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COMBINATION THERAPY WITH FLUTAMIDE AND CASTRATION (LHRH AGONIST OR ORCHIECTOMY) IN ADVANCED PROSTATE CANCER: A MARKED IMPROVEMENT IN RESPONSE AND SURVIVAL

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Summary—Eighty-seven previously untreated patients with clinical stage D2 (bone metastases) prostate cancer have received the combination therapy with a pure antiandrogen and an LHRH agonist (or orchiectomy) as first treatment in a multicentre study for up to 34 months (average = 16.2 months). A positive objective response assessed according to the criteria of the US NPCP has been observed in all cases. Pain disappeared in all patients within 1 month and performance become normal in all (including 2 bedridden patients) within 4 months. Progression of the disease after a period of remission has been observed in only 8 patients. Only one patient has died from prostate cancer while 3 have died from other causes. The probability of continuing response and survival at 2 years for the patients who receive the combination treatment (Kaplan–Meier's method) is 81 and 91%, respectively. By contrast, in the randomized group who had orchiectomy alone, 4 of 7 have died from prostate cancer ($P < 0.05$ as compared to combination therapy). In addition to a marked improvement in the remission rate and survival, combination therapy maintains a good quality of life, hot flashes and a decrease or loss of libido being the only side-effects.

INTRODUCTION

Despite being the second cause of death due to cancer in men [1], carcinoma of the prostate has remained a devastating disease against which medicine has had only limited success. Due to the presence of bone metastases in the majority of patients at the time of diagnosis, the possibility of treatment of the primary tumor by surgery and/or radiotherapy is limited to a small proportion of cases, while, for all others, hormonal therapy and sometimes chemotherapy are the only alternatives [2, 3].

The results of chemotherapy have been disappointing [4]. The most promising advance in the treatment of prostatic cancer has been the demonstration of the role of testicular androgens by Huggins and his colleagues in 1941 [5]. These observations opened a new era in the treatment of this disease and were based on the following straightforward rationale: "In many instances, a malignant prostatic tumor is an overgrowth of adult epithelial cells. All known types of adult prostatic epithelium undergo atrophy when androgenic hormones are greatly reduced in amount or inactivated. Therefore, significant improvement should occur in the clinical condition of patients with far advanced prostate cancer subjected to castration or estrogen administration [6].

Since the reports of Huggins and his colleagues [5, 6], the treatment of advanced prostate cancer has been centered on the inhibition or neutralization of androgens of testicular origin by orchiectomy or the administration of estrogens. Unfortunately, the results obtained in the numerous studies performed since 1941 [4, 7–11] have not met the original expectations. In fact, it is now well recognized that only 60–80% of patients show some remission for a limited time interval following neutralization of testicular androgens, thus leaving 20–40% of patients without any demonstrable improvement in their disease. Moreover, in those who initially respond, relapse of the disease is usually seen within 6 to 24 months [12] and 50% of the patients are then expected to die within the next 6 months [13, 14]. In addition, orchiectomy is often psychologically unacceptable and estrogens cause side effects such as gynecomastia, fluid retention, myocardial ischaemia and thromboembolism [9, 15]. The side effects of the two current forms of hormonal therapy and their questionable influence on survival left most physicians undecided about the real benefits of hormonal therapy. There was thus the clear need for a more efficient and better tolerated therapy.

The unexpected finding that agonists of luteinizing hormone-releasing hormone (LHRH) cause a blockade in testosterone secretion accompanied by a loss in prostate weight in experimental animals [16, 17] offered the possibility of an advantageous replacement for orchiectomy and estrogens for the treatment of prostate cancer. In men, following an initial but transient period of stimulation, testicular serum androgens are reduced to castration levels during chronic treatment with these peptides [17–24]. However, despite the lack of side effects of LHRH agonists, one cannot expect any improvement in

prognosis over the already well known effects of orchiectomy, since the effect of these peptides is limited to the blockage of testicular androgens.

Following detailed animals studies, we have applied the combined treatment with an LHRH agonist (or surgical castration) in association with a pure antiandrogen for the treatment of 87 previously untreated patients having clinical stage D2 (bone metastases) prostate cancer. The duration of treatment extends from 6 to 34 months with an average of 16.2 months. Some patients were also randomly assigned to orchiectomy alone, the entry into this group being stopped when survival became significantly different.

PATIENTS, MATERIALS AND METHODS

From March 1982 to September 1984, 94 patients with histology-proven prostatic adenocarcinoma and bone metastases visualized by bone scintigraphy (stage D2) took part in this multicentre study after written informed consent. The criteria for inclusion and exclusion were those of the US NPCP [14]. Of the 87 previously untreated stage D2 patients who had combination therapy, 77 received the combination treatment with the LHRH agonist [D-Trp^6, des-Gly-NH_2^{10}]LHRH ethylamide (Tryptal) or [D-Ser(TBU)^6, des-Gly-NH_2^{10}]LHRH ethylamide (Buserelin) in association with the pure antiandrogen 2-methyl-*N*-[4-nitro-3-(trifluoromethyl)phenyl]propanamide (Flutamide, Euflex) while 10 had orchiectomy (instead of LHRH agonist) in association with the antiandrogen. No difference in the clinical response was observed between chemical or surgical castration. Twenty patients were originally started randomly with the Flutamide analog, 5,5-dimethyl-3-[4-nitro-3-(trifluoromethyl)phenyl]-2,4-imidazolidione (RU23908, Anandron). However, the occurrence of visual side effects in 70% of the patients receiving Anandron has led to an early change from Anandron to Flutamide and to the almost exclusive use of Flutamide in all patients since June 1983.

The LHRH agonists were injected subcutaneously at the daily dose of 500 μg at 0800 h for 1 month followed by a 250 μg daily dose while Flutamide was given three times daily at 0700, 1500 and 2300 h at the dose of 250 mg orally. The antiandrogen was started one day before first administration of the LHRH agonist or orchiectomy.

During the course of the study, seven patients were randomly assigned to orchiectomy alone. The conditions of entry were the same as described above except that patients had to accept orchiectomy and LHRH agonist treatment. It was agreed at the start that entry into the orchiectomy alone arm would be stopped as soon as a significant difference in survival would be obtained. When a lack of objective response or tumor progression was noted in the orchiectomy-alone patients, treatment with Flutamide was started. All patients were followed to determine survival.

Complete clinical, urological, biochemical and radiological evaluation of the patients was performed before starting treatment as described [24]. The initial evaluation included history, physical examination, bone scan, transrectal and transabdominal ultrasonography of the prostate, ultrasonography of the abdomen, chest roentgenogram and skeletal survey and sometimes computerized axial tomography (CAT) of the abdomen and pelvis as well as excretory urogram (IVP). Performance status and pain were evaluated on a scale of 0–4. The follow-up was as described [24]. The criteria of the U.S. National Prostatic Cancer Project were used for assessment of objective response to treatment [14]. Statistical significance was measured according to the multiple-range test of Duncan–Kramer [25] and the Fisher's exact test [26], when appropriate. All results are shown as the means $\pm$ SEM of duplicate determinations on individual samples. The probability of continuing response and survival was calculated according to Kaplan and Meier [27].

RESULTS

In order to examine in detail the changes in serum testosterone following combined treatment with a pure antiandrogen and an LHRH agonist versus the effect of similar treatment with the anti-androgen in association with orchiectomy, the serum levels of testosterone in each group are illustrated in Figs 1 and 2, respectively. As well illustrated in Fig. 1, the serum concentration of testosterone increased from 4.93 ± 0.35 to 7.42 ± 0.68 ng/ml (151% of control, $P < 0.01$) between days 1 and 4 following the start of treatment with the LHRH agonist. On days 5–10, the serum levels of testosterone were decreased to 5.78 ± 0.51 ng/ml, this value being still at 21% above control ($P < 0.05$). Thereafter, the concentration of serum testosterone decreased to 46% of control on

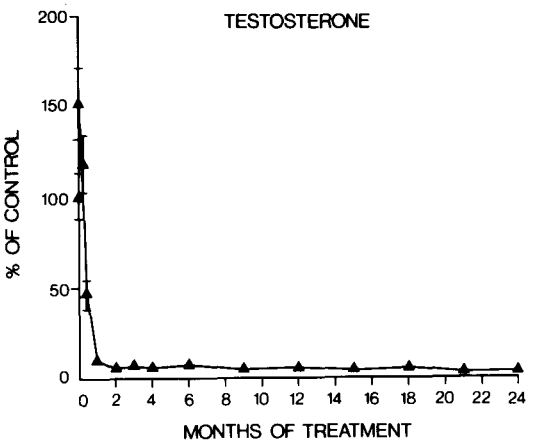

Fig. 1. Changes in serum testosterone in previously untreated patients having clinical stage D2 prostate cancer receiving the combined therapy with a pure antiandrogen and an LHRH agonist. The pretreatment values of serum testosterone were 4.93 ± 0.35 ng/ml (77 patients).

days 11–15 ($P < 0.01$) and to 9.85% of control at 1 month. Thereafter, the concentration of serum testosterone remained inhibited to values ranging between 3.2 and 6.9% of control ($P < 0.01$).

It can be seen in Fig. 2 that following orchiectomy, there was an immediate fall in serum testosterone from 3.37 ± 0.45 to 0.42 ± 0.19 ng/ml on days 1–4 ($P < 0.01$), the first time interval studied. Thereafter, serum concentrations of testosterone remained reduced between 1 and 21 months of treatment to mean concentrations ranging between 0.20 ± 0.13 and 0.40 ± 0.07 ng/ml ($P < 0.01$), these values being between 5.9 and 12% of control.

It was also of great interest to see the rapid decrease in the serum concentration of the four adrenal steroids which act as precursors for the biosynthesis of testosterone and 5α-dihydrotestosterone in the prostate cancer tissue. From basal values of 915 ± 75 ng/ml, the serum concentration of dehydroepiandrosterone sulfate (DHEA-S) is already decreased to 73% of control ($P < 0.05$) between days 1 and 4 of treatment and reaches 61% at 1 month ($P < 0.01$). Thereafter, the mean concentration of circulating DHEA-S remains at 60% of control or lower ($P < 0.01$).

The serum levels of dehydroepiandrosterone (DHEA) follow a pattern almost superimposable to that of DHEAS. In fact, from basal values of 2.18 ± 0.17 ng/ml, the concentration of serum DHEA decreases progressively to reach 63% of control after one month of treatment ($P < 0.01$). Thereafter, the concentration of DHEA remains approximately constant at mean values ranging between 46 and 67% of control ($P < 0.01$).

An even more striking inhibitory effect is observed on the serum concentration of androst-5-ene, 3β,17β-diol (Δ^5-diol) [Fig. 3]. From basal values of 0.59 ± 0.07 ng/ml, the serum concentration of this adrenal steroid decreases to 44% of control at 1 month ($P < 0.01$). Thereafter, the mean serum concentration of Δ^5-diol remains at values ranging between 36 and 50% of control ($P < 0.01$) during most of the treatment period. The serum levels of androstenedione (Δ^4-dione) follow a similar pattern (data not shown). It is of great interest to see that the serum concentration of cortisol remains constant during the whole period of combined antihormonal treatment, the pretreatment value being 184 ± 6.65 ng/ml. During the whole course of treatment, the mean values vary only between 170 ± 7.10 and 215 ± 11.9 ng/ml.

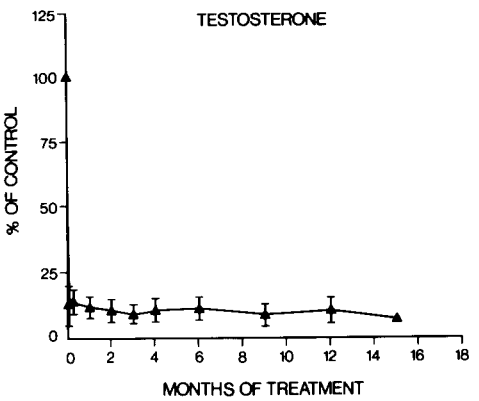

Fig. 2. Changes in serum testosterone in previously untreated patients having clinical stage D2 prostate cancer receiving the combined therapy with a pure antiandrogen and orchiectomy. The pretreatment values of serum testosterone were 3.37 ± 0.45 ng/ml (10 patients).

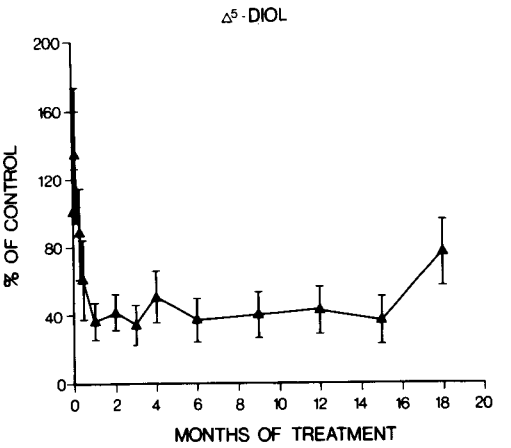

Fig. 3. Changes in serum Δ^5-diol in previously untreated patients having clinical stage D2 prostate cancer receiving the combined therapy with a pure antiandrogen in association with orchiectomy or an LHRH agonist. The pretreatment values of serum Δ^5-diol were 0.59 ± 0.07 ng/ml (15 patients).

Starting in March 1982, 87 previously untreated patients with histology-proven prostatic carcinoma and bone metastases identified by bone scan and X-ray received the combined treatment for more than 6 months as first therapy. Only 1 patient was excluded from evaluation (interruption of treatment). Pain was present in 52 patients, the pain being moderate in 24% [21] and severe requiring antalgic positions or movements in 25% of them [22]. Seven patients (8%) had pain requiring the use of a wheel chair for their displacement and 2 patients were totally bedridden. The pain subsided completely in all cases during the first month of treatment.

Almost all patients displayed at various levels prostatism which was improved during the first 2 months of treatment. The rectal examination revealed an enlarged and a hard prostate in 85% of the patients. In all of them, the volume of the gland regressed and its consistency improved to become small and soft during the first 6 months.

Of the 87 patients, 50.6% [44] had a normal activity. Twenty-three patients (26%) were symptomatic but ambulatory while 11 patients (12.6%) stayed in bed for less than 50% of the time and 7 (8%) stayed in bed more than 50% of the time, 2 of them being totally bedridden. The performance returned to normal in 64, 88, 96 and 100% of the patients after 1,

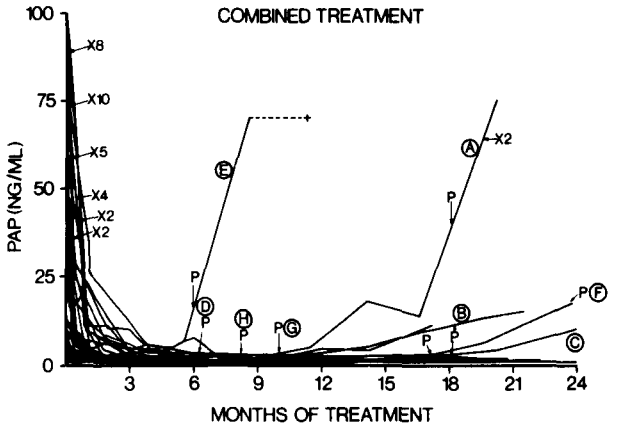

Fig. 4. Effect of combined antihormonal treatment on serum prostatic acid phosphatase (PAP) levels in previously untreated patients having clinical stage D2 prostate cancer. In a group of 87 patients, 77 (88.5%) had serum PAP levels above 2.0 ng/ml at the start of treatment. P indicates time of objective progression of the disease by bone scan and/or ultrasonography for local progression at the prostatic level. × indicates that the value shown should be multiplied by the indicated number while + indicates time of death. The circled letter identifies the patient.

2, 3 and 4 months of treatment, respectively. The 2 patients who were bedridden became ambulatory after 2 months of treatment.

Figure 4 illustrates the changes in serum prostatic acid phosphatase (PAP) levels following the start of combination antihormonal treatment. The serum levels of PAP were initially elevated in 77 of the patients (88.5%), the values ranging between 1.0 and 896 ng/ml, the normal being <2.0 ng/ml. In all cases, the start of treatment was followed by an extremely rapid fall in serum PAP, a decrease to 41 and 24% of control being already reached on days 1 to 4 and 5 to 10 ($P < 0.01$) after the start of treatment, respectively. In patients treated for 6 and 9 months, serum PAP values had returned to normal in 90 and 95% of the cases, respectively. Following remission, an elevation in serum PAP levels has so far been observed in only 6 of the 87 patients.

Bone scintigraphy performed 4–6 months after the start of treatment was an absolute requirement for inclusion of the patients in one of the categories of objective responses. An example of the changes in bone scintigraphy in a patient who showed a complete response at 6 months of treatment is illustrated in Fig. 5. Although serum PAP levels have decreased to normal in 17 of the 19 cases last included into the study before 4 months of treatment, follow-up bone scintigraphy was not yet available for these 19 patients who could not be included as evaluable responders in Table 1. It can be seen in this table that with an average duration of treatment of 16.2 months (from 6 to 34), 16 of 67 patients (24%) have already shown a complete response with normalization of the bone scan, serum PAP as well as disappearance of any clinical symptom or sign of prostate cancer. Twenty-eight patients (42%) have shown a partial response with a decrease by more than 50% in the number of increased areas of uptake at bone scintigraphy and a return to normal of serum PAP in all cases. The remaining 23 patients (34%) have shown an improvement or stabilisation of their disease confirmed by bone scan (Table 1A). Of all the patients who received the combination therapy at start of treatment, only 8 have shown progression of the disease after remission and only 1 has died from prostate cancer. In at least 2 of these patients, a lack of compliance could be documented.

Figure 6 illustrates the probability of continuing response in the group of 87 patients who received the combined treatment as first therapy. Quite remarkably, the probability of having a continuing positive response at 2 years (calculated according to Kaplan and Meier[27]) is 81%.

As mentioned earlier, it was felt important to

Table 1. Comparison of the response to orchiectomy alone and to the combined antihormonal treatment in newly diagnosed patients with clinical stage D2 prostate cancer (the criteria of objective response of the U.S. National Prostatic Cancer Project (NPCP) were used)

Month of treatment mean (limits)	Number of patients	Objective response				Relapse (previous responses)	Deaths from prostate cancer	Deaths from other causes
		Complete	Partial	Stable	Progression			
A. Combined treatment								
16.2 (6–34)	67	16 (24%)	28 (42%)	23 (34%)	0 0%	8 (11.9%)	1 (1.5%)	3 (4.5%)
B. Orchiectomy alone								
19 (12–29)	7	0	1 (14%)	3 (43%)	3 (43%)	4 (100%)	4 (57%)	0

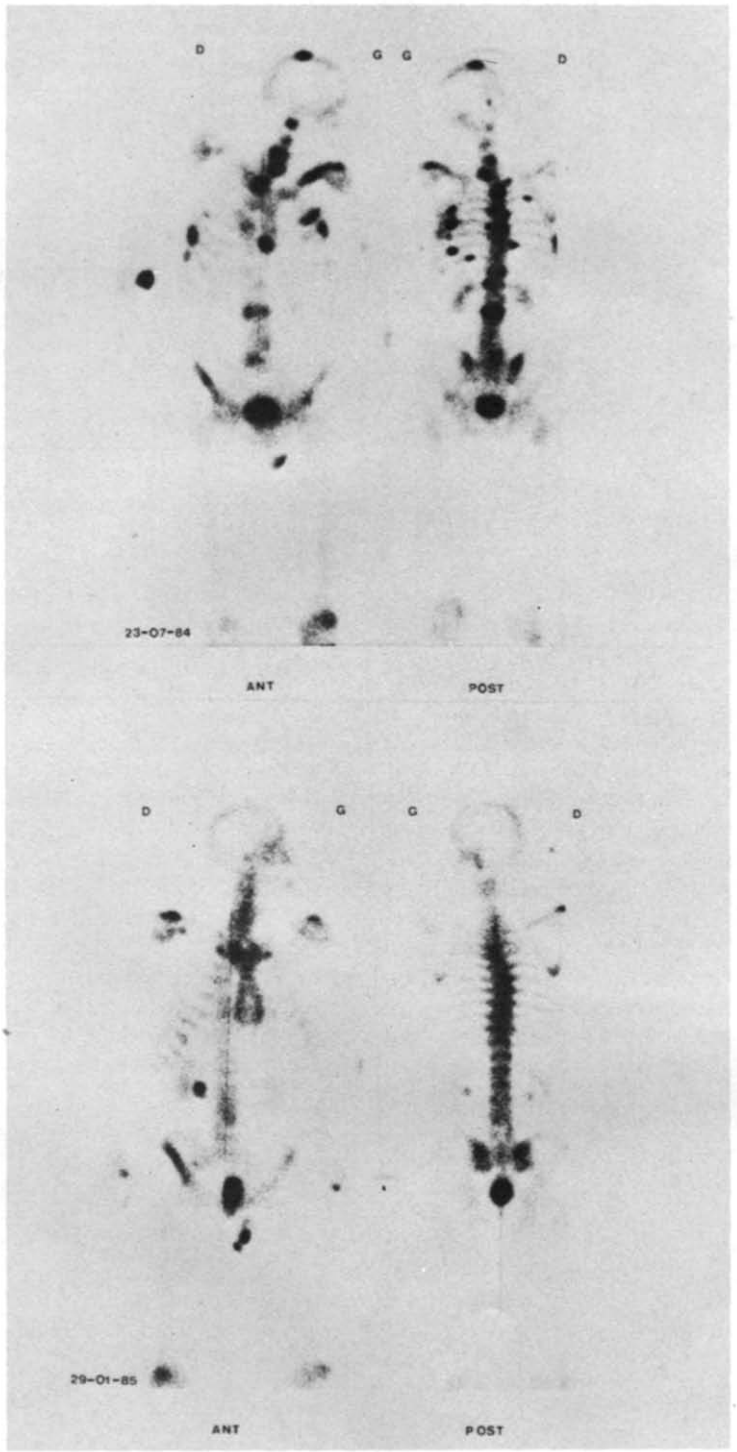

Fig. 5. Bone scans with ^{99m}Tc-labelled methylene diphosphonate of patient treated with the pure antiandrogen Flutamide and the LHRH agonist [D-Trp^6]des-Gly-NH_2^{10}]LHRH ethylamide. (A) Before treatment on July 23rd, 1984, showing disseminated bone metastases; (B); January 29th, 1985, 6 months after the start of combined antihormonal therapy. Note the disappearance of all areas of increased uptake.

include a randomized group of patients with orchiectomy alone before such a randomized study became ethically unacceptable due to the evidence of a higher risk in the group receiving no antiandrogen. Such a study should eliminate any potential bias related to our population of patients. The finding of a rate of response to orchiectomy similar to the previous studies would then permit a comparison of

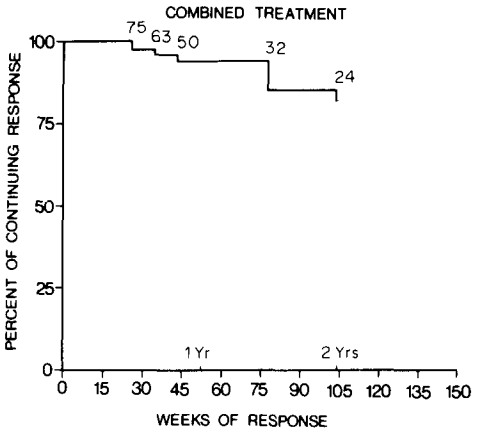

Fig. 6. Probability of continuing positive response following combined antihormonal therapy in previously untreated patients having clinical stage D2 prostate cancer (calculated according to Kaplan and Meier for 87 patients).

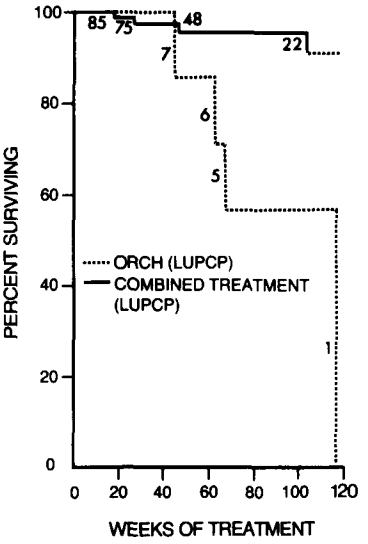

Fig. 8. Comparison of the probability of survival (Kaplan–Meier method) following orchiectomy alone and combination therapy in previously untreated patients having clinical stage D2 prostate cancer. Entry into the orchiectomy group was stopped when the difference became significant at 18 months with 3 out of 7 patients having died from their cancer ($P < 0.05$).

the effect of combination treatment with the numerous previous and contemporary studies on the effect of orchiectomy and estrogens alone.

The changes in serum PAP levels in the group of patients who had orchiectomy alone are shown in Fig. 7. In the 4 patients who had serum PAP levels above 10 ng/ml at the start of treatment (43, 575, 35 and 20 ng/ml), (patients nos 2, 3, 4 and 5, respectively), a progressive but relatively slow decrease was seen during the first 11 months. The serum PAP values did however remain above normal in all these 4 cases. Of the 3 patients who had slightly elevated serum PAP levels (below 10 ng/ml) at the start of treatment, the concentration of serum PAP temporarily decreased to normal in 2 cases.

The most dramatic but expected finding in this study of the effect of orchiectomy alone is that 4 out of the 7 patients have already died from their cancer at 11.5, 16, 17 and 29 months respectively, while the 3 remaining patients show progression of the disease. The objective response following orchiectomy alone is summarized in Table 1B. Comparison of the probability of survival following orchiectomy alone and the combination therapy is illustrated (according to Kaplan–Meier method) in Fig. 8.

At each visit, the patients answered a detailed questionnaire concerning any possible symptom or sign of intolerance to the drugs. Hot flashes were

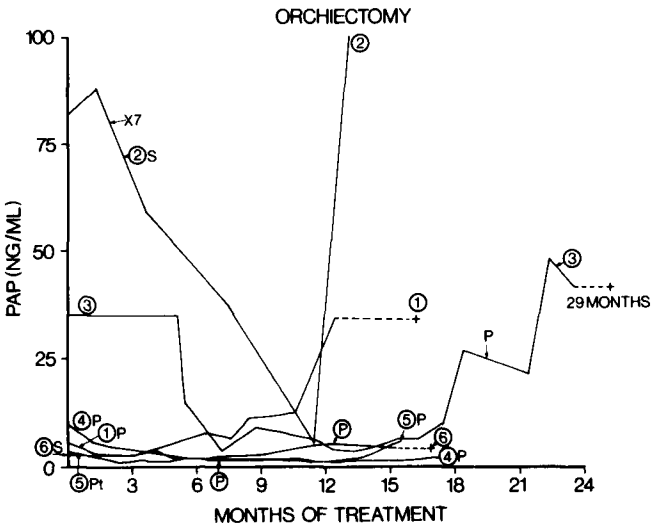

Fig. 7. Effect of orchiectomy alone on serum PAP levels in previously untreated patients having clinical stage D2 prostate cancer. P indicates objective progression of the disease, Pt means partial response, S indicates stable disease while + indicates time of death. × indicates that the value shown should be multiplied by the following number. Circled numbers are for patient identification.

described spontaneously by the patients in approx 50% of the cases after 1–3 months of treatment. Usually, the severity of the hot flashes decreased with time and disappeared within 2 years. A decrease or loss of libido was observed in approx 75% of patients. However, it should be mentioned that in 25% of the patients, libido and potency are maintained.

A side-effect not related to the neutralization of androgens is that approx 70% of patients treated with Anandron showed a delay to obtain good vision when coming from a bright area. While the upper limit of normal of the photostress test in patients of that age is 1 minute, the delay observed in some patients treated with Anandron was increased up to 25 min. However, upon cessation of Anandron treatment and change to Flutamide, those symptoms rapidly disappeared in all cases.

DISCUSSION

The use of a pure antiandrogen at the start of treatment eliminates the unnecessary risks of disease flare which are known to occur in a significant proportion of patients treated with an agonist alone [28, 29]. It seems obvious that exposure of the tumor cells to supraphysiological levels of androgens represents an increased stimulus for the tumor to grow and to metastasize. The present data clearly show that the pure antiandrogen permits to take advantage of the well tolerated LHRH agonists as substitutes for orchiectomy and estrogens by eliminating the risk of disease flare [30].

Since the present study has rigorously applied the criteria of the US NPCP [14] for determining the rate of objective response, the results can be confidently compared with those obtained in study 500 of the NPCP [4] as well as with those more recently reported by the Leuprolide Study Group [29]. In addition, the present results observed following orchiectomy alone are in agreement with all the data previously obtained by the groups who studied the effects of orchiectomy or estrogens [4, 8, 10, 11, 29].

Combined androgen blockade at the start of treatment in previously untreated stage D2 patients has led, so far, to a more than 95% positive objective response as compared to 81% following DES or orchiectomy in the NPCP-500 trial [4]. Initial response rates of 86 and 85% have been obtained with Leuprolide and DES alone, respectively, in the recent study of the Leuprolide Study Group [29]. In addition to the improved percentage of positive responses at the start of treatment, another most important aspect of the effect of the combination treatment is the marked increase in the duration of the positive response. With an average of 16.2 months of treatment, progression has been seen in only 8 patients or in 9.2% of the cases. In study-500 of the NPCP, only 40% of the patients were in remission after 18 months of treatment [4], thus indicating progression or relapse of the cancer in 60% of the patients as compared to 12% in the present study (Fig. 9).

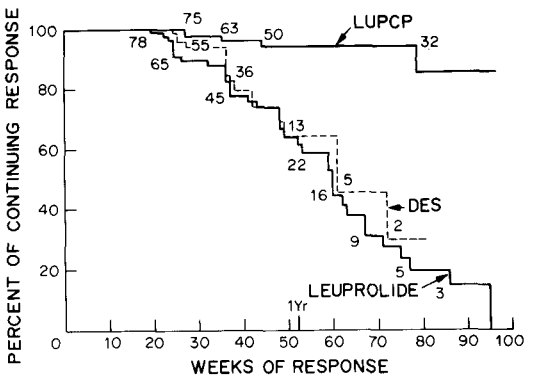

Fig. 9. Comparison of the probability of continuing response following combination therapy and the administration of Leuprolide alone [29] or DES [29].

While the percentage of patients still in remission at 2 years is 81% with the combination therapy, it has already decreased to 0% with Leuprolide at 22 months and to only 30% at 18 months with DES [24] (Fig. 9). There is thus a remarkable advantage of the combination therapy, not only on the percentage of initial responses, but ever more strikingly, upon the duration of the positive response.

The most impressive result is however that observed on survival and quality of life. In fact, only one patient has died from prostate cancer while 3 have died from other causes. When considering the group of 25 patients who have been in the study for at least 2 years, the global death rate is decreased to 9% as compared to values of 40–54% following medical or surgical castration. A contemporary study with Buserelin alone has shown a death rate of 81% at 2 years [31].

A most important conclusion of this study is that previously untreated prostate cancer, even at the metastatic stage, is exquisitely sensitive to androgens. These data clearly support the direct measurements of DHT in prostatic cancer tissue [32] which indicate that following DES or orchiectomy, a significant amount of androgens are left.

The most likely explanation for the difference between the present results and those of previous studies is that previous hormonal therapy was limited to the neutralization of androgens of testicular origin by surgical castration and/or estrogens while the present approach achieves more complete blockade of androgens of both testicular and adrenal origin at the start of treatment. A large number of reports have shown that neutralization of adrenal androgens has beneficial effects on prostate cancer [33]. However, in the past, medical or surgical adrenalectomy or hypophysectomy was never performed as a first approach in combination with blockade of testicular androgens. The neutralization of adrenal androgens was always achieved as a second step following the lack of response to castration or when relapse of the disease had occurred after a period of remission [33].

An unexpected but most important additional

benefit of combined antiandrogen treatment is that it inhibits by approx 50% the serum levels of adrenal steroids responsible for the formation of active androgens in prostatic cancer tissue, especially dehydroepiandrosterone (DHEA), DHEA-sulfate (DHEA-S), androstenedione and androst-5-ene-3β,17β-diol. This approx 50% decrease in the serum levels of precursor steroids should lead to a similar decrease in the level of active androgens in the prostatic cancer, thus decreasing the stimulatory androgenic influence on cancer growth. This 50% decrease in local androgens should facilitate the inhibitory action of the antiandrogen. It is thus quite remarkable that the combination treatment, in addition to completely blocking testicular androgen secretion as well as the peripheral action of androgens, can also achieve a partial medical adrenalectomy limited to androgen precursors and not affecting the secretion of cortisol. In order to minimize the development of androgen-sensitive tumors which are induced by the low androgen levels remaining in the prostate following castration alone [33], it is suggested that the future in the treatment of prostate cancer should aim at a complete blockade of the secretion and/or action of androgens of both testicular and adrenal origin at the start of treatment.

Although more complete inhibition of androgens remains a possibility, the results obtained using the combined use of an LHRH agonist and a pure antiandrogen already show marked advantages over previous therapies limited to partial neutralization of androgens. It is also hoped that the present principles of complete hormonal blockade at the start of treatment could be rapidly applied to other hormone-sensitive cancers, especially breast cancer.

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