A Comparison of Diethylstilbestrol or Orchiectomy With Buserelin and With Methotrexate Plus Diethylstilbestrol or Orchiectomy in Newly Diagnosed Patients With Clinical Stage D_2 Cancer of the Prostate

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From April 1983 to March 1985, 265 patients with newly diagnosed metastatic prostate cancer were randomized to one of three treatment protocols: (1) diethylstilbestrol (DES) or bilateral orchiectomy, (2) the leutinizing hormone-releasing hormone (LHRH) analog buserelin, or (3) methotrexate plus DES or orchiectomy. In 261 evaluable patients there was no significant difference in survival between the three groups. However, progression-free survival (PFS) was significantly different ($P < 0.0005$, log-rank test). Of the possible pairwise comparisons for PFS, two showed significance: buserelin was inferior to DES/orchiectomy ($P < 0.05$) and buserelin was inferior to methotrexate plus DES/orchiectomy ($P < 0.0001$).
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SINCE 1941, WHEN HUGGINS AND HODGES demonstrated the palliative effects of hormone manipulation in prostate cancer, hormone therapy has been the mainstay of treatment for metastatic disease.[1,2] About 70% to 80% of patients show definite clinical improvement and relief from symptoms of variable duration.[2,3] Major issues such as timing and form of endocrine therapy remain unresolved.[2–4] Also, whether hormone therapy significantly alters the course of prostate cancer has been questioned.[4]

Because of the limited duration of response to hormone therapy and because of other questions regarding its impact on survival, the early use of hormone therapy and chemotherapy has been an attractive approach to the management of newly diagnosed metastatic prostate cancer.[5] Consideration of the nature and implications of prostate tumor cell heterogeneity of hormone or hormone-resistant tumor cells supports this concept.[5] This article documents the third National Prostatic Cancer Treatment Group [NPCTG] study of such early combination therapy *versus* alternative forms of hormone therapy in newly diagnosed patients with metastatic prostate cancer.

Materials and Methods

From April 1983 to March 1985, 265 patients with newly diagnosed clinical Stage D_2 carcinoma of the prostate who had not had hormone treatment or chemotherapy were entered into the National Prostatic Cancer Treatment Group Protocol 1700. The results of this study are based on data available as of July 1, 1987. Patients were randomized into one of three treatment groups: (1) diethylstilbestrol [DES] 1 mg orally three times daily or bilateral orchiectomy; (2) buserelin (HOE 766, Hoechst-Roussel Pharmaceuticals, Somerville, NJ) 500 mg three times daily subcutaneously (SC) for 7 days, then 200 mcg SC daily or 400 mcg three times daily with intranasal

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TABLE 1. The Pretreatment Status of Patients at Entry in National Prostatic Cancer Project Protocol 1700

Category	Treatment			
	DES/ ORCH	Buserelin	MTX + DES/ ORCH	Total
Treated and evaluated for response	47	91	73	211
No treatment	1	4	5	10
Insufficient treatment	2	8	—	10
Major compliance deviation	1	4	1	6
Ineligible and not treated	1	1	2	4
Data missing	4	3	17	24
Total	56	111	98	265

MTX: methotrexate; DES: diethylstilbestrol; ORCH: bilateral orchiectomy.

applicator; and (3) methotrexate (MTX) 40 mg/m^2, intravenously (IV) on day 1, 60 mg/m^2 on day 8 and every 14 days thereafter, plus DES 1 mg orally three times daily or bilateral orchiectomy.

Not reported in this study will be observations on serum leutinizing hormone (LH) levels, serum follicle-stimulating hormone (FSH) levels, serum 17-β-estradiol levels, serum 17-β-estradiol levels, testosterone, and other studies including thyroxin levels and cortisol levels. The purpose of these studies was to ensure patient compliance and the achievement of suitable levels of testosterone at castration points in all patients on the LH/RH agonist, DES, or orchiectomy. As this was the case and will be reported elsewhere, it will not be included in this report (Buserelin (HOE-766) report Hoechst Pharmaceutical Products, March 2, 1987).

Patients who initially received DES and were then or-

TABLE 2. Status of Several Conditions or Variables at Entry for Evaluable Patients According to Treatment in National Prostatic Cancer Project Protocol 1700

Variable	Treatment*							
	DES/ORCH		Buserelin		MTX + DES/ ORCH		Total	
	No.	%	No.	%	No.	%	No.	%
Performance status								
Normal activity	20	36	46	42	47	49	113	43
Ambulatory	26	47	46	42	34	35	106	41
In bed <50%	5	9	8	7	5	5	18	7
In bed >50%	2	4	8	7	1	1	11	4
Bedridden 100%	1	2	—		—		1	1
Missing	1	2	2	2	9	9	12	5
Total	55		110		96		261	
Initial pain								
None	16	29	34	31	37	38	87	33
Mild	24	43	47	43	40	42	111	43
Moderate	13	24	25	22	10	10	48	18
Severe	1	2	2	2	—		3	1
Missing	1	2	2	2	9	9	12	5
Total	55		110		96		261	
Initial acid phosphatase								
Not elevated	8	14	21	19	16	16	45	17
Elevated	45	82	85	77	67	70	197	76
Missing	2	4	4	4	13	13	19	7
Total	55		110		96		261	
Initial alkaline phosphatase								
Not elevated	19	35	32	29	36	38	87	33
Elevated	32	58	73	66	44	46	149	57
Missing	4	7	5	5	16	17	25	10
Total	55		110		96		261	
History of cardiovascular disease								
No	29	52	64	58	49	51	142	54
Yes	25	46	44	40	38	40	107	41
Missing	1	2	2	2	9	9	12	5
Total	55		110		96		261	

MTX: methotrexate; DES: diethylstilbestrol; ORCH: bilateral orchiectomy.

* Four ineligible patients excluded from this table.

TABLE 3. Hematologic Toxicities According to Treatment in National Prostatic Cancer Project Protocol 1700

	Treatment*							
	DES/ORCH		Buserelin		MTX + DES/ ORCH		Total	
Toxicity	No.	%	No.	%	No.	%	No.	%
Anemia (abnormal = Hgb < 10.5 mg/dl)								
No toxicity	41	76	72	68	48	53	161	64
Toxicity	4	7	15	14	22	24	41	16
Remained abnormal	5	9	11	10	11	11	27	11
Missing	4	7	8	8	10	11	22	9
Total	54		106		91		251	
Leukocyte (abnormal = < ±4.000/μl)								
No toxicity	42	78	87	83	47	52	176	70
Toxicity	6	11	10	9	31	34	47	19
Remained abnormal	2	4	1	1	3	3	6	2
Missing	4	7	8	8	10	11	22	9
Total	54		106		91		251	
Platelets (abnormal = <100,000/μl)								
No toxicity	49	91	98		75	82	222	88
Toxicity	1	2	—	93	5	6	6	2
Remained abnormal	—		—		—		—	
Missing	4	7	8	8	11	12	23	9
Total	54		106		91		251	

MTX: methotrexate; DES: diethylstilbestrol; ORCH: bilateral orchiectomy; Hgb: hemoglobin.

* 14 untreated patients not included in this table.

chiectomized due to complications of therapy were considered to be protocol compliant and fully evaluable. The study design called for a total of 245 patients, which was the number of patients accrued.

Practical concerns such as different schedules and drug routes in the treatment groups prevented blinding of the study. The NPCTG response criteria (published elsewhere) were used to evaluate patient response.[6] As presented in this protocol, these criteria for the evaluation of therapy define progression of disease as the "appearance of new areas of malignant disease by bone scan."[6] By this definition, a patient who initially presents with multiple lesions on a bone scan that are completely resolved at a later date is considered to be in progression if there is one new area of disease. These criteria were developed before the recognition of phenomena such as the "flare" known to be caused by LH-RH compounds.[7,8] Thus, any patient with a new lesion in this study was considered a progression. All patients were observed and follow-up data was reported. It was not necessary or considered appropriate to classify a patient to have a flare response and later to reclassify the patient as a progression or new progression. The statistical analyses to evaluate the data were generally known and accepted methods.[8-10]

Results

A total of 265 patients were randomized to the three treatment groups of Protocol 1700 before entry to the study was closed in March 1985. The summary of eligibility and treatment compliance is shown in Table 1. There were four patients (2%) randomized to this protocol who were considered to be ineligible based on the entry criteria; none of these patients were treated. In addition, there were 10 eligible patients who did not receive treatment.

All eligible patients entered in the protocol (261) were included in comparisons of pretreatment characteristics and treatment efficacy. All patients who received protocol treatment regardless of eligibility (251) were included in the evaluation of toxicities. Table 2 illustrates the pretreatment characteristics of the patients. Clinical presentation with initial pain occurred less frequently and with less severity in the methotrexate group ($P < 0.05$). No other pretreatment characteristics of any group are significantly different.

Hematologic toxicities are shown in Table 3. They were not believed to be severe, as defined by our criteria. Tables 4 and 5 depict the observed non-hemic toxicities. Gastrointestinal toxicity, which was manifested by nausea and vomiting and/or anorexia, was observed much more frequently in patients receiving methotrexate ($P < 0.001$). Diarrhea was also more common in the methotrexate group. There was no significant difference in cardiovascular toxicity for any of the treatment groups. Ten complete regressions were reported: one on buserelin, three

TABLE 4. Non-Hemic Toxicities According to Treatment in National Prostatic Cancer Project Protocol 1700

	Treatment*							
	DES/ORCH		Buserelin		MTX + DES/ ORCH		Total	
Toxicity	No.	%	No.	%	No.	%	No.	%
Nausea and vomiting								
None	44	82	87	82	41	45	172	69
Mild-moderate	7	13	8	8	35	39	50	20
Severe	—		1	1	6	6	7	3
Missing	3	5	10	9	9	10	22	9
Total	54		106		91		251	
Anorexia								
None	41	76	77	73	48	53	166	66
Mild-moderate	9	17	17	16	26	27	52	20
Severe	1	2	2	2	8	9	11	4
Missing	3	5	10	9	9	10	22	9
Total	54		106		91		251	
Diarrhea								
None	46	85	89	84	64	70	199	79
Mild-moderate	5	9	7	7	17	18	29	12
Severe	—		—		1	1	1	1
Missing	3	6	10	9	9	10	22	9
Total	54		106		91		251	
Hypertension								
None	45	83	81	76	64	70	190	76
Mild-moderate	6	11	15	14	17	19	38	15
Severe	—		—		1	1	1	1
Missing	3	6	10	10	9	10	22	9
Total	54		106		91		251	
Edema of the extremities								
None	31	57	75	71	53	58	159	63
Mild-moderate	19	35	20	19	27	30	66	26
Severe	1	2	1	1	2	2	3	2
Missing	3	6	10	9	9	10	22	9
Total	54		106		91		251	

MTX: methotrexate; DES: diethylstilbestrol; ORCH: bilateral orchiectomy.

* 14 untreated patients not included in this table.

on DES/orchiectomy, and six on Methotrexate plus DES/orchiectomy.

The analysis of survival by treatment (Fig. 1) indicates that 58 of the 261 eligible patients (22%) have died. There is no difference in survival between the groups as determined by the log-rank statistical analysis. Figure 2 shows the progression-free survival curves. The analysis shows that 136 of 261 eligible patients (52%) failed to respond or progressed. The progression-free survival is significantly different in the treatment groups ($P < 0.0005$ log-rank statistics). Of the possible pairwise comparisons, two show significance: buserelin *versus* DES/orchiectomy ($P < 0.05$) and buserelin *versus* methotrexate plus DES/orchiectomy ($P < 0.0001$). While progression-free survival was highest in the methotrexate plus DES/orchiectomy group, it was not significantly greater than that in the DES/orchiectomy group ($P = 0.28$).

Discussion

This was the third NPCTG trial in which the role of early combined chemotherapy plus hormone therapy was studied in comparison to hormone therapy alone in the treatment of metastatic prostate cancer.[11,12] The first was NPCTG Protocol 500 in which previously untreated patients with Stage D_2 prostate cancer were randomized to the following three groups: (1) DES 1 mg orally three times a day or orchiectomy; (2) DES plus cyclophosphamide at 1 g/m^2 IV every 3 weeks; or (3) estramustine phosphate (Emcyt, Roche, Nutley, NJ) at 600 mg/m^2 orally, daily in three divided doses plus Cytoxan (Bristol Oncology, Syracuse, NY) (same dose in each group).[11] In 246 evaluable patients objective response rates, evaluated initially at 12 weeks were similar in all three groups. However, chemotherapy appeared to have a limited effect on

TABLE 5. Additional Non-Hemic Toxicities According to Treatment in National Prostatic Cancer Project Protocol 1700

	Treatment*							
	DES/ORCH		Buserelin		MTX + DES/ ORCH		Total	
Toxicity	No.	%	No.	%	No.	%	No.	%
SGOT (abnormal = > ±0 IU)								
No toxicity	38	70	50	47	47	52	135	54
Toxicity	10	18	36	34	25	28	71	28
Remained abnormal	3	6	12	11	6	6	21	8
Missing	3	6	8	8	13	14	24	10
Total	54		106		91		251	
Bilirubin (abnormal = >0.8 mg/dl)								
No toxicity	46	85	75	71	65	71	186	74
Toxicity	4	7	16	15	10	11	30	12
Remained abnormal	1	2	7	7	3	3	11	4
Missing	3	6	8	8	13	14	24	10
Total	54		106		91		251	
Serum creatinine (abnormal = >1.2 mg/dl)								
No toxicity	29	54	42	40	23	25	94	38
Toxicity	8	15	20	19	30	33	58	23
Remained abnormal	14	26	36	34	28	31	78	31
Missing	3	5	8	8	10	11	21	8
Total	54		106		91		251	
BUN (abnormal = >20 mg/dl)								
No toxicity	30	56	39	37	32	35	101	40
Toxicity	9	17	42	40	26	29	77	31
Remained abnormal	11	20	17	16	21	23	49	20
Missing	4	7	8	8	12	13	24	10
Total	54		106		91		251	

* 14 untreated patients not included in this table.
MTX: methotrexate; DES: diethylstilbestrol; ORCH: bilateral orchiectomy; SGOT: serum glutamic oxaloacetic transaminase; BUN: blood urea nitrogen.

overall survival in comparison to hormone therapy alone.[11] A more positive effect of chemotherapy on survival was seen in the patients who had pain at diagnosis.[11] There were no detectable differences in survival between the alternative forms of hormone treatment. Toxicity in the chemotherapy groups in particular was not considered excessive.[11]

The second NPCTG study of hormone therapy alone *versus* hormone therapy plus chemotherapy *versus* chemotherapy in newly diagnosed stage D_2 prostate cancer was NPCTG Protocol 1300, the results of which were recently published.[12] A total of 296 evaluable patients were randomized to one of three treatment arms: (1) DES 1 mg three times daily or bilateral orchiectomy; (2) estramustine phosphate (Emcyt) 600 mg/m^2 orally daily; (3) cyclophosphamide 1 g/m^2 IV every 3 weeks plus DES 3 mg/day plus 5-fluorouracil (5-FU) 350 mg/m^2 IV weekly. In this study there were no significant detectable differences in the treatment groups in the distribution of objective, short-term responses or in overall survival regardless of the presence of pain at entry into the study. Hematologic toxicity was significantly higher in patients receiving cyclophosphamide plus 5-FU plus DES/orchiectomy.[12]

The current study (NPCTG Protocol 1700) was the final group study of early combination therapy in previously untreated patients. Methotrexate was chosen as the reference chemotherapy agent based on the results of National Prostatic Cancer Project (NPCP) Protocol 1100, in which an initial response rate of 41% was reported in patients with hormone-refractory prostate cancer.[13] Toxicity of methotrexate at 60 mg/m^2 every 2 weeks was considered to be acceptable in that study.[13]

Buserelin is a synthetic peptide analog of the natural gonadatrophin releasing hormone leutinizing hormone-releasing hormone (LHRH). As with other LHRH analogs, side effects of buserelin treatment are primarily limited to hot flashes and decreased libido in most patients.[8] A brief elevation in testosterone levels for 1 to 3 days after starting treatment may cause or increase bone pain, but testosterone levels then progressively fall to castrate levels over a 2- to 4-week period.[8] Some preliminary studies

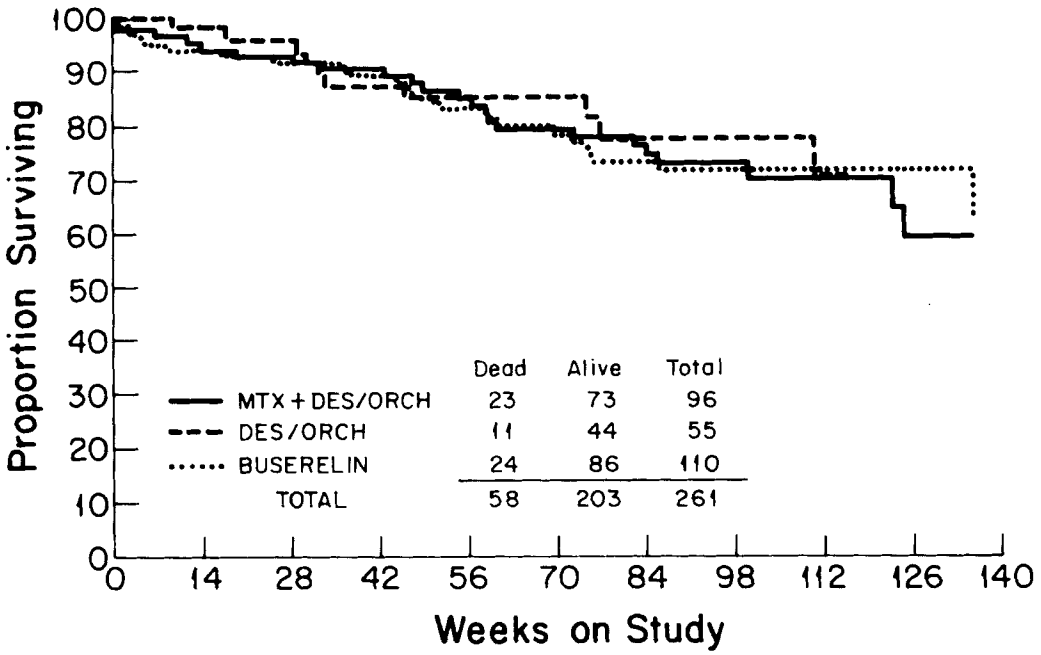

FIG. 1. Survival records of 261 patients with newly diagnosed metastatic prostate cancer receiving one of three therapies.

have suggested that LHRH analogs are as effective as estrogens or orchiectomy in the management of metastatic prostate cancer, at least in terms of initial clinical responses.[8,14,15]

From the results of the current study it can be concluded that there is a significant difference in the three treatment groups in progression-free survival. Methotrexate plus DES/orchiectomy showed the best progression-free survival, followed by DES/orchiectomy. Both of these groups were significantly different in terms of progression-free survival from the buserelin group. The reason for these differences is uncertain. It may be that the early progressions observed in the buserelin group were solely the result of the LHRH "flare" phenomenon.[8] Perhaps these flare-induced progressions have little clinical importance and will not be related to overall survival or quality of life.[14,15]

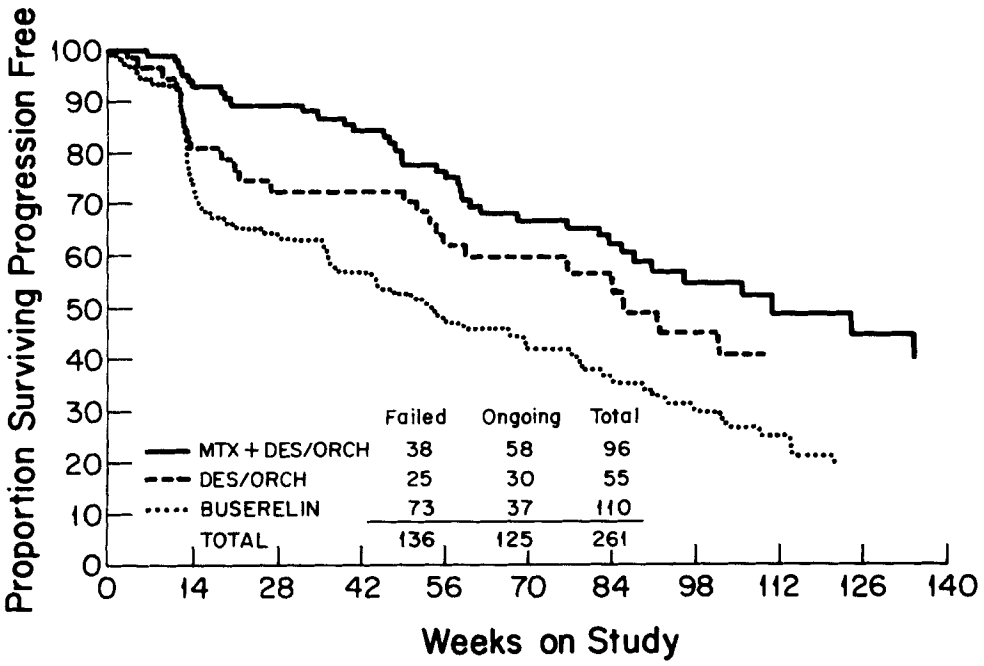

FIG. 2. Differences in progression-free survival, and the patients treated by one of the three randomized therapies.

Further study will be necessary to definitely resolve this issue.

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