of some growth factors that can affect cell signal transmission. By blocking AR, it can not suppress this androgen mechanism. In addition, adrenal source sex androgen has been reported to have no direct impact on the prostate and PCa. These studies indicate that the curative effect of MAB is no better than the LHRH-a in terms of molecular biology and cytology.

Men with PCa live longer than men with other cancers, and the survival period of most PCa patients is more than three years. When choosing the treatment method, the patient's economic condition, drug side effects and other factors should be considered. In this study, we found no significant difference in terms of the major known side effects (namely, feminine breast (P=0.660), breast tenderness (P= 0.455), decreased libido (P=0.667) and osteoporosis (P=0.188) between the LHRH-a and MAB groups. However, the LHRH-a group had significantly lower occurrence of hot flushes (P=0.035), anaemia (P<0.001), abnormal liver enzymes (P<0.001), fatigue (P=0.009) and constipation (P=0.004) compared with the MAB group. Taken together, our findings showed that LHRH-a should be used once every four weeks. In addition, the drug should be injected every four weeks. Oral drugs should also be taken daily. Patient compliance was good and the cost was low in the LHRH-a group.

In this study, we first compared the solitary curative effects and side effects of LHRH-a and MAB in middle late-staged PCa patients enrolled at the First Affiliated Hospital of Nanjing Medical University in China. The efficacy of LHRH-a therapy was similar to that of MAB therapy. However, the former had lower incidence of side effects and was less expensive compared with the latter. This finding provides a new way of thinking in the clinical practice of individualised endocrine treatment of PCa.

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Disclosure of conflict of interest

None.

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