Original Research Article

Effect of combined use of atorvastatin and hormonal therapy on serum prostate-specific antigen, urinary function, and quality of life of early prostate cancer patients in intensive care unit

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Abstract

Purpose: To determine the effects of combined use of atorvastatin and hormonal therapy on serum levels of prostate-specific antigen (PSA), urinary function parameters, and quality of life (QOL) of intensive care unit (ICU) patients with early prostate cancer (PCa).

Methods: The clinical data for 90 PCa patients treated in ICU of Chenzhou First People's Hospital, Chenzhou, China from July 2019 to July 2020 were retrospectively analyzed. The patients were divided into a reference group given intensity-modulated radiotherapy (n = 45), and a study group treated with intensity-modulated radiotherapy + atorvastatin + hormonal therapy (n = 45) sequentially as they were admitted. After the treatments, serum PSA levels of the patients were measured using enzyme-linked immunosorbent assay (ELISA), while QOL was measured based on Expanded Prostate Cancer Index Composite (EPIC). Urinary parameters were determined by measuring various urodynamic indicators.

Results: Compared with the reference group, the study group had significantly lower post-treatment serum levels of PSA and blood lipids, higher levels of urinary function indicators (except for residual urine volume), and higher scores in IIEF-5 and EPIC (p < 0.001).

Conclusion: These results demonstrate that the combined use of atorvastatin and hormonal therapy is a reliable method for improving urinary function and QOL in early PCa patients. Moreover, the combined treatment has potentials for reducing serum levels of PSA and blood lipids in PCa patients. These findings may be useful in the establishment of improved therapy for early PCa.

Keywords: Atorvastatin, Hormonal therapy, Early prostate cancer, Serum PSA, Urinary function, Quality of life

INTRODUCTION

Prostate cancer (PCa) is the most frequent malignant tumor in elderly men worldwide, with mortality ranking 5th among male malignancies, and first among genito-urinary tumors [1]. The incidence of PCa in China has increased significantly in recent years due to increases in

the population of the aged, and changes in dietary habits. Radical prostatectomy, the first choice of current treatment for PCa, controls the differentiation and proliferation of tumor cells and prolongs survival of the patients [2]. However, since most PCa patients are in old-age category, with impaired body function and intolerance to surgery, radical prostatectomy does not result in satisfactory curative effect [3]. Studies have shown that PCa is androgen dependent. Thus, hormonal therapy may be a better treatment option for the disease. It has been confirmed that levels of lipid metabolism are associated with viability of tumor cells. Indeed, PCa patients often show evidence of abnormal lipid metabolism [4]. Hyperlipidemia facilitates the development and progression of cancer cells. Therefore, it may be reasonably speculated that inhibiting the growth of tumor cells by controlling lipid metabolism in PCa patients may be beneficial for the clinical treatment of the disease.

Atorvastatin, a drug used to regulate blood lipids, reduces cholesterol biosynthesis and controls the level of lipid metabolism. The effectiveness of atorvastatin has been demonstrated in elderly patients with diabetic nephropathy [5]. However, the effect of combined use of hormonal therapy and atorvastatin on PCa has not been investigated. In this study, the effects of combined treatment with atorvastatin and hormonal therapy on serum PSA, urinary function and QOL in ICU patients with early PCa were investigated.

METHODS

General patient profiles

The clinical data for 90 PCa patients treated in ICU of *Chenzhou First People's Hospital* from July 2019 to July 2020 were retrospectively analyzed. The patients were divided into reference group and study group, based on their order of admission, with 45 patients in each group. This study was approved by the ethics committee of Chenzhou First People's Hospital (approval no. 20190547), and followed the guidelines of Declaration of Helsinki [6].

Inclusion criteria

Patients in the following categories were included in the study: subjects meeting the diagnosis criteria for PCa in Diagnosis and Treatment Specifications for Prostate Cancer [7], and were diagnosed after pathological biopsy of the prostate, with clinical manifestations such as micturition urgency, hematuria, and frequent micturition; patients with NM stages of T1 and T2, without symptoms of clinical metastasis and local lymphadenectasis; subjects who were treated in ICU, and those who did not receive hormonal and immuno-related therapies before the present study.

Exclusion criteria

Patients whose conditions were complicated with diseases resulting in failure of major organs such as heart, liver and kidney, or failure of other important organs; patients with immune dysfunction or acute or chronic infections; patients with cognition impairment or mental disease; patients who failed to complete the treatment regime, and those who were unwilling to participate in the study.

Treatments

After admission, patients in the two groups received ICU treatment, and corresponding intervention measures were established according to their actual condition and clinical cases. These treatments included nutritional support, fluid infusion and oxygen treatment. Moreover, the patients' vital signs were monitored. If any changes in signs occurred, timely intervention was carried out and the changes were reported to the attending doctor. In addition, there was frequent communication with the family members of the patients to enable them understand the function of the ICU so as to enhance compliance [8].

Patients in the reference group received intensity-modulated radiotherapy during their ICU stay. Positioning was done under a simulated CT machine, generally from L2 to 10 cm from the lower sciatic rim. The clinical target volume (CTV) included sub-clinical lesions such as prostate and bilateral seminal vesicles. The pelvic lymph node drainage area was delineated to avoid any invasion. The planning target volume (PTV) was delineated based on the CTV: 0.5 cm external exposure was conducted upwards, downwards, and to the left and right. In view of the fact that the rectum is behind the prostate, only 0.3 cm was enlarged at the front and back. At the same time, the adjacent parts susceptible to radiation such as the bulb of penis, femoral head, rectum and bladder were delineated. Integrated block was used for conformal radiation and correction of non-homogeneous tissues. The medical linear accelerator (model: XHA600C; Shandong Shinva Medical Instrument Co. Ltd.) was used for treatment. The irradiation dose used for CTV was 2.23 Cy each time, 5 times per week, and the

total dose was 78 Gy. The irradiation dose for PTV was 2.17 Cy each time, 5 times per week, with a total dose of 76 Gy. Rectum and bladder $V_{70} < 25$ %, femoral head $V_{50} < 5$ %, and pubis $V_{70} < 25$ % were carried out.

In addition to the above treatments, patients in the study group received atorvastatin in combination with hormonal therapy. More than 5 months before intensity-modulated radiotherapy, goserelin (NMPA approval no. J20160052; AstraZeneca Pharmaceutical Co. Ltd; specification: 3.6 mg/bottle/box) was subcutaneously injected at a dose of 3.6 mg each time, once every four weeks. After radiotherapy, 50 mg of the anti-androgen drug bicalutamide (NMPA approval no. J20150050; AstraZeneca Pharmaceutical Co. Ltd.; specification: 50 mg × 20 tablets/box) was given once daily. When the serum PSA level was reduced to below 0.2 ng/mL and remained stable for 3 months, the drug was discontinued, and 10 mg of atorvastatin (NMPA approval no. H20051408; Pfizer Pharmaceutical Co. Ltd.; specification: 20 mg) was administered once daily for 30 consecutive days.

Evaluation of indicators/parameters

Serum PSA and blood lipid indicators

After treatment, fasting venous blood (5 mL) was collected. The blood samples were allowed to coagulate, after which they were centrifuged to obtain sera. Serum PSA concentration was measured with ELISA kits (Shanghai Jingkang Bioengineering Co. Ltd.) according to the protocol specified on the kit manual. The serum levels of triglycerides (TG), total cholesterol (TC), and low-density lipoprotein cholesterol (LDL-C) were measured with an Automatic Biochemical Analyzer [model: BK-400; Biobase Biodustry (Shandong) Co. Ltd.], using assay kits purchased from Shanghai Fusheng Industrial Co. Ltd.

Urinary function

One month after treatment, various urodynamic indicators i.e., peak urinary flow, residual urine volume, bladder compliance, and maximum urethral pressure, were determined.

Erectile function and sexual desire

Erectile function and sexual desire after treatment were evaluated by international index of erectile function-5 (IIEF-5) [9]. The scores on this scale ranged from 0 to 24 points. A score less than 21 points indicated erectile dysfunction (ED).

Quality of life (QOL)

One month after the treatments, QOL was evaluated in the patients using the Expanded Prostate Cancer Index Composite (EPCI) which covered scores for symptoms in the domains of intestinal function, hormonal function, urine passage and sexual function [10]. The total score for each domain was 100 points, with a higher score representing higher QOL.

Statistical analysis

In this study, the data were processed with the professional statistical software SPSS version 24.0, while GraphPad Prism 7 (GraphPad Software, San Diego, USA) was used for graphics. Enumeration data are expressed as numbers and percentages [n (%)], and were compared using chi square (χ^2) test. Measurement data are presented as mean ± standard deviation (SD), and were compared between the two groups using Student's t-test. Differences were considered statistically significant at $p < 0.05$.

RESULTS

Patients' profiles

No notable differences were observed in patient profiles such as mean age, TNM stages, maximum urethral pressure, and degree of educational attainment between the two groups ($p > 0.05$), as outlined in Table 1.

PSA levels

After treatment, the mean serum PSA values of the study and reference groups were 15.47 ± 1.59 and 22.30 ± 2.97, respectively. Thus, post-treatment mean serum PSA level was lower in the study group than in the reference group ($p < 0.001$, Figure 1).

Urine passage

All urinary function indicators, except residual urine volume, were higher in the study group than in the reference group after treatment ($p < 0.001$, Table 2).

IIEF-5 score

After treatment, the IIEF-5 scores were significantly higher in the study group (21.34 ± 1.4) than in the reference group (16.47 ± 1.53, $p < 0.001$).

Table 1: Comparison of patient profiles

Parameter	Study group	Reference group	χ^2	*P*-value
Mean age (years)	65.49±3.26	65.52±3.19	0.044	0.965
BMI (kg/m^2)	21.26±0.46	21.31±0.52	0.483	0.630
TNM stage			0.185	0.667
T1	28 (62.22)	26 (57.78)		
T2	17 (37.78)	19 (42.22)		
Gleason score (points)	6.48±1.28	6.51±1.25	0.112	0.911
Prostate volume (cm^3)	31.27±4.38	31.31±4.46	0.043	0.966
Mean duration of disease (months)	3.28±0.73	3.31±0.69	0.200	0.842
Peak urine flow (mL/sec)	5.18±0.26	5.22±0.31	0.663	0.509
72 h frequency of urination	51.23±2.36	51.28±2.42	0.099	0.921
Maximum urethral pressure (cm H$_2$O)	22.37±1.36	22.42±1.29	0.179	0.858
Smoking history			0.189	0.664
Yes/No	29/16	27/18		
Drinking history			0.443	0.506
Yes/No	28/17	31/14		
Marital status				
Married	39 (86.67)	38 (84.44)	0.090	0.764
Unmarried	2 (4.44)	4 (8.89)	0.714	0.398
Divorced	4 (8.89)	3 (6.67)	0.155	0.694
Educational degree				
College	4 (8.89)	5 (11.11)	0.124	0.725
High school	39 (86.67)	37 (82.22)	0.338	0.561
Primary school	2 (4.44)	3 (6.67)	0.212	0.645
Place of residence			0.403	0.525
Urban area	26 (57.78)	23 (51.11)		
Rural area	19 (42.22)	22 (48.89)		

Table 2: Comparison of post-treatment urinary parameters (mean ± SD, n = 45)

Group	Peak urinary flow (mL/s)	Residual urine volume (mL)	Bladder compliance (cm H$_2$O)	Maximum urethral pressure (cm H$_2$O)
Study	16.28±2.37	72.17±9.27	27.39±2.36	37.28±3.46
Reference	12.35±2.35	95.47±8.19	23.17±2.25	33.27±3.16
t	7.899	12.636	8.682	5.741
P-value	<0.001	<0.001	<0.001	<0.001

Table 3: Comparison of blood lipid levels (mean ± SD, n = 45)

Group	TC	LDL-C	TG
Study	9.48±1.47	6.47±0.83	5.48±0.73
Reference	16.35±1.36	11.26±0.76	10.43±0.85
t	23.012	25.551	29.636
P-value	<0.001	<0.001	<0.001
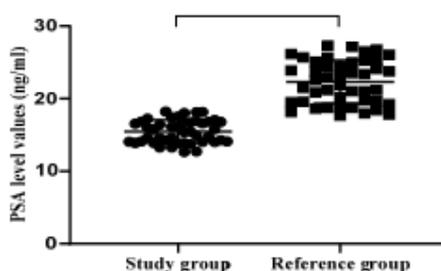
Figure 1: Between-group comparison of serum PSA level after treatment. *$P < 0.001$, ($t = 13.600$), vs study group

Blood lipid levels

Post-treatment levels of TC, LDL-C and TG were lower in the study group than in the reference group ($p < 0.001$, Table 3).

EPCI scores

After treatment, EPCI scores were significantly higher in the study group than in the reference group ($p < 0.001$), as presented in Table 4.

Table 4: Between-group comparison of EPCI scores after treatment (points, mean ± SD, n = 45)

Group	Urine passage	Intestinal function	Sexual function	Hormonal function
Study	74.53±4.29	82.16±3.82	72.54±4.62	81.23±4.71
Reference	69.26±4.37	74.27±3.27	62.28±4.18	75.25±4.28
T	5.773	10.526	11.047	6.303
P-value	<0.001	<0.001	<0.001	<0.001

DISCUSSION

Prostate cancer (PCa) is a frequent malignancy in men aged 50 years and above, and it is a main cause of cancer-related death in men [11]. Presently, the incidence of PCa and the associated mortality rates have increased in China. A study has shown that the incidence of PCa depends significantly on androgen levels, and it was suggested that PCa may be radically cured if patients at the early stage receive timely medical or surgical treatment. However, at the advanced stage of the disease, androgens cannot be blocked in a timely manner using surgery or drugs, leading to poor treatment effect [12]. Therefore, early PCa diagnosis and treatment are of great importance. Intensity-modulated radiotherapy, a common treatment for early-stage PCA with high conformality, further increases the target irradiation dose and reduces radiation damage to surrounding tissues, resulting in better clinical outcomes than conventional radiotherapy [13]. The proliferation of PCa cells is dependent upon androgens, implying that hormonal therapy occupies an important position in the treatment of prostate cancer [14].

The combined use of goserelin and bicalutamide is the classical regimen for hormonal therapy. It blocks the hypothalamic - pituitary - adrenal axis (HPA axis) and luteinizing hormone, and reduces serum testosterone levels, thereby suppressing the progression of PCa [15]. In another study, it was also demonstrated that the combined use of radiotherapy and hormonal therapy was more effective in reducing PCa recurrence and prolonging the overall survival of PCa patients, when compared with the use of radiotherapy alone [16]. Moreover, it has been shown that most PCa patients exhibit abnormal lipid metabolism, with hyperlipidemia contributing to the occurrence and progression of cancer cells, a finding which may be beneficial in the clinical treatment of PCa [17]. In the present study, the clinical data of ICU patients with early PCa were retrospectively analyzed. Patients in both groups received intensity-modulated radiotherapy, while those in the study group received additional combined treatment with atorvastatin and hormonal therapy. The results obtained revealed significantly lower mean PSA level in the study group. The changes in serum levels of PSA, a single chain glycoprotein, reflects therapeutic effect in PCa tissues [18]. Atorvastatin suppresses androgen biosynthesis and inhibits PCA tumor tissue proliferation, thereby reducing serum PSA level. Urinary dysfunction, a common complication in PCa patients, causes upper urinary tract lesions, impairs kidney function, and leads to life-threatening renal failure [19].

In this study, treatment of the PCa patients with combination of atorvastatin and hormonal therapy resulted in normal differentiation and apoptosis of the surviving tumor cells. The patients became free from hormone dependence, with improved condition and accelerated recovery of urinary function [20]. Post-treatment comparison of QOL between the two groups showed that the various EPCI scores were higher in the study group, indicating that PCa was controlled and the QOL was enhanced by the combined treatment with atorvastatin and hormonal therapy.

Limitations of the study

There was no diversity in the source of subjects investigated in this study, since the enrolled subjects were in the same hospital. In addition, the study period was short, and the toxic and side effects of the treatments on patients were not evaluated. Therefore, the conclusion arising from the present study requires validation through further research.

CONCLUSION

The use of atorvastatin and hormonal combination therapy for the treatment of ICU patients with early PCa reduced serum PSA levels, improves urinary function, and enhances QOL. Further studies in this direction will be beneficial for establishing a better therapy for PCa.

DECLARATIONS

Funding

None provided.

Ethical approval

None provided.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Conflict of Interest

No conflict of interest associated with this work.

Contribution of Authors

We declare that this work was done by the authors named in this article, and all liabilities pertaining to claims relating to the content of this article will be borne by the authors. Li Xiao and Jiaoe Liao conceived and designed the study, collected, analyzed and interpreted the experimental data, drafted the manuscript and revised the manuscript for important intellectual content. Both authors read and approved the final manuscript.

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