# Dual Interim Report of Low-dose Estramustine Phosphate (EMP) Monotherapy and Very Low-dose EMP Therapy Combined with LH-RH Agonist for Previously Untreated Advanced Prostate Cancer

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**KEY WORDS:** low-dose EMP monotherapy, very low-dose EMP with LH-RH agonist, previously untreated prostate cancer, advanced prostate cancer, estramustine phosphate

## ABSTRACT

**Purpose:** To assess the efficacy and toxicity of oral estramustine phosphate (EMP) administration, low-dose EMP monotherapy (Study 1) and very low-dose EMP therapy combined with luteinizing hormone-releasing hormone (LH-RH) agonist (Study 2) were conducted in previously untreated advanced prostate cancer and the interim data were compared between the 2 studies.

**Materials and Methods:** Studies 1 and 2 were independently performed beginning in June 1999 and November 2001, respectively. Study 1 comprised 87 patients including 85 assessable patients; all 87 patients selected for Study 2 were assessable. Low-dose EMP monotherapy (2 capsules/day or 280 mg/day) was used in Study 1 and very low-dose EMP (1 capsule/day or

140 mg/day) combined with LH-RH agonist was used in Study 2.

**Results:** Overall prostate specific antigen (PSA) response rates in Studies 1 and 2 were 92.3% and 90.4%, respectively, and overall toxicity rates were 48.2% and 23.0%. EMP discontinuation due to side effects was encountered more often in Study 1 (42.4%) than in Study 2 (16.1%).

**Conclusions:** Although the follow-up periods were too short to evaluate all parameters, our data indicate that the overall PSA response rate was comparable between both studies. However, rates in overall toxicity and drug discontinuation were higher in Study 1 than in Study 2. We consider Study 2 very promising for the treatment of previously untreated advanced prostate cancer because it will not only achieve a high PSA response rate but also lessen overall toxicity rate. Further long-term follow-up is required to assess the results of these studies.

## INTRODUCTION

Estramustine phosphate (EMP) is a potent drug for the treatment of prostate cancer that was introduced in the early 1970s. It was originally synthesized to allow selective delivery of the alkylating agent into estrogen receptor–positive cancer cells.[1] The compound was initially thought to have dual estrogenic and cytotoxic activity.[2] Although the cytotoxic activity was thought to be due to nornitrogen mustard, EMP was later proved to interfere with cellular microtubule dynamics but devoid of alkylating effect. After oral intake, EMP is rapidly dephosphorylated at the C17 position of the steroid to yield estramustine and estromustine in vivo. Estramustine preferentially enters prostate epithelial cells where it binds to cellular components of tubulin as well as to microtubule-associated proteins (MAPS),[1] which are essential to growth of microtubules.[3] In addition, estramustine and estromustine are further metabolized to estradiol and estrone, respectively, which suppress the pituitary-gonadal axis, resulting in decline of plasma testosterone level.

Since its introduction, EMP has been evaluated mainly for hormone-refractory advanced prostate cancer (HRPC) alone or in combination with a variety of anticancer agents,[4-8] because EMP exhibits a potent activity against prostate cancer even after treatment failure with conventional hormone therapies. Many investigations have confirmed a 30% to 35% objective response rate in HRPC patients on EMP monotherapy of 560 to 1260 mg/day (4-9 capsules/day) in 2 to 3 divided doses.[4] An EMP-based chemotherapy regimen, especially in combination with docetaxel, exhibited a satisfactory overall PSA response rate of 77% with median survival time of 16.8 months,[9] and many investigators are looking for more promising regimens to achieve better outcomes.

On the other hand, a small number of trials have been performed using EMP monotherapy for previously untreated advanced prostate cancer (PUAPC). In 1980, Andersson et al[10] reported a meta-analysis of 228 PUAPC patients on conventional EMP monotherapy (conventional dosage equals administration of 4-9 EMP capsules/day). They found an overall response rate of as high as 84%. However, adverse side effects were severe and frequent, especially in gastrointestinal (35%-46%)[11,12] and cardiovascular (36%)[13] toxicities, some of which were fatal. The high frequency of serious adverse side effects prompted the European Organization for Research and Treatment of Cancer group (EORTC) to attempt low-dose

EMP monotherapy (280 mg/day or 2 capsules/day) for PUAPC in 1984[14] because the toxicity was known to decrease in a dose-dependent manner. They found low-dose EMP monotherapy very effective for PUAPC with overall response rate of 89%, which was comparable to that of DES monotherapy of 3 mg/day. However, adverse side effects were marked in both monotherapies of EMP and DES, whose cardiovascular fatalities amounted to 5 out of 125 and 9 out of 123, respectively. The frequent severe adverse side effects discouraged urologists to pursue further EMP monotherapy as well as DES monotherapy. At around the same time, LH-RH agonist was developed and introduced into clinical practice. It showed a high response rate (86%-88%) with virtually no toxicity compared with EMP monotherapy.[15,16] Thereafter, EMP treatment was virtually waived for treating PUAPC patients even in low-dose monotherapy.

Recently, we re-evaluated the efficacy of EMP monotherapy for PUAPC patients because it was determined in 1990 that EMP forms insoluble calcium phosphate salt when taken with dairy products,[17] by which mechanism the amount of EMP absorption from the intestine could be reduced. In this case, the dose of EMP could be greatly decreased by taking EMP without concomitant intake of meals or dairy products. By using this mode of drug administration, we expected that low-dose EMP could achieve adequate serum levels to exert the same anticancer effect as conventional dosage without causing severe adverse side effects.[18] On the basis of the above-mentioned rationale, a new protocol was conducted to administer 2 capsules/day for PUAPC patients.[9] This protocol was designated low-dose EMP monotherapy (Study 1). However, the interim data of Study 1 suggested that even 2 capsules/day of EMP can occasionally cause severe adverse side effects after follow-up of 2 years despite very good response rate. Considering the interim data, a second project was undertaken by adopting a treatment program of very low-dose EMP (1 capsule/day) combined with LH-RH agonist (Study 2) in expectation of minimizing adverse side effects as well as maximizing antitumor activity. Although the time of follow-up was short and the 2 studies were conducted independently at different periods, results in 2 interim data of Studies 1 and 2 are presented and compared in detail.

## STUDY 1. LOW-DOSE EMP MONOTHERAPY IN PUAPC PATIENTS

### Patients and Methods

***Patient Evaluation and Eligibility***. Eligible patients had newly found advanced prostate cancer and were required to have a histological diagnosis of adenocarcinoma of the prostate, stage C, D1, or D2. Minimum serum PSA to be entered in this treatment project was 10 ng/mL. Clinical stages were evaluated from digital rectal examination (DRE), transrectal ultrasonography, X-rays, bone scintigraphy, and pelvic computed tomography (CT).

All patients were recruited from our department and 22 affiliated hospitals. Prior to enrollment, each patient underwent a baseline physical examination, including assessment of performance status (PS) according to ECOG Performance Status Criteria. Laboratory data (blood urea nitrogen, creatinine, lactate dehydrogenase, alkaline phosphatase, serum glutamic oxaloacetic transaminase [GOT], glutamic pyruvic transaminase [GPT], testosterone [TST], estradiol [$E_2$], Luteinizing hormone [LH], follicle-stimulating hormone [FSH] and prostate specific antigen [PSA]) were also determined before

treatment. After enrollment, the same laboratory tests were performed every week during the first month and once a month thereafter. Radiological examinations were done every 6 months after initiation of the treatment. Eligible patients were required to be within normal CBC and liver function. Patients had to have PS of 0 to 2. Patients could not have significant active concurrent medical illness or malignancy precluding EMP treatment, particularly, patients who had a history of cardiovascular event or ulcerative disorders in the intestine were excluded from this project. Histamine $H_2$ receptor antagonist (famotidine 40 mg/day) and aspirin (81 mg/day) were administered concomitantly with EMP for prophylaxis of gastric ulcer and thromboembolism, respectively. All patients were informed of the investigational nature of this study and had to sign and give written informed consent.

***Response Assessment.*** To be assessable cases for PSA response, EMP administration was required for more than 8 weeks. When PSA decreased below the detectable level it was designated PSA complete response (CR) and PSA partial response (PR) was defined as normalization of PSA ($0 < PSA < 4$ ng/mL). These responses were confirmed if a single determination of PSA entered the each corresponding level. PSA incomplete response (IR) was indicated as PSA > 4 ng/mL over the entire treatment period. The state of disease progression was defined as either of the following: regrowth of the prostate, the appearance of new lesions on computed tomography or bone scintigraphy, or a rise in the PSA level of > 4 ng/mL on 3 consecutive measurements, where the first determination of PSA ≥ 4 ng/mL was considered PSA failure. In cases of IR, the next point after the nadir was defined as the point of disease progression, where PSA rise in 3 consecutive measurements was identified.

***Treatment Plan.*** Patients received oral EMP of 280 mg/day (2 capsules/day) in 2 divided doses. EMP was taken at least 1 hour before and 2 hours after meal or dairy products. Toxicity was graded according to the National Cancer Institute common toxicity criteria. Patients were treated until disease progression, the development of treatment-limiting toxicity or withdrawal of consent. Treatment was discontinued in the presence of grade 3 to 4 adverse side effects. In these cases, other hormonal therapy such as maximum androgen blockade was started with cessation of EMP. However, in most cases patients were treated at the physician's discretion. All patients are being followed until death.

***Statistical Analyses.*** Survival curves were fitted using the Kaplan-Meier method and compared by the log rank test.[19] In two-tailed tests, $P$ values $< 0.05$ were considered statistically significant. Values were expressed as mean ± standard deviation or as median.

**Results**

***Patient Characteristics.*** Between June 1, 1999 and October 31, 2001, 87 patients were enrolled in Study 1. The pretreatment characteristics of these patients are listed in Table 1. Of the 87 patients, 85 were assessable for toxicity and 78 were assessable for PSA response, survival, and disease progression. Two patients were lost to follow-up early in this project. In 7 patients, severe toxicity developed within 8 weeks of therapy and they were evaluable only for toxicity. The remaining 78 patients continued to take EMP for at least 8 weeks. In the 85 patients assessable, the median age was 75 years (range 53-89). Patients in clinical stages C, D1 and D2 were 32, 10, and

**Table 1.** Patient Characteristics in Studies 1 and 2

| | Study 1 | Study 2 |
|---|---|---|
| | No. | No. |
| Total patients enrolled | 87 | 87 |
| Assessable patients | 85 | 87 |
| Patients evaluable for | | |
| biological response | 78 | 83 |
| toxicity | 85 | 87 |
| Age (yrs) | | |
| Median (mean) ± SD | 75 (74) ± 8.6 | 72 (72) ± 8 |
| Range | 53-89 | 55-89 |
| Stage | | |
| C | 32 | 43 |
| D1 | 10 | 10 |
| D2 | 43 | 34 |
| Cell differentiation | | |
| Well | 16 | 9 |
| Moderately | 37 | 36 |
| Poorly | 32 | 42 |
| Performance status (ECOG) | | |
| PS 0 | 65 | 70 |
| PS 1 | 12 | 13 |
| PS 2 | 8 | 4 |
| PS 3 | 0 | 0 |
| PS 4 | 0 | 0 |
| Baseline PSA value (ng/mL) | | |
| Median (mean) ± SD | 80.1 (285) ± 582 | 60.8 (505) ± 1557 |
| Range | 10-3,910 | 10-11,000 |

43, respectively. Adenocarcinomas were well differentiated in 16 patients, moderately in 37 patients, and poorly in 32 patients. Of the 85 assessable patients, 77 had a PS of 0 or 1 with an exceptional PS 2 in 8 patients. The median and mean baseline PSA values were 80.1 and 285 ng/mL (range 10-3910), respectively.

***Overall Changes in the Mean Serum PSA, $E_2$, TST, LH, FSH, GOT and GPT.*** Serum PSA decreased to within normal range by 2 months but later showed slight fluctuation (Figure 1). Serum $E_2$ rapidly increased to around 30,000 pg/mL within 2 weeks and remained high between 25,000 to 30,000 pg/mL, while serum TST declined to an undetectable level within 4 weeks and remained at a very low level (Figure 2). Serum LH and FSH decreased to an undetectable level by about 1 month with exceptional rise in 2 months (Figure 3). Thereafter, they showed slight fluctuation but remained almost at the bottom. Serum GOT and GPT transiently increased approximately in 2 months in 26 cases, but remained within upper normal range thereafter (Figure 4).

These data implicate that low dose EMP can, quickly and adequately, suppress the pituitary gonadal axis and the effect can be maintained for more than 30 months.

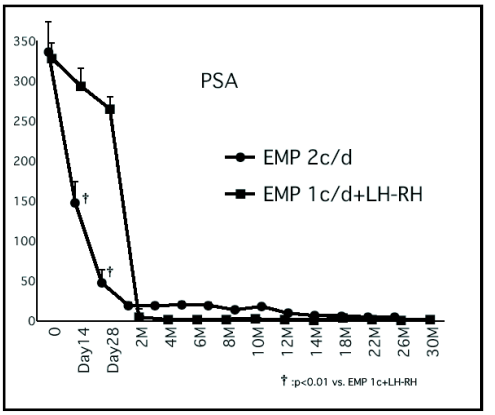


**Figure 1.** Serum PSA change on low-dose EMP monotherapy and very low-dose EMP therapy combined with LH-RH agonist for previously untreated advanced prostate cancer. Values are represented by mean ± standard error.

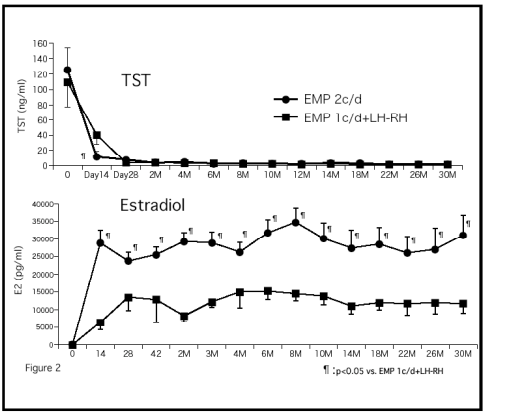


**Figure 2.** Serum testosterone and estadiol changes on low-dose EMP monotherapy and very low-dose EMP therapy combined with LH-RH agonist for previously untreated advanced prostate cancer. Values are represented by mean ± standard error.

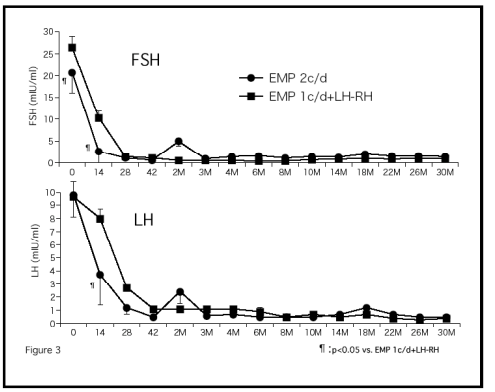


**Figure 3.** Serum FSH and LH changes on low-dose EMP monotherapy and very low-dose EMP therapy combined with LH-RH agonist for previously untreated advanced prostate cancer. Values are represented by mean ± standard error.

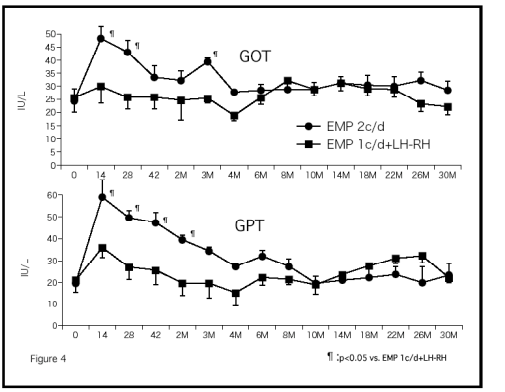


**Figure 4.** Serum GOT and GPT changes on low-dose EMP monotherapy and very low-dose EMP therapy combined with LH-RH agonist for previously untreated advanced prostate cancer. Values are represented by mean ± standard error.

***Clinical Outcomes.*** As of October 31, 2003, the mean observation time was 652 ± 467 days (range: 88-1620) (Table 2). The mean EMP administration time was 446 ± 442 days (range: 7-1585). Of the 78 assessable patients for PSA response, 40 and 32 had complete and partial PSA response, respectively. Total PSA response rate of complete and partial response was 92.3% (72/78), while PSA incomplete response rate was only 7.7% (6/78). The mean time to PSA normalization (< 4 ng/mL) was 67 ± 85 days which was slightly shorter ($P < 0.05$) than the time to nadir (80 ± 113 days). During the follow-up period, disease progression was experienced in 26 patients (33.3%), of whom PSA failure was observed in 24 (30.8%), regrowth of the prostate in 1 (1.3%) and new bony lesion in 1 (1.3%). A total of 21 patients died during the observation period. Eleven died of prostate cancer including 1 small cell cancer of the prostate, and

**Table 2.** Clinical Outcomes in Studies 1 and 2

| | Study 1 | Study 2 |
|---|---|---|
| Mean observation time | 652 ± 467 day | 412 ± 183 day |
| Range | 88-1,620 day | 46-766 day |
| Mean dosage time | 446 ± 442 day | 265 ± 170 day |
| Range | 7-1,585 day | 5-730 day |
| **PSA response** | **No. of patients (%)** | **No. of patients (%)** |
| | N = 78 | N = 83 |
| Complete response (PSA: nondetectable) | 40 (51.3%) | 41 (49.4%) |
| Partial response (0 < PSA < 4 ng/mL) | 32 (41.0%) | 34 (41.0%) |
| Incomplete response (PSA ≥ 4 ng/mL) | 6 (7.7%) | 8 (9.6%) |
| Mean time to PSA normalization | 67 ± 85 day* | 83 ± 79 day |
| Mean time to nadir | 80 ± 113 day† | 164 ± 96 day |
| **Disease progression** | **26 (33.3%)** | **7 (8.4%)** |
| PSA failure | 24 (30.8%) | 7 (8.4%) |
| Prostate regrowth | 1 (1.3%) | 0 (0%) |
| new bony lesion | 1 (1.3%) | 0 (0%) |
| Death from prostate cancer | 11 (14.1%) | 0 (0%) |
| Death from other causes | 10 (12.8%) | 0 (0%) |
| **Cause specific survival** | **724 ± 93 day** | **376 ± 95 day** |
| **Overall survival** | **809 ± 82 day** | **403 ± 126 day** |

*$P < 0.05$ compared with Study 2
†$P < 0.01$ compared with Study 2

another 10 died of diseases other than prostate cancer. Of the 10, 3 died of embolism in pulmonary, cerebral, and coronary artery, respectively. The cause of death in another 7 were pneumonia in 3, gastric cancer in 2, esophageal cancer and suicide in 1 each. Cause specific survival (Figure 5) and overall survival (Figure 6) were 724 ± 93 days and 809 ± 82 days, respectively. During the entire follow-up period, 3 patients died from gastrointestinal cancers including 2 gastric and 1 esophageal cancers.

***Toxicity.*** Toxicities are listed in Table 3. Gastrointestinal symptoms (nausea, vomiting, anorexia, and stomachache) were the most frequently encountered, in 23 of 85 cases, followed by 7 peripheral edemas. The third most frequent toxicity was liver dysfunction in 5 cases. In addition, 26 cases demonstrated initial transient rise in transaminases less than 150 IU/mL during the first 3 months, which did not necessitate cessation of EMP administration. The fourth most frequent toxicities were cerebral infarction in 4 and congestive heart failure in 4, followed by 2 pulmonary infarctions, 2 arrhythmias, and 2 skin rashes. Treatment-related death was seen in 1 case of sudden death (1.2%: 1/85) due to pulmonary embolism. Overall adverse

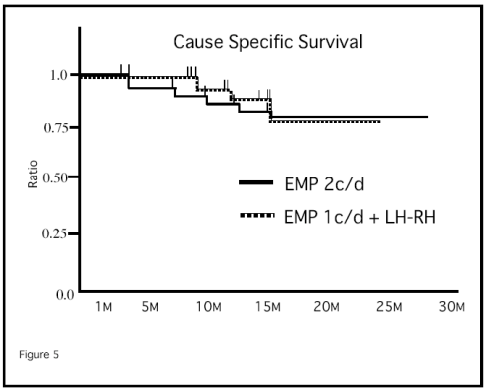


**Figure 5.** Cause specific survival in Studies 1 and 2.

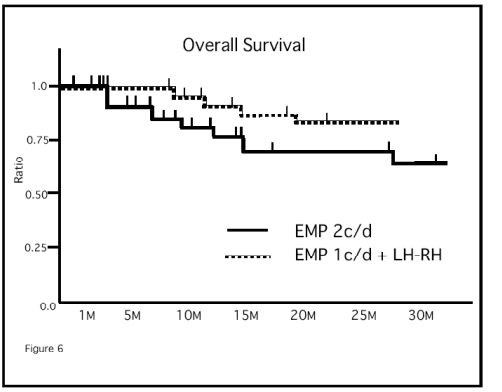


**Figure 6.** Overall survival in Studies 1 and 2.

side effects were documented in 41 of 85 cases (48.2%). As a result, EMP treatment had to be discontinued in 36 of 85 cases (42.4%). Gynecomastia and impotence, though the grade differed from case to case, were experienced in the majority of cases studied.

## STUDY 2. VERY LOW-DOSE EMP THERAPY COMBINED WITH LH-RH AGONIST IN PUAPC PATIENTS

### Patients and Methods

Patient evaluation and eligibility; and response assessment were quite same as Study 1.

***Treatment Plan.*** Patients took oral EMP dose of 140 mg/day (1 capsule/day) in the morning 2 hours following breakfast without dairy products. After 4 weeks of oral EMP treatment, LH-RH agonist injection (3.75 mg leuprorelin acetate or 3.6 mg goserelin acetate) was initiated and was continued once in 4 weeks thereafter along with maintenance of oral EMP intake. Other treatment plan was the same as in Study 1.

***Statistical Analyses.*** Identical to Study 1.

### Results

***Patient Characteristics.*** Between November 1, 2001 and June 30, 2003, 87 patients were enrolled in this treatment project. The pretreatment characteristics of these patients are listed in Table 1. Of the 87 patients, all were assessable for toxicity and 83 were assessable for PSA response, survival and disease progression. Four patients suffered from severe toxicity within 8 weeks of therapy and they were evaluable only for toxicity. The remaining 83 patients continued to take EMP for at least 8 weeks. In the 87 patients assessable, the median age was 72 years (range 53-89). Patients in clinical stages C, D1, and D2 were 43, 10 and 34, respectively. Adenocarcinomas were well differentiated in 9 patients, moderately in 36 patients, and poorly in 42 patients. Of the 87 assessable patients for toxicity, 83 were in PS of 0 or 1 with exceptional PS 2 in 4 patients. The median and mean baseline PSA values were 60.8 and 505 ng/mL (range 10-11,000), respectively.

***Overall Changes in the Mean Serum PSA, E2, TST, LH, FSH, GOT and GPT.*** Serum PSA slowly decreased to about 270 ng/mL in 1 month and rapidly went down to within normal range by 2 months. Thereafter, it remained undetectable (Figure 1). Serum estradiol rapidly went up to about 13,000 pg/mL in 1 month and remained from 10,000 to 15,000 pg/mL thereafter (Figure 2). Serum testosterone declined to an undetectable level by 1 month, and remained so for the entire follow-up period (Figure 2). Serum LH and FSH

**Table 3.** Toxicities and EMP Discontinuation in Studies 1 and 2 for Previously Untreated Advanced Prostate Cancer Patients

| | **Study 1** (n = 85) Total (%) No. of EMP Discontinuation (%) | | **Study 2** (n = 87) Total (%) No. of EMP Discontinuation (%) | |
|---|---|---|---|---|
| | (grades 1-4)* | (grades 3 and 4) | (grades 1-4)* | (grades 3 and 4) |
| gastrointestinal symptoms | 23 (27.1%) | 19 (22.4%) | 8 (9.2%) | 5 (5.7%)† |
| peripheral edema | 7 (8.2%) | 4 (4.7%) | 3 (3.4%) | 1 (1.1%) |
| liver dysfunction | 5 (5.9%) | 5 (5.9%) | 0 (11.5%) | 7 (8.0%) |
| [ initial rise in GOT/GPT | 26 (30.6%) | | 23 (26.4%) ] | |
| cerebral infarction | 4 (4.7%) | 3 (3.2%) | 0 (0%) | 0 (0%) |
| congestive heart failure | 4 (4.7%) | 2 (2.4%) | 0 (0%) | 0 (0%) |
| arrhythmia | 2 (2.4%) | 0 (0%) | 0 (0%) | 0 (0%) |
| pulmonary embolism | 2 (2.4%)∓ | 2 (2.4%) | 0 (0%) | 0 (0%) |
| skin rash | 2 (2.4%) | 1 (1.2%) | 0 (0%) | 0 (0%) |
| decrease in platelet count | 0 (0%) | 0 (0%) | 1 (1.1%) | 1 (1.1%) |
| **Overall toxicities?** | | | | |
| **adverse side effects** | **41/85 (48.2%)** | | **20/87 (23.0%)** | |
| **EMP discontinuation** | **71/85 (83.5%)** | | **30/87 (34.5%)** | |
| Due to side effects | 36/85 (42.4%) | | 14/87 (16.1%) | |
| Due to other causes | 9/85 (10.6%) | | 9/87 (10.3%) | |
| EMP refractory | 26/85 (30.6%) | | 7/87 (8.0%) | |
| **Drug continuation** | **14/85 (16.5%)** | | **57/87 (65.5%)** | |

*National Cancer Institute common toxicity criteria.
†One of the 5 patients suffered from severe hematemesis.
∓One of the 2 patients died of pulmonary embolism.

decreased to an undetectable level by about 1 month and remained undetectable thereafter (Figure 3). Serum GOT and GPT transiently increased in 2 months in 23 cases, but were kept within normal range during the period of follow-up (Figure 4).

***Clinical Outcomes.*** As of October 31, 2003, the mean observation time was 412 ± 183 days (range: 46-766) (Table 2). The mean EMP administration time was 265 ± 170 days (range: 5-730). Of the 83 assessable patients for PSA response, 41 and 34 had complete and partial PSA response, respectively. Total PSA response rate of complete and partial response was 90.4% (75/83), while the PSA incomplete response rate was only 9.6% (8/83). The mean time to PSA normalization (< 4 ng/mL) was 83 ± 79 days which was much shorter ($P < 0.05$) than the time to nadir (164 ± 96 days). During the follow-up period, disease progression was experienced in 7 patients (8.4%) and all of them had PSA failure devoid of regrowth or new bony lesion. A total of 3 patients died during the observation period—2 died of prostate cancer and 1 died of lung cancer. Cause specific survival (Figure 5) and overall survival (Figure 6) were 376 ± 95 and 403 ± 126 days, respectively. During the entire follow-up period, no patient suffered from gastrointestinal cancers.

***Toxicity.*** Toxicities are listed in Table 3. Liver dysfunction was encountered in 10 out of 87 cases. In addition, there were 23 cases of initial transient rise in transaminases less than 150 IU/mL during the first 3 months without cessation of EMP administration. The second most frequent toxicity was gastrointestinal symptoms (nausea, vomiting, anorexia, and stomachache), including 1 case of hematemesis just 7 days after EMP administration. Peripheral edema was the third most frequent toxicity; it was observed in 3 patients followed with 1 case of decline in platelet count. However, neither cardiovascular infarction nor congestive heart failure has been seen so far in this series. No treatment-related deaths were observed during the follow-up period. Overall adverse side effects were recorded in 20 of 87 cases (23.0%), of which 14 cases (16.1%) had to discontinue EMP administration. Slight gynecomastia and high-grade impotence were documented in most cases.

## DISCUSSION

At the beginning of this series of EMP therapy, low-dose EMP monotherapy was considered based on the assumption that low-dose EMP not only exerts an anticancer effect by adopting a new mode of intake but also by decreasing adverse side effects. However, a considerable number of side effects were encountered and drug compliance was inadequate in Study 1, but a satisfactory response rate (92.3%) was obtained. For the next step, very low-dose EMP therapy combined with LH-RH agonist (Study 2) was employed in an attempt to lessen side effects as well as to achieve high PSA response rate. This assumption appears to have been almost fulfilled in Study 2. As the entry characteristics in both study groups are comparable with respect to all major parameters, comparisons between both studies are discussed below though the follow-up period in Study 2 is much shorter than Study 1. We believe it will not be valueless to compare Studies 1 and 2, in spite of independently conducted and non-randomized studies.

### Comparison Between Studies 1 and 2

***Overall Changes in the Mean Serum PSA, E2, TST, LH, FSH, GOT and GPT.*** In general, changes in those parameters were similar in both study groups but were milder in Study 2. Serum PSA in Study 1 quickly declined to a low level in 1 month, while that in Study 2 decreased moderately during 1 month and then rapidly declined to an undetectable level in 2 months (Figure 1). The reason for the rapid decrease from 1 to 2 months may be attributed to LH-RH agonist injection at 1 month. Judging by the results, 2 capsules/day of EMP might be able to decrease serum PSA quite rapidly but 1 capsule/day of EMP might not. However, serum PSA was entirely stable in undetectable level following LH-RH agonist administration in Study 2; on the contrary, that in Study 1 was rather unstable within low level. The former may be explained by the medical castration effect of LH-RH agonist in Study 2 and the latter may be influenced by low EMP compliance in Study 1. Serum estradiol went up rapidly within 1 month in both studies and remained high between 25,000 to 30,000 pg/mL and between 10,000 to 15,000 pg/mL in Studies 1 and 2, respectively (Figure 2). That in Study 1 was more labile than that in Study 2, which may indicate that 1 capsule/day of EMP is more compliant than 2 capsules/day of EMP. On the other hand, 2 capsules/day of EMP can maintain serum estradiol about 2 times higher than that in Study 2. Serum level of estradiol can be a good indicator for the drug compliance of EMP.[9] Serum testosterone decreased rapidly to castrated level in 4 weeks in

**Table 4.** Comparison of Response and Toxicity Among Various Therapeutic Modalities in Previously Untreated Advance Prostate Cancer

| | Overall n | PSA response | Overall toxicity | EMP discontinuation | Lethal cases |
|---|---|---|---|---|---|
| **EMP 4 cap/day (conventional dosage)** | | | | | % (n) |
| Takayasu (1980)[20] | 172 | 89% | 65%*(0 %)† | 9% | 0 |
| Takenaka (2001)[21] | 20 | 85% | 55% (0%) | 30% | 0 |
| **EMP 2 cap/day (low dosage)** | | | | | |
| Smith (1984)[14] (EMP 4 2 cap/day) | 25 | 90 % | 62% | 13% | 4% (5) |
| Saito (2001)[22] (EMP 4 or 2 cap/day) | 26 | 83% | 27% (0%) | 12% | 0 |
| **DES (3 mg/d)** | | | | | |
| Smith (1984)[14] | 123 | 94% | 55% | 2% | 10% (12) |
| Leuprolide Gr. (1984)[15] | 101 | 85% | 39% (11%) | 13% | 0 |
| **CAB** | | | | | |
| Iversen (1990)[23] | 129 | 83% | 23% (61%) | 6% | 0 |
| Tyrrell (1991)[16] | 287 | 89% | 47% (14%) | 22% | 0 |
| Eisenberger (1998)[24] | 698 | 74% | 21% (10%) | 5% | 0 |
| **LH-RH agonist** | | | | | |
| Leuprolide Gr. (1984)[15] | 98 | 86% | 8% (52%) | 3% | 0 |
| Tyrrell (1991)[16] | 284 | 88% | 15% (12%) | 2% | 0 |
| Saito (2001)[22] | 35 | 80% | 9% (0%) | 3% | 0 |
| **Castration** | | | | | |
| Eisenberger (1998)[24] | 687 | 62% | 14% (10%) | 1% | 0 |
| Iversen (1990)[23] | 133 | 69% | 8% (54%) | 0% | 0 |
| **Current study** | | | | | |
| Study 1 (EMP 2 cap/d) | 87 | 92.3% | 48.2% | 42.4% | 1%(1) |
| Study 2 (EMP 1 cap/d + LH-RH agonist) | 87 | 90.4% | 23.0% | 16.1% | 0 |

*Percent of overall toxicity excluding hot flashes and gynecomastia.
†Percent of hot flashes in the total cases examined

both studies (Figure 2). Serum LH and FSH declined to an undetectable level within almost 1 month and remained almost stable at undetectable level (Figure 3). Serum GOT and GPT transiently increased once during the first 3 months following EMP administration, after which those data remained within the normal range, though the levels of serum GOT and GPT in Study 1 are a little higher than the Study 2 (Figure 4). Moreover, the amplitude of initial rise was more marked in Study 1 than in Study 2. The difference of amplitude might imply that the higher the serum level of EMP, the more the damage to liver cells.

***Clinical Outcomes.*** Total PSA response rates of complete and partial response were excellent both in Study 1 (92.3%) and Study 2 (90.4%), which is in accordance with our former report (93.4%),[9] and is rather superior to other reports (62%-94%) (Table 4).[14, 15, 20-25] PSA incomplete response (7.7%) in Study 1 was as low as that (9.6%) in Study 2. The mean time to PSA normalization (67 ± 85 days) in Study 1 was significantly shorter ($P < 0.05$) than that (83 ± 79

days) in Study 2. Likely, the mean time to PSA nadir (80 ± 113 days) in Study 1 is much shorter ($P < 0.01$) than that (164 ± 96 days) in Study 2. These results might indicate not only inadequacy for reducing serum PSA with 1 capsule/day EMP alone but also the necessity of combination with delayed LH-RH agonist in Study 2. During the follow-up period, disease progression was more often encountered in Study 1 than in Study 2, though the follow-up period was much longer in the former than the latter. It will not be meaningful at this time to compare mean cause specific survival, mean overall survival, and disease progression rate because the follow-up period is much different between the 2 studies. In the next report, these parameters should be discussed in detail.

***Toxicity.*** Toxicities among various therapeutic modalities are listed in Table 4. Overall toxicities were more common (48.2%) in Study 1 than that (23%) in study 2. Takenaka et al[21] reported that overall toxicity rate was 55% on EMP monotherapy of 4 capsules/day. Taking these combined data into consideration, toxicity of EMP seems to increase in a dose dependent manner like serum estradiol level does. Moreover, 1 case of fatal pulmonary embolism was seen in Study 1, while no such serious averse side effects were encountered in Study 2. In the report of EORTC,[14] cardiovascular side effects were documented in 36% including 5 fatal cases on low-dose EMP monotherapy, while there were 12 deaths on DES monotherapy (44%). These data suggest that our studies are superior to EORTC in terms of fatal cardiovascular toxicity, which is more prominent in Study 2. Likewise, gastrointestinal toxicity in Study 1 (27.1%), which is in accordance with the report of EORTC (26%),[14] was much higher than that in Study 2 (9.2%). In addition, gastrointestinal toxicity reported by Takayasu et al[20] is 36%, which was conducted on 4 capsules/day of EMP. These data support that gastrointestinal toxicity depends on EMP dosage, too. EMP administration was discontinued due to adverse side effects in 36/87 (41.4%) in Study 1 and in 14/87 (16.1%) in Study 2. It seems that side effects requiring EMP discontinuation occur more often in Study 1 than in Study 2. As a result, toxicities are in general milder in Study 2 than in Study 1 and depend on EMP dosage. In terms of toxicity, very low-dose EMP administration seems to be superior to other varieties of EMP dosage.

**Comparison of Response and Toxicity Among Various Therapeutic Modalities in Previously Untreated Advanced Prostate Cancer**

In general, overall PSA response rates (74%-94%) in various therapeutic modalities (Table 4) are excellent except for a slightly lower response rate (62%-69%) in castration alone. In terms of toxicity, therapies using EMP and DES showed higher toxicity (27%-65%) than that (8%-47%) in CAB, LH-RH agonist and castration.

With regard to our current studies, Study 2 can be regarded as a kind of CAB therapy using steroidal antiandrogen and its response rate (90.4%) appears to be comparable or rather superior to CAB therapy (78%-89%)[23,24,26] with nonsteroidal antiandrogen (Table 4). In Study 2, rate of adverse events leading to withdrawal from therapy (16.1%) is almost equivalent to that[16,23,24] in CAB therapy with nonsteroidal antiandrogen (5%-22%). In contrast, Study 1 showed very high withdrawal rate (41.4%) from therapy in spite of achieving high PSA response rate (92.3%). Although monotherapy using LH-RH agonist provides good PSA response rate (80%-88%),[16,22,25] as well as very low side effects (8%-15%)[15,16,22] and very low rate (2%-3%)[16]

of drug discontinuation, its overall survival rate at 5 years (20%-34%) is so far slightly inferior to that in CAB therapy (20%-42%).[26] Recently, Noguchi et al[27] reported that 4 capsules/day of EMP with LH-RH agonist showed better progression-free survival than CAB with 375 mg/day of flutamide. As they report, we consider Study 2 to be more promising than CAB alone, because Study 2 has a dual action of CAB and anticancer effect. However, we could not, at this time, discuss our interim data of progression-free survival in Studies 1 and 2 because of brief observation time. A longer follow-up will be necessary to elucidate the true outcomes in Studies 1 and 2. We will report on these outcomes in the near future.

## SUMMARY

Although follow-up periods were very short, Studies 1 and 2 exhibited excellent PSA response rates. However, rates of adverse side effects and EMP withdrawal were significantly higher in Study 1 than in Study 2. In addition, it was elucidated that not only serum level of estradiol but also the rate of toxicity increased in a dose-dependent manner. Since most patients found it difficult to take 2 capsules/day of EMP constantly, Study 2 is superior to Study 1 in every respect. All results of Study 2 are comparable or rather superior to those in CAB treatment but those in Study 1 are not satisfactory except for PSA response rate. As Study 2 belongs to a kind of CAB treatment with steroidal antiandrogen as well as with anticancer activity, it can be a promising treatment modality for PUAPC in the future. We have to follow-up our patients for a longer period and clarify the true outcomes, especially in Study 2.

## REFERENCES


1. Smith DC. Chemotherapy for hormone refractory prostate cancer. *Urologic Clinics North America.* 1999;26:323-331.
2. Perry CM, McTavish D. Estramustine phosphate sodium. A review of its pharmacodynamic and pharmacokinetic properties, and therapeutic efficacy in prostate cancer. *Drugs Aging.* 1995;7:49-74.
3. Olmstead J: Microtubule associated proteins. *Ann Rev Cell Biol.* 1986;2:419-455.
4. Van Poppel H, Baert L. The present role of estramustine phosphate in advanced prostate cancer. In*: European Organization for Research and Treatment of Cancer. Genitourinary Group Monograph 10—Urological Oncology: Reconstructive Surgery, Organ Conservation, and Restoration of Function.* Hoboken, NJ: Wiley-Liss, Inc; 1991;323-341.
5. Hudes G. Estramustine-based chemotherapy. *Semin Urol Oncol.* 1997;15:13-19.
6. Pienta KJ, Fisher EI, Eisenberger MA, et al. A Phase II trial of estramustine and etoposide in hormone refractory prostate cancer: A Southwest Oncology Group trial (SWOG 9407). *Prostate.* 2001;46:257-261.
7. Kelly WK, Curley T, Slovin S, et al. Paclitaxel, estramustine phosphate, and carboplatin in patients with advanced prostate cancer. *J Clin Oncol.* 2001;19:44-53.
8. Petrylak DP, Macarthur RB, O'Connor J, et al. Phase 1 trial of docetaxel with estramustine in androgen-independent prostate cancer. *J Clin Oncol.* 1999;17:958-967.
9. Kitamura T, Nishimatsu H, Hamamoto T, Tomita K, Takeuchi T, Ohta N. EMP combination chemotherapy and low-dose monotherapy in advanced prostate cancer. *Expert Rev Anticancer Ther.* 2002;2:59-71.
10. Andersson L, Berlin T, Boman J, et al. Estramustine versus conventional estrogenic hormones in the initial treatment of highly or moderately differentiated prostatic carcinoma. A randomized study. *Scand J Urol Nephrol.* 1980;55:143-145.
11. Benson RC Jr, Gill GM. Estramustine phosphate compared with diethylstilbestrol: a randomized, double-blind, crossover trial for stage D prostate cancer. *Am J Clin Oncol.* 1986;9:341-351.
12. Hauchecorne J. French multicentre study on the use of estramustine phosphate versus diethylstilbestrol. In: *Prostate Cancer, Part B: Imaging Techniques, Radiotherapy, Chemotherapy and Management Issues.* New York, NY; Alan R. Liss Inc; 1987:229-234.
13. Kuss R, Khoury S, Richard F, Fourcade F, Frantz P, Capelle JP. Estramustine phosphate in the treatment of advanced prostatic cancer. *Brit J Urol.* 1980;52:29-33.
14. Smith PH, De Pauw M, Robinson M, et al. EORTC Urological Group: Estramustine

phosphate in prostate cancer. EORTC experience: preliminary results of Protocol 30762. *Urology.* 1984;6(suppl):64-68.

15. The Leuprolide Study Group: Leuprolide versus diethylstilbestrol for metastatic prostate cancer. *N Engl J Med.* 1984;311:1281-1286.
16. Tyrrell CJ, Altwein JE, Klippel F, et al. A multicenter randomized trial comparing the luteinizing hormone-releasing hormone analogue Goserelin Acetate alone and with Flutamide in the treatment of advanced prostate cancer. *J Urol.* 1991;146:1321-1326.
17. Gunnarsson PO, Davidsson T, Andersson S-B, Backman C, Johansson S-A. Impairment of estramustine phosphate absorption by concurrent intake of milk and food. *Eur J Clin Pharmacol.* 1990;38:189-193.
18. Kitamura T. Necessity of re-evaluation of estramustine phosphate sodium (EMP) as a treatment option for first-line monotherapy in advanced prostate cancer. *Int J Urol.* 2001;8:33-36.
19. Marubini E, Valsecchi MG. Analyzing survival data from clinical trials and observational studies. Chichester, UK: John Wiley & Sons Ltd; 1995.
20. Takayasu H, Shida K, Momose S, et al. Clinical study on the treatment of prostatic carcinoma with Estracyt. *Nishinihon J Urol.* 1980;42:715-731.
21. Takenaka I, Soramoto S, Kagawa S, et al. Multicenter randomized clinical trial comparing estracyt mono-therapy with combined androgen blockade therapy (CAB) in the treatment of advanced prostate cancer. *Nishinihon J Urol.* 2001;63:1-9.
22. Saito S, Nakajima J, Nakajima Y, et al. Clinical efficacy of Leuprolide Acetate and combined treatment with Estramustine for advanced prostate cancer. *Jpn J Urol.* 2001;92:682-693.
23. Iversen P, Christensen MG, Friis E, et al. A phase III trial of Zoladex and Flutamide versus orchiectomy in the treatment of patients with advanced carcinoma of the prostate. *Cancer.* 1990;66(5 suppl):1058-1066.
24. Eisenberger MA, Blumenstein BA, Crawford ED, et al. Bilateral orchiectomy with or without Flutamide for metastatic prostate cancer. *N Engl J Med.* 1998;339:1036-1042.
25. Fourcade RO, Cariou G, Coloby P, et al. Total androgen blockade with Zoladex plus Flutamide vs. Zoladex alone in advanced prostatic carcinoma: Interim report of a multicenter, double-blind, placebo-controlled study. *Eur Urol.* 1990;18(suppl 3):45-47.
26. Samson DJ, Seidenfeld J, Schmitt B, et al. Systematic review and meta-analysis of monotherapy compared with combined androgen blockade for patients with advanced prostate carcinoma. *Cancer.* 2002;95:361-376.
27. Noguchi M, Noda S, Yoshida M, et al. Estramustine may offer benefits over Flutamide in chemohormonal therapy for metastatic prostate cancer. *Int J Urol.* 2004;11:103-109.