

Combination Therapy with Flutamide and the LHRH Agonist [D-Trp⁶, des-Gly-NH₂¹⁰]LHRH Ethylamide in Stage C Prostatic Carcinoma

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Summary—A series of 115 previously untreated patients displaying clinical stage C prostatic carcinoma with no evidence of distant metastases received combination therapy using the antiandrogen flutamide and the LHRH agonist [D-Trp⁶, des-Gly-NH₂¹⁰]LHRH ethylamide; the average follow-up was 3.9 years. Twenty-eight patients showed treatment failure with a probability of disease-free survival of 91.2% at 2 years. Twenty patients died from prostate cancer and 10 from other causes, the survival probability being 93.4% at 2 years. Local control was achieved rapidly in all patients. Urinary obstruction and hydronephrosis were corrected in all cases. When compared with data obtained after single endocrine therapy (orchiectomy or oestrogens) or radiotherapy, the treatment failure rate at 2 years was more than 3.0-fold lower after combination therapy (8.8%) than monotherapy (28.4%). The death rate 2 years after the start of combination therapy was 6.6% and was on average 22.2% (3.6-fold higher) in the studies using monotherapy (orchiectomy or oestrogens) or radiotherapy. The present data suggest that treatment of prostate cancer with combination therapy before clinical evidence of dissemination of disease permits more efficient control of local disease and a decreased rate of progression to metastatic disease.

A considerable proportion of patients have clinical stage C disease at the time of first diagnosis of prostate cancer (Schmidt *et al.*, 1986). The standard forms of treatment for these patients have been radiotherapy, radical prostatectomy and immediate or delayed partial androgen deprivation (orchiectomy or oestrogens) (Flocks *et al.*, 1975; Paulson *et al.*, 1984). During recent years, however, a decrease in the use of standard hormonal therapy, especially oestrogens, has been observed for the treatment of stage C disease (Schmidt *et al.*, 1986) and several studies have revealed the importance of cardiovascular side effects secondary to oestrogen therapy in prostate cancer (VACURG, 1967; Hedlung *et al.*, 1980; Glashan and Robinson, 1981). The VACURG (1967) study showed that among patients who died from heart disease or cerebrovas-

cular accident, 62% were treated with oestrogens and only 38% underwent orchiectomy, a 24% difference attributable to oestrogens. Another study showed that 15% of patients treated with oestrogens died from cardiovascular complications during the first year of therapy, an incidence which is comparable to the risk of death from cancer itself (Glashan and Robinson, 1981).

We have shown that the lipoprotein profile resulting from combination therapy is more favourable than that observed following orchiectomy and especially oestrogen therapy (Moorjani *et al.*, 1987; 1988). Oestrogen therapy induced hypertriglyceridaemia, while hypercholesterolaemia and elevated total and LDL apolipoprotein B levels were associated with orchiectomy. Combination therapy, on the other hand, had no effect on plasma lipids and apolipoprotein B concentrations, while VLDL lipoprotein apolipoprotein B decreased and

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LDL apolipoprotein B increased. Since combination therapy offers an advantageous serum lipid profile during long-term management of prostatic cancer patients, and knowing that delaying treatment permits further tumour cell dedifferentiation and the development of tumour heterogeneity (Grayhack and Kozlowski, 1980), we have studied the effect of combined antihormonal therapy using the antiandrogen flutamide and the LHRH agonist [D-Trp⁶, des-Gly-NH₂¹⁰]LHRH ethylamide in 115 previously untreated patients with clinical stage C prostate cancer. Comparison is made with published results using the conventional approaches.

Patients and Methods

Since September 1982, 115 men with histology-proven carcinoma of the prostate were included in the study after written informed consent. The average age upon entry was 70 years (range 57–88) and the average follow-up was 1427 days (range 19–3502). Complete clinical, urological, biochemical and radiological evaluation of the patients was performed before starting treatment (Labrie *et al.*, 1987). 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 occasionally computed axial tomography (CT scan) of the abdomen and pelvis as well as intravenous urography (IVU) and pedal lymphography. Follow-up was performed at intervals of 1, 3 and 6 months and then every sixth month (Labrie *et al.*, 1987). The last evaluation included in this report took place on April 30, 1992. In this group of patients, 4 (3.5%) discontinued therapy on their own before the first evaluation at 3 months, 2 stopped because of medical intolerance (rise of hepatic enzymes) and 1 was treated for less than 3 months; 108 patients were therefore evaluated for their response to combination therapy with the LHRH agonist [D-Trp⁶, des-Gly-NH₂¹⁰]LHRH ethylamide in association with the pure antiandrogen 2-methyl-N-[4-nitro-3(trifluoromethyl)phenyl]propanamide (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 3 times daily at 0700, 1500 and 2300 h at a dose of 250 mg orally. The antiandrogen was started 1 day before the first administration of the LHRH agonist.

Seventy patients (60.9%) had a needle biopsy and the diagnosis was made after transurethral resection

of the prostate (TURP) in the 45 remaining patients. At histology, 35 patients (30.4%) were graded as having well differentiated disease, 50 (43.5%) moderately well and 27 (23.5%) poorly differentiated disease; 2 had anaplastic disease (1.7%) and 1 was unknown (Table 1). The stage of each tumour was assessed by rectal examination according to the staging system of Whitmore (1973). Six patients had negative exploratory lymphadenectomy. Lymphangiograms and staging regional lymphadenectomy were not performed routinely. Hydronephrosis was present in 8 patients (6.9%) and low urinary tract obstruction was found in 4 (3.5%). No patient had detectable regional lymph node invasion at transabdominal ultrasonography or CT scan.

Table 1 Demographic Data and Baseline Profile of 115 Stage C Prostate Cancer Patients

Histological grade	No. of patients	PAP (> 2 ng/ml)
Well differentiated	35	15
Moderately differentiated	50	22
Poorly differentiated	27	15
Anaplastic	2	1
Unknown	1	0

All patients had negative isotopic bone scan and skeletal bone survey. Serum prostatic acid phosphatase measured by radioimmunoassay was elevated in 53 patients (48.8%) (Table 1), thus representing a greater risk (Paulson *et al.*, 1982). External radiotherapy to the prostate had been performed in 18 patients (15.6%) but all were showing local progression at the start of combination therapy. Treatment failure or progression was defined according to Paulson *et al.* (1984): appearance of a positive bone scan and/or elevation of serum prostatic acid phosphatase and/or specific antigen on 2 consecutive follow-up visits and/or appearance of parenchymal or soft tissue extension and/or appearance of groin or supraclavicular adenopathy. The criteria defining a positive response were as follows:

Regression

One of the following criteria:

1. Disappearance of urinary obstruction.
2. Decrease of cancer-related hydronephrosis ($\geq 50\%$).
3. Regression of prostate volume ($\geq 50\%$) and/or improvement in the consistency ($\geq 50\%$).

And all of the following:

1. No new lesion.
2. Serum PSA ≤ 0.2 $\mu\text{g/l}$ (or equivalent to those of female subject) and/or normal serum PAP level.
3. No significant cancer-related deterioration in weight ($\geq 10\%$), symptoms, or performance status.

Stable

1. PSA level decreased, though need not return to normal and/or serum PAP level decreased.
2. No new site of disease.
3. Decrease ($< 50\%$) or stability of prostate cancer-related hydronephrosis.
4. Decrease of cancer-related urinary obstruction.
5. Stability of the volume and consistency of the prostate.
6. No significant cancer-related deterioration in weight ($\geq 10\%$), symptoms or performance status.

A positive response required positive evaluation on at least 2 consecutive visits.

Student's *t* test was used to evaluate the difference between means. The probabilities of continuing response and survival were calculated according to Kaplan and Meier (1958). The multiple regression and stepwise variable selection to assess the validity of various prognostic factors was performed by a step by step selection (SAS Institute, 1986).

Results

As shown in Table 2, all evaluable patients showed a positive objective response to treatment. After an average follow-up period of 1427 days or 3.9 years, 28 patients had a relapse (Fig. 1). The probability of continuing response calculated according to Kaplan and Meier (1958) is 98.4, 91.2, 85.8, 78.2, 74.3, 63.5, 60.4 and 56.4% years at 1, 2, 3, 4, 5, 6, 7 and 8 years respectively.

The evolution of survival in the same group of patients is illustrated in Figure 2. When all causes of death are included, the calculated survival rate is $96.9 \pm 1.8\%$ (SEM), $93.4 \pm 2.6\%$, $85.5 \pm 3.9\%$,

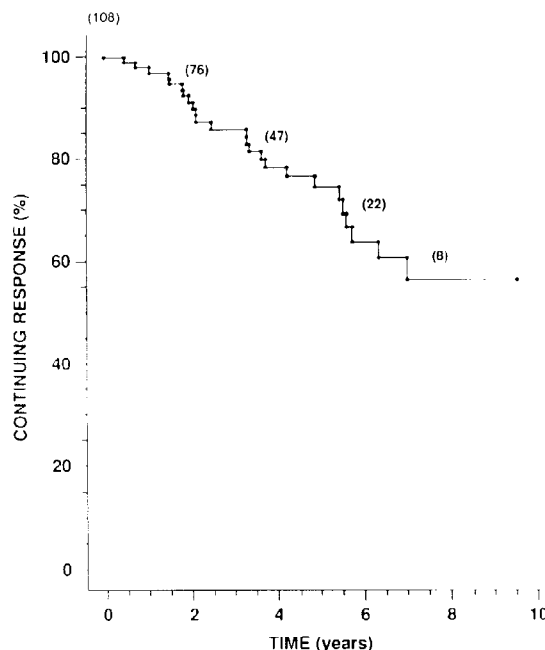


Fig. 1 Probability of continuing response in clinical stage C prostate cancer patients receiving combination therapy. Numbers in parentheses represent patients at risk.

$82.7 \pm 4.3\%$, $69.7 \pm 5.5\%$, $67.7 \pm 5.7\%$, $65.4 \pm 5.9\%$, $51.2 \pm 6.1\%$ at 1, 2, 3, 4, 5, 6, 7 and 8 years respectively. Twenty patients have died from prostate cancer and 10 from other causes (5 from myocardial infarct, 1 from pneumonia, 1 from suicide, 2 from cerebrovascular accidents and 1 from cardiac surgery complications); all 10 patients had been examined at this prostate cancer clinic within 6 months before death and were then found to be clinically free of disease, except for 1 man who died from a myocardial infarct 15 days after a local recurrence had been diagnosed.

Among the 108 patients evaluated in this study, 18 (16.7%) decided on their own to stop hormonal combination therapy while they were responding; 12 patients mentioned a financial problem and the 6 others did not give any reason. Three had abnormally elevated liver enzymes (twice the upper

Table 2 Best Objective Response in Previously Untreated Stage C Prostate Cancer Patients receiving Combination Therapy

No. of patients	Duration of treatment (days) Median (Range)	Best objective response		
		Regression (%)	Stable (%)	Progression
108	1427 (19-3502)	95 (88)	13 (12)	0

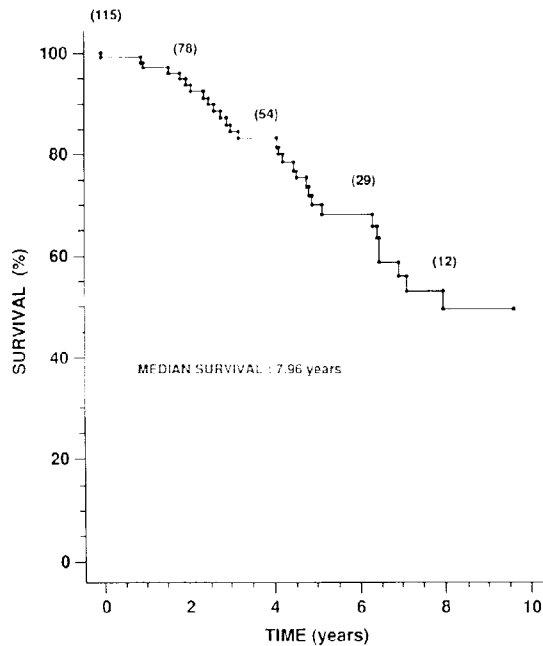


Fig. 2 Probability of survival in clinical stage C prostate cancer patients receiving combination therapy. Numbers in parentheses represent men at risk.

normal limits) 3 months after beginning therapy, but they continued on combination therapy and liver enzymes were normal at 6 months.

Serum prostatic acid phosphatase, which was elevated in 53 patients at the start of treatment, became normal in 44, 59, 91 and 97% at 1, 2, 3 and 6 months respectively after the beginning of combination therapy. In all patients except 2 the volume of the prostate rapidly regressed during the first year of treatment. Changes in prostate volume were confirmed by transrectal ultrasonography of the prostate in most patients. The low urinary tract obstruction present in 4 patients was corrected by treatment in all cases and in these patients the transurethral catheter was removed less than 21 days after the beginning of combination therapy (Emond *et al.*, 1989). Hydronephrosis, originally present in 8 patients, disappeared within 6 months of therapy.

At each visit the patients answered a detailed questionnaire concerning symptoms or signs of intolerance to the drugs. Haematology and biochemistry parameters were also checked. Haematocrit and haemoglobin values decreased by $8.3 \pm 1.5\%$ and $7.7 \pm 1.5\%$ respectively after 12 months of treatment ($P < 0.01$) and remained stable thereafter. In this connection it should be recalled that

androgens stimulate erythropoiesis in animals and man. Moreover, androgen receptors have been found in erythroblasts from bone marrow (Alexanian, 1969; Claustres and Sultan, 1988). Thus the hypoandrogenicity induced by the treatment might well be responsible for the lowering of haematocrit and haemoglobin levels. Platelet and white blood counts remained normal.

Hot flushes and a decrease or loss of sexual potency and libido were observed in 80 and 75% of patients respectively. Less than 5% complained of loose bowel movement or diarrhoea during the first months of therapy; in no case was it necessary to stop treatment. Dyspepsia was also observed in a few patients ($< 3\%$). This symptom was relieved when the antiandrogen was taken concomitantly with food. Hepatic toxicity, usually reflected by a 3-fold increase in liver enzymes, mainly SGOT and SGPT, was observed in 5 patients (Gomez *et al.*, 1992).

Discussion

The therapeutic aim in stage C prostate cancer is local control of the tumour and prolongation of the disease-free interval (Tomlinson *et al.*, 1977; Gibbons *et al.*, 1979). The present data show that local control of the disease was rapidly achieved in all patients without important side effects (except for liver toxicity). In the 3 patients with a low urinary tract obstruction the catheter was removed within 3 weeks after starting treatment, thus showing a rapid regression of the cancer at the prostatic level.

It is well known from previous studies that stage C prostate cancer patients run a high risk of early progression of the disease and short survival (Whitmore, 1973; Tomlinson *et al.*, 1977; Grayhack and Kozlowski, 1980; Paulson *et al.*, 1984). The present findings of 28 patients who had progression of disease after an average follow-up of 3.9 years is very encouraging. At 3 years the probability of a continued response in 85.8%.

The present data indicate that the early administration of combination therapy using a pure antiandrogen (flutamide) in association with medical castration ([D-Trp⁶, des-Gly-NH₂¹⁰]LHRH ethylamide) to stage C prostate cancer patients has advantages over standard therapies and delayed treatment (Cupps *et al.*, 1980; Smith *et al.*, 1986; Pavone-Macaluso *et al.*, 1986). The previous studies used comparable criteria of inclusion and similar parameters of response and it therefore seemed appropriate to compare the results previously obtained by standard therapy with those achieved

in the present study. In most reports, however, the number of patients who underwent treatment for 3 years is too small and so 2 years of treatment have been used as the time of comparison.

Comparison with similar studies shows that the percentage of treatment failure after 2 years' treatment with combination therapy was 8.8%, while 24 and 32% of patients progressed to stage D2 after radiotherapy and delayed hormonal therapy respectively (Paulson *et al.*, 1984). Cupps *et al.* (1980) showed that 2 years after radiotherapy the rate of progression to stage D2 was 18%. In a more recent study, 22% of stage C patients progressed to stage D2 after 2 years of treatment with Estracyt or DES (Smith *et al.*, 1986). In another study, the rate of progression to stage D2 at 2 years was 34, 40 and 56% after treatment with cyproterone acetate, DES and medroxyprogesterone acetate respectively (Pavone-Macaluso *et al.*, 1986). When all of the above data on monotherapy are combined (275 patients), the rate of treatment failure at 2 years was on average 28.4%, *i.e.* 3 times higher than that observed in the present study (8.8%).

Although progression to stage D2 is an early sign of treatment failure, it is interesting to compare, at this stage of our study, the survival rate observed under combination therapy with the results obtained in other studies using monotherapy. The death rate at 2 years with combination therapy was 6.6%; it was, on average, 34% (5.5-fold difference) at the same time interval following treatment with DES or Estracyt (Smith *et al.*, 1986). In the other EORTC study, the death rates after 2 years' treatment with cyproterone acetate, DES and medroxyprogesterone acetate were 12, 22 and 31% respectively (Pavone-Macaluso *et al.*, 1986). When the above data are pooled (513 patients), the average death rate at 2 years was 22.2% with standard therapy compared with only 6.6% in the present study (3.3-fold difference).

Our original clinical studies (Labrie *et al.*, 1982, 1990; Labrie, 1991), recently confirmed by other groups (Béland *et al.*, 1988; Crawford *et al.*, 1989; Denis, 1992; Janknegt *et al.*, 1992), demonstrated the advantages of combination therapy in patients with stage D2 prostate cancer. The present data indicate, as previously suggested (Dupont *et al.*, 1988), that combination therapy is even more advantageous when applied earlier in the disease. Similar conclusions have been reached by Crawford *et al.* (1989) for stage D2 patients with minimal disease.

The following 9 variables, namely age, method of diagnosis (needle biopsy or TURP), previous

loco-regional radiotherapy, hydronephrosis, urinary obstruction, size of the prostate estimated by DRE, histopathological grade and serum PAP level at start, were used to determine predictive factors for the remission and survival times. None of these factors was found to be statistically significant as predictor of either continuing response or survival when performing multiple regression analysis. However, the univariate analysis indicates that disease-free survival for patients with hydronephrosis at the start of combination therapy gives significant *P* values (Dupont *et al.*, 1988) by both the log rank and the Wilcoxon tests (Peto and Peto, 1972). Similarly, patients who had TURP displayed a tendency to a lower probability of survival, median survival time being 7.13 years, while in those where the biopsy was obtained by needle the median survival time remains undefined.

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