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ORCHIDECTOMY VERSUS BUSERELIN IN COMBINATION WITH CYPROTERONE ACETATE, FOR 2 WEEKS OR CONTINUOUSLY, IN THE TREATMENT OF METASTATIC PROSTATIC CANCER. PRELIMINARY RESULTS OF EORTC-TRIAL 30843.

H. J. DE VOOGT,[1] J. G. M. KLIJN,[2] U. STUDER,[4] F. SCHRÖDER,[3] R. SYLVESTER,[5] M. DE PAUW[5] and Members of the EORTC-GU Group

[1]Department of Urology, Free University Hospital, Amsterdam, [2]Daniel den Hoed Clinic, Rotterdam, [3]Department of Urology, Erasmus University, Rotterdam, The Netherlands, [4]Department of Urology, Inselspital, Bern, Switzerland and [5]EORTC Data Center, Brussels, Belgium

Summary—This prospective randomized phase III trial compares orchidectomy as standard androgen-deprivative therapy of advanced (metastatic) prostatic cancer with treatment using the LHRH agonist Buserelin® administered as nasal spray 3 daily doses of 400 μg, and combined with cyproterone acetate (CPA) 3 daily doses of 50 mg orally for 2 weeks initially to prevent flare-up of the disease, or continuously as complete androgen blockade. The trial was closed to entry in September 1989 when 367 patients were recruited. Patients were stratified for performance status (WHO) and metastatic status prior to randomization. According to patient and disease characteristics spreading of patients over the 3 arms was without statistical significant differences. Ineligibility was 5 and 4% of the patients were only partly evaluable. In March 1990 a first, preliminary analysis was performed. At that time 207 patients were off-study for progression or death and median follow-up was 1 yr. As to time-to-progression and survival there were no significant differences between the 3 arms. The meaning of this in regard to results of other trials with complete androgen blockade is discussed.

INTRODUCTION

The EORTC-GU group, having performed three phase III trials on the endocrine management of advanced prostatic cancer [1–3] decided in 1984 to start 2 new trials in which LHRH agonists could be compared to standard therapy, in the form of surgical castration (orchidectomy). Several phase II and pilot studies [4, 5] had indicated that LHRH-a could be regarded as a satisfactory medical castration with virtually no side effects. In addition, the work of Labrie [6] necessitated clinically controlled (randomized) trials to see whether complete androgen blockade by adding steroidal or non-steroidal (so-called "pure") antiandrogens to medical or surgical castration, induced a better survival or a longer time of progression-free disease. Since we had documented in a previous pilot study [7], that flare-up of the disease through the initial high serum-testosterone levels, caused by LHRH-a, could be adequately prevented by adding antiandrogens during the first two weeks, a third arm of medical castration only was combined with cyproterone acetate during the first two weeks.

MATERIAL AND METHODS

From November 1984 to September 1989 patients with metastatic prostatic cancer could be entered into the trial, provided they did not have any second primary malignancy and had not been treated endocrinologically before and had a performance status not higher than 2 on the WHO scale. Skeletal metastases and/or lymphnode/soft tissue metastasis had to be proven by bone-scan and X-ray or cytodiagnostically. Previous radiotherapy or surgical intervention (for relief of obstruction or radical prostatectomy) were permitted. After stratification for performance and metastatic status patients were randomized to receive: (a) orchidectomy, (b) Buserelin 3 daily doses of 0.5 mg subcutaneously for 1 week, followed by 3 daily doses of 400 μg intranasal spray,

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combined with CPA 3 daily doses of 50 mg for 2 weeks, (c) same as (b) but CPA 3 daily doses of 50 mg continuously, to be administered orally.

Strict criteria for response and progression were defined. The primary tumor (prostate) could be measured by transrectal echography, CT-scan, or digital examination. Lymphnodes could only be measured by CT-scan. Soft tissue metastases by direct measurement or X-ray. Bone metastases were screened every 6 months by bone-scan. Only new hot spots were accepted as an objective sign of progression. Subjective or aspecific criteria for response were: performance status and pain; serum-levels of hemoglobin; prostatic acid phosphatase; alkaline phosphatase; and PSA (optional). Serum testosterone levels were measured to monitor therapy compliance.

Although objective progression had to be confirmed by repeated X-rays or bone-scans which often took 1–3 months, the time of first signs of progression were always noted and used to define time-to-progression. All randomized patients whether later on ineligible, drop-outs by protocol violation or only partly evaluable, were kept on follow-up for survival.

RESULTS

In September 1989 when 367 patients were entered into the trial by 25 institutions, the trial was closed to entry. Table 1 gives a list of the institutions that entered all eligible patients. In March 1990 a first preliminary statistical analysis was done. Table 2 gives the status of evaluation. Median time of follow up at that moment was 1 year. Regarding patient- and disease-characteristics the spreading of patients over the 3 arms did not reveal significant differences. Tables 3, 4 and 5 present these characteristics. Toxicity consisted mainly of hot flushes which were present in 25% of the patients after 6 weeks, gradually increasing to 53% for follow up, but being the least in the patients on the continuous combination arm (40%). Gynaecomastia, which after 6 weeks was seen only in the combination arm in 3 patients, later increased to 7%. Only 3 patients in total had to stop treatment because of gastro-intestinal complaints or nasal irritation.

Table 6 gives the presence of pain at entry, again showing an equal distribution over the 3 arms. From those patients that had no pain at entry 92% remained pain-free after 6 weeks of therapy, while 8% reported pain. From the patients who had mild pain at entry 59% were pain free after 6 weeks, 36% still had mild pain and 5% were worse. From the patients who had severe pain 71% were better after 6 weeks, 25% had no change and 4% got worse.

Table 1. Eligible patients by institution

Inselspittal, Bern	49
VU, Amsterdam	48
Erasmus University, Rotterdam	34
J. Gutenberg, Mainz	27
Ramaz, Carpi Modena	23
Chu, Toulouse	23
AMC, Amsterdam	21
ZUIDERZ., Rotterdam	14
OLVG, Amsterdam	14
RRTI, Rotterdam	11
PR, Hull	11
CS La Paz, Madrid	10
St James Hospital, Leeds	9
AVL, Amsterdam	8
Varese	7
St Maria, Lisbon	7
St Franc., Roosendaal	6
W.A., Den Bosch	6
AZ, Leiden	5
St Maartens, Kortrijk	5
Sternberg, Rome	5
Refaja, Dordrecht	3
Palermo	3
AZ, Gent	1
Total	349

Table 2. Status of evaluation by the study coordinator

No. of patients randomized	367
No. of patients off-study	207
No. of patients evaluated	193
Ineligible	18 (5%)
Partly evaluable	15 (4%)
Fully evaluable	160

Table 3. Patient characteristics (302 patients)

Age (yr)	
<60	= 29 (10%)
60–69	= 97 (32%)
70–74	= 66 (22%)
75–79	= 66 (22%)
⩾80	= 44 (15%)
WHO perf. status	
0	= 159 (52%)
1	= 114 (38%)
2	= 28 (9%)
3	= 1 (1%)
Metastatic pain	
None	= 139 (46%)
Mild	= 100 (35%)
Moderate	= 51 (17%)
Severe	= 8 (3%)
Intractable	= 4 (1%)
Chronic diseases	
Cardiovascular	= 129 (43%)
Respiratory	= 46 (15%)
Paget's disease	= 7 (2%)
Musculo-skeletal	= 22 (7%)
Other	= 25 (8%)

Table 4. Disease characteristics (302 patients)

T category	
0	= 6 (2%)
1	= 9 (3%)
2	= 30 (10%)
3	= 143 (47%)
4	= 102 (34%)
X	= 12 (4%)
N category	
0	= 71 (23%)
1	= 8 (3%)
2	= 13 (4%)
3	= 6 (2%)
4	= 80 (27%)
X	= 124 (41%)
Histology grade	
1	= 32 (10%)
2	= 129 (43%)
3	= 133 (44%)
X	= 8 (3%)

Table 5. Disease characteristics (302 patients)

Site of metastases	
None (N4 only)	= 23 (8%)
Bone	= 268 (89%)
Visceral	= 14 (5%)
Soft tissue	= 1 (1%)
Alkaline phosphatase	
≤ 1.25 N	= 140 (46%)
1.26–2.5 N	= 67 (22%)
2.6–5 N	= 47 (16%)
5.1–10 N	= 26 (9%)
> 10 N	= 17 (6%)
Unknown	= 4 (1%)
Acid phosphatase	
≤ 1.25 N	= 56 (19%)
1.26–2.5 N	= 52 (17%)
2.6–5 N	= 47 (16%)
5.1–10 N	= 36 (12%)
> 10 N	= 103 (34%)
Unknown	= 7 (2%)

As to response, the time is still too short to give meaningful results. As shown in Table 2 already 207 patients were off-study because of progression and/or death. 113 patients died and Table 7 gives the cause of deaths, 75% of which were due to malignant disease. Finally in Figs 1 and 2 the curves of time-to-progression and survival are shown and as can be seen there is no statistical difference whatsoever between the 3 treatment arms.

DISCUSSION

As far as toxicity and side effects are concerned this trial does not differ in outcome from most other trials in which LHRH-a are used. The monitoring of serum-T levels indicated that medical castration was reached at 6 weeks in all cases and that these T levels remained low as long as Buserelin was taken. The compliance with nasal spray was very satisfactory and does not need to be less than with depot injections. It can be concluded that treatment with Buserelin is as good as with any other LHRH agonist.

Bearing in mind that this is a preliminary analysis there is a remarkable difference with trial 30853 of the EORTC-GU group, which used Zoladex® (depot) in combination with flutamide [8] and showed a significant difference in time-to-progression in favor of this combination, but not in survival. As well as with the so-called Crawford study [9] where leuprolide was used as single therapy compared with in combination with flutamide. In this last trial a significant difference of 3–6 months in time-to-progression and survival was found in favor of the combination.

The only difference between our trial and the Crawford study, apart from the use of a different brand of LHRH-a and a pure antiandrogen,

Table 6. Pain at entry on study

	Orchid. (%)	BUS + CPA 2 wks (%)	BUS + CPA Cont. (%)	Total (%)
None	44 (42)	47 (48)	48 (48)	139 (46)
Mild	38 (36)	29 (30)	33 (33)	100 (33)
Moderate	19 (18)	16 (16)	16 (16)	51 (17)
Severe	2 (2)	4 (4)	2 (2)	8 (3)
Intractable	1 (1)	2 (2)	1 (1)	4 (1)
Total	104	98	100	302

Mild = non-narcotic analgesics occasionally required; moderate = non-narcotic analgesics regularly required; severe = narcotic analgesics occasionally required; intractable = narcotic analgesics regularly required.

Table 7. Cause of death

	Orchid. (%)	BUS + CPA 2 wks (%)	BUS + CPA Cont. (%)	Total (%)
Malig. disease	27 (66)	30 (81)	27 (77)	84 (74)
Cardiovascular	8 (20)	6 (16)	3 (9)	17 (15)
Other/unknown	6 (14)	1 (3)	5 (14)	12 (11)
Total	41	37	35	113

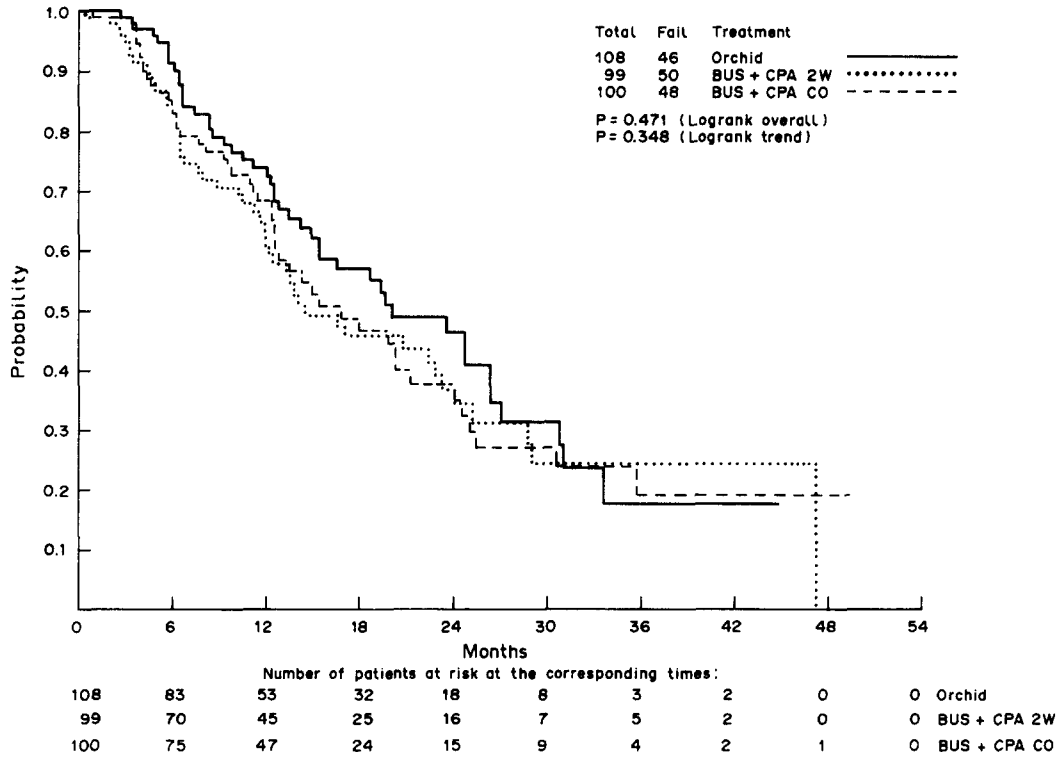

Fig. 1. Time-to-progression.

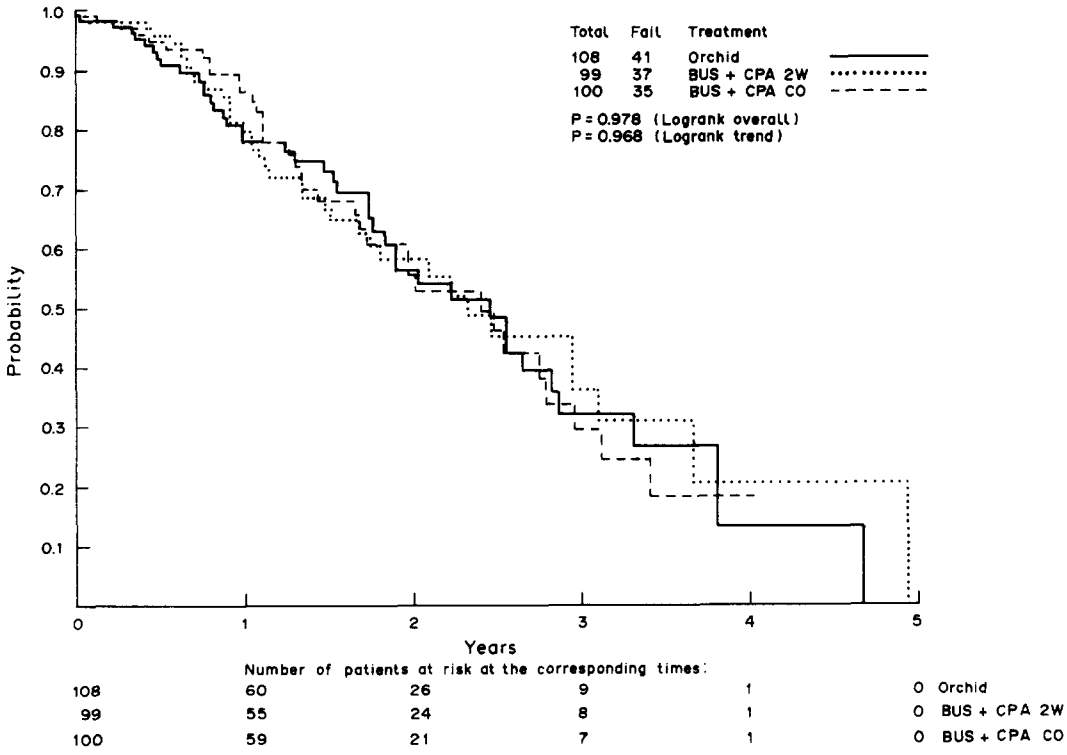

Fig. 2. Duration of survival.

are the serum-T levels during the first weeks. They were high in the leuprolide-only arm and could have caused a flare up, which even if not clinically detectable, could have acted upon the disease progression. Already in the first preliminary analysis this trend could be demonstrated, while it is absent in our study.

In conclusion this means that there still is no definite proof of the complete androgen blockade being more efficient than standard androgen-deprivation therapy. In addition the significance of serum-T levels in the treatment of advanced prostatic cancer is still far from clarified.

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