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SESSION IV

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Experiences with doxo/epirubicin and medroxyprogesterone acetate (MPA) in prostatic cancer

Abstract Maximal androgen blockade (MAB) has been reported to prolong the time to progression and the duration of survival in metastatic prostatic cancer. The addition of epirubicin to MAB in such patients seems to improve the therapeutic results further. The beneficial effect of combining castration with epirubicin in metastatic cases appears questionable. In comparing the time to progession in patients treated with MAB ± epirubicin versus castration ± epirubicin or estramustine, many studies reveal similar figures. Whether the results after treatment are actually improved remains controversial. In hormone-refractory cases, medroxyprogesterone acetate (MPA) alone seems superior to estramustine or prednisolone treatment. Combining MPA and epirubicin improves the results, but even if the improvement is of clinical value, it is nonetheless of limited magnitude.

Key words Epirubicin · Medroxyprogesterone acetate · Prostatic cancer

Introduction

The incidence of prostatic cancer is increasing throughout the world. At diagnosis, more than 50% of patients present with metastatic or locally advanced disease. In all, 70%–80% of them will respond to androgen deprivation with orchiectomy, estrogens, or luteinizing hormone-releasing hormone (LHRH) agonists and experience successful palliation of pain and an improved performance status. However, 10% will die within 6 months and 50% will live for less than 2 years. Recently, Crawford and Nabors [5] and Denis et al. [6] have reported increased duration of survival by applying the concept of maximal androgen blockade. The effect of such treatment, however, remains controversial. When the tumor is progressing after initial androgen deprivation, it is considered hormone-resistant and rarely responds to second-line endocrine therapy. Androgen deprivation thus offers effective palliation, which is generally of short duration, and new therapeutic concepts are mandatory.

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Steroidal antiandrogen treatment and chemotherapy in prostatic cancer

MPA in advanced prostatic cancer

Progesterones such as cyproterone acetate (CPA) and medroxyprogesterone acetate (MPA) are steroidal antiadrogens. Using high doses of MPA, Tomic et al. [15] produced a profound decrease in serum testosterone concentration in men. The serum testosterone level was reduced by 97%, which is more pronounced than the decrease reported earlier in patients after orchiectomy or during estrogen treatment. These findings suggest MPA to have a hypothalamo-pituitary-testicular and adrenal effect. In addition, progesterones block androgen receptors and inhibit 5-α-reductase. Accordingly, it could be expected to be at least as efficiant as estrogens or orchiectomy in the treatment of advanced prostatic cancer.

A prospective randomized multicenter study by the European Organization for Research and Treatment of Cancer (EORTC) compared oral CPA, i.m. MPA and diethylstilbestrol (DES) in patients with advanced prostatic cancer [12]. The 5-year survival rates were 38% for DES, 32% for CPA, and 14% for MPA; thus, MPA and CPA were not found to be superior to DES in such patients. Similar results were reported by Bouffioux [3], who compared 500 mg MPA given i.m. for 2 weeks followed by 100 mg given orally per day with 3–5 mg DES per day in locally advanced or metastatic cases. A subjective improvement

was experienced by 85% of the patients in both groups. MPA thus appeared less efficient than DES in previously untreated advanced prostatic cancer. However, higher doses of MPA might have been more effective. In elderly men with advanced prostatic cancer having cardiovascular problems, MPA treatment may be considered an alternative to estrogen therapy.

Combining androgen deprivation and steroidal antiandrogen treatment has been reported in a limited number of randomized trials, but no advantage for the combination therapy has been found.

MPA in hormone-refractory disease

In hormone-refractory diseases Johansson et al. [10] have reported on a prospective randomized study including 105 patients. All patients had metastatic disease and had progressed on initial androgen deprivation. The patients were randomized to receive either 1000 mg MPA i.m. for 15 days followed by 1000 mg i.m. weekly or estramustine phosphate at 280 mg b.i.d. Evaluation was made according to the criteria of the Scandinavian Prostatic Cancer Group (SPCG). Regarding time to further progression and duration of survival, no difference was found. However, 25% of the MPA-treated patients experienced remissions lasting for 12–56 weeks as compared with 8% of the patients given estramustine phosphate. MPA produced significantly more remissions. The authors' clinical impression was also that the MPA-treated patients experienced better palliation. Fosså et al. [8] compared 500 mg MPA b.i.d. with 5 mg prednisolone given four times a day and reported similar experiences. Thus, in hormone-refractory cases, MPA produced more remissions, gave better palliation, improved the performance status, and reduced pain as compared with estramustine and prednisolone but had no impact on survival. Side effects were rather few, but edema and cardiovascular complications were observed in several patients.

Fosså et al. [8] reported a flare reaction in 10% of 40 patients, and Johansson et al. [10] reported increasing pain in 3 of 51 MPA-treated patients. In our study combining MPA and epirubicin, flare was seen in only 2 of 75 patients included in that treatment arm [1]. Epirubicin may have partly inhibited this reaction, but this suggestion is only speculative.

Doxo/epirubicin in hormone-refractory disease

Applying the concept that hormone-insensitive cells are responsible for tumor progression and death and in an attempt to reduce side effects, especially cardiotoxicity, Torti et al. [16] treated 25 patients suffering from hormone-refractory prostatic cancer with doxorubicin. The patients received 20 mg/m^2 i.v. weekly. According to National Prostatic Cancer Project (NPCP) criteria, an 84% response rate was recorded at 12 weeks. The majority of the patients, however, experienced only stable disease [partial responce (PR), 4; stable disease (SD), 17; progressive disease (PD), 4)]. These results were supported by Robinson et al. [14] using 10 mg/m^2 doxorubicin, by Fosså et al. [9] using 20 mg/m^2 Adriamycin, and by Burk et al. [4] and Elomaa et al. [7] using 25 mg/m^2 epirubicin, all of whom found a clear improvement in performance status and pain relief. Complications of doxo/epirubicin given on a weekly basis were very few. Myelotoxicity, gastrointestinal complaints, and stomatitis were minimal, and the incidence of alopecia was lower than predicted. However, in contrast to the initial findings of Torti et al. [16], the other authors observed a small number of cardiovascular complications. Later, Torti et al. [17] combined doxorubicin and cisplatin, but the results did not improve as compared with those obtained using doxorubicin alone. Thus, no advantage was found for combination therapy; combinations of cytotoxic drugs have not generally been superior to single-drug regimens, and adverse effects increase when cytotoxic drugs are combined.

MPA and epirubicin in hormone-refractory disease

In an attempt to improve the therapeutic results in hormone-refractory disease, the possibility of combining chemotherapeutic and hormonal regimens has been suggested. Applying this concept in a three-arm study, Tveter et al. [18] randomized 79 patients to receive 280 mg estramustine b.i.d., 20 mg i.v. epirubicin weekly plus 500 mg MPA b.i.d., or 20 mg i.v. epirubicin weekly plus placebo. The patients were evaluated according to the SPCG criteria regarding response. Improvements in pain and performance status were evaluated separately. According to this group of investigators, estramustine had no significant effect on pain or performance status. Epirubicin-treated patients experienced a significant improvement in pain and performance status, and this was more pronounced in patients receiving the MPA-epirubicin combination. In patients treated with MPA-epirubicin a significant prolongation of the time to progression and/or death was also observed. The duration of response was short and the median time to progression or death was 2 months for the estramustine patients, 3 months for the epirubicin + placebo group, and 5 months for the MPA-epirubicin group (Fig. 1).

Our investigative group conducted a similar study comparing the results of estramustine and MPA + epirubicin treatment [1]. We used the higher dose of estramustine recommended by Benson and Gill [2] (12 mg/kg daily) and also 20 mg/m^2 epirubicin i.v. weekly, in contrast to the lower doses used by Tveter et al. [18]. The principal aim of the study was to compare the time to progression between the treatment modalities. The criteria for progression recommended by the SPCG were used. Patients were sequentially allocated to different groups according to grade, stage, and performance status, thereby reducing by 10% the number of patients needed for reliable statistical analysis. A total of 145 patients were evaluated in this 2-arm study. The progression-free period was rather short and the proportion of patients showing no tumor progression after 4, 8, 12, and 16 months was 66%, 17%, 17%, and

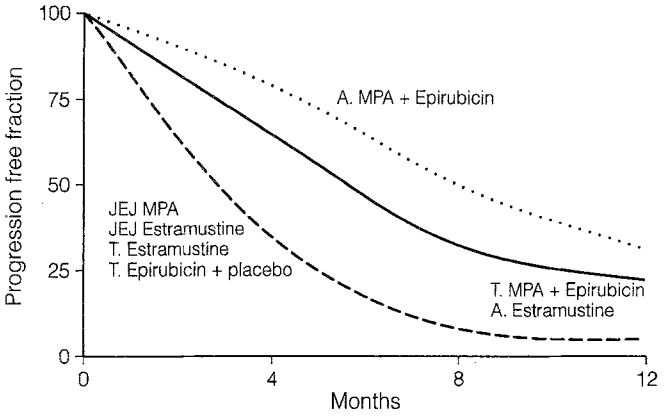

Fig. 1 Time to progression as determined in 3 studies on hormone-refractory prostatic cancer (*JEJ* Johansson et al. [10], *T* Tveter et al. [18], *A* Anderström et al. [1])

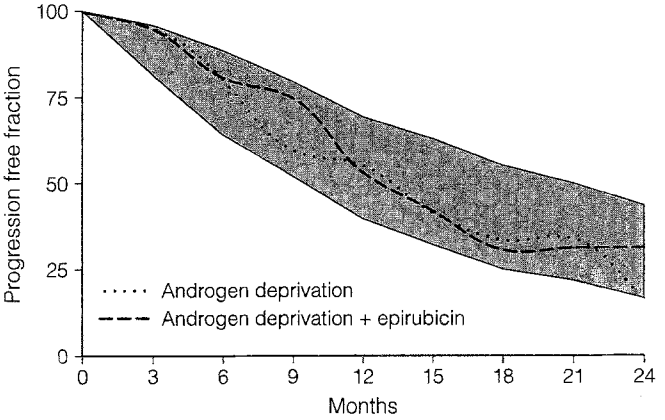

Fig. 2 Time to progression as determined in newly detected metastatic cancer. The results of practically all studies on metastatic prostatic cancer are within the *shaded area*

15%, respectively, in the estramustine-phosphate group and 80%, 49%, 29%, and 18%, respectively, in the MPA-epirubicin group (Fig. 1). The difference in hazard functions was clearly significant ($P = 0.013$, two-sided Gehans test). Our impression was that the MPA-epirubicin-treated patients experienced an improvement in pain and performance status. No difference in survival was detected.

Thus, MPA-epirubicin significantly improved the treatment of patients with hormone-refractory prostatic cancer. These findings are supported by an experimental study by Landström et al. [11], who showed MPA + epirubicin to be significantly more effective in reducing tumor volume in Dunning rats as compared with either drug alone. Side effects occurred rather frequently in our study [1], with 17 MPA + epirubicin-treated patients and 22 estramustine-treated patients experiencing adverse effects. Many of them were of minor significance, but 8 patients in the MPA-epirubicin group experienced heart failure, which was clinically significant in 6 cases. Among the estramustine-treated patients, 9 developed heart failure, which was severe in 2 cases and moderately severe in 4 cases. The risk of cardiotoxicity should not be neglected.

Epirubicin in newly detected advanced prostatic cancer

At our institution we are presently conducting a randomized study comparing castration ± epirubicin given i.v. at 20 mg/m^2 weekly. Patients have been entered in this study over a 2.5-year period, and accrual is ongoing. A preliminary interimistic analysis shows a progression-free interval very similar to that reported by Crawford and Nabors [5] and Denis et al. [6] in advanced prostatic cancer. After 1 year, about 50% of the patients in both groups have progressed. No difference between the hazard functions of the different groups has been observed, but the observation period has thus far been short and the intended number of patients for inclusion has not yet been reached.

An interesting study by Plummer [13] using maximal androgen blockade (MAB) ± epirubicin in 145 patients has been reported. Patients received castration + flutamide ± epirubicin given i.v. at 25 mg/m^2 weekly for 18 weeks. Although this study has not yet been finally reported, it showed significant differences in the response rate and in survival but not in the time to progression using NPCP criteria. From our findings and from the results reported by Plummer [13], it appears possible that epirubicin is more efficient when combined with MPA or MAB, which is in accordance with the experimental results of Landström et al. [11]. Further studies are needed, however, before this suggestion can be confirmed or rejected.

Discussion

During the last 10 years a huge number of drugs and drug combinations have been tested in advanced prostatic cancer. Despite this extensive testing, the results are often contradictory and different clinical studies are difficult to compare due to the different response criteria and different doses used. Furthermore, varying criteria for inclusion have been used.

In advanced prostatic cancer, Crawford and Nabors [5] and Denis et al. [6] have reported a prolongation of both the time to progression and the duration of survival using MAB. The improvement was even more obvious in patients with minimal metastatic disease. In other studies, however, these findings have not been confirmed. Plummer [13] have compared MAP ± epirubicin in similar patients and have found that patients in the combination arm survive longer and that this interesting combination needs further evaluation. However, a comparison of the progression-free survival obtained in these studies with that obtained by Benson and Gill [2], who reported estramustine phosphate to be superior to orchiectomy or DES in D_2 patients, reveals that the progression-free survival curves are very similar in all studies. Also, the preliminary data obtained in our study comparing orchiectomy ± epirubicin are almost identical and fall within the same range (Fig. 2).

The question as to whether any of the treatment regiments suggested is actually superior to the others remains controversial. However, it seems reasonable to apply these therapeutic concepts in patients with minimal metastatic disease. The high costs of such combination therapy will no doubt have a restraining effect on its general application. Combining MPA with androgen deprivation in metastatic cancer does not seem to improve the therapeutic efficacy. In hormone-refractory disease, however, Johansson et al. [10] found MPA to increase significantly the number of remissions as compared with estramustine phosphate. Their impression was that the MPA-treated patients obtained better palliation, and this was also the finding of Fosså et al. [8], who compared MPA with prednisolone treatment. MPA-treated patients had more remissions, obtained better palliation, and experienced an improved performance status and reduced pain. These factors are important in the palliation of patients with hormone-resistant prostatic cancer, whose expected survival is limited. MPA is easy to give orally and produces a limited number of complications that are mainly of minor importance.

In applications of the concept that hormone-insensitive cells are responsible for further tumor progression and death, the use of doxo/epirubicin has resulted in a clear improvement in performance status and pain relief in several nonrandomized studies. These initial reports have later been sustained by prospective randomized studies comparing the effect of epirubicin ± MPA with estramustine phosphate. From the study of Tveter et al. [18] and from our study [1], it is obvious that patients receiving the combination therapy benefit significantly from the treatment and experience an improved performance status, pain relief, and a prolonged time to progression; however, the duration of survival is not prolonged. In our study [1], the progression rates during the 1st year were reduced by 12%–32%. In our opinion the improvement for the MPA-epirubicin-treated patients is of clinical importance. The initiation of this type of treatment earlier in the course of prostatic cancer may prove to be more effective and should be evaluated in clinical studies.

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