Eur J Cancer Clin Oncol, Vol. 24, No. 12, pp. 1869–1878, 1988.
Printed in Great Britain

0277–5379/88$3.00 + 0.00

Important Prognostic Value of Standardized Objective Criteria of Response in Stage D2 Prostatic Carcinoma

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Abstract—*One hundred and eighty-six previously untreated patients with clinical stage D2 prostate cancer have been followed according to the criteria of objective response of the National Prostatic Cancer Project (NPCP). All patients received combination therapy with the antiandrogen Flutamide and the LHRH agonist (D-Trp^6, des-Gly-NH$_2^{10}$]LHRH ethylamide (or surgical castration, 10 patients) as first treatment. Forty-nine patients (26.3%) achieved a complete response as best response while 56 (30.1%) and 69 (37.1%) patients had partial and stable responses, respectively, and only 12 patients (6.5%) did not respond to treatment. The median times required to achieve stable, partial and complete responses were 155, 183 and 401 days, respectively. The best response achieved has a major influence on the probability of continuing response and survival. While the 50% probability of continuing response is more than 3 years for the complete responders, it is reduced to 630 and 517 days for partial and stable responders, respectively. While the non-responders have a median life expectancy of 10.0 months, this value is increased to 30.3 and 37.8 months for the stable and partial responders, respectively. The best probability of survival is for the complete responders with a 95.9% probability of survival at 3 years. There is no significant correlation between the time required to achieve a best response (phase 1) and the duration of the response before progression occurs (phase 2) or the time between progression and death (phase 3) for any of the categories of responses. A longer period of time required to achieve a complete response is associated with a longer survival. When analysis is made, in an attempt to predict response, of the baseline characteristics of the patients before treatment, a low number of bone metastases and better performance status are associated with a greater chance of achieving a complete response while partial, stable and progression responses cannot be predicted from the baseline characteristics. The present data show the importance of standardization of the objective criteria of response to treatment in advanced prostate cancer. Thus, the patients who achieve a complete response have a much more favorable prognosis while partial and stable categories of response have a closely similar prognosis which is inferior to the complete responders. Moreover, the present data indicate that the stable category of response has an important prognostic value which is almost superimposable and not statistically different from the partial response in terms of duration of response and survival. The presence of a low number of bone metastases is a major prognostic factor which favors complete responses and suggests the advantages of early treatment before dissemination of the disease.*

INTRODUCTION

INTENSIVE EFFORTS have been devoted by many groups during recent years to the development and standardization of objective criteria of response in advanced (stage D2) prostate cancer [1–4]. Reliable, precise and universally accepted criteria of response should greatly facilitate the successful development of new modalities of therapy of prostate cancer, a disease which has become the leading cancer (with lung cancer) with an annual incidence rate of 98,000 new cases predicted in 1988 in the United States [5].

Since we had the opportunity to study a large number of previously untreated patients with stage D2 prostate cancer using the NPCP criteria [2, 3], we have analyzed in detail the predictive value of

Accepted 12 July 1988.

the four categories of objective responses, namely complete, partial, stable and progression, achieved in patients who received combination therapy as first treatment. Potential relations between different phases of the responses and probability of continuing response as well as survival are investigated in detail. The present data demonstrate the clinical importance of objective categorization of the patients in order to predict duration of response and survival. The value of the stable category of response is also clearly illustrated.

PATIENTS AND METHODS

All patients had histologically confirmed clinically advanced (stage D2) prostate cancer and were entered into the study after written informed consent. The criteria of inclusion and exclusion were those of the NPCP [2, 3], except that a life expectancy of at least 90 days and normal blood cell counts were not used as criteria of exclusion. All 199 consecutive patients presenting with previously untreated (no previous endocrine therapy or chemotherapy), stage D2 prostate cancer were thus included, the only exclusions being the presence of a second cancer (3 cases). The patients with very advanced disease and a short life expectancy were not excluded in order to more closely mimick the situation found in usual urological practice.

Of the 199 previously untreated stage D2 patients who had combination therapy, 189 received the combination treatment with the LHRH agonist [D-Trp^6,des-Gly-NH$_2$^{10}]LHRH ethylamide (Tryptex) in association with the pure antiandrogen 2-methyl-*N*-[4-nitro-3(trifluoromethyl)phenyl]propanamide (Flutamide, Euflex, Eulexin) while 10 had orchiectomy (instead of LHRH agonist treatment). 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 exclusive use of Flutamide in all patients since June 1983.

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 the first administration of the LHRH agonist or orchiectomy. Recent kinetic data [6] and knowledge of the rapid change of sensitivity to androgens of tumors exposed to low androgens [7–9] indicate that the optimal time of administration of Flutamide should be 2 h before first injection of the LHRH agonist or orchiectomy. This schedule will thus be followed in the future.

It should be added that, contrary to what is usually done in many studies, combination therapy with Flutamide and the LHRH agonist was continued at the time of relapse, the rationale being that interruption of the combination therapy would permit the growth of tumors kept under control by such treatment, thus adding to the burden of tumors unresponsive to the treatment and responsible for the signs of relapse. Moreover, in order to block the

Table 1. Prostate cancer program. Schedule of visits and tests (Stage D2)

0 D/M/Y	3 D/M/Y	6 D/M/Y	9 D/M/Y	12 D/M/Y	15 D/M/Y	18 D/M/Y
	21 D/M/Y	24 D/M/Y	30 D/M/Y	36 D/M/Y	42 D/M/Y	48 D/M/Y

	DURATION OF TREATMENT (MONTH)												
	0	3	6	9	12	15	18	21	24	30	36	42	48
Consent form		/	/	/	/	/	/	/	/	/	/	/	/
Medical history		/	/	/	/	/	/	/	/	/	/	/	/
Physical examination		X	X	X	X	X	X	X	X	X	X	X	X
Clinical follow-up													
Hematology													
Serum biochemistry													
PAP + PSA													
Urinalysis													
LH, FSH, Prolactin Testicular & adrenal steroids													
Flowmetry													
Skeletal survey		/	X	/		/	X	/		X		X	
Bone scan		/		/		/		/					
Liver scan	X	/	X	/	X	/	X	/	X	X	X	X	X
I.V.P.	X	/	X	/	X	/	X	/	X	X	X	X	X
Chest X-Ray		/		/		/		/					
C.A.T. scan		/	X	/	X	/	X	/	X	X	X	X	X
N.M.I.	X	/	X	/	X	/	X	/	X	X	X	X	X
Ultrasound of the abdomen		/		/		/		/					
E.K.G.		/	/	/		/	/	/		/		/	
Prostatic biopsy		/	/	/	X	/	/	/	X	/	X	/	X
Prostatic ultrasonography													

X When indicated

secretion of adrenal androgens, aminoglutethimide is added routinely at the time of relapse, at the dose of 250 mg every 8 h in association with a low dose of hydrocortisone acetate (10 mg at 0700 h, 5 mg at 1500 h at 5 mg at 2300 h). The tolerance to aminoglutethimide and low doses of hydrocortisone is good.

The initial evaluation included medical history, physical examination, hematology, serum biochemistry, urinalysis, flowmetry, chest X-ray, bone scan, skeletal survey, ultrasonography of the prostate and abdomen, and, when indicated, computerized axial tomography (CAT), nuclear magnetic resonance imaging (NMRI), and intravenous pyelogram (IVP) (Table 1). As illustrated in detail in Table 1, the same tests were performed after 3 and 6 months of treatment and then every 3rd or 6th month, depending upon the evolution of the disease. Bone scans were evaluated by an independent group of radiologists unaware of the treatment of the patients. All measurements of serum prostatic acid phosphatase (PAP) and prostatic specific antigen (PSA) as well as serum levels of testicular steroids, adrenal steroids and pituitary hormones were performed at the Laboratory of Molecular Endocrinology, Laval University Medical Center, Quebec City.

The first reported evaluation of positive objective response is at 3 months of treatment. Patients were considered as non-responders if there was no objective stabilization or regression of their disease at that time period, even though there had been subjective benefits (Table 2). Performance status and pain were evaluated on a scale of 0–4 according to the ECOG criteria (Table 3). Among the 199 patients included in this study, one was lost to follow-up (he had a complete response when last seen), three decided on their own to stop therapy while they were responding (1 complete, 1 partial and 1 stable) and treatment was interrupted in three other patients for intolerance (2 had diarrhea and 1 developed a pulmonary fibrosis).

Statistical significance was measured according to the chi-square, the one-way analysis of variance [10], the Kruskal–Wallis, test the Kolmogorov–Smirnov two-sample test and the Mann–Whitney test [11], when appropriate. The probabilities of continuing response and survival were calculated according to Kaplan and Meier method [12] and the significance assessed by the log-rank test [13].

RESULTS

Demographic data and baseline profiles for patients who received the combination therapy (LUPCP, Laval University Prostate Cancer Program) and those of study 500 of the NPCP [14] who had orchiectomy or received DES are shown in Table 4. While the age of the patients, baseline pain, baseline performance status and soft tissue metastases are not significantly different, it can be seen that a larger number of patients in the present study had elevated serum prostatic acid phosphatase (PAP) value (89 vs. 67%, $P < 0.01$), which is considered to be a factor contributing toward a poorer prognosis. Moreover, no statistical difference in the clinical response was observed between chemical or surgical castration.

Table 5 indicates that 49, 56 and 69 patients achieved complete, partial and stable responses respectively, as their best response, while 12 patients (6.5%) did not respond to treatment (progression). Figure 1 illustrates the time required to achieve stable, partial and complete objective responses in previously untreated stage D2 prostate cancer patients who received the combination therapy with Flutamide and LHRH agonist [D-Trp^6]LHRH ethylamide or orchiectomy as first treatment. The median times for response are 155, 183 and 401 days for stable, partial and complete

Table 2. Objective response to therapy in stage D2 prostate cancer according to the National Prostatic Cancer Project (NPCP) Criteria (slightly modified from Slack et al. [2, 3])

COMPLETE RESPONSE (CR)

All of the following criteria:
1. Tumor masses, if present, totally disappeared and no new lesions appeared.
2. Elevated acid phosphatase, if present, returned to normal.
3. Osteolytic lesions, if present, recalcified.
4. Osteoblastic lesions, if present, disappeared, with a negative bone scan.
5. If hepatomegaly is a significant indicator, there must be a complete return in liver size to normal - i.e. no distention below both costal margins at the xiphoid process during quiet respiration without liver movement, and normalization of all pretreatment abnormalities of liver function, including bilirubin, SGOT and γ-GT.
6. No significant cancer-related deterioration in weight (>10%), symptoms, or performance status.

PARTIAL RESPONSE (PR)

Any of the following criteria:
1. Recalcification of one or more of any osteolytic lesions.
2. A reduction by 50% in the number of increased uptake areas on the bone scan (always required if bone metastases are identified by bon scan).
3. Decrease of 50% or more in cross-sectional area of any measurable lesions (except in the prostate where 50% regression is not sufficient by itself).
4. If hepatomegaly is a significant indicator, there must be at least 30% reduction in liver size indicated by a change in the measurements, and at least a 30% improvement of all pretreated abnormalities of liver function, including bilirubin, SGOT and γ-GT.

All of the following:
5. No new site of disease.
6. Acid phosphatase returned to normal.
7. No deterioration in weight (>10%), symptoms, or performance status.

OBJECTIVELY STABLE (S)

All of the following criteria:
1. No new lesion occurred and no measurable lesion increased more than 25% in cross-sectional area.
2. Elevated acid phosphatase, if present, decreased, though need not have returned to normal.
3. Osteolytic lesions, if present, did not appear to worsen.
4. Osteoblastic lesions, if present, remained stable on the bone scan (less than 25% increase in uptake).
5. Hepatomegaly, if present, did not appear to worsen by more than a 30% increase in the measurements, and symptoms of hepatic abnormalities did not worsen including bilirubin, SGOT and γ-GT.
6. No significant cancer-related deterioration in weight (>10%), symptoms, or performance status.

OBJECTIVE PROGRESSION (P)

Any of the following criteria:
1. Significant cancer-related deterioration in weight (>10%), symptoms, or performance status.
2. Appearance of new areas of malignant disease by bone scan or x-ray or in soft tissue by other appropriate techniques.
3. Increase in any previously measurable lesion by greater than 25% in cross-sectional area.
4. Development of recurring anemia, secondary to prostatic cancer.
5. Development of ureteral obstruction

NOTE: An increase in acid or alkaline phosphatase alone is not to be considered an indication of progression. These should be used in conjunction with other criteria

Table 3. Scoring system for subjective response

Performance status (ECOG)	
Fully active	0
Active, capable of light work/domestic tasks	1
Restricted: in bed < 50% of time: capable of self-care	2
Restricted: in bed > 50% of time: limited self-care	3
Bedridden	4
Analgesic requirement	
None or no requirement for analgesics	0
Non-narcotic analgesics - occasional	1
- regular	2
Oral or parenteral narcotic analgesics - occasional	3
- regular	4
Assessment of pain	
None	0
Slight mild: little interference with non-strenuous activities	1
Quite bad: interferes with daily activities and or sleep	2
Severe: distracted by pain for much of the time	3
Intolerable: dominates existence	4

Table 4. Demographic data and baseline profiles for patients of the studies using the combination therapy with [D-Trp^6]LHRH ethylamide and Flutamide (LUPCP) and ORCH/DES (study NPCP-500) [5]

	LUPCP	NPCP-500
Total evaluated	199	83
Age (years)		
Mean	66	67
Median	65	66
Range	38-86	43-104
Baseline Pain		
Present	126 (63%)	47 (57%)
Absent	73 (37%)	31 (37%)
Not specified	0	5 (6%)
P-value (Chi-square)		.64
Baseline Performance Status		
Normal	113 (57%)	37 (45%)
Symptomatic	53 (27%)	32 (39%)
Bedridden < 50%	19 (9%)	8 (10%)
Bedridden > 50%	10 (5%)	6 (7%)
Bedridden 100%	4 (2%)	0 (0%)
P-value (Mann-Whitney)		.14
Elevated PAP (> 2ng/ml)		
Yes	177 (89%)	56 (67%)
No	22 (11%)	27 (33%)
P-value (Chi-square)		< .01
Soft Tissue Metastases		
Yes	62 (31%)	24 (29%)
No	137 (69%)	59 (71%)
P-value (Chi-square)		.71

responses, respectively, the differences being highly significant ($P < 0.01$) between each pair of curves (complete vs. partial, complete vs. stable and partial vs. stable). Table 6, third column (phase 1), expresses the same data as average numbers of days, instead of median values. Moreover, in this table and in Table 7, the patients within each category of response are divided into disseminated and non-disseminated bone metastases. The importance of this subclassification will be indicated during subsequent discussions.

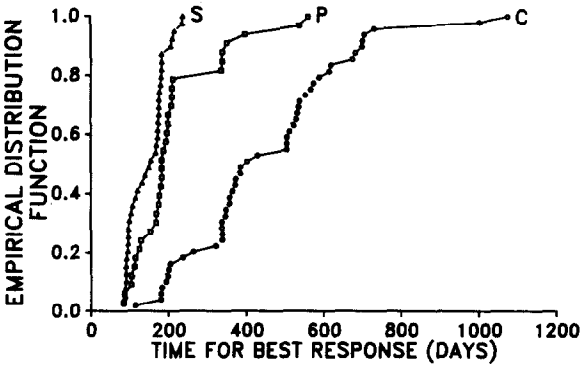

Fig. 1. Time for achieving best objective response (stable, partial or complete) in previously untreated stage D2 prostate cancer patients who received the combination therapy as first treatment. P < 0.01 between each pair of curves (complete vs. partial, complete vs. stable and partial vs. stable) according to Kolmogorov–Smirnov (2-sample test).

Table 5. Best objective response (complete, partial, stable and progression) achieved in 186 previously untreated patients with prostate cancer who received combination therapy as first treatment. The slightly modified NPCP criteria of response (see Table 3) were used

Age mean (limits)	Months of treatment mean (limits)	Best objective response			
		complete	partial	stable	progression
66 (38-86)	26 (3-59)	49 (26.3%)	56 (30.1%)	69 (37.1%)	12 (6.5%)

The probability of continuing response according to the best response category is illustrated in Fig. 2. As can be seen in this figure, the best response achieved has an influence on the probability of continuing response. In fact, while for complete responders, the 50% probability of continuing response is more than 3 years, it is reduced to 630 days for partial responders and to 517 days for stable disease. While the difference between complete responders and any of the other two groups is highly significant (log-rank test, $P < 0.0001$), there is no statistical difference between the results obtained in patients who had a partial response and those who had stable disease as best response. The same conclusion can be reached from Table 6 where the average duration of remission is approximately twice as long for complete responders as compared to those who had partial or stable responses (one-way analysis of variance after logarithmic transformation of the data, $P < 0.0001$). It should be noted that this difference is a minimal value since

Table 6. Mean duration of the three phases of responses according to category of the best response achieved (complete, partial, stable and progression) in previously untreated stage D2 prostate cancer patients

Best response	According to number of bone metastases (sample size)	PHASE 1[1] Time for best response mean ± SEM	PHASE 2 Duration of best response mean ± SEM	PHASES 1+2 Duration of remission mean ± SEM	PHASE 3 Duration of progression means ± SEM	PHASES 1+2+3 Duration of survival means ± SEM
		DAYS				
Complete	Not diss.[2] (44)	444 ± 27	563 ± 51	1007 ± 52	-	1081 ± 53
	Diss. (5)	522 ± 166	351 ± 104	874 ± 249	-	1048 ± 223
Partial	Not diss. (19)	226 ± 24	306 ± 42	532 ± 50	454 ± 75	985 ± 92
	Diss. (14)	200 ± 35	296 ± 34	496 ± 59	250 ± 52	746 ± 80
Stable	Not diss. (28)	153 ± 9	302 ± 28	456 ± 31	366 ± 42	822 ± 52
	Diss. (11)	128 ± 12	239 ± 62	366 ± 70	124 ± 25	490 ± 74
Progression	Not diss. (9)	-	-	-	-	383 ± 103
	Diss. (3)	-	-	-	-	295 ± 17

[1] As defined in Fig. 4.

[2] Refers to the fact than bone lesions can be counted individually in contrast with disseminated disease where no visible limit between lesions can be seen, giving an homogeneous image of uptake of 99 mTc-labelled methylene diphosphonate.

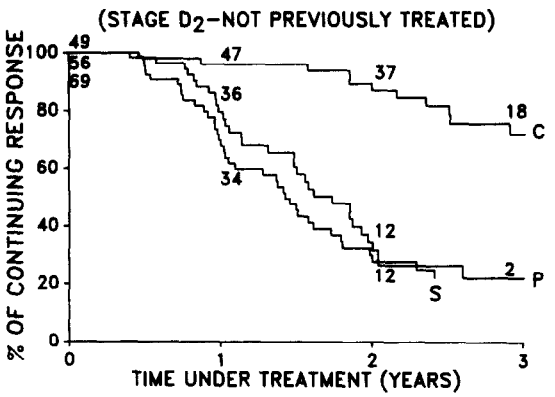

Fig. 2. Probability of continuing response according to category of best response achieved (complete, partial or stable) in previously untreated stage D2 patients who received combination therapy as first treatment.

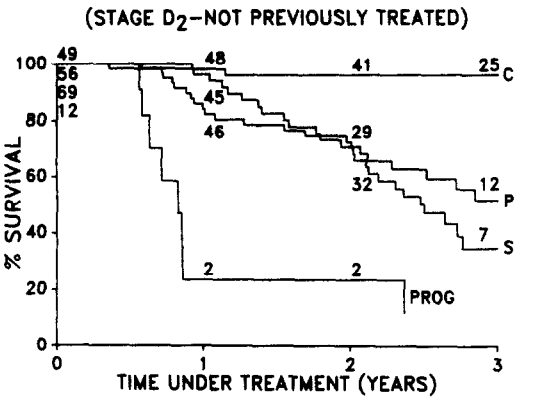

Fig. 3. Probability of survival according to the best objective response achieved (complete, partial, stable and progression) in previously untreated stage D2 prostate cancer who received combination therapy as first treatment.

the majority of complete responders are still in remission while all partial and stable responders in this table have progressed.

The probability of survival for each category of response is shown in Fig. 3. While the small group of non-responders (progression) had a median life expectancy of only 10.0 months, the best probability of survival was obtained with the complete responders with a 95.9% probability of survival at 3 years. Intermediate prognosis for survival was obtained for the partial and stable categories of response. Again, while the complete responders had a highly significant (log-rank test, $P < 0.0001$) better prognosis for survival than the other groups, there was no difference between partial and stable responders. The poor prognosis of non-responders is highly different (log-rank test, $P < 0.0001$) from that of any of the other three groups.

In the responders, there are three distinct phases of response, namely the time required to achieve the best response (phase 1), the duration of the best response (phase 2) and the time between progression (or relapse) and death (phase 3) (Fig. 4). It thus becomes of interest to study the possible correlation between these three different phases for each category of best responses. We will analyze the results obtained when excluding the stable and partial responders still in remission since it is likely that some of these patients will transfer into a better category of response before progression of the disease or death from another cause. In other words, some of these patients have not yet achieved their best possible response. The analysis is thus limited to patients who have definitively obtained their best response.

We thus analyzed the correlation between the

Table 7. Mean duration of the three phases of response according to category of the best response achieved (complete, partial, stable and progression) in previously untreated stage D2 prostate cancer patients who received combination therapy as first treatment (including partial and stable responders still in remission)

Best response	According to number of bone metastases (sample size)	PHASE 1 Time for best response mean ± SEM	PHASE 2 Duration of best response mean ± SEM	PHASES 1+2 Duration of remission mean ± SEM	PHASE 3 Duration of progression means ± SEM	PHASES 1+2+3 Duration of survival means ± SEM
		DAYS				
Complete	Not diss. (44)	444 ± 27	563 ± 51	1007 ± 52	-	1081 ± 53
	Diss. (5)	522 ± 166	351 ± 104	874 ± 249	-	1048 ± 223
Partial	Not diss. (36)	216 ± 21	359 ± 41	575 ± 46	-	815 ± 68
	Diss. (20)	174 ± 26	259 ± 31	433 ± 48	-	608 ± 74
Stable	Not diss. (55)	145 ± 7	372 ± 44	517 ± 47	-	703 ± 53
	Diss. (14)	120 ± 10	223 ± 49	343 ± 56	-	440 ± 64
Progression	Not diss. (9)	-	-	-	-	383 ± 103
	Diss. (3)	-	-	-	-	295 ± 17

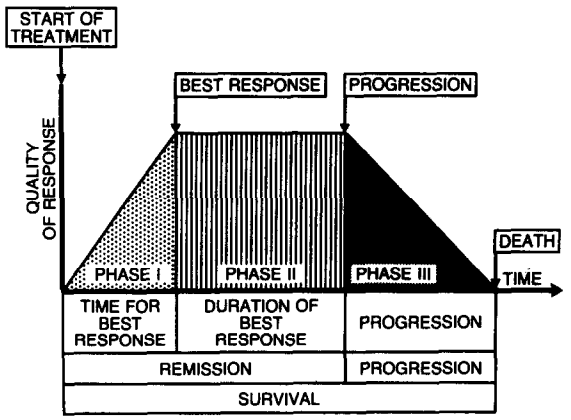

Fig. 4. Schematic representation of the three phases of response to treatment in advanced prostate cancer, namely the time required to achieve the best response (phase 1), the duration of the best response (phase 2) and the time between progression (or relapse) and death (phase 3). The total remission time is the sum of phases 1 and 2 while survival includes all three phases between diagnosis and death.

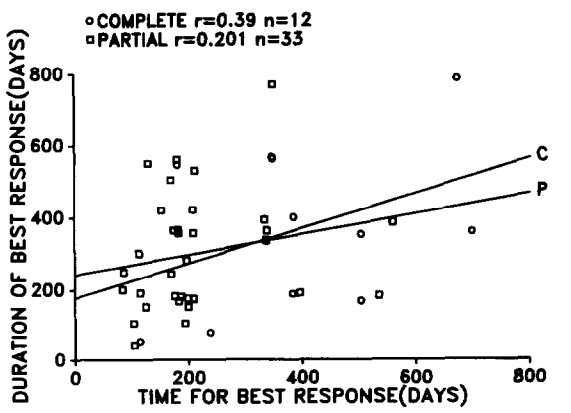

Fig. 5. Distribution of time for best response (abcissa) and duration of best response (ordinate) for complete (○), and partial (□) responders. Only patients who have achieved their best possible response and have thus progressed are included.

different phases of response within each category of response. First, analysis of the relation between time for best response (phase 1) and duration of the best response (phase 2) shows no significant correlation between these two variables for any of the three categories of responses. In other words, the time required to reach any best response has no significant effect on the duration of the response achieved. Figure 5 illustrates the distribution of phases 1 and 2 for complete and partial responses who have relapsed with no apparent positive correlation.

It is also of interest to investigate a possible correlation between the time required to achieve best response (phase 1) and the time interval between the start of relapse (or progression) and death from prostate cancer (phase 3). Analysis of the data, however, shows that the time period between progression and death has no significant correlation with the time interval required to achieve best response (phase 1) or with the duration of that best response (phase 2) (data not shown).

Since, as illustrated above, the best response achieved has an important prognostic value for duration of response and survival, it is of interest to attempt to predict response from the baseline characteristics of patients before starting treatment. It is apparent from Table 8 that a low number of bone metastases gives better chances of achieving a complete response. In the group of 49 complete responders, 44 had a median of 3.5 bone metastases while the median values were 8, 8 and 9 bone metastases for the partial, stable and progression categories (Kruskal–Wallis test, $P = 0.0006$). For partials, stables and progressors, the median number of bone metastases at start of treatment was not significantly different. Moreover, only five complete responders had diffuse bone metastases for a low percentage of 10% while diffuse bone metastases were present in 42, 28 and 25% of partials, stables

Table 8. Relationship between the number of bone metastases, pain, performance status, elevated serum prostatic acid phosphatase and the characteristics of the best objective response achieved in previously untreated stage D2 prostate cancer patients who received combination therapy as first treatment (excluding partial and stable responders still in remission, since a proportion of these patients are likely to change for a better category of response before progression or death)

Best response	No. of Pts.	Age Mean (SEM)	No. of bone metastases median or dissiminated (DISS)	No. of pts with tissues metastases		PAP (≥2ng/ml) elevated	Pain present	Performance status abnormal
				Lung	Liver			
Compl.*	44	63.7 (0.9)	3.5	4	0	38	24(55%)	13(30%)
	5 (10%)	71.0 (4.6)	DISS	1	0	5	5(100%)	4(80%)
Part.	19	65.7 (1.8)	8	0	0	17	13(68%)	10(53%)
	14 (42%)	70.0 (2.3)	DISS	2	0	14	12(86%)	11(79%)
Stable	28	66.8 (1.8)	8	0	0	24	20(71%)	11(39%)
	11 (28%)	67.6 (2.6)	DISS	1	0	11	11(100%)	10(91%)
Progr.	9	63.3 (2.8)	9	0	2	9	6(67%)	5(56%)
	3 (25%)	63.0 (3.5)	DISS	1	0	3	3(100%	2(67%)

* Includes 35 patients still in remission, one lost to follow-up and one who ceased treatment.

and progressors (chi-square test, $P = 0.010$). Diffuse bone metastases thus significantly decrease the chance of achieving a complete response.

In parallel with the number of bone metastases, the absence of pain showed a tendency to be more frequently associated with a complete response, although the difference did not reach statistical significance between any group. It is of interest to notice that pain was present in 31 of the 33 patients (94%) who had diffuse bone metastases at the start of treatment while the incidence was reduced to 55% in the complete responders who had a median of 3.5 bone metastases and to about 70% in the three other groups who had larger numbers of 8 or 9 bone metastases.

Normal performance status, however, was associated with a better chance of a complete response ($P = 0.055$, chi-square test). Again, disseminated bone metastases were accompanied by a high (82%) incidence of abnormal performance status while only 39% of patients with a more limited number of bone metastases had an abnormal performance status (chi-square test, $P < 0.02$). Another interesting observation is that all patients with diffuse bone metastases on bone scintigraphy had elevated serum prostatic acid phosphatase levels. There was no age difference between the categories of response.

As illustrated in Table 9, inclusion of the baseline values of the 23 partial and 30 stable responders still in remission had no significant effect on the baseline variables and their relation with the objective response achieved under treatment, the main conclusions being that a low number of bone metastases and the absence of diffuse bone metastases as well as a better performance status are associated with a better probability of complete response while the baseline parameters cannot predict between partial, stable and progression responses.

In Table 9, all patients are included with the understanding that the number of complete and partial responses is likely to increase before progression or death from patients still in the stable and partial response categories at the time of analysis. The data concerning the partial and stable patients still in remission have been added to avoid the possibility that these patients who have already progressed or achieved their best response (Table 8) could represent an unfavorable subpopulation. Although not providing definitive proof, the absence of a significant effect upon addition of the patients still in remission suggests an absence of bias in Tables 6 and 8.

DISCUSSION

The present data clearly demonstrate the clinical importance of categorizing the patients treated for advanced prostate cancer according to strict objective criteria of response in order to more accurately predict duration of response, quality of life and survival. The dramatic advantages of obtaining a complete response are clearly illustrated while the stable category of response which has been criticized on many occasions, has benefits which are almost as good as those of the partial response.

Duration of the positive response has obvious implications for quality of life and survival. As

Table 9. Relationship between the number of bone metastases, pain, performance status, elevated serum prostatic acid phosphatase and the characteristics of the best objective response achieved in previously untreated stage D2 prostate cancer patients who received combination therapy as first treatment (including partial and stable responders still in remission)

Best response	No. of Pts.	Age Mean (SEM)	No. of bone metastases median or dissiminated (DISS)	NO OF SOFT TISSUES METASTASES		PAP (2≥ng/ml) elevated	Pain present	Performance status abnormal
				Lung	Liver			
Compl.*	44	63.7 (0.9)	3.5	4	0	38	24	13
	5 (10%)	71.0 (4.6)	DISS	1	0	5	5	4
Part.	36	67.4 (1.4)	8	0	0	32	21	15
	20 (36%)	70.5 (1.8)	DISS	2	0	19	18	14
Stable	55	65.7 (1.3)	6	0	0	46	31	14
	14 (20%)	66.7 (2.3)	DISS	1	0	14	12	11
Progr.	9	63.3 (2.8)	9	0	2	9	6	5
	3 (25%)	63.0 (3.5)	DISS	1	0	3	3	2

* Includes 35 patients still in remission, one lost to follow-up and one who ceased treatment.

illustrated in Fig. 2, the 50% probability of continuous response for complete responders is more than 3 years while it is of 630 and 517 days, respectively, for partial and stable responders. There is in fact no significant difference in the duration of response for partial and stable responders although there is a tendency for a more favorable evolution for the partial responders.

The most meaningful difference is however on survival. As can be seen in Fig. 3, while only three deaths from prostate cancer occurred during the first 3 years in the group of 49 complete responders for a 95.9% probability of survival at 3 years, the 50% probability of survival is 37.8 and 30.3 months for the partial and stable responders, respectively. In study 500 of the NPCP, where the patients received standard therapy (orchiectomy or DES), the median survival for partial and stable responders was 34.4 and 37.2 months, respectively [3, 6]. Comparison of the data of NPCP study 500 where standard hormone therapy was used and our data using the combination therapy indicate that different degrees of androgen blockade lead to different proportions of responses (more complete and less progression with the combination therapy) [15]. However, it appears that a category of response obtained by either standard or combination therapy has the same prognostic value. In other words, a complete or partial response obtained by standard or combination therapy has the same prognostic value for duration of response and survival. The difference between treatments resides exclusively in the ability of the combination therapy to achieve more complete responses and less non-responders than standard therapy.

In another study, for the small number of patients who became partial after stabilization, the life expectancy was similar to that of those who remained stable [3]. In the same study, the probability of survival for complete responders was significantly superior to that of all other groups while that of non-responders was significantly poorer than all other groups. In fact, all available results indicate close similarity of the prognosis for stable and partial responses.

The criteria outlined in Table 2 take into account the fact that metastatic prostatic cancer almost invariably involves osteoblastic lesions [16] which are best evaluated by bone scintigraphy [17, 18]. Skeletal survey, in addition to confirming bone scan for osteoblastic lesions, permits follow-up of the rare osteolytic lesions. The criteria for evaluating soft tissue metastases are also included.

Although there is debate about the prognosis of patients having metastases limiting to bone vs. those having soft tissue lesions [19], it seems clear that the prognosis is poorer for those who have lesions in the lungs, liver or bone, compared with those with disease limited to distant lymph nodes [20]. CT and NMI scan are becoming routinely used for assessing changes in pelvic lymph node metastatic changes. The availability of new technology, especially transrectal ultrasonograpy, is likely to be an important improvement in monitoring evolution of local disease [21].

The value of the objective criteria developed by

the NPCP and used in most recent clinical trials is also supported by the constancy of the results observed following equivalent endocrine treatments namely orchiectomy, estrogens and LHRH agonists alone [5, 22, 23]. The objective criteria of response of stage D2 prostatic cancer developed by the NPCP have been reviewed periodically to adjust to new findings, the last version [2, 3] appearing as Table 2. The EORTC criteria of response [4] are, to a very large extent, identical to those developed by the NPCP. While complete response is the same for both sets of criteria, the differences are the following:

(a) Partial response: The NPCP criteria require a decrease of 50% or more in cross-sectional area of any measurable lesion while the EORTC criteria require a decrease of 50% or more in at least 50% of all measurable lesions. Moreover, while the NPCP requires a reduction by 50% in the number of increased uptake areas on the bone scan, the EORTC criteria of partial response are limited to a recognizable decrease in activity shown on at least two successive scans. Since bone metastases are present in more than 95% of patients having stage D2 disease, the NPCP criteria of partial response are somewhat more severe than those of EORTC.

(b) For NPCP, stable disease indicates that no measurable lesion increases more than 25% in cross-sectional area while for the EORTC, an increase of less than 50% in either direction is classified as no change.

(c) Progression: For the NPCP, an increase in any previously measurable lesion by greater than 25% in cross-sectional area is classified as progression while an increase of 50% or more is required for progression according to the EORTC.

Since both sets of criteria show minimal differences, it appears justifiable to propose the universal use of common objective criteria which have been used and tested in the largest series of clinical studies of stage D2 prostate cancer. We have thus chosen the NPCP criteria [2, 3] with minor changes, namely the addition of 'except at the prostatic level' for criteria 3 of partial response. In fact, since refinements in ultrasonography now permit accurate measurement of local prostatic tumor size and that local tumor regression is a general finding after combination therapy, the number of partial responders would be markedly increased if a 50% reduction in the local prostatic tumor is to be sufficient by itself to enter into the category of partial responders. We feel that in the presence of bone metastases, a 50% reduction in the number of increased uptake areas on the bone scan is required before classification as partial response.

The existence of prostatic tumors having variable growth rates is well recognized [2, 3, 24]. Although no precise data are available, it is felt that the dichotomy between fast-growing and slow-growing tumors is less clear when distant metastases have appeared [25]. Although no data are available on the progress rate in the absence of treatment, it is well recognized that the growth rate varies in patients receiving the same endocrine therapy, thus indicating heterogeneity of androgen-sensitivity and/or growth rate.

The heterogeneity of growth rate or, in other words, the presence of fast- and slow-growing tumors, is at the basis of the problems of stable disease. The category of stable disease has generated much discussion among urologists and oncologists. In fact, while stable disease is included as positive response along with complete and partial responses by the US NPCP [2, 3], the EORTC did not consider stable disease as a positive objective response [4]. The stable category reflects a halt in the progressive state of the disease [1]. Patients who do not continue to worsen during the first 3 months of evaluation are termed 'stable'. The dispute about the category of stable patients originates from the uncertainty about the number of patients who would remain stable in the absence of treatment. Since no patients in disease progression are left untreated, it is unlikely that such clinical data will ever become available to settle this issue. However, when comparison is made between different treatments, the occurrence of stable disease should be equally distributed among groups and the use of this category of response appears valid. Moreover, the present data clearly demonstrate the prognostic value of the stable category of response with probabilities of continuing response and survival being almost superimposable to those of partial response (Figs. 2 and 3).

While the NPCP criteria include patients in the stable category after 3 months of treatment, we have extended this period to 6 months and only patients showing no progression and no change at 6 months are included in the category of stable response. Although particularly slow growing tumors could well show no change at 6 months despite some real but undetectable growth, their proportion in the stable category is likely to be minimal.

Despite the uncertainty about the role of treatment in the proportion of patients who show stable disease, it is clear that this category has a major prognostic value and should be used. The remaining question is the inclusion of stable disease in the responders along with partial and complete responses. Considering the almost superimposable survival rates of the partial and stable categories, it seems logical to include stable responders in the group of responders. However, it seems essential to

always indicate the distribution of patients among complete, partial and stable responses in order to provide a more informative description of the effect of therapy. The vast experience gained in the objective evaluation of stage D2 prostate cancer patients by a large number of investigators provides us (Table 2) with objective criteria of response which, although still not perfect, permit a precise and clinically valid assessment of the effect of new therapies.

REFERENCES

1. Schmidt JD, Johnson DE, Scott WW, Gibbons RP, Prout GR Jr, Murphy GP. The National Prostatic Cancer Project: chemotherapy of advanced prostatic cancer, evaluation of response parameters. *Urology* 1976, **7**, 602–610.
2. Slack NH, Murphy GP, Participants in the National Prostatic Cancer Project. Criteria for evaluating patient responses to treatment modalities for prostatic cancer. *Urol Clin North Am* 1984, **11**, 337–342.
3. Slack NH, Brady MF, Murphy GP, Investigators in the National Prostatic Cancer Project. Stable versus partial response in advanced prostate cancer. *The Prostate* 1984b, **4**, 401–415.
4. Pavone-Macaluso M, De Voogt HJ, Viggiano G *et al.* Comparison of diethylstilbestrol, cyproterone acetate and medroxyprogesterone acetate in the treatment of advanced prostatic cancer: final analysis of a randomized phase III trial of the European Organization for Research on Treatment of Cancer Urological Group. *J Urol* 1986, **136**, 624–631.
5. Cancer Statistics, CA-A Cancer Journal for Clinicians: *Am Cancer Soc* 1988, **37**, no. 1.
6. Simard J, Luthy I, Guay J, Bélanger A, Labrie F. Characteristics of interaction of the antiandrogen flutamide with the androgen receptor in various target tissues. *Mol Cell Endocrinol* 1986, **44**, 261–270.
7. Labrie F, Veilleux R. A wide range of sensitivities to androgens develops in cloned Shionogi mouse mammary tumor cells. *The Prostate* 1986, **8**, 293–300.
8. Luthy I, Labrie F. Development of androgen resistance in mouse mammary tumor cells can be prevented by the antiandrogen flutamide. *The Prostate* 1987, **10**, 89–93.
9. Labrie F, Veilleux R, Fournier A. Low androgen levels induce the development of androgen hypersensitive cell clones in Shionogi mouse mammary carcinoma cells in culture. *J Natl Cancer Inst* 1988, in press.
10. Armitage T. *Statistical Methods in Medical Research.* Oxford, Blackwell, 1971.
11. Conover WJ. *Practical Nonparametric Statistics*, 2nd edn. New York, J. Wiley & Sons, 1980.
12. Kaplan EJ, Meier P. Non parametric estimation from incomplete observations. *Am Stat Ass J* 1958, **53**, 457–481.
13. Cox DR, Oakes D. *Analysis of Survival Data.* London, Chapman and Hall, 1984.
14. Murphy GP, Beckley S, Brady MF *et al.* Treatment of newly diagnosed metastatic prostate cancer patients with chemotherapy agents in combination with hormones versus hormones alone. *Cancer* 1983, **51**, 1264–1272.
15. Labrie F, Dupont A, Bélanger A. LHRH agonists and antiandrogens in prostate cancer. In: Ratliff TL, Catalona WJ, eds. *Genitourinary Cancer.* Boston, Martinus Nijhoff, 1987, 157–200.
16. Whitmore WF. The natural history of prostatic cancer. *Cancer* 1973, **32**, 1104–1112.
17. Pollen JJ, Gerber K, Ashburn WL, Schmidt JD. The value of nuclear bone imaging in advanced prostatic cancer. *J Urol* 1984, **125**, 222–223.
18. Slack NH, Murphy G, Participants of the National Prostatic Cancer Project. Criteria for evaluating patient responses to treatment modalities for prostatic cancer. *Urol Clin North Am* 1980, **11**, 337–342.
19. Eagen RT, Hahn RG, Myers RP. Adriamycin (NSC-123127) versus 5-fluorouracil (NSC-19893) and cyclophosphamide (NSC-6721) in the treatment of metastatic prostate cancer. *Cancer Treat Rep* 1976, **60**, 115–117.
20. Slack NH, Bross IDJ. The influence of site of metastatis on tumor growth and response to chemotherapy. *Br J Cancer* 1975, **32**, 78–86.
21. Lee F, Littrup PJ, Kumasaka G, Borlaya GS, McLeary RD. The use of transrectal ultrasound in the diagnosis, guided biopsy, staging and screening of prostate cancer. *Radiographics* 1987, **7**, 627–629.
22. The Leuprolide Study Group. Leuprolide versus diethylstilbestrol for metastatic prostate cancer. *New Engl J Med* 1984, **311**, 1281–1286.
23. Smith JA, Glode LM, Wettlaufer JN *et al.* Clinical effects of gonadotropin-releasing hormone analogue in metastatic carcinoma of the prostate. *Urology* 1985, **20**, 106–112.
24. Franks LM. Etiology, epidemiology, and pathology of prostatic cancer. *Cancer* 1973, **32**, 1092–1095.
25. Flocks RH. Clinical cancer of the prostate. *JAMA* 1965, **193**, 559–562.