Original Paper

Combination Therapy Combining Low Dose Cisplatin and Regional Hyperthermia for Treatment of Progressive Hormone Refractory Prostatic Carcinoma

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Abstract : The aim of the work presented here was to evaluate the efficacy and safety of a new regimen which combines weekly cisplatin-based chemotherapy and regional hyperthermia for the treatment of advanced hormone-refractory prostate cancer. Cisplatin (10 mg/body weight) was administered intravenously at weekly intervals one hour before regional hyperthermia, and was applied for a maximum of 10 cycles. Therapy was discontinued after the first 10 cycles in patients who responded, or in cases of stable disease, and was resumed as soon as any signs of progression were noted. Of the 15 patients evaluated, 6 were confirmed to have achieved a greater than 50% decrease in prostate specific antigen (PSA) levels (40.0%). The median response duration was 19.5 months, and the median time to progression was 9.0 months. Reduction of pain along with improvement in the quality of life were seen. Pain was reduced in 7 patients who were symptomatic at the beginning of the study. Of the 15 patients, 9 resumed therapy after the planned 10 original cycles of therapy. Of these, 9 received 10 mg of docetaxel/mg body weight. 4 patients had prostatic specific antigen (PSA) levels under 4 ng/ml (26.7%), and 2 patients exhibited stable disease. The regimen was well tolerated, and minor general fatigue (NCI-CTC grade I) was recognized in 3 patients, but no anemia or thrombocytopenia was observed. The results of this study suggest the feasibility and tolerability of using the combination of weekly cisplatin administration along with regional hyperthermia. This combined therapy led to a rapid and long lasting decrease in PSA levels and palliative responses in patients with advanced hormone-refractory prostate cancer.

Key Words : hormone refractory prostate cancer, low dose chemotherapy, regional hyperthermia

Introduction

Hormone refractory and progressive prostate carcinomas are difficult to treat with chemotherapy or radiation, and therefore have a poor prognosis. A new therapeutic modality is described here which consists of combination therapy combining low dose cisplatin chemotherapy and regional hyperthermia delivered with a Thermotron RF8. A high dose based systemic chemotherapy would be able to shrink

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a tumor of this size in a short period, but would not be effective for producing an increase in long term survivals¹⁾. Takahashi et al have shown that low dose chemotherapy may not shrink tumor sizes, but can protect against metastasis into other regions, and improve long survival¹⁾. Induction of such a cytostatic phase in cancer therapy is critically important : it is the most rational approach in treating many cases of solid tumors and certainly deserves more attention. Regional hyperthermia is recognized as being useful in the treatment of malignant tumors, and immunological responses are generated after hyperthermia, and hyperthermia also leads to the production of heat shock proteins²⁾. Moreover, intracellular concentrations of anti-cancer drugs can increase after hyperthermia exposure³⁾. Therefore, it is possible that the effects of anti-cancer drugs could be enhanced by hyperthermia⁴⁾.

Patients and methods

Patient characteristics :

Fifteen patients (age : 47-80, mean : 69.67years old) were enrolled from April, 2004 to January, 2007 and were treated in the Nagoya Prostatic Center. These patients were all classified as having stage D2 progressive and hormone-refractory prostate carcinomas, and their Gleason scores ranged from 7 to 9 (Table I). None of cases had received radiation or surgery before the treatments used here. Total androgen blockade (TAB) hormone therapy based on LH-RH agonists were tried in all of these cases and it was confirmed that the anti-androgen withdrawal syndrome (AWS) was negative. Informed consents were obtained from each patient, and each patient agreed to undergo a combined chemo-hyperthermia regimen. Their PSA levels measured before treatments ranged from 20.0 ng/ml to 210.0 ng/ml. Performance status in patients before the treatments were : grade 2, 2 cases ; grade 1, 5 cases ; grade 0, 8 cases.

Table I. Patient characteristics

Case No.	Age	Stage	Pathology	(Gleason score)	PS	Pre-treatment	Metastasis
1	80	D2	mod	(8)	0	TAB	bone, lung, LN
2	65	D2	mod	(7)	0	TAB	bone, LN
3	72	D2	por	(8)	1	TAB	bone, LN
4	74	D2	por	(9)	0	TAB	bone, lung, LN
5	74	D2	mod	(7)	0	TAB	bone, LN
6	70	D2	por	(8)	1	TAB	bone, LN
7	59	D2	por	(9)	2	TAB	bone, LN
8	75	D2	mod	(7)	0	TAB	bone, LN
9	75	D2	mod	(7)	0	TAB	bone, LN
10	72	D2	por	(9)	2	TAB	bone, lung, LN
11	61	D2	mod	(7)	0	TAB	bone, LN
12	75	D2	mod	(7)	0	TAB	bone, LN
13	76	D2	mod	(7)	1	TAB	bone, LN
14	72	D2	mod	(7)	1	TAB	bone, LN
15	45	D2	por	(9)	1	TAB	bone, LN

Pre-treatment : previous treatment
PS : performance status
TAB : total androgen blockade
LN : lymphnodes

Treatment method

Ten mg of cisplatin dissolved in 500 ml of saline was given intravenously one hour before hyperthermia. Hyperthermia was delivered using an 8 MHz radio frequency with a Thermotron RF-8 to heat the entire pelvic cavity with capacitive heating with two electrodes. The heated area covered a 30 cm diameter, and the radiofrequency range was varied from 500 to 800 watts to generate temperatures of over 42.0 degrees centigrade. This was monitored with a thermocouple inserted into the rectal cavity. The treatment schedule required 30-50 minutes for each patient once a week for a total 10 treatments. The effects of concurrent cisplatin-based regional hyperthermia was judged according to “General Rules for Clinical and Pathological Studies on Prostate Cancer, 3rd Edition, 2001”, and by monitoring changes in prostate specific antigen (PSA) levels. PSA levels (Tandem R) were the main criterion used for judging response, and levels were compared before and after treatments : a complete response was defined as observing PSA levels decrease to below standard acceptable levels (4.0 ng/ml) ; a partial response was defined as elevated PSA levels decreasing more than 50% from initial values, but not to standard levels ; no change : elevated PSA levels decreased less than 50% or increased up to 25%. Progressive disease was defined as : PSA levels increased more than 25% from levels observed before treatments, or that the accepted PSA levels became elevated to abnormally high levels after treatments.

Statistical analysis :

Statistical analysis utilized the student T-test and Spearman’s rank correlation.

Results

Clinical results obtained by monitoring PSA levels revealed that there was a complete response (CR) in 4 cases (26.7%), a partial response (PR) in 2 cases (13.3%), and no change (NC) in 6 cases (40.0%), and progressive disease (PD) in 3 cases (20.0%). The CR plus PR ratio was 40.0%. The mean survival time for patients with concurrent cisplatin-based hyperthermia ranged from 10 months to 36 months in those who responded to the treatments. Patients exhibiting complete responses had a mean survival time of 27 months. Patients exhibiting a partial response had a mean survival time of 20.0 months, and the group exhibiting no change had a mean survival time of 15.0 months. Patients with progressive disease had a mean survival time of 8.6 months (Table II). Relationships between PSA levels before treatments and the treatment results are shown in Table III. Those with PSA levels less than 50 ng/ml before

Table II. Clinical effects and survival of patients receiving combination therapy

Clinical effects	(no. of cases)	duration of survival (months)	Mean survival (months)
complete response	(4)	12-36	(27.0)
partial response	(2)	10-30	(20.0)
no change	(6)	8-24	(15.0)
progressive disease	(3)	6-10	(8.6)

Relationship between clinical results and survival of patients receiving combination therapy Patients who experienced better clinical results from the treatment exhibited longer survival times than those who did not exhibit good clinical results. P=0.0099, γ =0.597.

Table III. Relationship between PSA levels and clinical effects

PSA (Tandem R : ng/ml)	CR	PR	NC	PD
4-50	4	2	3	0
50-100	0	0	3	0
100-	0	0	0	3

Relationships between PSA levels and clinical results. Low level PSA groups exhibited better clinical effects than groups with higher PSA levels. $P=0.0025$. $\gamma=0.8160$

treatment included 4 cases exhibiting a complete response, 2 cases exhibiting partial response, and 3 cases with no changes out of 9 patients. Three patients who had PSA levels of 50-100 ng/ml did not respond and exhibited no changes. 3 patients who had PSA levels of over 100 ng/ml exhibited progressive disease, and all 3 died from the disease. Of the 15 patients treated, 9 resumed therapy after the planned 10 cycles of therapy ; and these 9 received 10 mg of docetaxel/body weight ; 4 patients had a prostate specific antigen response under 4 ng/ml (26.7%) ; and 2 patients had stable disease. Six patients among those who exhibited a complete response and partial response were treated with regional hyperthermia once a week for maintenance therapy. The regimen was well tolerated, and minor general fatigue (National Cancer Institute-Common Toxicity Criteria=NCI-CTC grade 1) in 3 patients was recognized, but no anemia or thrombocytopenia was observed. Pain was reduced in 9 patients who were symptomatic at the beginning of the treatments.

Discussion

Patients with hormone-refractory and progressive prostate carcinomas are difficult to treat. Because these patients display metastasis in multiple sites such as bone, lung or lymph nodes, such patients suffer from prostate cancer along with other complications, such as heart disease and lung disease. Therefore severe systemic chemotherapy can not be tolerated in patients with progressive prostate cancer. Therapeutic options for patients with hormone-refractory prostate cancer (HRPC) are second-line hormonal therapy and chemotherapy. Approximately 25% of the patients with HRPC respond to second line-hormonal therapy or chemotherapy, but such a response is a short-lived phenomenon usually not exceeding 4 months in duration. A number of clinical trials have evaluated the role of single-agent and combination chemotherapies in the treatment of HRPC, and have demonstrated encouraging results regarding disease control and improvement in the quality of life^{5,6)}. Docetaxel and estramustine were compared to treatment with mitoxantrone and prednisone for HRPC, and an improvement in the median survival time of nearly two months was seen with docetaxel and estramustine, when compared to treatment with mitoxantrone and predonisolone⁷⁾. However, side effects of these combination therapies including neutropenic fevers, nausea and vomiting, and cardiovascular events were common⁸⁾. Recently low dose chemotherapy has been recognized as being able to prevent metastatic lesions *via* mechanisms involving epithelial growth factor (EGF) or fibloblast growth factor (FGF). These results indicated that low dose chemotherapy could not suppress the tumor, but could suppress metastasis, resulting in longer median survival times. Takahashi *et al*¹⁾ have reported that low dose chemotherapy had minimum side effects and could be administered repeatedly, therefore improving long term survival. Biweekly

administration of low-dose docetaxel can be considered an effective non-toxic therapy option for patients with HRPc as reported by Karavasilis *et al*⁹⁾ who saw decreases of PSA levels of more than 50% in 38 treated patients, with a median response duration of 4.5 months. The current work reported here used a combined therapy with hyperthermia and chemotherapy, termed chemo-hyperthermia, and involved using cisplatin or other anti-cancer agents whose cytotoxic effects are enhanced by hyperthermia⁴⁾. This approach appears to be useful, even with low dose chemotherapy, because intracellular drug concentrations can be effectively increased by hyperthermia *via* enhanced cellular membrane permeability¹⁰⁾. Hoshi *et al*¹¹⁾ described the use of low dose cisplatin and UFT which resulted in a decrease of over 50% in PSA levels in 16 (50%) out of 32 patients with HRPc. A UFT combination was compounded with tegafur and uracil, where tegafur is a masked compound of 5-FU, which is converted to 5-FU in the liver by microsomal P-450. A combination therapy with low-dose cisplatin and 5-FU was considered to be useful, because it is possible that cisplatin could act to interfere with the intra-cellular transport of methionine, and prevent the synthesis of DNA¹¹⁾. Better results have been reported in terms of PSA decreases (up to 80%) with docetaxel plus high-dose calcitriol. A large randomized trial is currently in progress to verify the possible advantage of this combination¹²⁾. This strategy was used with a plan to stop after the first 10 treatment cycles. If no responses were obtained with this combination, other drugs such as docetaxel were to be administered along with regional hyperthermia. Regional hyperthermia has been used for the treatment of malignant disease in the lung, stomach and pancreas^{13,14)}. Tumor cells can be killed by heat using radiofrequency hyperthermia with temperatures ranging from 42-45°C, while mild hyperthermia of less than 42°C can act to enhance the effects of administered anti-cancer drugs¹⁰⁾. In addition, hyperthermia can lead to the production of heat shock proteins (HSP70 and HSP 90) and enhanced immunological activity¹⁴⁾. Tumors and lymph nodes metastases which were not heated directly have disappeared after hyperthermia¹⁴⁾. The relationship between clinical effects and survival showed that the complete response (CR) group and partial response (PR) group demonstrated better long survivals than the no change (NC) group and progressive disease (PD) group. Patients among the CR, PR, NC groups have survived during the present trials, but there are no survivors in the PD group. Even patients exhibiting no changes have experienced longer survival periods. The performance status (PS) did not decrease in any of the cases. Two cases with PS 2 scores improved to PS 1 after the treatments. These results indicate that tumor dormancy therapy is important for obtaining long survival, even if a shrinkage in tumor size can not be obtained by treatment with chemo-thermotherapy. The regimen was well tolerated. Minor general fatigue (NCI-CTC grade 1) in 3 patients was recognized, but no anemia or thrombocytopenia was not observed. The results reported in this study suggests that the combination of weekly cisplatin and regional hyperthermia can lead to a rapid and long lasting decrease in prostate-specific antigen levels, and to palliative responses in patients with advanced hormone refractory prostate cancer.

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