Safety of Megestrol Acetate in Palliating Anorexia-Cachexia Syndrome in Patients with Castration-Resistant Prostate Cancer

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INTRODUCTION

In 2012, Jung et al. (1) announced that an estimated 11,016 new cases (9.3% of total cancers in men) of prostate cancer would be diagnosed in Korea and that approximately 1,540 men (3.4%) would be expected to die from prostate cancer. Although, Korean men have one of the lowest rates of prostate cancer in the world, the onset of prostate cancer has been sharply increasing since 1999 (2). Approximately 15% of men with prostate cancer present with metastatic disease, and 30% of men with localized disease treated with definitive local therapy subsequently develop metastatic disease (3). While the great majority of patients with metastatic disease demonstrate a temporary response to androgen deprivation therapy (ADT), eventually all patients develop castration-resistant prostate cancer (CRPC) and virtually all prostate cancer deaths are due to the development of metastatic CRPC (4, 5). During recent years, docetaxel-based chemotherapy has been used as a standard treatment in patients with metastatic CRPC (6-8). Despite several studies demonstrating that it helps to increase the survival, the prognosis is poor in that the median survival time from the starting point of treatment is merely 16 to 20 months (8).

Cachexia is one of the most frequent effects of malignancy, with up to one-half of untreated cancer patients losing some weight and approximately one-third losing more than 5% of their original body weight (9). Cachexia is a pathological state of loss of skeletal muscle and fat; it occurs in the presence of underlying illness (10) and usually indicates that patients with advanced prostate cancer and suffering from cachexic symptoms, will need some palliative support.

A potential role for megestrol acetate (MA) in the treatment of patients with prostate cancer was suggested after documentation of its capacity to lower the luteinizing hormone, follicle-stimulating hormone, and testosterone in men who underwent transurethral resection of the prostate for benign prostatic hypertrophy (11). MA, a synthetically derived progesterone, blocks androgen receptors and lowers the serum androgen levels through inhibition of the release of luteinizing hormone and 5 alpha-reductase (12). However, it has been reported that MA has limited activity on PSA in patients with CRPC (13). Also, MA has a powerful effect on appetite; it is currently administered to improve appetite and to increase weight in cancer-associated cachexia (14). MA is also the most extensively studied agent for treating cancer-associated anorexia and has a well-established track record for alleviating this symptom and for promoting weight gain in patients with advanced cancer (15, 16).
Mutations in the androgen receptor gene have been identified in tissue samples from patients with advanced prostate cancer and represent a possible mechanism underlying the development of CRPC (17). It has been also reported that mutation in the steroid binding domain of the androgen receptor was found in the human prostatic carcinoma cell line or in tissue from men with advanced prostate cancer (18). In this context, three case reports showed rapid progression of advanced CRPC during palliative treatment with MA for cancer cachexia (19). Therefore, MA might induce the proliferation of CRPC via the mutated androgen receptor.

Even though MA has been used in clinical practice for palliating cancer cachexia anorexia syndrome in patients with CRPC, to our knowledge, there have no studies which demonstrated the influence of the cumulative doses of MA on survival in patients with CRPC and who were receiving docetaxel-based chemotherapy. Therefore, we retrospectively investigated the effect of MA on DSS in patients with CRPC and who were receiving docetaxel-based chemotherapy.

**MATERIALS AND METHODS**

**Patient population**

We studied 126 patients with CRPC who had received docetaxel-based chemotherapy and prednisone at our institution between July 2003 and June 2009. However, 17 of these patients were found to be ineligible, 10 owing to < 3 docetaxel cycle, and seven because of a > 3 ECOG performance status. All 109 eligible patients had histologic proof of adenocarcinoma of the prostate and progressive visceral metastases or progressive regional lymph node disease after ADT, as determined by the individual investigators.

Demographic information, date of prostate cancer diagnosis, baseline laboratory findings, the cumulative doses of MA, concomitant hormonal therapy, and date of the last follow-up or death were taken directly from the medical charts. The baseline ECOG performance status was estimated according to the clinical progress notes at the beginning of docetaxel-based chemotherapy. We defined CRPC in the following cases: when the serum testosterone is castration levels; three consecutive rises of PSA two weeks apart and resulting in two, 50% increases over the nadir; PSA progression observed despite secondary hormonal manipulation or for at least four weeks of antiandrogen withdrawal; and bone metastases and soft tissue metastases progression (20).

The number of docetaxel cycles was divided by the median value: ≤ 7 vs > 7. The ECOG performance status and the Gleason score were evaluated 1-2 vs 3 and ≤ 7 vs 8-10, respectively. We classified patients into two groups according to the existence of other predicting variables such as visceral metastases, lymph node metastasis, bone metastasis, and concomitant hormonal therapy administered during the docetaxel-based chemotherapy.

**Docetaxel-based chemotherapy**

The scheduled interval in our study was three weeks, at which time patients received 75 mg/m² of docetaxel (Taxotere, Aventis) as a one-hour intravenous infusion and prednisone 5 mg was given orally six hours before and six hours after treatment. Pretreatment supportive medications were given according to our institutional practice. Dose adjustment was performed according to toxicity.

**Megestrol acetate dosage**

Patients complaining of cachexic symptoms received 800 mg MA daily. The cumulative doses of MA were investigated from their medical chart, and the calculation of MA was counted from the date of the beginning of docetaxel-based chemotherapy to the date of the last follow-up. Patients were classified into three different groups based on the median amount (18,400 mg) of the MA dose administered cumulatively as follows: 68 patients who were not administered MA (group 1); 21 patients who received low dose MA (total ≤ 18,400 mg; group 2); and 20 patients who received high dose MA (total > 18,400 mg; group 3).

**Statistical analysis**

Differences in the basic demographic variables were compared using Pearson’s chi-square test and the one-way ANOVA using Scheffe’s test as post-hoc analysis. Quantitative data were expressed as the mean value (± standard deviation) or median value (range). To evaluate the effect of cumulative doses of MA on DSS, the relative risks and the 95% CI were calculated as HR derived from the Cox proportional hazards regression model. Survival curves were generated by means of the Kaplan-Meier estimates, and differences in survival were compared using the log-rank test. For all statistical analyses, P < 0.05 was considered significant, and all P values were two-sided. SPSS®, version 12.0 was used for the statistical analysis.

**Ethics statement**

The study protocol was approved by the institutional review board of Asan Medical Center (IRB No. 2012-0047), and the need for informed consent was waived.

**RESULTS**

The demographic and baseline characteristics of our study patients are shown in Table 1. The mean baseline PSA, Hb, and ALP were 121.4 ng/mL, 11.8 g/dl, and 160.2 IU/L, respectively. The mean number of docetaxel cycles was 8.6, and 41 (37.6%) patients received MA in order to relieve their cachexic symptoms. Visceral metastases and lymph node metastasis were found in 21 (19.3%) and 50 (45.9%) of our patients, respectively,
Demographics and baseline data

Table 1.

| Characteristics                  | Group 1 (n = 68) | Group 2 (n = 21) | Group 3 (n = 20) | P value* |
|----------------------------------|-----------------|-----------------|-----------------|---------|
| Mean age ± SD, years (median, range) | 68.4 ± 7.4 (69, 45-87) | 68.4 ± 7.1 (68, 45-87) | 68.4 ± 7.1 (71, 51-86) | 0.977† |
| Mean cumulative doses of MA, mg (range) | 0 (0-18,400) | 3,200 (800-18,400) | 40,800 (21,600-163,200) |         |
| ECOG performance status, n (%) | 1-2 96 (88.1) | 16 (76.2) | 18 (90.0) | 0.172 |
| Bone metastasis, n (%) | Yes 100 (91.7) | 19 (90.5) | 19 (95.0) |         |
| Lymph node metastasis, n (%) | Yes 50 (45.9) | 2 (10.0) | 2 (10.0) | 0.038 |
| Mean number of docetaxel cycles ± SD (median, range) | 8.6 ± 4.6 (7, 3-32) | 8.3 ± 5.1 (7, 3-32) | 8.6 ± 3.9 (8, 3-20) |         |

Baseline characteristics according to the cumulative doses of MA

Table 2.

| Characteristics                  | Group 1 (n = 68) | Group 2 (n = 21) | Group 3 (n = 20) | P value* |
|----------------------------------|-----------------|-----------------|-----------------|---------|
| Mean age ± SD, years (median, range) | 68.4 ± 7.4 (69, 45-87) | 68.2 ± 6.5 (70, 56-80) | 68.4 ± 7.4 (71, 51-86) | 0.977† |
| Mean cumulative doses of MA, mg (range) | 0 (0-18,400) | 3,200 (800-18,400) | 40,800 (21,600-163,200) |         |
| ECOG performance status, n (%) | 1-2 96 (88.1) | 16 (76.2) | 18 (90.0) | 0.172 |
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Visceral metastases, n (%)

| Characteristics                  | Group 1 (n = 68) | Group 2 (n = 21) | Group 3 (n = 20) | P value* |
|----------------------------------|-----------------|-----------------|-----------------|---------|
| Mean age ± SD, years (median, range) | 68.4 ± 7.4 (69, 45-87) | 68.2 ± 6.5 (70, 56-80) | 68.4 ± 7.4 (71, 51-86) | 0.977† |
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Table 3 shows the univariate and multivariate Cox proportional analysis for DSS. In the univariate Cox regression analyses, no variable was a statistically significant predictor for DSS after starting docetaxel-based chemotherapy, except for lung metastasis and the docetaxel cycles (HR: 3.001, 95% CI: 1.258-7.142, P = 0.013; and HR: 0.633, 95% CI: 0.408-0.982, P = 0.041, respectively). In multivariate Cox regression analysis using backward the elimination method, the docetaxel cycles was only significant factor (HR: 0.578, 95% CI: 0.318-0.923, P = 0.016).

Survival status is available for 109 patients. Fifty-four of 68 patients in the group 1 have died, 14 of 21 patients in the group 2 have died, and 7 of 20 patients in the group 3 have died, respectively. When comparing DSS using the Kaplan-Meier, there were no statistically significant survival differences among the three groups, with a median overall survival time of 19.3 months and bone metastasis was detected in 100 (91.7%) of these patients.

Table 2 presents the demographic and baseline characteristics of the three groups. There were 109 eligible patients with a median age of 69 yr (range 45 to 87), including 68 (range 45 to 87), 70 (range 56 to 80), and 71 yr (range 51 to 86) in groups 1, 2, and 3, respectively (P = 0.977). The median MA dose was 3,200 mg (range 800 to 18,400) in group 2 and 40,800 mg (range 21,600 to 163,200) in group 3.

Table 3 shows the univariate and multivariate Cox proportional analysis for DSS. In the univariate Cox regression analyses, no variable was a statistically significant predictor for DSS after starting docetaxel-based chemotherapy, except for lung metastasis and the docetaxel cycles (HR: 3.001, 95% CI: 1.258-7.142, P = 0.013; and HR: 0.633, 95% CI: 0.408-0.982, P = 0.041, respectively). In multivariate Cox regression analysis using backward the elimination method, the docetaxel cycles was only significant factor (HR: 0.578, 95% CI: 0.318-0.923, P = 0.016).
Table 3. Cox proportional hazards model of disease-specific survival

| Variables                                      | Univariate HR (95% CI) | P value | Multivariate HR (95% CI) | P value |
|------------------------------------------------|------------------------|---------|--------------------------|---------|
| Age (median) (yr)                              |                        |         |                          |         |
| > 70 vs ≤ 69                                   | 0.864 (0.553-1.350)    | 0.522   |                          |         |
| ECOG performance status                        |                        |         |                          |         |
| 3 vs 1-2                                       | 0.946 (0.498-1.795)    | 0.865   |                          |         |
| Bone metastasis                                |                        |         |                          |         |
| Yes vs No                                      | 0.971 (0.446-2.115)    | 0.941   |                          |         |
| Lymph node metastasis                          |                        |         |                          |         |
| Yes vs No                                      | 1.492 (0.913-2.392)    | 0.097   |                          |         |
| Liver metastasis                               |                        |         |                          |         |
| Yes vs No                                      | 0.481 (0.186-1.202)    | 0.115   |                          |         |
| Lung metastasis                                |                        |         |                          |         |
| Yes vs No                                      | 3.001 (1.258-7.142)    | 0.013   | 1.215 (0.263-3.372)      | 0.133   |
| Baseline Hb (median) (g/dL)                    |                        |         |                          |         |
| > 12.0 vs ≤ 12.0                               | 1.089 (0.705-1.683)    | 0.700   |                          |         |
| Baseline PSA (median) (ng/dL)                   |                        |         |                          |         |
| > 42 vs ≤ 42                                   | 0.788 (0.502-1.237)    | 0.301   |                          |         |
| Baseline ALP (median) (IU/L)                   |                        |         |                          |         |
| > 86 vs ≤ 86                                   | 1.063 (0.689-1.639)    | 0.784   |                          |         |
| Gleason score                                  |                        |         |                          |         |
| 8-10 vs ≤ 7                                    | 1.242 (0.626-2.431)    | 0.533   |                          |         |
| Docetaxel cycles (median)                      |                        |         |                          |         |
| > 7 vs ≤ 7                                     | 0.633 (0.408-0.982)    | 0.041   | 0.578 (0.318-0.923)      | 0.016   |
| Concomitant hormonal therapy                    |                        |         |                          |         |
| Yes vs No                                      | 0.770 (0.491-1.206)    | 0.253   |                          |         |
| Cumulative doses of MA                         |                        |         |                          |         |
| Group 2 vs Group 1                              | 0.962 (0.531-1.743)    | 0.905   | 0.852 (0.512-1.361)      | 0.812   |
| Group 3 vs Group 1                              | 1.106 (0.606-2.008)    | 0.744   | 1.063 (0.629-2.163)      | 0.753   |

HR, hazard ratio; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; Hb, hemoglobin; PSA, prostate-specific antigen; ALP, alkaline phosphatase; MA, megestrol acetate.

Fig. 1. Kaplan-Meier survival curve for disease-specific survival. There was no significant difference among the three groups (log rank $P = 0.546$).

Fig. 1. Kaplan-Meier survival curve for disease-specific survival. There was no significant difference among the three groups (log rank $P = 0.546$).

The median, DSS time was 21.2 months in group 1, 20.4 months in group 2, and 16.8 months in group 3, respectively. The one year, DSS rate was 73.0% in group 1, 84.2% in group 2, and 67.1% in group 3, respectively, and the two year, DSS rate was 46.8% in group 1, 44.3% in group 2, and 16.3% in group 3, respectively (Fig. 1).

DISCUSSION

In our study, we attempted to investigate the effect of cumulative doses of MA on the DSS in cachexic patients with CRPC who were receiving docetaxel-based chemotherapy. However, our study has several limitations. First, although we attempted to carefully select our study population, the problems inherent in a retrospective study are unavoidable and can influence the results. Secondly, as MA was mostly administered for the improvement of cachexic symptoms rather than as a secondary hormonal manipulation in prostate cancer, MA might be prescribed according to the demand of patients complaining of cachexic symptoms rather than based on the decisions of physicians. In addition, follow-up studies were not carried out focusing on weight gain, pain relief, and the quality of life enhancement. On the basis of the data from other studies using high doses of MA, several theoretical side effects should be considered and include weight gain, thromboembolic disorders, edema, lipid changes, cardiovascular disease, and the possible influence of MA on bone structure. In addition, male impotence has been reported with high doses of MA (21).
To our knowledge, however, there have been no studies reviewing DSS according to the cumulative doses of MA in patients with CRPC and who are receiving docetaxel-based chemotherapy. Although several, early clinical trials conducted in men who failed first-line hormonal therapy using 160 mg MA daily as secondary hormonal manipulation, have been examined recently (22, 23), the purpose of MA to be used as the second-line hormonal therapy for advanced prostate cancer, was considerably decreased. In our study, we administered MA to treat cancer-associated cachexia in approximately one-third of the patients with CRPC and who were receiving docetaxel-based chemotherapy. However, there are still concerns whether MA might stimulate prostate cancer cell growth via mutated androgen receptors in patients with CRPC. Dawson et al. demonstrated that withdrawal responses might occurred with steroidal and non-steroidal antiandrogens, as they observed a significant decrease in PSA in response to the withdrawal of MA (24). Tassini et al. also reported the cases of three patients with advanced “hormone-resistant” prostate cancer, each of whom had rapid disease progression during their treatment with MA for cancer-associated cachexia. However, when MA was discontinued for inefficacy reasons, serum PSA values quickly stopped increasing, bone pain decreased, and patient performance status improved (19). Although it was not case regarding the administration of MA in patients with CRPC, one case report showed that patients with prostate cancer who were given MA for symptomatic relief of hot flashes after administration of a luteinizing hormone-releasing hormone analog, experienced a PSA value which declined more than 60% when MA therapy was stopped (25). Perhaps the functional changes in the androgen receptors have been hypothesized, and antiandrogens may act on the mutated androgen receptor, thus having a promoting role on tumor growth and progression of the disease under total androgenic blockade.

The recommended MA doses range for appetite enhancement from 40mg three times daily, to 30 min before meals, to 800 mg once a day. MA has demonstrated dose-dependent improvements (starting at 160 mg/day) in appetite, fatigue, and general well-being in more than 60% of the patients studied (26, 27). Approximately 480-800 mg/day is optimal for weight gain, although it is prudent to start at a lower dose and titrate upward as adverse effects and expense are dose-related (28). In our study, 800 mg of MA was administered equivalently and daily in order to improve appetite in nearly all patients, and which is relatively higher than the 640 mg administered in other study for high-dose patient groups (13). In fact, patients who administered MA might seem to be more likely to have advanced disease and poorer comorbidity than those who did not administered MA. However, compared to patients who did not administer MA there were no significant differences with regard to visceral or bone metastasis or to the ECOG performance status noted in our study. When comparing DSS using the Kaplan-Meier method, there was no statistically significant difference among the three groups. Also, in multivariate Cox regression analysis after adjusting the influencing factors for patients with CRPC and receiving docetaxel-based chemotherapy, the cumulative doses of MA were not an independent factor predicting DSS.

Dawson et al. reported that one noteworthy example of toxicity in their trial was the apparent flare in bone pain in 7% of the patients with CRPC. Therefore, although MA may occasionally be beneficial, they concluded that the potential for pain flare as well as other serious complications such as thrombosis, hypertension, and hyperglycemia, makes the standard use of MA in clinical practice inadvisable (13). In our study, although it was not a randomized prospective study, the result demonstrating that relatively higher doses of MA proved to be safe, is expected to be very helpful and supportive in the cachexia management of patients with CRPC when considering the fact that the prevalence of cachexia increases from 50% to more than 80% before death and that in more than 20% of patients, cachexia is the main cause of death (29).

In Korea, more than half of newly diagnosed prostate cancer is of an advanced stage (30). Therefore, it is a noteworthy fact that MA has been safely used for patients with CRPC when considering the considerable number of those who complain of cachexic symptoms. Finally, chemotherapy has traditionally been used in patients with CRPC, however, treatment of metastatic CRPC after progression on docetaxel-based chemotherapy is a challenging clinical scenario with only limited availability of treatment options. Some recent studies are in progress regarding other second-line systemic treatment for patients with metastatic CRPC that progressed following docetaxel-based chemotherapy (31). We think that further evaluation of the relationship between other promising, post-docetaxel agents and MA will be especially worthy of note in the near future.

In conclusions, MA administered in patients with CRPC as an adjuvant treatment in docetaxel-based chemotherapy intended to treat anorexia-cachexia syndrome, did not affect the DSS. Therefore, MA can be considered as a safe, adjuvant treatment for anorexia-cachexia syndrome in patients with CRPC.

DISCLOSURE

The authors have no conflicts of interest to disclose.

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