RESEARCH COMMUNICATION

Advantages of Second Line Estramustine for Overall Survival of Hormone-Refractory Prostate Cancer (HRPC) Patients

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Abstract

There is no effective standard therapy for the treatment of hormone refractory prostate cancer (HRPC), and treatments vary among different medical institutions with efforts to improve results. The present retrospective investigation was performed to assess the outcomes of second line, third line, and fourth line therapies. A total of 142 patients with HRPC were treated at Nagoya City University Hospital and its affiliate hospitals during the 10 years between October 1996 and August 2006. Patient background and treatments given after hormone refractory phase were determined, with especial attention to 50% or greater decrease rates of serum PSA levels and other variables with three common regimens based on: estramustine phosphate (EMP); diethylstilbestrol diphosphate (DES); and dexamethasone (DEX). With second line therapy for HRPC, the response rate was highest with EMP, whereas best outcomes were apparent with DES as a third line or fourth line therapy. However, overall survival for all cases and particularly with those having a poorly differentiated lesion, was best with EMP in any time period. Although there is no generally established optimal treatment for HRPC, our analysis supports the efficacy of EMP based on second line therapy response rates and optimal prognosis with longer term use.

Key Words: HRPC - hormone therapy - second line therapy

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Introduction

Almost all prostate cancers are initially androgen dependent and metastatic cases in particular are treated mainly with hormone therapy. This generally provides favorable therapeutic effects, but the duration of positive responses is mostly limited to 2-3 years. After this, a hormone refractory phase is entered in which no particular treatment is effective, resulting in cancer death after about 1-2 years in the majority of cases in the United States and Europe (Soloway et al., 1989; Kelly et al., 1993; Vogelzang et al., 1998; Halabi et al., 2003). Currently, treatment for hormone refractory prostate cancer (HRPC) is one of the major issues in the area of prostate cancer management. However, there is no established effective standard therapy. In addition, targets of treatments vary widely, some aiming at cancer shrinkage and prolonged survival as far as possible, while others are simply conducted for relief in cancer pain to improve the patient's quality of life (QOL). Under these circumstances, it is natural that therapy varies among different medical institutions. Treatments for HRPC include: (1) addition of antiandrogen; (2) therapy discontinuation or modification in antiandrogen therapy; (3) estrogen therapy like DES; (4) glucocorticoid therapy, (5) chemotherapy, (6) herbal therapy, (7) gene therapy, or other new therapy methods alone or in combination.

Treatments for HRPC often employ a 50% reduction in PSA levels as an index for therapeutic response, and re-increase in PSA warrants therapy modification. Although the validity of prostate specific antigen (PSA) for assessing therapeutic effects has been questioned, a 50% or more reduction in serum levels may indicate prolonged survival, according to previous reports (Kelly et al,. 1993; Smith et al., 1998). If the initial treatment given for HRPC (i.e., second line therapy) is not effective with regard to this criterion, or requires modification because of adverse effects or other reasons, another third line therapy may be indicated. Optimal timing for therapy initiation and appropriate end points remain unclear.

In the present study, we therefore retrospectively investigated the methods and the results of the treatments given to the patients with HRPC at Nagoya City University Hospital and its affiliate hospitals, in order to determine the second line therapy which might offer the best outcomes. We also assessed the influence of third and fourth line therapies. Grouping was made into EMP, DES and DEX, but since DES is no longer available, the

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discussion was focused on EMP and DEX.

Patients and Methods

A total of 142 patients with HRPC were treated at Nagoya City University Hospital and its affiliate hospitals during the 10 years from October 1996 to August 2006. The investigation was focused on patient background before the hormone refractory phase and the treatments given after it had begun. The Post-Relapse Therapy investigation variables were as follows:

1 Mean duration of therapy
2 Response rate (PSA response)
3 Mean duration of response
4 PSA nadir level (mean)
5 Time to PSA nadir (mean)
6 PSA improvement rate
7 Pain improvement rate
8 Incidence of adverse effects

A hormone refractory phase was defined as recurrence or worsening of the disease after response to androgen deprivation therapy was no longer evident. The date of hormone refractory phase was thus defined as the earliest date when three consecutive increases in PSA level were noted. The clinical stage and pathological grade of each prostate carcinoma were defined according to the Whitmore-Jewett classification and the WHO grading system (Sobin et al., 1997). The Kaplan-Meier method was employed to calculate the probability of survival and the different parameters were compared using the log-rank test. All p values were 2-sided, and those <0.05 were considered as statistically significant. All of the statistical analyses were performed using the SPSS version11.0 software.

Results

Patient Background before the Hormone Refractory Phase

The mean age was 74.0 years (53-94) and the PSA level at diagnosis of prostate cancer was 196.0ng/mL (2-12400). Clinical stage was as follows: Stage A in 1 patient (0.7%), Stage B in 9 (6.3%), Stage C in 12 (8.5%), Stage D1 in 6 (4.2%), and Stage D2 in 96 (67.6%), and unknown in 18 (12.7%).

Histopathological grade at initial diagnosis was 'well differentiated', 'moderately differentiated', 'poorly differentiated', and unknown in 4 (2.8%), 45 (31.7%), 74 (52.1%), and 19 (13.4%) of cases, respectively.

As for symptoms, cancer specific pain was present in 57 (40.1%) and not present in 74 (52.2%). Performance status was classified into 2 groups: '0-2' and '3-4', accounting for 107 (75.4%) and 9 (6.3%), respectively. Each of the four series of second line, third line, and fourth line therapies for HRPC was here regarded as a separate treatment regimen, although there was naturally some overlap. The numbers of cases are summarized in Table 1.

The median duration of follow-up was 21.2 (1.1-73.1) months.

Table 1. Pretreatment Patient Characteristics

Median age, years (range)		74.0	(53-94)
Median PSA, ng/ml (range)		196.0	(2-12400)
Primary histological grade			
	well differentiated	4	(2.8%)
	moderately differentiated	45	(31.7%)
	poorly differentiated	74	(52.1%)
	unknown	9	(13.4%)
Clinical stage	A	1	(0.7%)
	B	9	(6.3%)
	C	12	(8.5%)
	D1	6	(4.2%)
	D2	96	(67.6%)
	unknown	18	(12.7%)
Performance status	0-2	107	(75.4%)
	3-4	9	(6.3%)
	unknown	26	(18.3%)
Pain	(+)	57	(40.1%)
	(-)	74	(52.2%)
	unknown	11	(7.7%)

Table 2. Number of Cases and PSA 50% or More Response Rate with Each Line of Therapy

Drug	Second line		Third line		Fourth line	
	No.	Positive	No.	Positive	No.	Positive
EMP	102	48.0	14	28.6	8	12.5
DES	24	29.2	11	36.4	10	30.0
DEX	16	37.5	15	33.3	9	44.4

Hormone Therapy before the Hormone Refractory Phase

Hormonal therapies given before relapse were as follows: MAB (maximum androgen blockade (Prostate Cancer Trialists' Collaborative Group., 1995; Caubet et al., 1997)) in 85 patients (54.9%), LH-RH agonist monotherapy in 2 patients (1.3%), estrogen preparations in 4 patients (2.6%), those combined therapy in 63 patients (40.6%), and unclear in 1 patient (0.6%). There was no significant variation in the type of hormone therapy among the three groups.

Mean Duration of Therapy for HRPC

With second line therapy, the mean durations for EMP, DES, and DEX were 9.0±9.1, 2.1±4.1, and 5.7±5.3 months, respectively, that for DES being significantly the shortest (statistically not significant). Regarding EMP, the mean duration was the longest when it was given as second line therapy (statistically not significant).

50% or more PSA Response Rates with the HRPC Treatments

The 50% or greater response rates for the HRPC cases are summarized in Table 2. The response rates of EMP, DES, and DEX as second line therapies for HRPC were 48.0%, 29.2%, and 37.5% respectively, with a significantly lower response rate to DES. Given the preponderance of EMP cases within those demonstrating a positive response we primarily focused on comparisons between this therapy and all others combined.

Overall Survival rate according to the Therapy and Response Category

Comparison of survival receiving EMP or the other

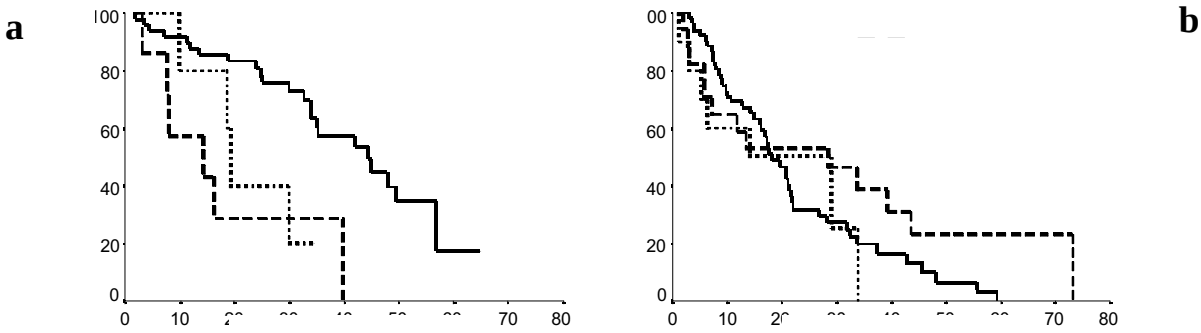

Figure 1. Overall Survival Rate of Responders and Non-Responders in Each Second Line Therapy for HRPC. a: Responders, b: Non-Responders

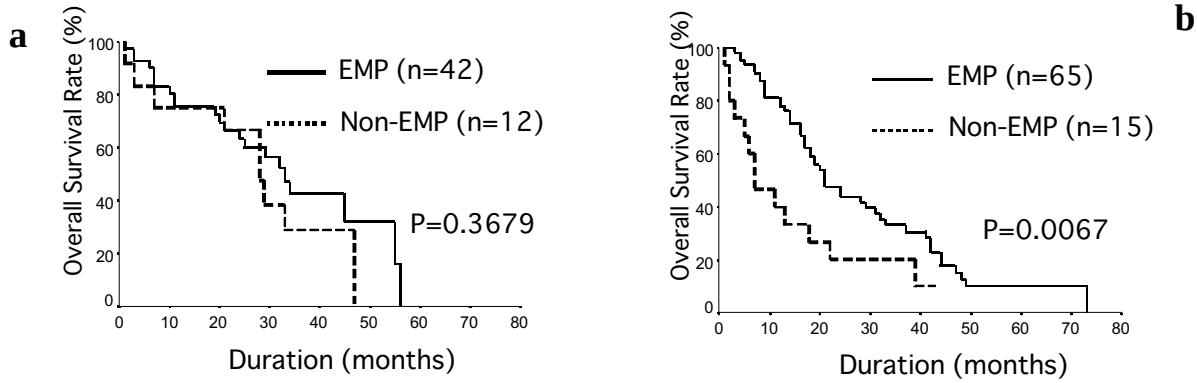

Figure 2. Overall Survival Rate Comparison between EMP and Others in Responders and Non-Responders. a: Well and Moderately Differentiated, b: Poorly Differentiated

regimens as second line therapies is shown in Figure 1a for responders and Figure 1b for non-responders. A significantly better prognosis for responders was evident with EMP as compared to the combined data for the other regimens (P=0.0033).

Overall survival rate according to histopathological grade

In comparison of assessable 123 cases in 142 responder and non-responder patients on the view point of received EMP or other regimens for any line therapy, improvement of overall survival with EMP was significant better in 'poorly differentiated' patients (shown in Figure 2b) (P=0.0178) than in those with other grade (shown in Figure 2a) (P=0.1893).

Discussion

From the results of the present study of HRPC cases in Nagoya, Japan, EMP appears to offer the best alternative as second line therapy. Even when given as third or fourth line treatment the results were comparable with those obtained using the other regimens and prognosis overall was best with EMP. Since response rates were poor independent of the fourth line regimen, our data confirmed the importance in selecting a treatment that can lead to response in second line or third line therapy for HRPC. It should of course be stressed that reduction in PSA levels may not always reflect prolonged overall survival, but our data for both PSA and survival were consistent. A Danish study (DAPROCA study 9002) (Iversen et al., 1997) of EMP versus placebo as second line treatment after orchiectomy in patients with metastatic HRPC demonstrated that 37.2% of 43 patients who showed a 50% or more PSA reduction were treated with EMP, and that the decrease in PSA correlated significantly with favorable cancer-specific survival.

Trials of EMP therapy for HRPC have used it in combination with other chemotherapeutic agents, such as vinblastine, etoposide, or paclitaxel, which may result in improvement of outcome (Soloway et al., 1983; Hudes et al., 1992; Dimopoulous et al., 1997). In combination trials, PSA response rates, defined as the percentage of patients with greater than 50% decline in PSA for a minimum of biweekly or monthly measurements, ranged from 31 to 54%. EMP is commonly associated with gastrointestinal side effects including nausea, vomiting and anorexia, but hematological adverse effects are rare. Soloway et al. reported an incidence of 37% for mild and severe adverse effects including nausea and vomiting with EMP and cisplatin treatment. In our analysis, approximately 30% of the patients enrolled needed to be discontinued due to the development of severe gastrointestinal symptoms.

According to the results of the present analysis, use of EMP in second line therapy for HRPC led to a high response rate, which is consistent with previous reports of relapsed cancer treatment. Hormonal therapy before hormone refractory phase was primarily either MAB or estrogen preparations, but EMP was commonly used as second line therapy for HRPC irrespective of the primary therapy, presumably because EMP is thought to be appropriate for the therapy for HRPC at various institutions based on various published reports (Soloway

et al., 1983; Smith et al., 1999; Hirano et al., 2005). The results of our analysis of response rate are also in favor of this conclusion. In the present analysis, although the time to PSA nadir and mean duration of therapy were longer in the EMP treated group, EMP was not particularly associated with onset of adverse effects, and its long term use should probably be encouraged whenever possible. Recently, taxane derivative anticancer drugs have been reported to be effective for the treatment of relapsed prostate cancer (Van Veldhuizen et al., 2003; Berry et al., 2004). Further study is now required in larger patient populations, like for instance a randomized controlled trial of efficacy comparing EMP monotherapy and combined taxane derivatives therapy as second line for HRPC.

Regarding DEX in the present analysis, the response rates did not differ with second line or third line use. But because of its low cost and high palliative potential, DEX therapy can be readily started on an outpatient basis. Its benefit for pain relief and/or improvement of cachexia associated with relapsed cancer has already been documented (Nishimura et al., 2000; Storlie et al., 1995). Use of DEX as third or fourth line therapy for relapse, also appears to be indicated.

Based on our analysis of relapsed cancer treatment in 142 patients, we cannot conclude one particular treatment method for HRPC should be established. Nonetheless, EMP as second line therapy for relapsed case was found to be favorable. In addition, DEX was indicated when it is given as subsequent therapy for HRPC.

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