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Combination Therapy with Flutamide and [D-Trp^6]LHRH Ethylamide for Stage C Prostatic Carcinoma

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Abstract—*Sixty-seven previously untreated patients presenting with clinical stage C prostatic carcinoma with no evidence of distant metastases received combination therapy using the antiandrogen Flutamide and the LRHH agonist [D-Trp^6]LHRH ethylamide for an average duration of treatment of* 23.5 *months. Only five patients have so far shown treatment failure with* 91.8% *of the patients still in remission at* 2 *years. Three patients have died from prostate cancer while three have died from other causes,* 93.5% *of the patients being alive at* 2 *years. Local control was achieved rapidly in all except one patient. Urinary obstruction and hydronephrosis were corrected in all cases. When comparing to recent data obtained after single endocrine therapy (orchiectomy or estrogens), or radiotherapy, the rate of treatment failure at* 2 *years is* 3.5*-fold lower after combination therapy* (8.2%) *than monotherapy* (28.4%). *The death rate at* 2 *years following start of the combination therapy is* 6.5% *while it is on average* 22.2% (3.4*-fold higher*) *in the studies using monotherapy (orchiectomy or estrogens) or radiotherapy. The present data suggest that treatment of prostate cancer with combination therapy before clinical evidence of dissemination of the disease permits a better response which is possibly explained, at least in part, by the lower degree of dedifferentiation and heterogeneity of the tumors.*

INTRODUCTION

FORTY to 50% of patients initially evaluated for prostate cancer present with stage C disease [1–3]. The therapeutical approaches proposed for these patients have been radiotherapy, radical surgery and immediate or delayed androgen deprivation (orchiectomy or estrogens).

Since it is likely that delaying treatment of prostate cancer permits further tumor cell dedifferentiation and the development of greater tumor heterogeneity [4, 5], we have studied the effect of combined antihormonal therapy using the antiandrogen Flutamide and the LHRH agonist [D-Trp^6]LHRH ethylamide in 70 previously untreated patients presenting with clinical stage C prostate cancer. Comparison is made with the results recently published using the conventional approaches.

PATIENTS AND METHODS

Since September 1982, 70 men with histology-proven adenocarcinoma of the prostate were entered into this study after written informed consent. Average age at entry in the study was 69 years (from 48 to 88 years) with a median follow-up of 666 days (62–1466). Complete clinical, urological, biochemical and radiological evaluation of the patients was performed before starting treatment as described [6]. The initial evaluation included history, physical examination, bone scan, transrectal and transabdominal ultrasonography of the prostate, ultrasonography of the abdomen, chest roentgenogram, skeletal survey and sometimes computerized axial tomography (CT scan) of the abdomen and pelvis as well as intravenous pyelography (IVP) and pedal lymphography. The follow-up was performed at 1, 3, 6 months and then every 6th month as described [6].The last evaluation included in this report was performed on August 1986.

In this group of patients, three (4.2%) stopped therapy on their own before first evaluation at 3 months. Sixty-seven patients could thus be evaluated for their response to combination therapy with the LHRH agonist [D-Trp^6,des-Gly-NH$_2$^{10}]LHRH ethylamide in association with the pure antiandro-

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Table 1. Demographic data and baseline profile of the 70 stage C patients

Differentiation	No. of patients	PAP ≥ 2 ng/ml	Hydronephrosis	Urinary obstruction
Well	22	12	1	0
Moderately	27	14	2	0
Poorly	19	13	5	3
Anaplastic	2	1	0	0

gen 2-methyl-N-[4-nitro-3-trifluoromethyl)phenyl] propanimide (Flutamide, Euflex, Eulexin). The LHRH agonist was injected subcutaneously at a 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 a dose of 250 mg orally. The antiandrogen was started 1 day before first administration of the LHRH agonist. Our recent data about the rapidity of changes of sensitivity of androgen-sensitive tumor cells to androgens [5] indicate that, in the future, the first pill or tablet of the antiandrogen should be given 2 h before first injection of the LHRH agonist or surgical castration.

Thirty-nine (55.7%) patients had a needle biopsy while the diagnosis was made after transurethral resection (TURP) in the 31 (44.3%) other patients. At histology, 22 (31.4%) were graded as having well, 27 (38.6%) moderately well, 19 (27.1%) poorly differentiated and two (2.9%) anaplastic disease. The stage of each tumor was assessed by rectal examination according to Whitmore's staging system [1]. Local extension was classified as stage C tumor in all patients before starting the combination therapy. Six (14.7%) patients had negative exploratory lymphadenectomy. Lymphangiograms and staging regional lymphadenectomy were not performed routinely. Hydronephrosis was found in eight (11.4%) patients and low urinary tract obstruction was present in three (4.3%) of them. Regional lymph nodes were detected in four (5.7%) patients by routine transabdominal ultrasonography. In these four patients, the presence of pelvic lymph node enlargement was confirmed by pedal lymphography or computerized axial tomography or both. All patients had negative isotopic bone scan and skeletal bone survey. Serum prostatic acid phosphatase measured by RIA was elevated in 40 (57.1%) patients (Table 1), thus representing a greater risk [7]. External radiotherapy to the prostate had been performed in six (8.6%) patients, but all were showing local progression at the start of combination therapy. Treatment failure was defined as described by Paulson *et al.* [3]: appearance of a positive bone scan and/or elevation of serum prostatic acid phosphatase on two consecutive follow-up visits and/or appearance of parenchymal or soft tissue extension and/or appearance of groin or supraclavicular adenopathy.

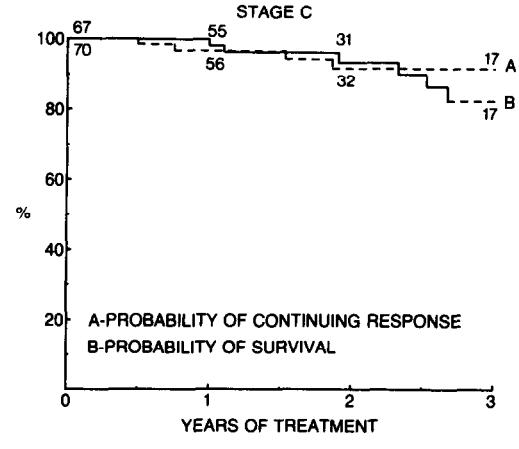

Fig. 1. Probabilities of continuing response (A) and survival (B) in patients with clinical stage C prostate cancer who received combination therapy with Flutamide in association with the LHRH agonist [D-*Trp*^{6}]*LHRH ethylamide.*

Of the sixty-seven patients evaluated in this study, six (8.6%) decided on their own to stop therapy while they were responding. They were then removed from further evaluation. LH (luteinizing hormone), FSH (follicle-stimulating hormone) and PRL (prolactin) were measured by radioimmunoassay as described [6, 8, 9]. Testosterone (T), dihydrotestosterone (DHT), dehydroepiandrosterone (DHEA), DHEA-sulphate (DHEA-S), androst-5-ene-3β,17β-diol (Δ^5-diol) and androstenedione (Δ^4-dione) were measured by radioimmunoassay as described [9, 10] after separation on LH-20 columns. Radioimmunoassay data were analyzed using a program based on model II of Rodbard and Lewald [11]. Statistical significance was measured according to the multiple-range test of Duncan–Kramer [12]. The probabilities of continuing response and survival were calculated according to Kaplan and Meier [13].

RESULTS

As shown in Fig. 1, all except one evaluable patients have shown a positive response to the treatment. Moreover, only five patients have shown progression or treatment failure to the combination therapy after an average treatment period of 714 days (Fig. 1). Details of demographic data and

Table 2. Demographic data and baseline profiles of the five patients who have shown treatment failure

Age	Differentiation	PAP ≥2 ng/ml	Hydronephrosis	Urinary obstruction	Duration of response (days)	Signs of relapse
83	Moderately well	1	0	0	1120	Bone metastasis + PAP
70	Well	0	0	0	556	Bone metastasis
65	Moderately well	1	0	0	677	Enlarged prostate + PAP
71	Poorly	1	1	1	273	Loco-regional involvement + PAP
88	Poorly	1	1	1	0	Bone metastasis + PAP

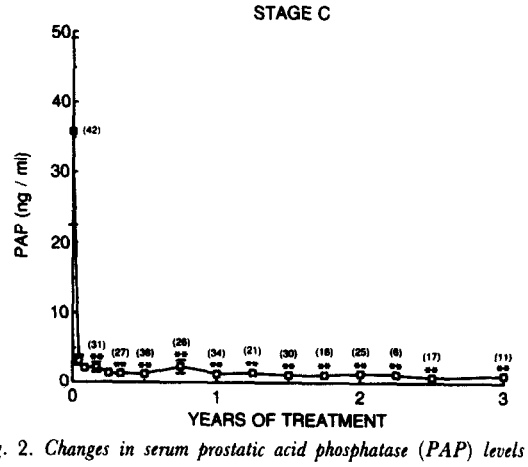

Fig. 2. Changes in serum prostatic acid phosphatase (PAP) levels in patients with clinical stage C prostatic cancer treated with combination therapy using Flutamide and the LHRH agonist [D-Trp⁶]LHRH ethylaminide.

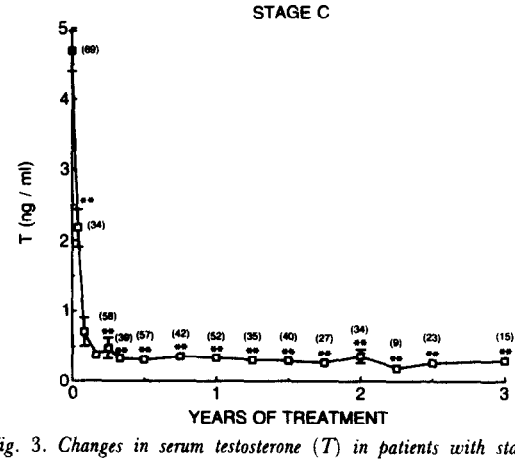

Fig. 3. Changes in serum testosterone (T) in patients with stage C prostatic cancer treated with combination therapy using Flutamide and the LHRH agonist [D-Trp⁶]LHRH ethylamide.

baseline profile of the five patients who had treatment failure are shown in Table 2. The evolution of survival in the same group of patients is illustrated in Fig. 1. The calculated survival rate is 98.2% and 93.7% at 1 and 2 years, respectively. Three patients died from prostate cancer while three died from other causes (myocardial infarct, pneumonia and suicide). All three patients had been examined at our Prostate Cancer Clinic within 6 months of death and had been found to be clinically free of disease.

As illustrated in Fig. 2, serum prostatic acid phosphatase which was elevated in 40 patients before starting treatment became normal in 44, 59, 91 and 96% of them, at respectively 1, 2, 3 and 6 months after the beginning of combination therapy. In all except one patient, the volume of the prostate rapidly regressed and its consistency became normal during the first 9 months of treatment at rectal examination. These changes were confirmed by ultrasonography of the prostate in most patients. The low urinary tract obstruction present in three patients was corrected by treatment in all cases. In all these patients, the transurethral catheter could be removed less than 21 days after the beginning of combination therapy. Hydronephrosis originally present in eight patients disappeared in all of them before 6 months of therapy.

The serum concentration of testosterone (T) decreased from 4.5 ± 0.2 to 0.6 ± 0.1 ng/ml one month after starting combination therapy ($P \leq 0.01$). Thereafter, serum testosterone remained at castration levels (Table 3, Fig. 3). A similar decrease in serum 5α-dihydrotestosterone was seen in these patients (from 0.7 ± 0.1 to 0.1 ± 0.01 ng/ml) ($P \leq 0.01$) (data not shown). Serum luteinizing hormone (LH) concentrations measured by radioimmunoassay decreased to approx. 50% of the control value at 1 month to approx. 35% of control between 4 and 36 months

Table 3. Effect of combination therapy on serum levels of pituitary, testicular and adrenal hormones (ng/ml)

Hormone	Months of treatment 0	1	2	3	4	6	9	12
	(ng/ml)							
LH	108 ± 6.0	52 ± 1.1	48 ± 3.0	43 ± 2	40 ± 5	43 ± 4	36 ± 4	44 ± 5.0
FSH	663 ± 57.0	171 ± 10	252 ± 30.0	238 ± 13.0	317 ± 57	332 ± 50	312 ± 44	363 ± 59.0
PRL	10.6 ± 0.5	10.8 ± 0.5	10.8 ± 0.5	11.5 ± 1.0	10.7 ± 0.6	10.6 ± 0.5	11.0 ± 0.6	11.4 ± 0.9
T	4.5 ± 0.2	0.64 ± 0.14	0.53 ± 0.13	0.41 ± 0.07	0.35 ± 0.06	0.27 ± 0.02	0.32 ± 0.03	0.30 ± 0.03
DHT	0.73 ± 0.14	0.14 ± 0.02	0.11 ± 0.03	0.11 ± 0.02	0.11 ± 0.02	0.15 ± 0.05	0.14 ± 0.04	0.07 ± 0.01
DHEA-S	852 ± 83.0	543 ± 77.0	614 ± 101	627 ± 106	599 ± 98	650 ± 110	762 ± 127	783 ± 139
DHEA	2.3 ± 0.2	1.5 ± 0.3	1.5 ± 0.3	1.2 ± 0.2	1.2 ± 0.1	1.6 ± 0.3	1.7 ± 0.3	1.7 ± 0.3
Δ^5-diol	0.66 ± 0.10	0.30 ± 0.05	0.31 ± 0.07	0.38 ± 0.06	0.30 ± 0.05	0.25 ± 0.05	0.33 ± 0.07	0.26 ± 0.04
Δ^4-dione	0.84 ± 0.11	0.42 ± 0.07	0.36 ± 0.08	0.34 ± 0.06	0.35 ± 0.05	0.35 ± 0.07	0.39 ± 0.07	0.33 ± 0.06
E_2(pg/ml)	23.2 ± 2.8	6.9 ± 1.2	6.3 ± 1.1	5.8 ± 1.0	7.5 ± 1.2	8.1 ± 1.5	11. ± 2.3	10.5 ± 1.3
Cortisol	182 ± 8.0	190 ± 6.0	190 ± 7.0	179 ± 6.0	190 ± 6.0	203 ± 7.0	209 ± 6.0	206 ± 9.0

Hormone	Months of treatment 15	18	21	24	27	30	33	36
	(ng/ml)							
LH	37 ± 4.0	43 ± 5.0	36 ± 2.0	35 ± 2.0	35 ± 2.0	32 ± 2.0	34 ± 5.0	36 ± 2.0
FSH	330 ± 58	372 ± 63.0	274 ± 25	269 ± 26	255 ± 26	223 ± 17	208 ± 42	213 ± 18
PRL	11.0 ± 0.9	11.3 ± 1.2	11.8 ± 0.6	10.8 ± 0.8	10.7 ± 1.8	10.0 ± 1.2	16.9 ± 7.6	9.7 ± 0.8
T	0.30 ± 0.03	0.26 ± 0.02	0.39 ± 0.09	0.39 ± 0.09	0.24 ± 0.03	0.30 ± 0.04	0.26 ± 0.03	0.40 ± 0.27
DHT	0.14 ± 0.03	0.17 ± 0.03	0.17 ± 0.03	0.13 ± 0.02	0.2 ± 0.05	0.20 ± 0.10	0.07 ± 0.01	0.11 ± 0.02
DHEA-S	669 ± 177	663 ± 229	548 ± 171	370 ± 94	350 ± 69	424 ± 117	371 ± 88	365 ± 119
DHEA	1.5 ± 0.3	1.4 ± 0.5	1.5 ± 0.5	1.6 ± 0.6	1.4 ± 0.2	1.7 ± 0.5	1.8 ± 0.4	0.9 ± 0.1
Δ^5-diol	0.39 ± 0.1	0.46 ± 0.08	0.37 ± 0.04	0.43 ± 0.06	0.39 ± 0.09	0.4 ± 0.09	0.2 ± 0.01	0.3 ± 0.7
Δ^4-dione	0.33 ± 0.05	0.41 ± 0.05	0.36 ± 0.05	0.48 ± 0.05	0.70 ± 0.16	0.60 ± 0.12	0.75 ± 0.2	0.51 ± 0.86
E_2(pg/ml)	14.3 ± 2.5	16.7 ± 3.3	11.0 ± 1.4	14.1 ± 2.0	19.0 ± 7.3	16.8 ± 3.3	11.0 ± 1.6	17.1 ± 7.0
Cortisol	206 ± 8.0	210 ± 7.0	206 ± 8.0	213 ± 10.0	194 ± 5.0	198 ± 10.0	181 ± 14.0	209 ± 16.0

of treatment. Follicle-stimulating hormone (FSH) serum levels rapidly decreased by 75% from 663 ± 57 to 171 ± 10 ng/ml 1 month after starting the combined administration of [D-Trp^6]LHRH ethylamide and Flutamide ($P \leq 0.01$). There was then a slight rise to 55% of the control value at 18 months, this rise being followed by a return to a low value at 30% of control after 36 months of treatment. Serum prolactin, on the other hand, remained unchanged throughout the 36-month period.

It is of interest to see that the serum concentration of estradiol (E_2) is markedly decreased during the combination therapy instead of being enhanced as reported when Flutamide was given alone [14]. The adrenal androgen precursors dehydroepiandrosterone (DHEA), DHEA-sulphate (DHEA-S), androst-5-ene-3β,17β-diol (Δ^5-diol) and androstenedione (Δ^4-dione) are lowered from 2.3 ± 0.2, 852 ± 84, 0.7 ± 0.1 and 0.8 ± 0.1 ng/ml to respectively 1.5 ± 0.3 (65%), 544 ± 77 (64%), 0.3 ± 0.1 (43%) and 0.4 ± 0.1 (50%) ng/ml after 1 month of therapy. Thereafter, the serum concentration of all four adrenal steroids remained at similar low values.

At each visit, the patients answered a detailed questionnaire concerning any possible symptom or sign of intolerance to the drugs as well as measurement of hematology and biochemistry parameters as mentioned under Patients and Methods. Hematocrit and hemoglobin values decreased by 8.3 ± 1.5 and 7.7 ± 1.5% at 12 months of treatment ($P \leq 0.01$) and remained stable thereafter. In connection with this observation, it might be relevant to recall that androgens stimulate erythropoiesis in animals and man [15, 16]. Therefore, the hypoandrogenicity induced by the treatment might well be responsible for the lowering of hematocrit and hemoglobin levels. Platelet as well as white blood counts remained normal.

Concerning the biochemical evaluation (SMA-18), serum uric acid levels significantly ($P \leq 0.05$) decreased by 20 and 25% after respectively 12 and 36 months of treatment. There was a tendency for an initial increase in the serum levels of SGOT, LDH, γ-glutamyl transferase and SGPT which remained within the normal range except in seven patients. In all cases, the values remained within 50% of the upper value of the normal range. All values were normal at 6 months and thereafter. All other biochemical parameters remained normal.

Hot flushes and a decrease or loss of sexual potency and libido were observed in respectively 80 and 75% of the patients. Less than 5% of patients complained of loose bowel movement or diarrhea during the first months of treatment, none of them requiring arrest of therapy. Dyspepsia was also observed in a few patients (≤3%). This symptom was relieved when the antiandrogen was taken concomitantly with food.

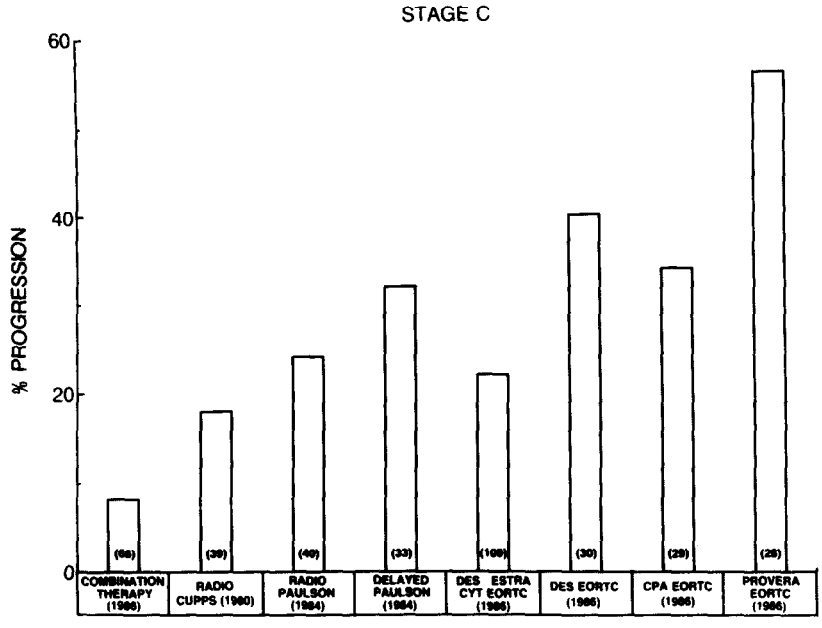

Fig. 4. Comparison of the probability of treatment failure (progression) in patients with stage C prostate cancer who received combination therapy with Flutamide and the LHRH agonist [D-Trp⁶]LHRH ethylamide (present data), radiotherapy [3, 21]. *delayed treatment* [3], *DES/Estracyt* [22], *DES* [23], *cyproterone acetate (CPA)* [23] *and medroxyprogesterone acetate (Provera)* [23].

DISCUSSION

The goal of therapy in stage C prostate cancer is local control of the tumor and prolongation of the interval free of disease [17, 18]. The present data show that local control of the disease was achieved rapidly in all except one patient (98.6%). In the three patients who had a low urinary tract obstruction, the catheter could be removed within 3 weeks after starting treatment, thus indicating a rapid regression of the cancer at the prostatic level.

Patients having stage C prostate cancer are well known to be at high risk for early progression of disease and short survival [1, 19, 20]. The present finding of only five patients who showed progression during the course of this study (Table 2) is very encouraging. These data indicating a low rate of treatment failure are well supported by the occurrence of only three deaths due to prostate cancer.

The present data suggest that administration of the combination therapy using a pure antiandrogen (Flutamide) in association with medical castration ([D-Trp⁶]LHRH ethylamide) at the time of diagnosis of stage C prostate cancer has advantages over standard therapies and delayed treatment [3, 21–23]. Since these recent studies have used comparable criteria of response, it seems appropriate and much more informative to compare the present data with the results obtained in those studies. Since, in most publications, the number of patients at 3 years of treatment is too small, it seems more appropriate to use 2 years of treatment as the time of comparison.

As illustrated in Fig. 4, the percentage of treatment failure at 2 years of treatment with the combination therapy is only 8.2% while 24 and 32% of patients have progressed to stage D2 after radiotherapy and delayed hormonal therapy, respectively [3]. Another study [21] shows that 2 years after radiotherapy, the rate of progression to stage D2 is 18%. In a more recent study, 22% of stage C patients had progressed to stage D2 after 2 years of treatment with Estracyt or DES [22]. In another recent study, the rate of progression to stage D2 at 2 years was 40, 34 and 66% after treatment with cyproterone acetate, DES and medroxyprogesterone acetate, respectively [23]. When all the above-mentioned data of monotherapy are combined (275 patients), the rate of treatment failure at 2 years is on average 28.4%, a value 3.5 higher than that observed in the present study (8.2%).

Although progression to stage D2 is the early sign of treatment failure, it is of interest to compare, even at this early stage in our study, the survival rate so far obtained under combination therapy with the results achieved in other studies using monotherapy. As illustrated in Fig. 5, the death rate at 2 years with combination therapy is 6.5% while it is, on average, at 34% (5.2-fold difference) at the same time interval following treatment with DES or Estracyt [22]. In the other EORTC study, the death rates at 2 years of treatment with cyproterone acetate, DES and medroxyprogesterone acetate were 12, 22 and 31%, respectively [23]. When the above-mentioned data are pooled (513 patients), the average death rate at 2 years is 22.2% with standard therapy as compared to only 6.5% in the

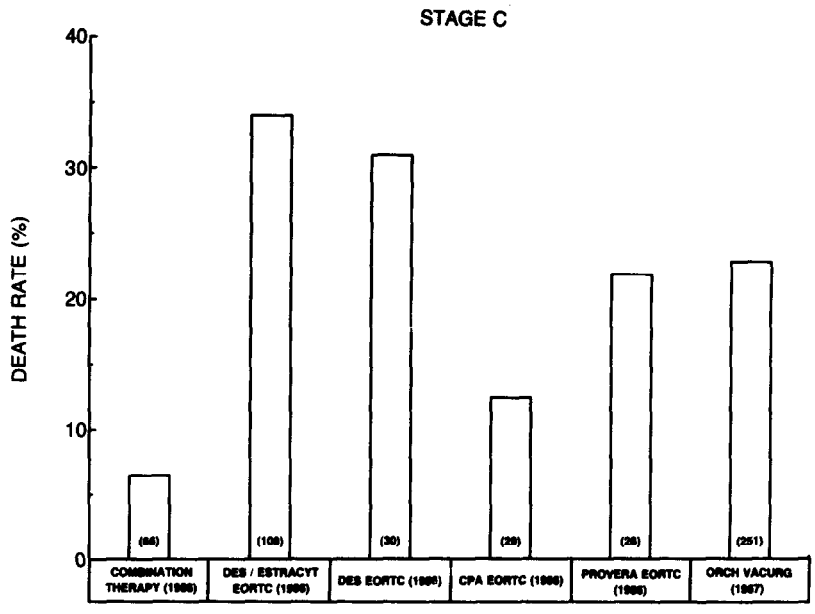

Fig. 5. Comparison of the probability of death in patients with clinical stage C prostate cancer who received combination therapy with Flutamide and the LHRH agonist [D-*Trp*^{6}]*LHRH ethylamide (present data), DES/Estracyt* [22], *DES* [23], *cyproterone acetate (CPA)* [23], *medroxyprogesterone acetate (Provera)* [24] *or orchiectomy* [31].

present study (3.4-fold difference).

The data summarized by Paulson [24] have indicated that in patients who had biopsy-proven pelvic lymph node extension, no difference in disease control could be obtained between radical prostatectomy, external beam radiation therapy or delayed androgen deprivation. Such data strongly suggest that once pelvic lymph nodes contain cancer cells, the prostatic tumor is usually disseminated at distance and the cancer can no longer be controlled by a treatment having only a local or regional impact. The role of radiation therapy in the treatment of prostate cancer was even more seriously questioned when it was observed that radiotherapy did not seem to alter significantly the subsequent appearance of bone or parenchymal spread in patients who were classified as stage C at the beginning of the study [24]. Moreover, previous studies have shown that there is no advantage in the concurrent use of standard hormonal manipulations with irradiation of the prostate in localized carcinoma [25–30]. Many studies have stressed the high frequency of serious cardiovascular side-effects caused by estrogen therapy [25, 31]. Such data suggest that one should seriously question the use of estrogens for the treatment of prostate cancer, especially since LHRH agonists can provide a similar blockade of testicular androgens without any of the serious complications of estrogens [32–36].

Our previous data have indicated the advantages of combination therapy in patients with stage D2 prostate cancer [6, 9, 33, 35]. The present data clearly suggest that combination therapy is even more advantageous when applied earlier in the disease. The recent experimental evidence indicating the development of a marked heterogeneity of the sensitivity to androgens in tumors *in vivo* as well as *in vitro* in cells in culture [5] provides strong support for the present clinical findings. We have in fact found that a marked heterogeneity of the responsiveness to androgens developed *in vivo* in the mouse androgen-sensitive Shionogi tumor, some cells being up to 1200 times more sensitive than others to the androgen DHT. Moreover, when a clone originating from a single cell was grown *in vitro* under defined conditions, the same heterogeneity of sensitivity to DHT developed rapidly [5].

Since every cancer cell division carries the risk of additional heterogeneity, it seems logical to expect a less favorable efficacy when the combined antiandrogen treatment is applied at a later stage of the disease. As much as early tumors are more likely to be composed of cells which resemble the original normal prostatic cell and thus respond well to androgen blockade, it is expected that advanced prostate cancer contains more clones of cells which have deviated from the normal phenotype and have acquired a different sensitivity to androgens (both hypersensitive and hyposensitive). In analogy with the experimental Shionogi tumor, the human prostatic tumors having a high sensitivity to androgens will be difficult to block since their high sensitivity to DHT permits them to grow on the small amounts of the androgen left free under antiandrogen treatment.

Although the present study is non-randomized and the possibility of a bias in the patient population exists, the exceptionally large difference observed

when comparing it to all available studies is highly suggestive of the advantages of the combination therapy over previous approaches. It should be mentioned that our population of patients is, if anything, less favorable since it includes stage C, D_0 and D_1 patients. In fact, due to the unavoidable limitations of the available staging techniques, no routine lymphography or staging pelvic lymphadenectomy was performed to differentiate between stages C and D_1. As shown by the finding of elevated serum PAP levels in 40 of 70 patients (57%), a maximum of 33% of our patients were still at stage C while 57% were at stage D_0 or D_1.

In agreement with previous suggestions [4], the present data provide strong support for early treatment of prostatic cancer by endocrine therapy. The highly probable arguments which, in our opinion, strongly support early combination therapy are the following: (1) untreated stage C or D prostate cancer is usually progressive; (2) minimizing tumor load is likely to facilitate individual immune antitumor defenses; (3) minimizing cancer cell division is likely to decrease the appearance of more undifferentiated cell clones resistant to antiandrogen blockade; (4) progressive disease is more likely to endanger the quality of life than the antiandrogen treatment; (5) early recognition of non- or poor responders to available antiandrogen blockade permits initiation of other therapies before deterioration of the general status of the patient.

When treatment is delayed until the disease has become symptomatic, the patient has to recover from one or more of the following complications: bone pain, anorexia, weight loss, urinary obstruction, cord compression and/or anemia. The argument for early administration of combination therapy is particularly strong when one considers the relative lack of undesirable side-effects of the treatment. In fact, in patients who do not accept orchiectomy, the possibility of achieving medical castration with LHRH agonists avoids all the cardiovascular problems associated with the use of estrogens [31, 37, 38] while the pure antiandrogen used in this study is devoid of significant side-effects. Hot flushes and a decreased or loss of potency and libido are usually found in patients receiving the combination therapy but it should be mentioned that these side-effects, essentially due to the blockade of androgen action, are not new and were also present with previous therapies, namely orchiectomy and treatment with estrogens.

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