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Comparison Between Continuous and Intermittent Administration of Estracyt in the Treatment of Carcinoma of the Prostate

W. Vahlensieck[1]*, G. Wegner[1], H.-D. Lehmann[2], G. Franzen[2], L. Steffens[3] and S. Wählby[4]

1 Department of Urology, University Hospital, Bonn
2 Cologne-Holweide Hospital and
3 St. Antonius-Hospital, Eschweiler, FRG, and
4 Medical Department, Research Laboratories, AB Leo, Helsingborg, Sweden

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Summary. Ninety-five patients with prostatic carcinoma, stages A–D and of all histological grades were randomized between a continuous and an intermittent treatment regimen of Estracyt^R (estramustine phosphate). 77 patients were evaluated (46 with continuous and 31 with intermittent therapy). Remissions were seen in 13 (28%) and (13%), respectively. Stable disease was recorded in 30 (65%) and 24 (77%), respectively. Progression experienced 3 (6%) and 3 (10%) respectively. 19% were unable to continue therapy due to intolerable gastrointestinal side effects (7 patients receiving continuous and 8 patients receiving intermittent therapy).

Key words: Prostatic cancer, Estracyt, Continous vs. intermittent administration, Therapeutic effect, Side effects.

Introduction

Estracyt^R (estramustine phosphate) has been reported to have a beneficial effect in advanced prostatic carcinoma. The drug has been most widely used in hormone resistant patients, where an objective response rate of 37% has been reported. About 45% of patients experience a subjective response [2, 8, 10, 11].

In addition, these reports [1–3] indicate that the response in previously untreated patients is very favorable with an overall response rate of approximately 90%. Objective response amounts to about 75% whereas the remaining 15% are subjective responses.

One mode of action of Estracyt is depression of gonadotropins resulting in low plasma testosterone levels, as well as influence on other hormones [4, 7]. This depression has been shown to occur with low dose of estramustine [4] and there are indications that depression persists 2–3 months after discontinuation of the therapy [3].

Based on the assumption that a reduced testosterone level is important for the clinical efficacy of Estracyt, we performed a randomized study to compare the efficacy of intermittent versus continuous treatment on newly diagnosed patients with carcinoma of the prostate from 1976 to 1982. A total 95 patients were randomized, and this report covers the evaluation up to 25 months of treatment. Preliminary reports of this study have been published [13, 14].

Materials and Methods

All patients entered into the study had histologically or cytologically confirmed carcinoma of the prostate. The patients were entered into the study immediately after diagnosis, irrespective of clinical stage. Patients with other malignant diseases, severe liver damage or with a platelet count less than 75,000/μl were excluded, as well as those who were in a terminal state.

Initial evaluation consisted of history and physical examination, full blood count, serum chemistry, urinalysis, chest and skeletal X-ray and bone scan, lymphangiography and excretory urography. All patients received prophylactic mammary irradiation. Routine periodic clinical evaluations, including full blood count, serum chemistry and urinalysis were performed after 2, 7, 13, 19 and 25 months. In addition, appropriate X-rays and bone scans were performed after 13 and 25 months. Further biopsies were also performed at these intervals.

Following classification according to primary tumor (T-category), *and* if metastases were detectable or not (N & M categories) *and* histopathological classification (G category), the patients were randomly allocated to *either* a continuous treatment regimen with 2 capsules b.i.d. (560 mg daily) for as long as a response was maintained, *or* an intermittent treatment regimen. In this latter regimen the patients received an initial period of two months of therapy and thereafter two months drug free period followed by one month on treatment in sequence. The dosage was 2 capsules b.i.d. (560 mg daily) during treatment periods.

The response criteria used were the same as those employed by the National Prostatic Cancer Project [12]. Effect was classified as remission when a significant reduction in primary tumor and metastases as well as normalization of elevated acid phosphatases was re-

* *Request for reprints:* Department of Urology, University Hospital, Sigmund-Freud-Straße 25, D-5300 Bonn 1, Federal Republic of Germany

Table 1. Patient characteristics at entry to study

	Continuous	Intermittent
No. randomized	51	44
Early drop-outs	5	13
Evaluable for effect	46	31
Age of evaluable patients		
median	69.0	68.5
range	50–77	56–79
T-category of evaluable patients		
T1	13	8
T2	15	14
T3	12	4
T4	6	5
N-category of evaluable patients		
N0	22	19
N1	2	5
N2	7	0
N3	1	3
N4	4	1
NX	10	3
M-category of evaluable patients		
M0	29	18
M1	17	13
M1a	0	0
M1b	2	2
M1c	4	0
M1d	11	11
G-category of evaluable patients		
G1	20	13
G2	11	8
G3	15	10

Table 2. Therapeutic effect of the two regimens of Estracyt with respect to T-, M-, and G-categories. (*R*, remission; *SD*, stationary disease; *P*, progression)

Patient category	Treatment regimen						X^2-lin trend
	Continuous			Intermittent			
	R	SD	P	R	SD	P	
T1–2, M0	5	17	0	0	16	0	$p = 0.119$
T1–2, M1	1	4	1	2	3	1	$p = 0.505$
T3–4, M0	2	5	0	0	2	0	$p = 0.951$
T3–4, M1	5	4	2	2	3	2	$p = 0.460$
Total	13	30	3	4	24	3	$p = 0.131$
G1	5	14	1	1	12	0	$p = 0.427$
G2	3	6	2	2	6	0	$p = 0.559$
G3	5	10	0	1	6	3	$p = 0.026$ (*)

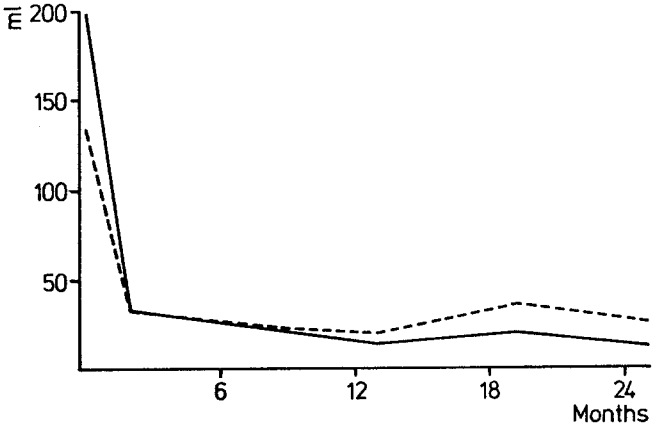

Fig. 1. Residual urine in patients with initially elevated values, excluding patients who have undergone TUR. Curves of mean values. —— Estracyt continuous, – – – Estracyt intermittent

corded at two assessments 6 months apart, and progression upon signs of deterioration such as appearance of new metastatic lesions or elevation of acid phosphatases. In all other cases the disease was judged as stable.

Of 95 randomized patients, 18 could not be evaluated for effect due to loss to follow-up before 2 months on study (6 patients), early adverse reactions (10 patients), death within 2 months (1 patient) and refused further treatment at 2 months' control (1 patient). Patient characteristics of 77 evaluable patients are shown in Table 1.

To detect differences in response between treatments, the X^2-test for linear trend, according to Armitage [1], was used. Duration of response and survival were defined as the period from start of treatment until observation of progressive disease or death, respectively. Differences between treatments with regard to response duration and survival, were analysed using the generalized Wilcoxon test as described by Gehan [5].

Results

The therapeutic effect in patients with regard to T- and M-categories as well as G-categories and total, is seen in Table 2. Such an extensive break-down of the patient material will Remissions were seen more often following a continuous treatment (28% vs 13%) whereas there was no statistically significant difference between stable disease (65% vs 77%) and progression (6% vs 10%) rate.

Duration of response is related to the time of observation of this study. No patient of the 17 in remission and 3/54 of patients in SD have experienced a progression. Two of three patients had advanced disease with skeletal metastases already at diagnosis and the third had a poorly differentiated tumor.

The effect of therapy on local disease may be seen from Fig. 1, which shows mean residual urine at different times in patients with residual urine before treatment. Patients who had a TUR were excluded. It can be seen that mean residual urine drops during the first two months of treatment and remains at a low level during the rest of the survey.

The therapeutic effect was assessed in patients with metastatic disease by measurement of acid prostatic phosphatases. Figure 2 shows the mean phosphatase values from the start of therapy up to 25 months later in patients with ini-

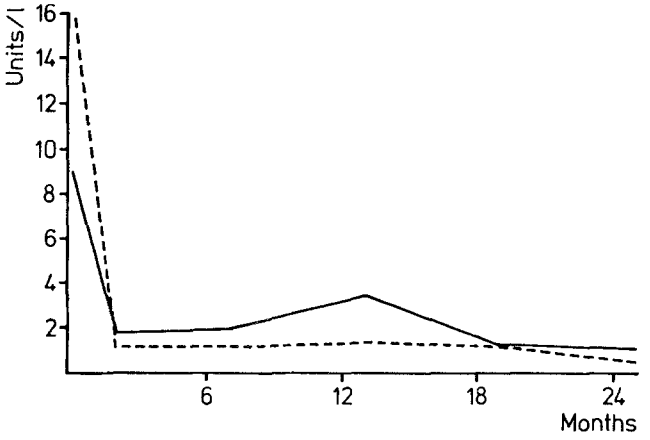

Fig. 2. Prostatic phosphatase values in patients with initially elevated values. Curves of mean values. —— Estracyt continuous, – – – Estracyt intermittent

Table 3. Adverse reactions. Figures represent number of patients. Figure in parenthesis indicates number of patients where treatment had to be withdrawn

Type of adverse reaction	Appearing within		
	first 2 months	Continuous	Intermittent
Gastrointestinal (nausea, vomiting)	19 (4)	9 (3)	10 (8)
Cardiovascular			
Edema	7 (1)	8 (1)	2
and/or Flebitis	1		4 (1)
and/or Embolism		1	
Liver (elevated transaminases and/or bilirubin)	3 (2)	2	1
Gynecomastia	23	19	14
Drug allergy	2	4	1
Others	0	5	2
No. of patients evaluable	88	50	38

tially elevated phosphatases. The main fall occurs during the first 2 months of therapy. Thereafter the phosphatases remain within normal limits.

Adverse reactions were evaluated in 88 patients. In recording adverse reactions, those appearing before two months of therapy are shown separately because the treatment up to this point is equal. Thereafter adverse reactions are shown with respect to treatment group. Table 3 shows a summary of adverse reactions and frequency of therapy withdrawal for that reason.

It was observed that transaminases (GPT and/or GOT) were influenced, with slightly elevated values at 2 months in 36 patients (41%). In the majority of cases, the elevated value did not exceed normal limits and returned to the initial level within 6–12 months (Fig. 3a). Only 6 patients experienced pathologically elevated values, resulting in withdrawal of medication in 2. Contrary to these findings, in 12/14 patients with initially elevated transaminases, a normalization occurred during treatment (Fig. 3b).

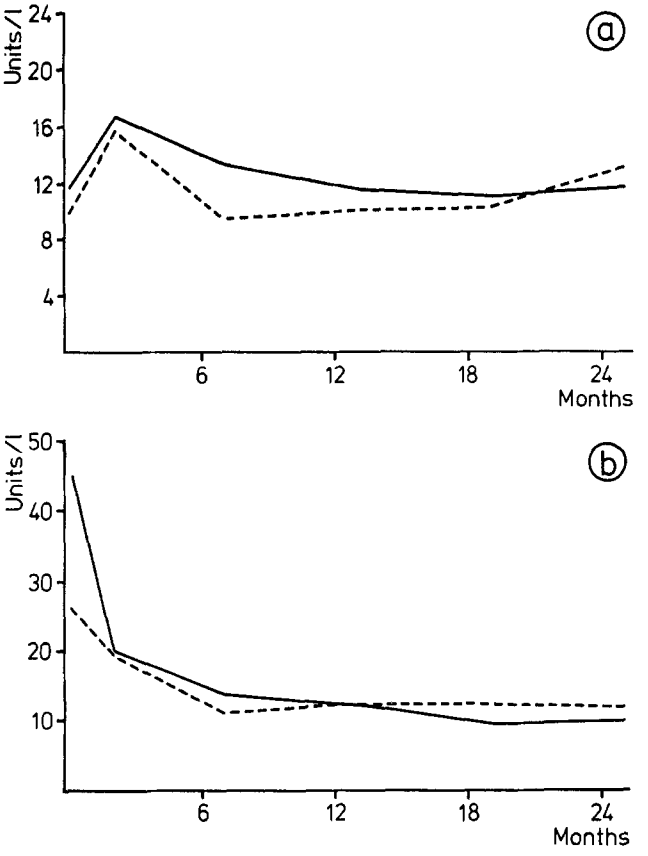

Fig. 3a, b. Serum aspartate-aminotransferase (s-GOT) in patients with (a) initially normal values and (b) initially elevated values. Curves of mean values. —— Estracyt continuous, – – – Estracyt intermittent

Two patients taking intermittent therapy experienced clinical depression clearly related to the treatment cycles, i.e. during treatment free periods the patients were in good psychological state. Of the remaining 5 patients with side effects, 2 had dry skin, 2 had orthostatism and 1 had pubic alopecia.

Discussion

As noted in several earlier studies, the therapeutic effect of Estracyt in previously untreated patients was found to be good with only 6 patients not responding to therapy; 92% of patients experiencing an effect. The rate of objective tumor regression was 22%. With respect to extent of disease, as reflected from T and M categories, no difference was found between the two therapeutic alternatives. When grouping the patients according to histology, it was found the same. The response rate agrees with earlier findings [8].

Of the adverse reactions, the gastro-intestinal disturbances were frequent (49% of patients) and were the major cause of treatment limitation, causing therapy tobe withdrawn in 15 patients (19%). It was surprising to note that of 10 patients with gastro-intestinal symptoms when given Estracyt intermittently, therapy still had to be withdrawn in 8 patients. The corresponding figures for the continuous treatment was 9 patients with only 3 having to cease treatment. These data support the findings of others [6] that during prolonged therapy with Estracyt an adaption to this kind of disturbance seems to occur.

The data on transaminases indicate a hepatic effect, which may be similar to the effect of diethylstilbestrol diphosphate [9]. The decrease in elevated transaminases may indicate regression of liver metastases.

The frequency of gynecomastia seemed to be high despite preventive measures of mammary irradiation prior to the initiation of therapy.

The conclusion of this study is that intermittent therapy is sufficient to control prostatic cancer as well as continuous therapy. Gastro-intestinal disturbances are more frequent when given Estracyt intermittently.

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Prof. Dr. W. Vahlensieck
Department of Urology
University Hospital
Sigmund-Freud-Straße 25
D-5300 Bonn 1
FRG