A Pilot Study of Quality of Life of Patients with Hormone-refractory Prostate Cancer after Gene Therapy

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Abstract. Background: The effects on quality of life (QOL) after a Phase I/II clinical trial of a combination of osteocalcin promoter-driven herpes simplex virus thymidine kinase (Ad-OC-TK) gene therapy and valacyclovir (VAL) were investigated for patients with hormone-refractory prostate cancer (HRPC). Patients and Methods: The QOL of six patients was prospectively assessed after gene therapy on days 0, 14, and 28. A modified questionnaire was created based on the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire’s prostate cancer-specific module (EORTC QLQ-PR25). Results: The scores of all items significantly improved along with the total score. Further, bodily pain was significantly reduced on day 28. Moreover, the rate of change in the serum prostate-specific antigen levels from day 0 to day 28 was significantly correlated with the rate of change in bodily pain. Conclusion: In this clinical trial, Ad-OC-TK plus VAL treatment significantly improved the short-term QOL and bodily pain of patients with localized recurrence or bone metastases of HRPC.

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Prostate cancer is a leading cause of cancer-related deaths in men, second only to lung cancer-related deaths in industrialized countries (1, 2). In advanced disease, androgen-deprivation therapy remains the best treatment. After a median response of 12 to 24 months, patients develop progressive hormone-refractory prostate cancer (HRPC) (3, 4). Therefore, the development of new therapies with a survival advantage and greater antitumor effects is necessary. Gene therapy is a good candidate among new therapies.

The phase I clinical trial of the combination therapy of osteocalcin promoter-driven herpes simplex virus thymidine kinase (Ad-OC-TK) and valacyclovir (VAL) for the treatment of HRPC was conducted previously at the University of Virginia (5). Between August 2003 and March 2006, a phase I/II dose-escalating clinical trial of intratumoral injections of Ad-OC-TK was performed on 6 patients with HRPC in order to assess the potential toxicity and therapeutic effects of this treatment at Kobe University Hospital (6, 7). In clinical oncological trials, the therapeutic effects on the tumor volume and the serum levels of tumor markers are frequently used as the primary therapeutic indices. However, recently, the assessment of quality of life (QOL) has become an important therapeutic index. Since prostate cancer generally has a protracted natural history, it is particularly important for patients with HRPC to receive therapies that preserve or improve QOL, delay the progression of disease caused by severe pain, and provide quality-adjusted clinical benefits (8). In this study, the short-
term QOL and bodily pain of patients with HRPC who were undergoing a clinical trial of the combination of Ad-OC-TK gene therapy plus VAL was evaluated.

Patients and Methods

Study design. The most important criteria for inclusion in the study were as follows: metastatic or locally recurrent prostate cancer; histologically confirmed adenocarcinoma; evidence of disease progression despite surgery, radiation, androgen-deprivation therapy, and/or conventional chemotherapy. Patients were required to have a measurable lesion demonstrated by imaging studies and a single selected lesion had to be amenable to intralesional injection of the therapeutic agent. Six patients were divided into low-dose and high-dose viral vector groups (3 patients at each dose level). Ad-OC-TK was injected directly into the localized recurrent tumor or the bone metastatic lesion under the guidance of transrectal ultrasonography (TRUS) or computed tomography (CT). The doses used were 2.5×10^9 (low-dose group: 3 patients) and 2.5×10^10 (high-dose group: 3 patients) plaque-forming units (PFU) on day 1 and day 8. The patients were given 1 g of VAL three times daily for 21 days.

Assessment of the short-term QOL and bodily pain. Since there was no questionnaire for assessing the short-term QOL in patients receiving gene therapy for HRPC, a questionnaire (Table I) was created based on the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire’s prostate cancer-specific module (EORTC QLQ-PR25) (9), which is widely used to assess QOL in patients of prostate cancer. The questionnaire comprised scores evaluating role limitations in work (2 items), physical or social functioning (4 items), interpersonal relationships (2 items), emotional functioning (3 items), and sleep/vitality (2 items) as well as the global health status (2 items). A higher median value obtained on the symptom scale indicated a higher number of symptoms or problems. All the patients answered the questionnaire by themselves on days 0 (pretreatment), 14 and 28. The patients indicated how true a statement had been for them over the previous 14 days using a 4-point scale as follows: 0, not at all; 1, a little bit; 2, quite a bit; 3, very much. All items were assigned equal weighing. All the patients also scored their bodily pain on a visual analogue scale (VAS) on days 0, 14 and 28 as follows: 0%, they did not experience any bodily pain; 100%, they experienced severe bodily pain (10).

Correlation of the change of PSA with QOL and bodily pain. The correlation of serum prostate-specific antigen (PSA) levels with short-term total QOL scores and bodily pain was assessed by measuring the rate of change (%) of the serum PSA levels, the short-term total QOL scores, and bodily pain from day 0 to day 28; these values were expressed as ΔPSA, ΔQOL, and ΔPain, respectively.

Statistical analysis. The short-term QOL scores of patients (nonparametric data) were analyzed by Friedman one-way ANOVA. The Spearman test was used to analyze the correlation of ΔPSA with ΔQOL and ΔPain. P<0.05 was considered to be statistically significant.

Results

Patient characteristics. The mean age of the patients was 68 years (range, 63-77 years). The mean pretreatment serum PSA level was 222.7 ng/mL (range, 46.6-455.5 ng/mL). Three patients (50% ) had been diagnosed with poorly differentiated adenocarcinoma and the other 3 (50% ) had been diagnosed with moderately differentiated adenocarcinoma. All the patients had multiple bone metastatic lesions. In addition, 2 patients (33.3% ) had locally recurrent lesions. Two patients (33.3% ) had undergone radical prostatectomy in the past and all the patients had been treated with androgen-deprivation therapy.

Short-term QOL and bodily pain. All 6 patients answered the questionnaires on days 0, 14 and 28. Table II shows the short-term QOL scores of role limitations in work, physical or social functioning, interpersonal relationships, emotional functioning and sleep/vitality along with a total score of all items as well as the global health status. As compared with day 0, the scores for the global health status (p<0.05), interpersonal relationships (p<0.01), emotional functioning (p<0.01) and sleep/vitality (p<0.01) were significantly

Table I. Questionnaire.

<table>
<thead>
<tr>
<th>Global health status</th>
</tr>
</thead>
<tbody>
<tr>
<td>• How much overall influence on your health?</td>
</tr>
<tr>
<td>• How much overall influence on your life?</td>
</tr>
<tr>
<td>Role limitation of work</td>
</tr>
<tr>
<td>• How much influence on your home activities such as cleaning, shopping and so on?</td>
</tr>
<tr>
<td>• How much influence at work and daily activity out of the home?</td>
</tr>
<tr>
<td>Role limitation of physical or social activities</td>
</tr>
<tr>
<td>• How much influence on physical activities such as strolling, running, sports and so on?</td>
</tr>
<tr>
<td>• How much influence on using a bus, a car, train, an airplane and so on?</td>
</tr>
<tr>
<td>• How much influence on your interactions with others?</td>
</tr>
<tr>
<td>• How much influence on calling or meeting your friends?</td>
</tr>
<tr>
<td>Personal relationship</td>
</tr>
<tr>
<td>• How much influence on the relation with your companion-partner?</td>
</tr>
<tr>
<td>• How much influence on your family life?</td>
</tr>
<tr>
<td>Emotional</td>
</tr>
<tr>
<td>• Did you feel depressed?</td>
</tr>
<tr>
<td>• Did you feel anxiety and become nervous?</td>
</tr>
<tr>
<td>• Did you become miserable?</td>
</tr>
<tr>
<td>Sleep/Vitality</td>
</tr>
<tr>
<td>• How much influence on your sleeping habits?</td>
</tr>
<tr>
<td>• Did you feel fatigue?</td>
</tr>
</tbody>
</table>

Answer questions scoring 0-3 (0: not at all; 1: a little bit; 2: quite a bit; 3: very much).
improved on day 28. Moreover, significant improvements in
the short-term QOL scores were demonstrated with respect
to the role limitations in work (day 14, \( p < 0.05 \); day 28,
\( p < 0.05 \)) and physical or social functioning (day 14, \( p < 0.05 \);
day 28, \( p < 0.01 \)). As compared with day 0, the total score of
all items was also significantly improved on day 28
(\( p < 0.01 \)). Moreover, as compared with day 0, the bodily pain
was significantly reduced on day 28 (\( p < 0.01 \)).

**Correlation of ΔPSA with ΔQOL and ΔPain.** Figure 1 shows
the changes in the serum PSA levels of all patients from a
period of 8 weeks before (–8 w) to 4 weeks after (4 w) the
initial vector injection. The correlation of the serum PSA
levels with the short-term total QOL scores and bodily pain
is shown in Figure 2A and Figure 2B, respectively. A
significant correlation was observed between ΔPSA and
ΔQOL (\( p < 0.05 \)); however, it was not observed between
ΔPSA and ΔPain.

**Discussion**

QOL instruments, including EORTC QLQ-PR25, have been
applied in several therapeutic trials of prostate cancer (8, 11,
12). The items in these questionnaires include questions
regarding urinary conditions, for example pollakiuria, dysuria,
and macrohematuria. In addition, these questionnaires are
employed for patients with prostate cancer at various stages.
In this study, however, patients who had undergone various
treatments – including radical prostatectomy, androgen-
deprivation therapy and/or conventional chemotherapy –
prior to gene therapy were targeted. In 4 patients, the lesions
that were injected with the vector were bone metastatic
lesions alone. This study aimed at assessing the effect of
gene therapy on bodily pain because most patients suffered
pain at the site of the vector-injected lesion. Moreover, there
have been no questionnaires that assess QOL in patients
receiving gene therapy for HRPC. Taking the above into
consideration, a questionnaire based on EORTC QLQ-PR25
questionnaire (Table I) was created and bodily pain was
assessed by using VAS.

QOL is increasingly being recognized as a measure for
assessing outcomes of therapeutic trials. Moreover, the
assessment of the clinical effects of therapy on QOL is

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**Table II. Scores of QOL and percentage of bodily pain.**

<table>
<thead>
<tr>
<th>Items</th>
<th>Pretreatment</th>
<th>Day 14</th>
<th>Day 28</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>QOL score</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Global health status</td>
<td>6.0 (5-7)</td>
<td>5.5 (5-6)</td>
<td>5.0 (4-6)*</td>
</tr>
<tr>
<td>Role limitations in work</td>
<td>6.0 (5-6)</td>
<td>4.5 (5-6)</td>
<td>4.0 (4-6)**</td>
</tr>
<tr>
<td>Physical or social functioning</td>
<td>11.0 (9-12)</td>
<td>8.5 (8-10)*</td>
<td>8.0 (6-10)*</td>
</tr>
<tr>
<td>Interpersonal relationships</td>
<td>6.0 (4-6)</td>
<td>5.0 (3-6)*</td>
<td>4.0 (3-6)**</td>
</tr>
<tr>
<td>Emotional functioning</td>
<td>7.5 (7-9)</td>
<td>7.0 (5-7)</td>
<td>5.0 (5-7)**</td>
</tr>
<tr>
<td>Sleep/Vitality</td>
<td>5.0 (4-6)</td>
<td>4.5 (4-6)</td>
<td>4.0 (4-5)**</td>
</tr>
<tr>
<td><strong>Total score</strong></td>
<td>42.0 (35-54)</td>
<td>34.0 (31-39)</td>
<td>30.5 (27-37)**</td>
</tr>
<tr>
<td>Bodily pain (%)</td>
<td>52.5 (10-70)</td>
<td>35.0 (5-50)</td>
<td>25.0 (5-50)**</td>
</tr>
</tbody>
</table>

Data are expressed as median (range); *\( p < 0.05 \), **\( p < 0.01 \).
indispensable in the evaluation of therapeutic trials (13). In several therapeutic trials for prostate cancer, the assessment of patients’ QOL was incorporated as a therapeutic index. In this study, it was demonstrated that Ad-OC-TK plus VAL treatment significantly improved the short-term QOL scores and the ΔQOL using the modified questionnaire statistically correlated with ΔPSA (Figure 2A). Therefore, although it will be necessary to compare the changes in QOL scores using the modified questionnaire to the changes in QOL scores of other typical questionnaires used for patients of HRPC, it is considered that the QOL of patients receiving Ad-OC-TK plus VAL treatment is worth assessing as a therapeutic index. Significant improvements in bodily pain were also observed. It is suggested that the clinical improvements may contribute to a significant improvement in bodily pain. Since the tumors of these patients displayed disease progression despite surgery, radiation, androgen-deprivation therapy and/or conventional chemotherapy, the serum PSA levels of all patients were very high prior to gene therapy. Following gene therapy, the serum PSA levels decreased in 2 patients, no change was observed in 1 patient and they were slightly increased in 2 patients (Figure 2A). In addition, the induction of cell apoptosis in the vector-injected lesions of 5 patients examined by anti-ssDNA antibody staining on day 28 was also found. However, a correlation between ΔPSA and ΔPain was not demonstrated in spite of the clinical effects observed in the vector-injected lesion (Figure 2B). In this study, the Ad-OC-TK vector was injected directly into one single localized recurrent tumor or bone metastatic lesion despite the fact that all the patients had multiple bone metastatic lesions. Especially in the case of patient 3, the pain in the non-vector-injected lesions increased on day 28. This fact might be one reason that a correlation between ΔPSA and ΔPain was not demonstrated.

Kornblith AB et al. assessed the QOL in HRPC patients treated with docetaxel, estramustine and low-dose hydrocortisone by using the FACT-P questionnaire, the Mental Health Inventory-17 (MHI-17) and the Brief Pain Inventory (BPI) (14). They assessed the QOL in HRPC patients by combination regimens that employed several questionnaires. There are a few reports regarding the QOL in HRPC patients using combination regimens; however, it might be necessary to combine several questionnaires or modify the prostate-specific questionnaire for assessing the QOL in HRPC patients receiving gene therapy because of the specificity of the patients’ pathologies and the treatment method.

In conclusion, it was demonstrated that Ad-OC-TK plus VAL gene therapy improved or preserved the short-term QOL and bodily pain of HRPC patients with metastatic or local recurrent tumors. These assessments may emerge as new therapeutic indices of gene therapy for HRPC.

References


