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EFFECT OF QIANLIE XIAOZHENG TANG, A CHINESE HERBAL DECOCTION, ON CASTRATION RESISTANT PROSTATE CANCER: A PILOT STUDY

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Abstract

Background: To examine the effect of Qianlie Xiaozheng Tang (QLXZT), a Chinese herbal decoction, on treating castration resistant prostate cancer (CRPC).

Materials and Methods: A total of 70 men with CRPC were recruited and randomly allocated into treatment groups (treated with QLXZT and conventional therapy) or control group (treated with conventional therapy) for 12 weeks treatment. Primary endpoint was serum prostate specific antigen (PSA) concentration. Secondary endpoints included patients' quality of life measured by Functional Assessment of Cancer Therapy-Prostate questionnaire, and prostate cancer-specific anxiety assessed by Memorial Anxiety Scale for Prostate Cancer.

Results: After a 12-week treatment, the PSA level in control group rose remarkably from 45.3 ± 17.0 to 76.0 ± 56.7 ng/ml (P=0.0015). By contrast, the PSA level in treatment group did not increase significantly (P>0.05). The scores of Functional Assessment of Cancer Therapy-Prostate in each domain changed significantly (P<0.05) in treatment group whereas the scores in control group did not differ from the baseline. In addition, the scores of Memorial Anxiety Scale for Prostate Cancer in treatment group dropped from 30.5 ± 4.7 to 27.0 ± 3.9 (P<0.001) while no significant difference was found between baseline and post-treatment in control group (P>0.05).

Conclusions: QLXZT could slow PSA progression, enhance quality of life and alleviate the prostate cancer-specific anxiety in patients with CRPC.

Key Words: Prostate Cancer; Traditional Chinese Medicine; Quality of Life; cancer-specific anxiety

Introduction

Study Population

All the patients were recruited from the Department of Urology, Guang An Men Hospital, China Academy of Chinese Medical Sciences between Jan. 2010 and Dec. 2012. Inclusion criteria were patients with histologically confirmed prostate cancer; age ranging from 50 to 75years; serum testosterone concentration lower than 50ng/dl; and prostate specific antigen (PSA) progression according to Prostate Cancer Working Group criteria (Bubley, Carducci et al., 1999, Scher, Halabi et al., 2008) (PSA more than 5.0 ng/ml followed by rising values in two or more consecutive measurements performed at least 1 week apart) or radiographic progression in soft tissue or bone with or without PSA progression. Exclusion criteria were patients with any history of cancers other than prostate cancer; impaired liver or renal function; and a history of psychiatric disorder.

The study protocol was approved by the institutional review board in Guang An Men Hospital (ethics permission number: 2010EC053) and it was designed according to the Declaration of Helsinki, the International Conference on Harmonisation. All study participants provided written informed consent.

Procedure

Patients who met the protocol eligibility criteria were allocated into treatment groups or control groups randomly, using a random number

generator in a 1:1 ratio. All the patients received chemical castration with luteinising-hormone-releasing hormone analogue: Goserelin Acetate (manufactured by AstraZeneca UK Ltd) 3.6mg subcutaneous injection once a month and second-line endocrine therapy: Megestrol Acetate Dispersible Tablets (manufactured by Qingdao Ruige Pharmaceutical Co. Ltd) 160 mg orally three times a day. Meanwhile, the patients in treatment group took QLXZT 200ml orally twice a day. The QLXZT was composed of Sheng Yi Ren (*Semen Coicis*) 40g, Zhi Huang Qi (*Astmgali Radix PraeparataCum*) 15 g, Huang Jing (*Polygonatum sibiricum*) 15g, Bai Hua She She Cao (*Hedyotis diffusa*) 15g, Tu Bei Mu (*Rhizoma Bolbostematis*) 15g, E Zhu (*Curcuma aeruginosa Roxb*) 10g, and Zhu Ling (*polyporus*)10g. All the decoctions were provided by the Department of Pharmacy, Guang An Men Hospital, China Academy of Chinese Medical Sciences, and were packed in opaque plastic bags with 200 ml for each one.

Clinical Assessment

The cancer stage was confirmed by pelvic CT or MRI, chest X-ray, and an isotope bone scan within 6 weeks before study entry. The PSA concentration in serum was measured and physical examination was undertaken within 1 week before study entry and at the end of 12 weeks to assess the clinical progression of CRPC (Scher, Halabi et al., 2008).

Evaluation of the Quality of Life

Patients' QOL was evaluated by Functional Assessment of Cancer Therapy-Prostate (FACT-P) (Esper, Mo et al., 1997) questionnaire (version 4). It includes five domains and is composed of 27 general questions and 12 items related to additional concerns of prostate cancer. Each question or item is answered on a scale from zero to four (0=not at all, 1=a little, 2=somewhat, 3=quite a lot, 4=very much). In addition, the prostate cancer-specific anxiety was assessed with the Memorial Anxiety Scale for Prostate Cancer (MAX-PC) (Roth, Nelson et al., 2006), which is composed of 18 questions. The answer of each question varies from zero to three (0=not at all, 1=rarely, 2=sometimes, 3=often). All the patients were asked to complete the questionnaires at the baseline and at the end of 12 weeks.

Statistical Analyses

Statistical analyses were performed using the JMP 9.0 software package (SAS Institute, Cary, NC, USA). Continuous variables were expressed as means ± standard deviation or median (interquartile range) while categorical variables were expressed as percentage and frequency. All analyses were based on the intention-to-treat (ITT) analysis set, which was defined as patients that have received at least one treatment. Differences between baseline and post-treatment in PSA level, the scores of MAX-PC and each domain in FACT-P were analyzed by paired t-test. Differences between two groups were evaluated by two sample t-test or Mann-Whitney U test. All reported *P*-values were two-sided, and $P<0.05$ was considered statistically significant.

Results

Seventy men (35 in treatment group and 35 in control group) were recruited in our study. Of those, two patients dropped out in treatment group because they took other Chinese patent medicine during the study period. Three patients dropped out in control group. One went abroad for seeking a better health-care service and two others underwent radiotherapy during the study period. *Table 1* shows the patients' demographic and no significant difference was detected between two groups.

After 12 weeks, the PSA level rose remarkably from 45.3 ± 17.0 ng/ml to 76.0 ± 56.7 ng/ml ($P=0.0015$) in control group. A slight increase of PSA level was also found in treatment group, but there was no significant difference between baseline and post-treatment (47.4±15.6 vs. 50.1±19 ng/ml). In terms of the change in PSA between baseline and post-treatment, control group presented a more significant elevation compared to the treatment group ($P<0.001$).

Table 1: Patient characteristics

Variables	Treatment group (33 cases)	Control group (32 cases)
Age (yrs)[a]	69 ± 5	70 ± 5
BMI [a]	22 ± 4	22 ± 3
History (months) [a]	23 ± 8	24 ± 7
Clinical Stage [b]		
T3	10（30%）	12（37%）
T4	23（70%）	20（63%）
N0	15（45%）	16（50%）
N1	18（55%）	16（50%）
M0	9（27%）	7（22%）
M1	24（73%）	25（78%）
Biopsy Gleason Score [b]		
7	7（21%）	6（19%）
8	13（40%）	11（34%）
9	11（33%）	12（38%）
10	2（6%）	3（9%）

[a] Values are given as mean ± standard deviation; [b] Values are given as frequency (percentage).

As is shown in *Table 2*, the scores of FACT-P in physical well-being, emotional well-being and additional concerns domains presented significant decreases, while the scores in Family/Social Well-being and functional well-being domains showed marked increases after 12-week treatment in treatment group. By contrast, the scores of FACT-P in each domain didn't show any significant difference in control group. With regard to the change from baseline to post-treatment, a more marked reduction in physical well-being, emotional well-being and additional concerns domains and a more significant rising in Family/Social Well-being and functional well-being domains were found in treatment group in comparison with ones in control group.

After 12-week treatment, the patients in treatment group presented a significant decrease in MAX-PC scores, which dropped from 30.5 ± 4.7 to 27.0 ± 3.9 ($P<0.001$). On the contrary, the scores in control group increased slightly, although there was no significant difference between baseline and post-treatment (31.1 ± 5.2 vs. 31.9 ± 5.2). In terms of the change in MAX-PC scores between baseline and post-treatment, treatment group had a significant reduction compared to control group ($P<0.001$).

Discussion

The main finding of our study is that QLXZT can suppress the PSA progression and improve QOL in patients with CRPC. In terms of specific QOL, QLXZT not only can enhance patients' physical function and alleviate bothersome symptoms, but also may relieve their prostate cancer-specific anxiety.

Some studies have shown that some Chinese herbal formulas are effective in treating prostate cancer. Of those, the most popular formula is PC-SPEC, which is a mixture of extracts from eight herbs (*Dendrantherma morifolium, Ganoderma lucidium, Glycyrrhiza uralensis, Isatis indigotica, Panax pseudo-ginseng, Rabdosia rubescens, Scutellaria baicalensis and Serenoa repens*). It was reported that PC-SPEC could inhibit prostate cancer cell growth in vitro and reduce PSA in patients with CRPC (Oh, Kantoff et al., 2004, Wadsworth, Poonyagariyagorn et al., 2003).

Table 2: Summary of FACT-P score at baseline and post-treatment.

	Baseline		Post-treatment		Change in value	
	Control group (n=32)	Treatment group (n=33)	Control group (n=32)	Treatment group (n=33)	Control group (n=32)	Treatment group (n=33)
Physical Well-being						
Mean ± SD	11.8 ± 2.3	11.1 ± 2.4	11.3 ± 2.1	9.0 ± 2.1	-0.4 ± 1.1	-2.1 ± 1.4
Median (IQR)	12.0 (2.0)	11.0 (4.0)	12.0 (3.0)	9.0 (3.5)*	-0.5 (1.0)	-2.0 (2.0)
	P=0.24[a]		*P*<0.001[a]		*P*<0.001[b]	
Family/Social Well-being						
Mean ± SD	13.2 ± 2.5	12.6 ± 2.1	13.4 ± 2.6	13.6 ± 2.3	0.2 ± 0.7	1.0 ± 1.0
Median (IQR)	14.0 (4.0)	13.0 (3.0)	14 (4.8)	14.0 (4.0)*	0.0 (1.0)	1.0 (2.0)
	P=0.37[a]		*P*=0.71[a]		*P*=0.0011[b]	
Emotional Well-being						
Mean ± SD	7.6 ± 1.3	7.3 ± 1.2	7.5 ± 1.2	6.5 ± 0.9	-0.1 ± 0.4	-0.8 ± 0.8
Median (IQR)	8.0 (1.0)	7.0 (2.0)	8.0 (1.0)	6.0 (1.0)*	0.0 (0.0)	-1.0 (1.0)
	P=0.29[a]		*P*<0.001[a]		*P*<0.001[b]	
Functional Well-being						
Mean ± SD	9.8 ± 2.6	11.1 ± 2.7	10 ± 2.9	12.7 ± 2.7	0.2 ± 0.6	1.6 ± 1.0
Median (IQR)	9.0 (3.0)	10.0 (4.5)	9 (3.3)	12.0 (3.0)*	0.0 (1.0)	2.0 (1.0)
	P=0.053[a]		*P*<0.001[a]		*P*<0.001[b]	
Additional Concerns						
Mean ± SD	20.2 ± 4.1	19.4 ± 3.6	19.9 ± 3.9	17.5 ± 2.7	-0.3 ± 0.9	-1.9 ± 1.4
Median (IQR)	19.5 (7.0)	19.0 (6.0)	19.5 (7.8)	18.0 (4.5)*	0.0 (1.0)	-2.0 (2.0)
	P=0.38[a]		*P*=0.046[a]		*P*<0.001[b]	

*$P<0.05$ vs. baseline; [a] Difference was analyzed by two sample t-test between two groups; [b] Differences were analyzed by Mann-Whitney U test between two groups.

SD: standard deviation; IQR: interquartile range.

However, it was withdrawn from the market in 2002 due to its supplement of estrogens, anticoagulants and analgesics (Kosty, 2004). QLXZT is an empirical formula invented by Professor Liu You-fang, the founder of Chinese Integrative Urology, according to his clinical experience of more than 40 years. Based on the theory of Traditional Chinese Medicine (TCM), it has the function of strengthening spleen to benefit the Qi, clearing heat and removing toxicity. In the formula, Sheng Yi Ren (*Semen Coicis*) is the Monarch with the function of invigorating spleen to eliminate dampness and removing heat to eliminate pura. Zhi Huang Qi (*Astmgali Radix PraeparataCum*) and Huang Jing (*Polygonatum sibiricum*), as the Ministers, take the effect of reinforcing the kidney and the spleen, invigorating Qi and nourishing Yin. And as the Assistants, Bai Hua She She Cao (*Hedyotis diffusa*), Tu Bei Mu (*Rhizoma bolbostematis*), E Zhu (*Curcuma aeruginosa Roxb*) and Zhu Ling (*polyporus*) expel pathogenic factors by clearing heat and detoxication and removing blood stasis. This formula presents a good example of the essential principle in treating cancers by TCM, supporting healthy energy to eliminate evils. Our previous studies have revealed that QLXZT can inhibit the tumor growth in nude mice and C57 mice model with hormone refractory prostate cancer (Zhang and Lin, 2005a, Zhang and Lin, 2005b). In current study, we found that QLXZT could suppress PSA progression in patients with CRPC, although it did not reduce the PSA concentration significantly. It indicates that QLXZT may slow the progression of CRPC.

Many early clinical trials regarding prostate cancer focused on survival rate as the primary endpoint. Over the past years, QOL has been another important outcome measure. Furthermore, QOL is of great concern to patients considering treatment options, because both disease burden and the side effects of treatment may result in negative impacts in patients' QOL(Resnick and Penson, 2012). A study has shown that long-term ADT is associated with poor QOL and psychosocial well-being (Chipperfield, Fletcher et al., 2013). Our previous study has shown that QLXZT can enhance the QOL in patients with advanced prostate cancer (Pang, Lu et al., 2010). In this study, we further found that QLXZT could improve the QOL of patients with CRPC in each domain. The potential mechanism might be related to two possible factors. On one hand, QLXZT slowed the disease progression and alleviated patients' symptoms. On the other hand, QLXZT relieved the negative effects of ADT on QOL.

It is reported that one-third patients with prostate cancer meet the criteria of anxiety disorder (Nelson, Weinberger et al., 2009). With disease progressing to CRPC, the majority of patients present psychological disorder. However, most urologists underestimate them (De Sousa, Sonavane et al., 2012), which result in these problems being remained and even deteriorated. Our study is the first to focus on the effect of TCM on relieving the anxiety associated with CRPC. We found that QLXZT had a positive effect on reducing patients' anxiety related to CRPC. The nucleus of TCM is the view of "harmony between Yin and Yang", which includes the harmony between physical function and psychological status. Therefore, the effect of QLXZT on relieving prostate cancer-specific anxiety may stem from this harmony between physical and mental status.

The important limitations of this study include small sample size, lack of a parallel placebo-control group and non-blind design. Another limitation is lack of the radiographic evaluation after 12-week treatment, which would be a burden for both patients and the insurance system.

Conclusion

Our study suggests that QLXZT may slow PSA progression, enhance the QOL and alleviate the prostate cancer-specific anxiety in patients with CRPC. QLXZT might be an alternative treatment for CRPC.

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