Correlation Between Pretreatment Serum Biochemical Markers and Treatment Outcome for Prostatic Cancer with Bony Metastasis

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Background: This study was undertaken to evaluate whether or not pretreatment serum biochemical markers are prognostic factors for prostatic cancer with bony metastasis in patients on hormonal treatment.

Methods: Between 1983 and 1998, 127 patients with prostatic cancer and bony metastasis were included for evaluation. Serum prostate-specific antigen, alkaline phosphatase, calcium (Ca), lactic dehydrogenase, inorganic phosphate, γ-glutamine transpeptidase, uric acid, albumin (Alb), iron, cholesterol (Cho), triglyceride, alanine aminotransferase, aspartate aminotransferase, and hemoglobin (Hb) were checked before treatment. The patients were divided into 2 groups according to their response (group 1, good response; group 2, poor response).

Results: There were 54 patients in group 1 and 73 patients in group 2. Pretreatment levels of serum Ca, Alb, Cho and Hb were higher in group 1 than in group 2, while the other parameters were lower in group 1 than in group 2; only pretreatment levels of serum Ca, Alb and Hb were significantly different between groups ($p < 0.05$). When stratified by tumor grading, patients in group 1 still had significantly higher pretreatment levels of Ca, Alb and Hb than those in group 2.

Conclusion: Higher pretreatment serum levels of Ca, Alb and Hb are good prognostic factors for patients with metastatic prostatic cancer on hormonal treatment, irrespective of tumor grading. [*J Chin Med Assoc* 2009;72(6):301–306]

Key Words: biochemical markers, prognosis, prostatic carcinoma

Introduction

Prostatic cancer is a leading cause of cancer mortality in males in the United States.[1] Prognostic factors for prostatic cancer including clinical, endocrinologic and pathologic factors have been reported previously.[2–7] Emrich et al reported that for survival time, the significant prognostic factors for advanced prostatic cancer were previous hormone response status, anorexia, elevated acid phosphatase, pain, elevated alkaline phosphatase (Alk-p), obstructive symptoms, tumor grade, performance status, anemia and age at diagnosis.[8] Smaletz et al demonstrated, by multivariate analysis, that Karnofsky performance status, hemoglobin (Hb), lactate dehydrogenase (LDH), Alk-p and albumin (Alb) were significantly associated with survival in patients with progressive metastatic prostate cancer after castration, whereas age and prostate-specific antigen (PSA) were not.[9]

We conducted a retrospective study to evaluate the correlation between pretreatment serum levels of biochemical markers, including Hb, PSA, Alk-p, calcium (Ca), LDH, inorganic phosphate (IP), γ-glutamine transpeptidase (γ-GT), uric acid (UA), Alb, iron (Ir),

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cholesterol (Cho), triglyceride (TG), alanine aminotransferase (ALT) and aspartate aminotransferase (AST), and the prognosis for prostatic cancer with bony metastasis in patients on hormonal therapy.

Methods

Between 1983 and 1998, 127 patients with good-to-moderate Karnofsky performance status who had prostatic cancer with bony metastasis and who were on hormonal treatment and received regular follow-up were included in this study. Prostatic cancer was confirmed by transrectal ultrasonography and biopsy or transurethral resection of the prostate, and bony metastasis was confirmed by whole-body bone scintigraphy. Patients who were not regularly followed-up or who only had suspicious lesions on bone scans or with poor control of diabetes mellitus or hypertension were excluded.

Body mass index (BMI), serum PSA, Alk-p, Ca, LDH, IP, γ-GT, UA, Alb, Ir, Cho, TG, ALT, AST and Hb were measured before treatment. Normal ranges were: Alk-p, 100–280 U/L; Ca, 8.1–10.7 mg/dL; LDH, 95–213 U/L; IP, 2.1–4.7 mg/dL; γ-GT, 8–60 U/L; UA, 2.5–7.2 mg/dL; Alb, 3.7–5.3 g/dL; Ir, 35–200 μg/dL; Cho, 125–240 mg/dL; TG, 20–200 mg/dL; ALT, 0–40 U/L; AST, 5–45 U/L; and Hb, 12–16 g/dL. Patients with BMI < 15 or > 40 were also excluded. For these patients, all of these serum biochemical markers were routinely checked at our hospital before hormonal treatment, and PSA was checked every 3 months after hormonal treatment. Of the 127 patients, 106 received orchiectomy and 21 were treated with diethylstilbestrol therapy, but no patient was on luteinizing hormone-releasing hormone agonist or total androgen blockade initially. The castration level of testosterone (< 0.2 ng/mL or 5% of the pretreatment level) was confirmed for all of the 127 patients on hormonal treatment during follow-up.[10]

Tumor grade was categorized as low (2–4), intermediate (5–6) or high (7–10) according to Gleason score. The 127 patients were divided into 2 groups according to their response after hormonal treatment. Treatment outcome was defined as follows. Group 1 attained a PSA nadir of < 4 ng/mL within 6 months after hormonal treatment or an undetectable level with no increase in PSA during follow-up for 2 times; and resolution or no change in previous metastatic lesion(s) on bone scintigraphy during follow-up. Group 2 had no PSA nadir of < 4 ng/mL within 6 months after hormonal treatment or had continuous increased PSA (20% increase of nadir) during follow-up for 2 times; and new metastatic lesion(s) or progression of previous lesion(s) demonstrated on bone scintigraphy during follow-up. Thus, group 1 comprised patients who had a good response after hormonal treatment and group 2 comprised patients who had a poor response.

The Mann-Whitney U test, Kruskal-Wallis test and multiple regression were used for statistical analysis, with $p < 0.05$ considered to show statistically significant difference.

Results

The mean age of the patients was 75.2 ± 6.3 years (range, 62–85 years), and the mean duration of follow-up was 30.7 ± 9.6 months (range, 10–120 months). There were 54 (42.5%) patients in group 1 and 73 (57.5%) patients in group 2. The overall survival rates at 12, 18, 24 and 60 months were 96.3%, 83.3%, 77.8% and 40.7% in group 1, and 56.1%, 16.4%, 12.3% and 2.7% in group 2, respectively. Significantly higher survival rate was noted in group 1 patients than in group 2 patients. There were 51 patients (42 in group 1, 9 in group 2) who survived ≥ 24 months, and 76 (12 in group 1, 64 in group 2) who survived < 24 months. A significantly higher survival rate was noted in group 1 patients than in group 2 patients. No significant differences were noted in age between groups 1 and 2 (75.1 ± 6.8 *vs.* 75.3 ± 6.0 years; $p = 0.72$), or among the 3 different tumor grades (73.8 ± 6.8 *vs.* 75.2 ± 6.7 *vs.* 75.5 ± 5.8 years; $p = 0.62$). There was also no significant differences in BMI between groups 1 and 2 (29.1 ± 7.8 *vs.* 28.7 ± 7.3; $p = 0.73$), or among the 3 different tumor grades (29.3 ± 7.9 *vs.* 27.9 ± 6.3 *vs.* 28.6 ± 7.1; $p = 0.65$). The distribution of grade overall and within groups 1 and 2 is shown in Tables 1 and 2. Patients with high tumor grade had significantly higher levels of γ-GT and TG. However, there were no significant differences in the other biochemical parameters among the 3 tumor grades (Table 1). Higher tumor grades were associated with a higher probability of having poorer response to hormonal treatment (Table 2).

The pretreatment serum levels of biochemical markers in groups 1 and 2 are listed in Table 3, while those in patients who survived ≥ 24 months or < 24 months are shown in Table 4. Pretreatment levels of serum Ca, Alb, and Hb were significantly higher in group 1 than in group 2, while the other parameters (except Cho) were lower (but did not reach statistical significance) in group 1 than in group 2 (Table 3). Also, according to multiple regression analysis, patients who survived ≥ 24 months had significantly higher pretreatment levels of serum Ca, Alb and Hb than those

Table 1. Pretreatment serum levels of biochemical markers by tumor grade*

	Tumor grade			$p^{\dagger}$
	Low ($n=24$)	Intermediate ($n=46$)	High ($n=57$)	
Alk-p (U/L)	250.3±87.3	224.1±330.2	242.5±325.1	0.91
Ca (mg/dL)	8.9±0.3	8.8±0.3	8.8±0.3	0.63
LDH (U/L)	274.5±152.8	220.6±118.7	248.2±110.5	0.24
IP (mg/dL)	3.2±0.4	3.4±0.5	3.3±0.4	0.46
γ-GT (U/L)	40.3±23.7	27.2±25.8	55.4±64.7	0.002‡
UA (mg/dL)	6.4±1.9	5.8±1.6	6.4±1.9	0.51
Alb (g/dL)	3.6±0.5	3.7±0.5	3.7±0.6	0.91
Ir (μg/dL)	65.5±37.2	74.3±32.9	91.1±37.2	0.07
Cho (mg/dL)	194.6±45.4	179.6±47.6	180.3±30.5	0.16
TG (mg/dL)	145.1±61.6	140±101.2	181.7±71.3	0.003‡
ALT (U/L)	18.1±11.5	26.2±44.3	30.5±33.0	0.29
AST (U/L)	29.4±15.7	36.4±46.9	34.1±25.2	0.65
Hb (g/dL)	12.1±1.3	11.4±1.1	10.6±1.5	0.07
PSA (ng/mL)	93.9±149.4	145.2±304.5	100.5±101.1	0.77

**Data presented as mean±standard deviation; †statistical analysis by Kruskal-Wallis test; ‡significant difference. Alk-p = alkaline phosphatase; Ca = calcium; LDH = lactic dehydrogenase; IP = inorganic phosphate; γ-GT = γ-glutamine transpeptidase; UA = uric acid; Alb = albumin; Ir = iron; Cho = cholesterol; TG = triglyceride; ALT = alanine aminotransferase; AST = aspartate aminotransferase; Hb = hemoglobin; PSA = prostate-specific antigen.*

who survived <24 months (Table 4). After stratifying by tumor grade, patients in group 1 still had significantly higher pretreatment levels of serum Ca, Alb and Hb than those in group 2 (Table 2). There was no significant difference in pretreatment serum PSA level among the different tumor grade and response groups, probably due to a large standard deviation of the data (Tables 1 and 3).

Discussion

Evaluating the clinical, pathologic and hormonal factors as prognostic indicators in prostatic carcinoma would provide a better understanding of the mechanism affecting disease progression,[11] and one of our previous studies reported that higher serum testosterone and lower luteinizing hormone, follicle-stimulating hormone and prolactin levels were good prognostic factors in patients with prostate cancer and bony metastasis on hormonal treatment.[12] That a higher tumor grade leads to a poor prognosis is obvious,[7] and was confirmed by this study. In order to reduce the bias of tumor grading, the grades were stratified for comparison.

The PSA nadir is an important indicator of response to hormonal treatment in patients with metastatic prostate cancer. Miller et al[13] stated that patients who reached a PSA nadir (<4 ng/mL) had a significantly longer remission than those who failed. Therefore, we used the PSA nadir as a factor to evaluate treatment outcome in this study. Patients with metastatic prostate cancer and poor performance status have poor prognosis after hormonal treatment.[9] In order to avoid this bias, only patients with good-to-moderate Karnofsky performance status were included in this study. Also, BMI, diabetes mellitus or hypertension are important confounders to the biochemical markers. Therefore, patients with BMI <15 or >40 or poor control of diabetes mellitus or hypertension were excluded.

Bone is the most common site of metastatic prostate cancer, and the prognosis for such patients is poor.[14] Imai et al stated that Alk-p, erythrocyte sedimentation rate and new extent of disease (based on bone scan) were significant prognostic factors in patients with prostate cancer and bony metastasis.[14] In this study, no significant difference in pretreatment serum Alk-p level was found among the different tumor grade and response groups because the standard deviation was large.

Tandon and Rizvi reported that hypocalcemia can be a manifestation of prostate cancer metastatic to bone.[15] Schwartz suggested that prostate cancer with bony metastasis might increase parathyroid hormone because calcium is transferred from serum into blastic bone.[16] Serum calcium is bound by Alb, so patients with lower Alb levels might present with lower calcium. Therefore, free calcium will be more valuable. However, in this study, we did not measure free calcium and found that patients with higher pretreatment serum Ca had better prognosis. Kuroda et al demonstrated that interleukin-6 might contribute to cachexia

Table 2. Pretreatment serum levels of biochemical markers in groups 1 and 2, stratified by tumor grade*

	Tumor grade								
	Low ($n=24$)			Intermediate ($n=46$)			High ($n=57$)		
	G1 ($n=16$)	G2 ($n=8$)	$p^{\dagger}$	G1 ($n=20$)	G2 ($n=26$)	$p^{\dagger}$	G1 ($n=14$)	G2 ($n=43$)	$p^{\dagger}$
Alk-p (U/L)	129.2±82.8	206.0±83.7	0.129	201.0±327.6	229.1±341.2	0.22	222.4±248.6	245.1±355.9	0.41
Ca (mg/dL)	9.0±0.2	8.7±0.3	0.004‡	9.1±0.2	8.7±0.2	<0.001‡	9.1±0.2	8.7±0.2	0.001‡
LDH (U/L)	248.7±112.1	326.2±220.1	0.371	202.4±60.5	231.4±150.3	0.41	218.2±44.7	263.1±128.8	0.91
IP (mg/dL)	3.2±0.4	3.3±0.3	0.768	3.3±0.6	3.4±0.6	0.71	3.3±0.3	3.4±0.5	0.21
γ-GT (U/L)	44.3±26.9	32.2±14.8	0.594	23.2±11.6	30.5±34.3	0.55	36.4±24.1	65.4±76.8	0.19
UA (mg/dL)	6.7±2.2	5.8±1.2	0.371	5.4±1.3	6.1±1.8	0.18	6.6±1.1	6.3±2.2	0.66
Alb (g/dL)	3.8±0.5	3.3±0.2	0.04‡	3.9±0.3	3.4±0.6	0.005‡	4.1±0.3	3.4±0.6	0.012‡
Ir (μg/dL)	68.1±37.2	60.4±41.1	0.513	75.4±25.8	76.5±36.8	0.95	83.3±28.1	95.4±40.1	0.70
Cho (mg/dL)	203.7±43.8	176.4±47.9	0.254	175.4±29.8	180.5±57.8	0.53	186.8±25.9	178.4±32.8	0.87
TG (mg/dL)	152.6±68.4	130.2±48.4	0.594	123.5±99.5	151.2±102.2	0.12	163.4±62.6	192.5±74.6	0.33
ALT (U/L)	22.3±10.6	9.8±9.0	0.075	14.2±9.6	32.5±5.2	0.31	25.8±12.8	33.1±38.8	0.63
AST (U/L)	25.6±13.2	37.0±19.0	0.165	28.4±23.7	41.5±57.6	0.09	32.1±15.7	34.5±28.1	0.71
Hb (g/dL)	12.6±1.4	11.0±1.0	0.04‡	12.1±1.3	10.6±1.2	0.002‡	11.9±0.9	10.7±1.1	0.012‡
PSA (ng/mL)	53.8±39.0	182.7±256.7	0.165	129.7±251.1	138.4±232.8	0.38	91.5±54.9	115.4±127.1	0.71

**Data presented as mean±standard deviation; †statistical analysis by Mann-Whitney U test; ‡significant difference. G1 = group 1, good response; G2 = group 2, poor response; Alk-p = alkaline phosphatase; Ca = calcium; LDH = lactic dehydrogenase; IP = inorganic phosphate; γ-GT = γ-glutamine transpeptidase; UA = uric acid; Alb = albumin; Ir = iron; Cho = cholesterol; TG = triglyceride; ALT = alanine aminotransferase; AST = aspartate aminotransferase; Hb = hemoglobin; PSA = prostate-specific antigen.*

Table 3. Pretreatment serum levels of biochemical markers in groups 1 and 2*

	Group 1 ($n=54$)	Group 2 ($n=73$)	$p^{\dagger}$
Alk-p (U/L)	194.76±273.2	242.1±331.0	0.095
Ca (mg/dL)	9.1±0.2	8.7±0.2	<0.001‡
LDH (U/L)	218.4±73.7	255.2±150.2	0.230
IP (mg/dL)	3.3±0.5	3.4±0.6	0.342
γ-GT (U/L)	31.2±20.4	43.8±54.7	0.413
UA (mg/dL)	6.0±1.6	6.2±2.0	0.822
Alb (g/dL)	3.9±0.4	3.5±0.5	<0.001‡
Ir (μg/dL)	75.8±29.6	82.8±39.6	0.512
Cho (mg/dL)	185.2±34.1	179.7±49.1	0.156
TG (mg/dL)	138.9±87.3	165.8±92.0	0.075
ALT (U/L)	20.2±11.0	31.2±29.2	0.891
AST (U/L)	29.2±20.2	39.5±47.5	0.109
Hb (g/dL)	12.1±1.3	10.8±1.2	0.001‡
PSA (ng/mL)	107.6±194.6	127.7±208.1	0.556

**Data presented as mean±standard deviation; †statistical analysis by Mann-Whitney U test; ‡significant difference. Group 1 = good response; Group 2 = poor response; Alk-p = alkaline phosphatase; Ca = calcium; LDH = lactic dehydrogenase; IP = inorganic phosphate; γ-GT = γ-glutamine transpeptidase; UA = uric acid; Alb = albumin; Ir = iron; Cho = cholesterol; TG = triglyceride; ALT = alanine aminotransferase; AST = aspartate aminotransferase; Hb = hemoglobin; PSA = prostate-specific antigen.*

Table 4. Pretreatment serum levels of biochemical markers by overall survival*

	Survival		$p^{\dagger}$
	≥24 mo ($n=51$)	<24 mo ($n=76$)	
Alk-p (U/L)	191.21±270.3	244.2±327.1	0.19
Ca (mg/dL)	9.2±0.2	8.6±0.2	0.05‡
LDH (U/L)	217.2±72.6	257.3±149.3	0.99
IP (mg/dL)	3.2±0.5	3.4±0.7	0.23
γ-GT (U/L)	30.9±19.3	44.2±53.6	0.17
UA (mg/dL)	5.9±1.5	6.3±1.9	0.26
Alb (g/dL)	4.0±0.4	3.4±0.4	0.05‡
Ir (μg/dL)	74.6±29.2	83.1±39.8	0.17
Cho (mg/dL)	184.7±33.8	179.7±50.2	0.34
TG (mg/dL)	137.5±86.8	166.7±92.2	0.28
ALT (U/L)	20.1±10.9	31.4±29.1	0.95
AST (U/L)	28.9±19.9	39.9±47.2	0.50
Hb (g/dL)	12.2±1.2	10.7±1.1	0.03‡
PSA (ng/mL)	105.4±191.2	128.2±204.5	0.40

**Data presented as mean±standard deviation; †statistical analysis by multiple regression; ‡significant difference. Alk-p = alkaline phosphatase; Ca = calcium; LDH = lactic dehydrogenase; IP = inorganic phosphate; γ-GT = γ-glutamine transpeptidase; UA = uric acid; Alb = albumin; Ir = iron; Cho = cholesterol; TG = triglyceride; ALT = alanine aminotransferase; AST = aspartate aminotransferase; Hb = hemoglobin; PSA = prostate-specific antigen.*

in patients with prostate cancer, and that patients with lower serum Alb, Cho and Hb had higher levels of interleukin-6.[17] In this study, we noted that patients with higher pretreatment serum Alb and Hb had better response after hormonal treatment. It seems that there is no correlation between the good prognostic parameters found in this study (high serum Ca, Alb and Hb) and in our previous study (high serum testosterone, lower prolactin, luteinizing hormone and follicle-stimulating hormone)[12] for prostatic cancer with bony metastasis under hormonal treatment. Hager et al reported that Cho may play a promotional role in prostate cancer development and progression.[18] Wuermli et al stated that hypertriglyceridemia may increase the risk of prostate cancer.[19] In this study, there was no significant difference in pretreatment serum Cho and TG between the 2 groups of patients, but patients with high-grade tumor had higher levels of TG. The exact mechanism needs further evaluation (maybe because of large standard deviation). Oral estrogen might have an influence on lipid profile and other biochemical parameters, but we used pretreatment level to avoid the effect of such an influence. Kapur suggested that hypophosphatemia could reduce the risk of aging men to develop prostatic cancer.[20] In this study, patients with better prognosis had lower IP level, but the difference was not significant. Patients with lower pretreatment serum LDH, γ-GT, UA, Ir, ALT and AST had better response after hormonal therapy, but again, the differences were not significant. The possible reason needs further investigation. Patients with high-grade tumor had significantly higher levels of γ-GT, but the difference between the 2 groups was not significant, which may be due to large standard deviation.

In conclusion, higher pretreatment levels of serum Ca, Alb and Hb were found to be good prognostic factors for patients with bone-metastatic prostatic cancer on hormonal treatment, irrespective of tumor grading.

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