

Clinical Trial Protocol

**THERAPY OPTIMIZATION TRIAL OF A COMBINATION OF
ORAL ESTRAMUSTINE PHOSPHATE (ESTRACYT®)
AND ORAL ETOPOSIDE (VEPESID®) IN
HORMONE RESISTANT METASTATIC PROSTATE CANCER**

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1. SUMMARY

Prostate cancer is one of the most common malignancies in men aged over 70 years and is still associated with a high rate of mortality. Though localized tumors are effectively controlled by locally effective means of treatment, treatment of metastatic prostate cancer remains unsatisfactory. Approximately 90 % of metastatic tumors respond to hormone therapy or orchiectomy, however, in most patients eventually resistance develops and disease progression ensues. Following the failure of orchiectomy or hormone therapy, patients have an estimated median survival of 6 to 9 months. In this group of hormone-refractory patients, the optimization of chemotherapeutic strategies has led to new treatment options.

Based on the following considerations, the efficacy of combined chemotherapy with estramustine phosphate (Estracyt®) and etoposide (Vepesid®) will be studied in an open, uncontrolled therapy optimization trial:

Estramustine phosphate is an effective agent in hormone resistant prostatic carcinoma with an overall response rate after single agent chemotherapy of 37%.

In vitro data suggested synergistic activity of estramustine phosphate (Estracyt®) and etoposide (Vepesid®). Estramustine has been shown to increase the amount of topoisomerase II DNA crosslinking induced by etoposide.

A recent clinical study by Pienta and coworkers turned out that the combination of oral estramustine phosphate (Estracyt®) and oral etoposide (Vepesid®) was both effective and well tolerated in patients with hormone-refractory prostatic cancer.

Estramustine phosphate (Estracyt®) yields only minor bone marrow suppression and can thus be combined with myelosuppressive chemotherapy. On the other hand, etoposide (Vepesid®) shows only minor cardiovascular and gastrointestinal toxicity and can be applied in elderly patients as well.

A treatment schedule with combination of oral estramustine phosphate (Estracyt®) and oral etoposide (Vepesid®) is convenient for both the physician and the patient, allowing for treatment on an outpatient basis.

The primary objective is to determine efficacy and side effects of combined chemotherapy with oral estramustine phosphate (Estracyt®) and oral etoposide (Vepesid®) in patients with hormone resistant prostate cancer. The primary response parameter are an at least 50 % reduction of the initial serum concentration of PSA in plasma as a measurable parameter and for subjective response the improvement of performance status or reduction of the pain score. Estracyt® will be applied as 140 mg capsules dosed as close to 10 mg/kg/d as the dosage form allows, split in three doses daily. Vepesid® will be given as 50 or 100 mg capsules per os in divided doses as close to 50 mg/m²/d as the dosage form allows. Both drugs are given for 21 days every 28 days. Combined treatment is continued until disease progression occurs.

2. INTRODUCTION AND RATIONALE

2.1 Cancer of the Prostate

Prostate cancer is one of the most common malignancies in men aged over 70 years [Balducci 1989, Frank 1991] and is still associated with a high rate of mortality [Soloway 1993, Hanks 1993]. It has recently become the second most commonly reported cancer of the male population in Europe and North America, and the estimated annual incidence of newly diagnosed cases in Europe is 85.000 cases per year [Denis 1990, 1993, Boring 1993]. The autopsy incidence of histologic prostate carcinoma is 14 % to 46 % in men over 50 years of age [Suen 1974].

Approximately 60 % of patients have localized cancer when first diagnosed. Most of these patients are asymptomatic or show symptoms of lower urinary tract obstruction [Frank 1991]. Advanced presentation includes bladder outlet obstructive symptoms with urinary retention, ureteral obstruction, anemia and cachexia. Bone pain is the most frequent complaint of patients with metastatic disease.

Digital rectal examination remains the gold standard for detection of prostatic carcinoma. For diagnosis, needle biopsy with histologic or cytologic examination is inevitable. Transrectal ultrasound allows for preoperative estimation of local tumor size. CT scans of pelvis and abdomen as well as bone scans and chest films are necessary for systemic tumor staging. Although the recent introduction of screening for elevated levels of prostate-specific antigen (PSA) has improved prostate cancer detection rates [Catalona 1994], many patients remain undiagnosed until the disease has progressed to a locally advanced or metastatic stage and is beyond the local control of radical prostatectomy or definitive radiotherapy [Bono 1990].

The TNM categories have been widely accepted for prostate cancer classification (**table 1**). Incidental finding by the pathologist and clinically unsuspected carcinoma is classified as stage T1. Clinically palpable lesions in the prostate are either stage T2a, T2b (involving one lobe) or T2c (involving two lobes). Extension beyond the prostatic capsule without evidence of metastases defines stages T3 or T4.

The vast majority of prostatic cancers are adenocarcinomas. Multiple grading systems are available, with the Gleason grading score being the most frequently utilized. It is based on both the tumor's glandular differentiation and growth pattern. The score ranges from 2 to 10 and has been shown to be predictive of associated lymph node metastasis (Paulson 1979).

Table 1: TNM classification for prostate carcinoma

Stage	Characteristics
T1	Clinically unapparent tumor, not palpable nor visible by imaging T1a Tumor an incidental histological finding in 5% or less of tissue resected T1b Tumor an incidental histological finding in more than 5% of tissue resected T1c Tumor identified by needle biopsy
T2	Tumor confined within the prostate T2a Tumor involves half of a lobe or less T2b Tumor involves more than half of a lobe but not both lobes T2c Tumor involves both lobes
T3	Tumor extends through the prostate capsule T3a Unilateral extracapsular extension T3b Bilateral extracapsular extension T3c Tumor invades seminal vesicle(s)
T4	Tumor is fixed or invades adjacent structures other than seminal vesicles T4a Tumor invades bladder neck and/or external sphincter and/or rectum T4b Tumor invades levator muscles and/or is fixed to pelvic wall
N1	Single lymph node metastasis < 2 cm diameter
N2	Single lymph node metastasis with a diameter of 2 - 5 cm or multiple < 5 cm
N3	Lymph node metastasis > 5 cm
M1	distant metastasis M1a Non-regional lymph node M1b Bone(s) M1c Other site(s)

The classic options of prostate cancer treatment include surgery, radiotherapy, hormonal treatment and chemotherapy. While 10-year-survival rates of 60 - 90 % are achieved in localized tumor stages, prognosis is considerably worse for patients with positive lymph nodes or distant metastasis (**table 2**). Given the short life-expectancy of elderly patients with advanced prostate cancer, palliation and improvements in the patient's overall performance (e.g., mobility, pain, ability to work) and, as a consequence, improvements in the quality of life, are likely to be as important to the patient as any modest improvement in survival.

Table 2: Prostate cancer: diagnosis, stage and prognosis [Scardino 1992]

Percentage of patients	Stage ¹	Characteristic	10-year cancer-specific survival rate
30 %	M1	distant metastasis	10 %
20 %	N1-3	lymph node metastasis	40 %
10 %	T3-T4	localized, extending beyond capsule	60 %
40 %	T1-T2	localized, limited to gland	80 - 95 %

¹ based on clinical stage, pelvic lymph node dissection, bone scan and alkaline phosphatase

2.2 Therapeutic Strategies in Prostatic Cancer

Localized tumors of the prostate require locally effective means of treatment. Radical prostatectomy with sampling of pelvic lymph nodes as well as supervoltage irradiation with a

dose of 60 Gy to 70 Gy are effective therapies in tumors limited to the prostatic gland or in locally invasive cancers with extracapsular spread [Frank 1991, Hanks 1993].

Treatment of metastatic prostate cancer has for almost 50 years focused on orchiectomy and administration of estrogens. Although there is a shortage of conclusive data on the etiology of prostate cancer, the hormone dependence of this tumor has been recognized in 1941, when Huggins and Hodges reported that orchiectomy induced the regression of metastatic disease [Huggins 1941]. Bilateral orchiectomy (surgical castration) is still acknowledged as a highly successful method of treating patients with metastatic prostate cancer. Estrogen therapy, usually administered as diethylstilbestrol 3 mg/d, represents a non-surgical alternative of treating patients with advanced prostate cancer. Both methods will remove 90 - 95 % of circulating testosterone [Vogelzang 1992, Shearer 1973].

Luteinizing hormone-releasing hormone agonists (LHRH analogs) have been shown to be equivalent to orchiectomy or estrogen therapy [Stege 1995]. However, they are associated with a transient increase in bone pain and outlet obstruction. Flutamide is a non-steroidal anti-androgen blocking the uptake and/or nuclear binding of androgens in target tissues. Combined androgen ablation (medical castration) using an LHRH agonist and flutamide has been shown to produce significantly better results, particularly in patients with minimal disease [Crawford 1989].

Overall, approximately 90 % of metastatic tumors respond to hormone therapy or orchiectomy. Side effects (including loss of libido, azoospermia and impotence) may compromise the quality of life in individual patients. Median survival is one to three years in ambulatory patients. Eventually resistance develops, possibly due to the emergence of hormone-independent cancer cells or mutations of androgen receptors and disease progression ensues [Balducci 1989, Van Poppel 1991].

Following the failure of orchiectomy or hormone therapy, patients have an estimated median survival of 6 to 9 months [Eisenberger 1985]. In hormone resistant patients, the optimization of chemotherapeutic strategies has led to new treatment options. Estramustine phosphate (Estracyt®) is one of the most active compounds in single agent chemotherapy trials. Other drugs used in prostate cancer chemotherapy include anthracyclines like doxorubicin, the vinca alkaloids vinblastine and vindesine, the epipodophyllotoxin etoposide (Vepesid®) as well as mitomycin-C. Standard alkylating agents and antimetabolites have produced minimal antitumor activity with objective response rates of less than 20 %.

2.3 Estramustine Phosphate (Estracyt®) in Prostatic Cancer

Estramustine phosphate (Estracyt®) is a complex of 17β -estradiol and a nonnitrogen mustard linked together by a carbamate ester bridge (**figure 1**).

Pharmacokinetic properties

Approximately 75 % of estramustine phosphate is absorbed after oral administration [Forshell 1988]. Intestinal uptake is markedly reduced by calcium ions, which form an insoluble calcium-phosphate salt with the drug. Oral estramustine phosphate should therefore not be administered with dairy products or other calcium-rich foods or drugs [Gunnarsson 1990]. The plasma elimination half-life of estramustine phosphate is short ($t_{1/2}=1.3$ hours). However, the plasma half-life of the active cytotoxic metabolite estromustine ranges between 8.9 and 22.7 hours [Gunnarsson 1984]. Both estramustine and estromustine are excreted via the biliary route [Kirdani 1975].

Preclinical activity

In vitro, estramustine phosphate demonstrated activity against human prostate cancer cell lines and animal models. Combinations of estramustine phosphate with topoisomerase II inhibitors, e.g. etoposide, have demonstrated synergistic cytotoxic activity [Pienta 1993].

Therapeutic efficacy: Single agent studies

Estramustine phosphate (Estracyt®) has been predominantly evaluated as a second line option in patients with hormone-refractory prostate cancer [Perry 1995]. Most patients included in these studies had symptomatic, histologically confirmed prostate cancer, and were aged between 40 and 85 years. All histological grades were studied, and the majority of patients showed advanced metastatic disease (T₃ and T₄, M₁). Estramustine phosphate (Estracyt®) was usually administered orally at dose levels between 560 and 840 mg/day. In most studies, responses were evaluated according to the United States National Prostate Cancer Project (US-NPCP) criteria [Murphy 1984]. Based on the fact, that changes in prostate-specific antigen (PSA) were recognized as a predictive indicator of clinical response to prostate cancer treatment [Naik 1994], in recent studies PSA levels were used for definition of response [Morote 1991, Yagoda 1991]. Overall, in non-comparative studies objective response rates ranging between 19 and 69 % have been reported with single agent therapy (**table 3**). An analysis of 634 patients with hormone resistant disease who received second line treatment with estramustine phosphate (Estracyt®) alone revealed a mean objective response rate of 37 % [Benson 1990]. Compared with results of other non-comparative studies, a high proportion of patients experienced objective responses and an improved subjective status (evaluated by a modified ECOG pain relief and performance status scale) within the first 6 months of treatment with estramustine phosphate (Estracyt®) [Benson 1979]. Thereafter, 33 % of patients remained in objective response [Benson 1979].

Table 3: Phase II non-comparative studies of estramustine phosphate (Estracyt®) as a single agent in patients with hormone-refractory prostate cancer

Treatment Estracyt®	Patients n	Evaluation criteria ¹	Response rates (%) ²				Reference
			OR	PR	SD	PD	
14 mg/kg/d p.o.	51	NPCP	69	10	59	31	[Benson 1979]
840 mg/d p.o.	30	NPCP	27	-	27	73	[Chisholm 1977]
600 - 900 mg/d p.o.	17	TS, M, PAP	35	35	n.g.	n.g.	[Fosså 1976]
560 - 840 mg/d p.o.	91	NPCP	31	n.g.	n.g.	69	[Jonsson 1977]
560 mg/d p.o.	15	TS, M	20	20	n.g.	n.g.	[Kuss 1980]
15 mg/kg/d p.o.	44	NPCP	19	19	n.g.	n.g.	[Mittelman 1976]
560 mg/d p.o.	21	PSA, PAP	67	n.g.	n.g.	33	[Morote 1991]
560 - 840 mg/d p.o.	31	DNAX	45	45	n.g.	n.g.	[Nagel 1983]
560 mg/d p.o.	32	TS, M, PAP	28	28	n.g.	n.g.	[Toulouse 1984]
14 mg/kg/d p.o.	42	PSA, PAP	38	14	24	62	[Yagoda 1991]

¹ NPCP National Prostate Cancer Project, TS tumor size, M metastasis, PSA prostate-specific antigen, PAP prostatic acid phosphate, DNAX cytology DNA analysis

² OR objective response, PR partial remission, SD stable disease, PD progressive disease, n.g. not given

Therapeutic efficacy: Combination chemotherapy

More recently, several non-comparative studies have evaluated the therapeutic efficacy of combinations of estramustine phosphate (Estracyt®) with either vinblastine, paclitaxel or etoposide as second line treatment in patients with hormone-refractory prostatic cancer (**table 4**). Declining values of prostate-specific antigen (PSA) were used to monitor clinical response. Objective response rates were higher and improvements in subjective parameters were greater than those achieved with single agent chemotherapy. Reductions in PSA levels of 50 % were reported in 46 to 61 % of patients and, in most studies, the decline in PSA levels was related to an improvement in subjective parameters such as the degree of pain.

Overall, the combination of estramustine phosphate (Estracyt®) and vinblastine seems to be a safe and effective combination in hormone-refractory prostate carcinoma. However, a higher incidence of myelosuppression was observed than with estramustine phosphate alone [Perry 1995]. Combination chemotherapy with estramustine phosphate (Estracyt®) and paclitaxel showed encouraging results as well, however, further studies with this combination are necessary [Hudes 1995].

On the basis of in vitro and in vivo data, which suggested a synergistic effect of estramustine and etoposide [Pienta 1993], combination therapy with these agents was performed in one study, yielding 50 % reduction in PSA levels in 79 % of patients. Moreover, a 45 % remission rate was observed in patients with measurable soft tissue disease [Pienta 1995].

Table 4: Phase II non-comparative studies of estramustine phosphate (Estracyt®) in combination chemotherapy in hormone-refractory prostate cancer

Treatment ¹	Patients n	Evaluation criteria ²	Response rates (%) ³				Reference
			OR	CR	PR	PD	
EMP 600 mg/m ² /d p.o. VBL 4 mg/m ² /wk i.v.	36	PSA, STLM	31	-	31	n.g.	[Hudes 1992]
EMP 600 mg/m ² /d p.o. PT 120 mg/m ² /96h i.v.	17	PSA, NMM, STLM	50	-	50	n.g.	[Hudes 1995]
EMP 15 mg/kg/d p.o. ETO 50 mg/m ² /d p.o.	52	PSA, STLM	40	25	15	30	[Pienta 1995]

¹ EMP estramustine phosphate (Estracyt®), VBL vinblastine, PT paclitaxel, ETO etoposide

² PSA prostate-specific antigen, PAP prostatic acid phosphate, BS bone scan,

NMM nodal metastases measurement, STLM soft tissue lesion measurement

³ OR objective response, CR complete PR partial remission, PD progressive disease, n.g. not given

Toxicity

The most frequently encountered adverse effects of oral estramustine phosphate (Estracyt®) therapy are nausea and vomiting in 15 - 45 % of patients. These are generally mild to moderate in nature, although more severe symptoms may require a reduction in dosage or discontinuation of treatment [Benson 1990, Slack 1984]. Cardiovascular complications (including ischemic heart disease, venous thromboembolism and cardiac failure) have been reported in 10 % of patients during the first 20 weeks of treatment and in 25 % of patients after more than 20 weeks of treatment [Slack 1984]. To minimize the risk of such complications, careful patient selection and prophylaxis with anticoagulants (aspirin) and diuretics have been suggested by some investigators [Hedlund 1987]. However, recent data demonstrate, that estramustine recipients are at lower risk of cardiovascular complications than recipients of conventional estrogen therapy [Benson 1986, Lundgren 1986, Voogt 1986]. Elevated serum transaminases, reversible upon the withdrawal of treatment, have been observed in about 10 % of patients during treatment with estramustine phosphate [Benson 1990, Slack 1984]. As with conventional estrogens, recipients of estramustine phosphate (Estracyt®) may experience gynecomastia [Benson 1990]. Estramustine phosphate (Estracyt®) is rarely associated with myelosuppression [Jonsson 1977, Mittelman 1976, Loening 1983, Murphy 1979, Soloway 1981].

Dosage and administration

The recommended oral dose of estramustine phosphate (Estracyt®) is 140 to 1400 mg/d, administered in 2 to 3 divided doses [Pharmacia 1994]. The recommended initial starting dose is 560 to 1120 mg/d in 3 divided doses, with adjustment according to therapeutic response and gastrointestinal tolerability. Treatment should be discontinued after 4 weeks if there is no response. Patients should be advised to take estramustine phosphate (Estracyt®) 1 hour before or 2 hours after meals. Patients should not consume dairy products, calcium-containing foods or calcium-rich drugs (e.g., calcium-based antacids) concomitantly with oral estramustine phosphate (Estracyt®).

2.4 Etoposide (Vepesid®) in Prostatic Cancer

Etoposide is an epipodophyllotoxin analogue leading to inhibition of topoisomerase II . The compound was clinically studied since 1971 and has demonstrated broad antitumor efficacy in various types of malignancies. Interference with topoisomerase II effects DNA strand breaks and mitotic arrest in the late S- or early G₂-phase of the cell cycle. Furthermore, metabolic activation of etoposide by microsomal liver enzymes leads to generation of free radicals, which again react with cellular DNA [O'Dwyer 1985].

After oral application, bioavailability of etoposide (Vepesid®) is about 50 %. The major part of the active drug is metabolized in the liver, the resulting metabolites do not show cytotoxic activity. About 30 - 40 % of the compound are eliminated via the kidneys, and about 15 % are excreted via the bile duct [Arbuck 1986].

Myelosuppression is the dose-limiting toxicity after application of etoposide (Vepesid®). Gastrointestinal side effects like nausea, vomiting and diarrhea were observed in 25 % of cases. Cardiovascular side effects, i.e., hypotension and arrhythmias, as well as fever and anaphylactoid reactions are mainly observed after rapid intravenous application. In less than 5 % of patients, transient hepatotoxicity is observed. Most patients show grade 3 alopecia. High doses of etoposide are given as induction therapy in hematopoietic stem cell or bone marrow transplantation and can be associated with mucositis and peripheral neuropathy [O'Dwyer 1985, Postmus 1984].

In prostatic cancer, single agent chemotherapy with etoposide (Vepesid®) showed only low response rates [Yagoda 1993]. However, recent in vitro data demonstrated a synergistic effect of estramustine and etoposide [Pienta 1993]. Both agents interact at the level of the nuclear matrix and inhibited growth of the prostatic adenocarcinoma models PC-3 and R3327 in vitro and in vivo.

Based on these data, Pienta and coworkers combined estramustine phosphate (Estracyt®) 15 mg/kg/d and etoposide (Vepesid®) 50 mg/m²/d, given orally in divided doses for 21 days every 28 days, in patients with hormone-refractory prostatic cancer. 52 patients were enrolled in the trial with a minimum follow-up of 40 weeks. In 20 patients with measurable soft tissue disease, 3 patients demonstrated a complete response (15 %) and 6 patients had a partial response (30 %) for > 2 months. Of 32 patients with disease limited to bone, eight (25 %) showed improvement and 12 (38 %) had stability in their bone scans. There was no difference in survival between patients who had an improved bone scan versus those with a stable bone scan, however, both groups had a significantly better survival than patients with progressive disease (p<0.001). There was no difference in survival between men with soft tissue- versus bone-only disease. Performance status was an important predictor of survival. Overall, thirteen men (25 %) demonstrated a decrease of at least 75 % and 28 men (54 %) an at least 50 % decrease in their pretreatment PSA [Pienta 1995].

2.5 Rationale

Based on the results as given above, the efficacy of combined chemotherapy with estramustine phosphate (Estracyt®) and etoposide (Vepesid®) will be studied in an open, uncontrolled therapy optimization trial. The following points are of major importance with regard to this study:

Estramustine phosphate (Estracyt®) is an effective agent in hormone resistant prostatic carcinoma with an overall response rate after single agent chemotherapy of 37 %.

In vitro data suggested synergistic activity of estramustine phosphate (Estracyt®) and etoposide (Vepesid®). Estramustine has been shown to increase the amount of topoisomerase II DNA crosslinking induced by etoposide.

A recent clinical study by Pienta and coworkers turned out that the combination of oral estramustine phosphate (Estracyt®) and oral etoposide (Vepesid®) was both effective and well tolerated in patients with hormone-refractory prostatic cancer.

Estramustine phosphate (Estracyt®) yields only minor bone marrow suppression and can thus be combined with myelosuppressive chemotherapy. On the other hand, etoposide (Vepesid®) shows only minor cardiovascular and gastrointestinal toxicity and can be applied in elderly patients as well.

A treatment schedule with combination of oral estramustine phosphate (Estracyt®) and oral etoposide (Vepesid®) is convenient for both the physician and the patient, allowing for treatment on an outpatient basis.

In the present study the clinical usefulness of combined chemotherapy with estramustine phosphate (Estracyt®) and etoposide (Vepesid®) will be evaluated in patients who have relapsed after primary androgen suppressive treatment (i.e. medical or surgical castration). The patients will be on a milk restricted diet. Prostate specific antigen is the primary response parameter and will be measured regularly. As secondary parameters objective response criteria and subjective well-being (life quality analysis) will be monitored.

3. OBJECTIVES

3.1 Primary Objective

The primary objective is to determine efficacy and toxicity of combined chemotherapy with oral estramustine phosphate (Estracyt®) and oral etoposide (Vepesid®) in patients with hormone resistant prostate cancer. The response parameters are: reduction of the initial serum concentration of PSA in plasma and improvement of performance status or reduction of pain. Estracyt® will be applied as 140 mg capsules dosed as close to 10 mg/kg/d as the dosage form allows, split in three doses daily. Vepesid® will be given as 50 or 100 mg capsules per os in divided doses as close to 50 mg/m²/d as the dosage form allows. Both drugs are given for 21 days every 28 days. Combined treatment is continued until disease progression or any of the discontinuation criteria (cf. 4.4.3) occur.

3.2 Secondary Objectives

- The following variables will be assessed as secondary objectives:
 - duration of the primary response parameter
 - time to progression
 - overall survival
 - toxicity
 - changes in alkaline phosphatase.

- The subjective response parameters pain and performance status are monitored by standardized life quality analysis (cf. Appendix VII).

- If measurable lesions are present, they will be monitored regularly for further analysis.

4. PATIENTS, MATERIALS AND METHODS

4.1 Trial design

This is an open, uncontrolled therapy optimization trial to assess the efficacy and tolerability of combined chemotherapy with oral estramustine phosphate (Estracyt®) and oral etoposide (Vepesid®) in patients with prostatic carcinoma progressing after androgen suppression (surgical or medical castration). The patients may have received either antiandrogens or corticosteroids as secondary systemic treatment. If antiandrogen has been given, the drug must have been discontinued for at least one month prior to study entry.

4.2 Study population

This is a therapy optimization study, and the total number of patients evaluable for the primary response parameter is aimed at 40 patients. If no response is observed within the first 14 patients, the study will be closed.

The planned number of patients was based on assumptions regarding the percentage of responders. This percentage was expected to lie somewhere in the range of 0-40%. For planning purposes, a percentage of responders of 20% was assumed. Stopping the study after 14 patients with no response has a probability of 4,4%, if the true percentage of responders is 20%.

With a total of 40 patients and a percentage of responders of 20%, the precision (standard error) of the estimated percentage of responders is 6,3%.

4.2.1 Source

This is a multicenter study. Adult patients with hormone resistant prostate cancer will be recruited from participating centers.

4.2.2 Inclusion criteria

Histologically proven carcinoma of the prostate (any T or N category) with evidence of progressive metastatic disease following primary hormonal treatment (surgical or medical castration).

PSA > 100 µg/l or a PSA value between 20 and 100 µg/l if it has increased by at least 100 % during the preceding two months.

The serum testosterone within the institution's castration level.

Patients on a medical castration therapy with an LHRH analogue will continue this treatment together with the estramustine phosphate (Estracyt®) and etoposide (Vepesid®) combination therapy.

Adequate bone marrow reserve:

- white blood cell count $3.0 \times 10^9/l$
- platelet count $100 \times 10^9/l$

If a depressed count is considered to be due to tumor invasion of the bone marrow, treatment may be initiated.

Performance status (WHO criteria) 0 - 2 (cf. Appendix V).

Patients irrespective of age with a minimum life expectancy of more than 90 days.

Written informed consent prior to trial entry

Age < 75 years

4.2.3 Exclusion criteria

Previous systemic chemotherapy except primary hormonal manipulation (orchectomy, LHRH). One trial with either antiandrogen or corticosteroids as secondary systemic treatment does not represent an exclusion criterion. If antiandrogens were given, the drug should have been discontinued for at least one month prior to protocol entry.

Patients receiving local palliative radiotherapy at the time of evaluation for this protocol are regarded as ineligible, but can be entered subsequently upon progression after local radiotherapy.

Prior surgery (total prostatectomy or transurethral resection) and previous local radiotherapy do *not* represent exclusion criteria.

A second malignancy apart from basal cell carcinoma of the skin.

Cardiovascular disorders, i.e., systemic congestive heart failure, stable or non-stable angina pectoris, myocardial infarction or stroke within the previous six months, uncontrolled hypertension or deep vein thrombosis.

Inadequate renal (creatinine 1.5 x upper limits of normal) or liver (bilirubin 1.5 x upper limits of normal) function.

4.3 Statistical methods

Since this is an uncontrolled study, only descriptive statistical analysis will be performed.

The primary efficacy parameter will be analyzed by calculating the number and percentage of responders, whereby response will be defined as an at least 50% reduction from the baseline value in the PSA concentration at any time point, which was measured at 2 separate successive occasions within a 3-week interval. For the percentage of responders a two-sided 95% confidence interval will be calculated.

Duration of response will be defined as the duration starting at the first time at which response was observed and lasting as long as response was observed without interruption. For nonresponders this duration will be calculated as 0. Duration of response will be summarized descriptively with mean, standard error, minimum, median, maximum, and quartiles.

For the classification of PSA into CR, PR, NC and PD, as described in section 4.7.3, for each patient the best attained class will be determined and the numbers and percentages of patients in each class will be calculated.

The time to progression will be defined as the time from the start of therapy to the first time PD (regarding PSA) was documented. It will be analyzed by calculating the Kaplan-Meier estimate of the survival distribution. Patients without PD will be regarded as censored observations with the last visit as censoring time.

PSA will be summarized in the time course with mean, standard error, minimum, median, maximum, and quartiles, including the summarization of changes from baseline.

The time to death will be summarized in the same way as the time to progression.

The classification of secondary efficacy parameters into CR, PR, NC, and PD will be analyzed in the same way as the corresponding classification of PSA.

Subjective response will be summarized by means of frequency tables.

Adverse events will be summarized by type and grade.

Toxicity and laboratory data will be analyzed by calculating the worst WHO grade per patient and then calculating absolute and relative frequencies.

Alkaline phosphatase will be summarized in the time course with mean, standard error, minimum, median, maximum, and quartiles, including the summarization of changes from baseline.

4.4 Trial Products

All agents used in this protocol are commercially available and therefore will be purchased by each center involved in the trial. The Investigator is responsible for appropriate storage and handling of the trial products as indicated in the approved package inserts of the trial products (cf. Appendix IX).

Estramustine phosphate (Estracyt®)

capsules, 140 mg each (Pharmacia)

mechanism of action: dual mechanism combining cytotoxic and estrogenic activities

application: per os

side effects: nausea, vomiting, cardiovascular toxicity, gynecomastia

Etoposide (Vepesid®)

capsules, 50 or 100 mg each (Bristol)

mechanism of action: epipodophyllotoxin, inhibiting topoisomerase II

application: per os

side effects: myelosuppression, anaphylactoid reaction, alopecia, hepatotoxicity.

4.5 Therapy

4.5.1 Treatment schedule

The patients will receive combination chemotherapy with oral estramustine phosphate (Estracyt®) and oral etoposide (Vepesid®). Estracyt® will be applied as 140 mg capsules dosed as close to 10 mg/kg/d as the dosage form allows, split in three doses daily. Suggested dose levels for Estracyt® are given in **table 5**. Vepesid® will be given as 50 or 100 mg capsules per os in divided doses as close to 50 mg/m²/d as the dosage form allows. Suggested dose levels for Vepesid® are given in **table 6**. Both drugs are given for 21 days every 28 days. Combined oral treatment is continued until disease progression or any of the discontinuation criteria (cf. 4.4.3) occur.

Table 5: Recommended doses of estramustine phosphate (Estracyt®)

Body weight (kg)	Estracyt® dose (mg)	Estracyt® 140 mg capsules
37 - 50 kg	140 - 140 - 140 mg	1 - 1 - 1
51 - 64 kg	140 - 140 - 280 mg	1 - 1 - 2
65 - 78 kg	140 - 280 - 280 mg	1 - 2 - 2
79 - 92 kg	280 - 280 - 280 mg	2 - 2 - 2
93 - 106 kg	280 - 280 - 420 mg	2 - 2 - 3

Table 6: Recommended doses of etoposide (Vepesid®)

Body surface (m ²)	Vepesid® dose (mg)	Vepesid® 50 mg capsules
<1.50	50 - 0 - 0 mg	1 - 0 - 0
1.50 - 2.49	50 - 0 - 50 mg	1 - 0 - 1
2.50	50 - 50 - 50 mg	1 - 1 - 1

Estramustine phosphate (Estracyt®) must not be taken together with milk or other dairy products. It should be taken at least 1 hour before or 2 hours after meals.

Patients treated for at least 9 weeks and patients progressing within 9 weeks after trial entry (early progression) are evaluable for efficacy. Treatment can be discontinued at any time in case of toxicity.

4.5.2 Dose Modifications

Dose modifications will not be performed. If relevant hematologic toxicity (white blood cell count below $3 \times 10^9/l$ or platelet count below $100 \times 10^9/l$) is observed, treatment is interrupted until the values are within the institutions normal values. If relevant non-hematologic toxicity (WHO grade 3, excluding alopecia) is observed, the patient will go off study and may receive further treatment at the discretion of the investigator.

4.5.3 Discontinuation of Therapy

Reasons for discontinuation of therapy are:

- Progressive disease at any point during therapy.
- Non-hematologic toxicity WHO grade 3 (excluding alopecia)
- Development of any other unacceptable toxicity or serious intercurrent disorder
- The patient wishes to discontinue the trial

Patients who discontinue the treatment will receive other treatment at the discretion of the investigator.

4.5.4 Concomitant Therapy

Concomitant therapy considered necessary for the patient's welfare (e.g. antibiotics, antiemetics, blood products etc.) may be given at the discretion of the Investigator. All such therapy must be recorded in the Case Report Form. No other drug under investigation may be used concomitantly. The patients are not allowed to participate concurrently in any clinical study. No other anticancer chemotherapy, hormonal therapy, radiotherapy or immunotherapy is permitted during the trial period.

4.6 Efficacy and Toxicity Assessments

There are several major endpoints to be considered during treatment of hormone resistant prostatic cancer [Newling 1988]:

- Response
- Time to progression
- Overall survival

The evaluation of objective response according to WHO criteria [Miller 1981] requires measurable or at least evaluable tumor masses. This is problematic in prostate cancer, since only 10 to 20 % of patients have measurable metastatic lesions. Bone scans of metastases are not suitable for response evaluation due to great variation of results. Furthermore, detection of treatment-related changes in bone metastasis requires long observation intervals [Smith 1990]. Similarly, the primary tumor is not suitable as an indicator lesion [Jones 1986].

Recently, the level of prostate-specific antigen (PSA) has been shown to reflect development of the disease [Stamey 1987, Siddal 1987]. The level of PSA correlates closely to the total tumor burden if the carcinoma is not too anaplastic. Recent data have demonstrated, that reduction of PSA level due to treatment is associated with prolonged survival in hormone resistant patients [Cooper 1990, 1991, Mulders 1992, Kelly 1993, van Rijswijk 1992, Sridhara 1993, Thibault 1993].

Therefore, PSA levels will be used as primary response parameters in this study. The used PSA-Assay (e.g. Hybritech) has to be documented. Furthermore, as secondary objectives time to progression and overall survival will be evaluated. If measurable disease is present, regular follow-up of lesions will be performed. Subjective response, i.e. relief of metastatic bone pain and improvement of the patient's general condition, are an important response criteria in this patient group. They will be measured as well and will be recorded routinely as part of the life quality analysis.

4.6.1 Baseline Assessments

All pretreatment evaluations are to be performed within 1 week prior to the start of treatment. Pretreatment evaluations include (cf. **table 7**):

Case history, including previous treatment and evidence of progression of disease prior to trial entry.

Physical examination including weight, pulse, blood pressure, body surface area, examination for lymphadenopathy etc. The presence or absence of edema must be noted. Performance status (cf. Appendix V) and life quality analysis (cf. Appendix VII) must be assessed.

An ECG must be performed. History of cardiac or cardiovascular disorders must be included.

Any preexisting toxicity symptoms (cf. Appendix VI) must be noted.

Hematologic examinations including white blood cell count, hemoglobin and platelets.

Blood chemistry: total bilirubin, alkaline phosphatase, SGOT, SGPT, blood urea nitrogen (BUN), creatinine, LDH, C-reactive protein, uric acid, glucose, sodium, potassium, calcium, creatinine kinase CK, prostate-specific antigen PSA, prostate acid phosphatase PAP, serum testosterone.

Infection work-up (urine analysis, chest X-ray, blood cultures, microbiology and virology assays as appropriate) should be done where appropriate.

Radioisotope bone scan is mandatory at study entry. X-ray of hot spots should be done if there is any doubt about the metastatic nature of hot spots. Intravenous urograms and ultrasound of the liver should be performed if clinically indicated. CT scan, MRI or caliper measurements of superficial palpable lesions should be performed, if measurable disease parameters are present.

4.6.2 Assessments during Therapy

Assessments during combination chemotherapy with estramustine phosphate (Estracyt®) and etoposide (Vepesid®) will be performed monthly and include (cf. **table 7**):

Case history, including history of any adverse events

Physical examination including weight, pulse, blood pressure, edema, examination for lymphadenopathy etc. Performance status (cf. Appendix V) and life quality analysis (cf. Appendix VII) must be assessed.

ECG should be repeated only if cardiovascular symptoms have occurred.

Hematologic examinations including white blood cell count, hemoglobin and platelets.

Blood chemistry: total bilirubin, alkaline phosphatase, SGOT, creatinine, LDH, prostate-specific antigen PSA.

White blood cells, hemoglobin and platelets will additionally be assessed every 14 days.

4.6.3 Follow-up Examinations

Follow-up examinations should be performed every 8 weeks after discontinuation of treatment and include (cf. **table 7**):

Case history, including history of any adverse events

Physical examination including weight, pulse, blood pressure, edema, examination for lymphadenopathy etc. Performance status (cf. Appendix V) and life quality analysis (cf. Appendix VII) must be assessed.

ECG should be repeated only if cardiovascular symptoms have occurred.

Hematologic examinations including white blood cell count, hemoglobin and platelets.

Blood chemistry: total bilirubin, alkaline phosphatase, SGOT, creatinine, LDH, prostate-specific antigen PSA.

A bone scan should be repeated at 6 months intervals, if metastases were detected at the baseline scan. Measurable lesions should be monitored by the methods applied at baseline (cf. 4.5.1)

Table 7: Efficacy and Toxicity Assessments

Assessment	before treatment	during treatment	follow-up
Case history	X	X	X
Physical Examination	X	X	X
Performance Status	X	X	X
Life Quality Analysis	X	X	X
Toxicity Symptoms	X	X	X
ECG	X	_1	-1
Hematology	X	X	X
Blood Chemistry	X	X	X
Infection work-up	_1	-1	-1
Radioisotope bone scan	X	-	_1
Measurable lesions	_1	-	-1

¹ only when appropriate

If a patient shows evidence of disease progression (cf. 4.6.4), he goes off study and may receive any treatment at the discretion of the investigator.

Patients with partial response or no change (cf. 4.6.4) should continue combined treatment until progression or unacceptable toxicity occurs.

4.7 Efficacy Criteria

Efficacy will be assessed by the primary response parameter PSA as well as various secondary response parameters. Patients are evaluable for response only if they have been treated for a minimum of 9 weeks of therapy.

4.7.1 Response Parameters

The measurable response parameter is at least 50 % reduction in the concentration of serum prostate-specific antigen (PSA) during combined therapy with oral estramustine phosphate (Estracyt®) and oral etoposide (Vepesid®). The 50 % decrease in PSA concentration must be measured on 2 separate occasions with a 3 week interval.

Furthermore subjective response as defined by improvement of performance status or reduction of pain score will be evaluated as well.

4.7.2 Secondary Response Parameters

The duration of the 50 % reduction in PSA and the time to progression will be measured and recorded for further analysis. Clinically measurable changes in soft tissue and the concentration of alkaline phosphatase in serum will be measured at each follow-up examination and recorded for further analysis. Additionally, overall patient survival and toxicity profiles will be recorded.

4.7.3 Response Classification

Response will be classified as follows:

PSA:

Complete Response (CR): normalization of PSA (considering the institution's normal limits) on two successive evaluations with a 3 week interval, documented over a period of at least 4 weeks

Partial Response (PR): Decrease from baseline PSA value by 50 % or more

No Change (NC): PSA values as compared to baseline 51 - 125 %.

Progression (PD): Increase by 25 % or more from baseline PSA.

Secondary parameters:

Complete Response (CR): Normalization of all parameters of disease (pain, performance status, measurable disease).

Partial Response (PR): Reduction (but not normalization) of pain, increase (but not normalization) of performance status, at least 50 % reduction in the sum products of the two largest perpendicular diameters of measurable lesions and no new lesions detectable.

No change (NC): unchanged pain score and performance status, unchanged status of measurable metastases (size 50 - 125 % of baseline)

Progression (PD): increase of pain score or reduction of performance status as assessed by life quality analysis, increase in size (>125 %) or number of measurable lesions.

4.8 Safety Assessment and Adverse Events

4.8.1 Safety Parameters

Variables to be measured for safety assessment and schedules of evaluations are given in **table 7**.

At each visit, patients will be asked if they have experienced any adverse event since the last visit. For purpose of the assessment, the following definition of adverse events applies: any undesirable clinical event occurring to a subject during a clinical trial, whether or not it is considered related to the investigational product, is to be reported as adverse event. This includes any change in the patient's condition or laboratory results, which has or could have a deleterious effect on the subject's health or well-being.

4.8.2 Safety Criteria

The criteria for grading toxicities are the WHO Toxicity Criteria (cf. Appendix VI). For each episode, the highest severity grade attained should be reported.

4.8.3 Special Patient Categories

The major aim of this trial is to evaluate efficacy and toxicity of a combination of estramustine phosphate (Estracyt®) and etoposide (Vepesid®) in patients with hormone resistant prostate cancer. All patients entered into the trial will be accounted for during the evaluation of results. However, for a more adequate analysis, the following patient categories require special characterization:

Early withdrawal: Patients taken off the trial before completion of one treatment course for any cause, will be considered non-evaluable for response, but will be evaluated for toxicity.

Early deaths: Patients who die within 3 weeks from the initiation of drug therapy, will be evaluated for toxicity and considered as non-evaluable for response.

4.8.4 Adverse Events

An Adverse Event is any undesirable clinical event occurring to a subject, during a clinical trial, whether or not it is considered related to the used product. This includes a change in a patient's condition or laboratory results which has or could have a deleterious effect on the patient's health or well being.

All Adverse Events should be recorded in the Case Report Forms. If no Adverse Event has occurred during the period concerned, this should be noted in the appropriate place. Adverse Events should be carefully monitored during the entire trial.

A Serious Adverse Event is an event which is life-threatening, has resulted in death, hospitalization (initial or prolonged), disability or congenital anomaly or has required intervention to prevent permanent impairment/damage (FDA definition).

Minimum requirements of data to be recorded are: type of event, duration of Adverse Event (start to end), dosage, severity, seriousness, action taken, outcome and, if appropriate, causality.

Serious Adverse Events must be reported within one working day by the Investigator to the Medical Department at Pharmacia & Upjohn, Erlangen (Tel.: 09131/621822; Fax: 09131/621820), regardless of the time that may have elapsed from the time the event occurred to when the Investigator first learns of it. An Adverse Event Report must be completed, signed and sent to Pharmacia & Upjohn within 7 working days.

Adverse events should be reported to Pharmacia&Upjohn even after the clinical trial has been finished, if in the judgement of the Investigator there might be an association between the event and the previous use of the product Estracyt®. In this regard patients must be followed at least for 4 weeks after the last treatment.

Expected consequences from treatment with cytotoxic drugs, like neutropenia, and established consequences from neutropenia, like fever and sepsis as related to administration of cytotoxic drugs, do not need an Adverse Event compilation. However, they should be documented in the CRFs and reported at the end of the trial.

An event need not be reported as a Serious Adverse Event if it represents only a relapse or an expected change or progression of the condition that was the cause of treatment without any other symptoms and signs than those present before treatment.

The appropriate Ethics Committee should be informed by the Investigator about Serious Adverse Events associated with the use of the products.

4.8.5 Withdrawal from Treatment

A patient should be withdrawn from the trial treatment if, in the opinion of the Investigator, it is medically necessary or it is the wish of the patient.

The reason for withdrawal should be clearly described and the patient should, whenever possible, irrespective of the reason for withdrawal, as soon as possible be examined.

4.8.6 Emergency Procedures

The Investigator is responsible for assuring that there are procedures and expertise available to cope with medical emergencies during the trial.

5. ETHICAL REQUIREMENTS

5.1 Declaration of Helsinki

The trial will be performed in accordance with the recommendations guiding physicians in biomedical research involving human subjects adopted by the 18th World Medical Assembly, Helsinki, Finland, 1964 and later revisions (latest revision by the 41st World Medical Assembly, Hong Kong, 1989)(cf. Appendix I).

The trial protocol and the locally used informed consent form (German language) has to be approved by the hospital Ethics Committee of each institution involved in the trial. Protocol amendments are to be submitted to the Ethics Committee prior to implementation. It is the responsibility of the Investigator to give required progress reports to the Ethics Committee, as well as report any Serious Adverse Events, life-threatening problems or deaths. The Ethics Committee must be informed of the termination of the Trial. All correspondence with the Ethical Committee should be filed by the Investigator and copies should be forwarded to Pharmacia&Upjohn.

5.2 Patient Information and Consent

It is the responsibility of the Investigator to give each patient (or the patient's legally authorized representative), prior to inclusion in the trial, full and adequate verbal and written information regarding the objective and procedures of the trial and the possible risks involved. The patients must be informed about their right to withdraw from the trial at any time. Written patient information (included as Appendix II to this protocol) should be given to each patient before enrollment. Furthermore, it is the responsibility of the Investigator to obtain signed informed consent from all patients prior to inclusion in the trial.

5.3 Patient Data Protection

The Investigator should keep a patient identification list, including sufficient information to link records, i.e. CRF and hospital records.

The patients should be informed that the data will be stored and analyzed by computer, that local regulations for the handling of computerized data will be followed and described in the written patient information and that identification of individual patients data will only be possible for the Investigator.

6. FURTHER REQUIREMENTS AND GENERAL INFORMATION

6.1 Liability and Insurance

For this therapy optimization trial with commercially available drugs, patient insurance is not necessary, as potential risks are covered by the general liability of the hospital and treating physician. On a voluntary basis, an additional insurance for participating patients will be provided, covering unexpected injuries, including death, that the use of the products may cause patients.

6.2 Staff Information

It is the responsibility of the Investigator to ensure that all personnel involved in the trial are fully informed of all relevant aspects of the trial, including detailed knowledge of and training in all procedures to be followed.

6.3 Protocol Reviews

The trial will not be started until approval of the protocol, the Patient Information and the Informed Consent Form has been obtained from the appropriate Ethics Committee. It is the responsibility of the Investigator to forward a copy of the written approval and, where possible, a list of the members, their titles or occupation, and their institutional affiliations, to Pharmacia.

6.4 Changes to the Final Trial Protocol

Any variation on procedure from that specified in the Final Trial Protocol may lead to the results of the trial being questioned and in some cases rejected. Any proposed protocol change must therefore be submitted for Ethics Committee approval and notification. Any protocol change should be documented in a Protocol Amendment.

6.5 Case Report Forms

A Case Report Forms (CRF) (cf. Appendix VII) is required and should be completed for each individual patient and signed.

Corrections of data should be made using one single line, leaving the corrected data clearly visible. The accurate data should be entered next to the inaccurate data. All changes should be initialed and dated by the Investigator. If corrections are performed by another member of the staff, the Investigator has to approve the correction. Corrections fluids are not allowed.

6.6 Record Retention

To enable further evaluations and/or audits from Health Authorities, the Investigator agrees to keep records, including the identity of all participating patients (sufficient information to link records, i.e., CRF and hospital records), all signed Informed Consent Forms, copies of all CRFs and detailed records of drug deposition. To comply with international regulations, the records should be retained by the Investigator for 15 years.

6.7 Reporting and Communication of Results

After completion of the trial, the statistical analysis will be performed. Based on these data the Principal Investigator will prepare a Clinical Trial Report. The report will form the basis for a manuscript intended for publication in a medical journal. All publications should be joint publications, as authors all investigators contributing more than 5 % of the patients as well as all members of the protocol committee will be included.

6.8 Timetable

The present trial should start accruing patients by January 1998 and close accrual within December 1999.

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8. APPENDICES

- I The Declaration of Helsinki (revised in Somerset 1996)
- II Patient Information and Informed Consent Form (German)
- III Ethics Committee Approval
- IV Insurance Policy
- V Performance Status (WHO criteria)
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- VII Case Report Form and Life Quality Analysis
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