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Platinum Priority – Prostate Cancer

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Locally Advanced and Metastatic Prostate Cancer Treated with Intermittent Androgen Monotherapy or Maximal Androgen Blockade: Results from a Randomised Phase 3 Study by the South European Uroncological Group

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Abstract

Background: Few randomised studies have compared antiandrogen intermittent hormonal therapy (IHT) with continuous maximal androgen blockade (MAB) therapy for advanced prostate cancer (PCa).
Objective: To determine whether overall survival (OS) on IHT (cyproterone acetate; CPA) is non-inferior to OS on continuous MAB.
Design, setting, and participants: This phase 3 randomised trial compared IHT and continuous MAB in patients with locally advanced or metastatic PCa.
Intervention: During induction, patients received CPA 200 mg/d for 2 wk and then monthly depot injections of a luteinising hormone-releasing hormone (LHRH; triptoreline 11.25 mg) analogue plus CPA 200 mg/d. Patients whose prostate-specific antigen (PSA) was $<$4 ng/ml after 3 mo of induction treatment were randomised to the IHT arm (stopped treatment and restarted on CPA 300 mg/d monotherapy if PSA rose to $\geq$20 ng/ml or they were symptomatic) or the continuous arm (CPA 200 mg/d plus monthly LHRH analogue).
Outcome measurements and statistical analysis: Primary outcome measurement was OS. Secondary outcomes included cause-specific survival, time to subjective or objective progression, and quality of life. Time off therapy in the intermittent arm was recorded.
Results and limitations: We recruited 1045 patients, of which 918 responded to induction therapy and were randomised (462 to IHT and 456 to continuous MAB). OS was similar between groups ($p = 0.25$), and noninferiority of IHT was demonstrated (hazard ratio [HR]: 0.90; 95% confidence interval [CI], 0.76–1.07). There was a trend for an interaction between PSA and treatment ($p = 0.05$), favouring IHT over continuous therapy in patients with PSA $\leq$1 ng/ml (HR: 0.79; 95% CI, 0.61–1.02). Men treated with IHT reported better sexual function. Among the 462 patients on IHT, 50% and 28% of patients were off therapy for $\geq$2.5 yr or $>$5 yr, respectively, after randomisation. The main limitation is that the length of time for the trial to mature means that other therapies are now available. A second limitation is that T3 patients may now profit from watchful waiting instead of androgen-deprivation therapy.
Conclusions: Noninferiority of IHT in terms of survival and its association with better sexual activity than continuous therapy suggest that IHT should be considered for use in routine clinical practice.

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1. Introduction

Prostate cancer (PCa) is one of the most commonly diagnosed cancers in men [1]. Incidence in recent years has been increasing worldwide and is expected to continue with the current ageing population; this increase poses a global major health and economic burden on society. Intermittent hormonal therapy (IHT) with antiandrogens is used increasingly to improve the quality of life (QoL) of PCa patients without diminishing the efficacy of chronic androgen-deprivation therapy (ADT). ADT is the current standard therapy for advanced PCa or cancer that has metastasised beyond the prostate. To maximise the efficacy and tolerability of ADT while reducing adverse events, it is possible for some patients to alternate treatment and off-treatment periods.

Few randomised studies have compared the efficacy of IHT with continuous therapy; however, available data suggest that IHT is at least as effective as continuous treatment in the management of advanced PCa with regard to both disease progression and overall survival (OS) [2–5]. Further potential benefits of IHT include reduced side-effects compared with continuous therapy, improved QoL (especially recovery of sexual potency), health care cost savings, and delayed emergence of hormonal refractoriness [6–8]. However, no randomised studies to date have assessed IHT delivered as monotherapy with antiandrogens (cyproterone acetate; CPA).

This study aimed to demonstrate the noninferiority of antiandrogen monotherapy with CPA IHT compared with continuous maximal androgen blockade (MAB) therapy.

The European Association of Urology recently acknowledged that intermittent ADT (IADT) is already offered to patients with advanced PCa and stated in its guidelines that IADT should no longer be considered experimental [1].

2. Patients and methods

South European Uroncological Group (SEUG) 9901, a phase 3 randomised trial, compared intermittent and continuous androgen suppression with respect to OS, time to loss of androgen dependence, symptom-free survival, and QoL. Patients were recruited in 31 centres in Portugal, Spain, Italy, Turkey, Greece, Slovakia, and the United Kingdom. All patients gave informed consent. The study opened in September 1999, with the first patient randomised in January 2000 and the last patient randomised in September 2007. Follow-up for this analysis ceased in October 2012.

2.1. Patients

Inclusion criteria were histologically confirmed prostate adenocarcinoma, cT3–cT4 M0 and M1, serum prostate-specific antigen (PSA) $\geq$4 ng/ml and $\leq$100 ng/ml, age $\leq$80 yr, World Health Organisation performance status 0–2, and normal liver function not suitable for definitive treatment. Exclusion criteria were previous hormonal therapy or chemotherapy, presence of another neoplasm (except skin, excluding melanoma), severe concomitant chronic disease, or expected follow-up difficulties. Prior surgery and radiotherapy were reasons for exclusion. Clinical stage was assessed by the investigator in each centre, and there was no central pathology review.

2.2. Intervention

All patients received induction therapy of CPA 200 mg/d for 2 wk, followed by monthly depot injections of a luteinising hormone-releasing hormone (LHRH) agonist (triptoreline 11.25 mg) plus CPA 200 mg/d. Patients whose PSA levels decreased to $<$4 ng/ml 14 wk after starting induction therapy were randomised to receive either IHT or continuous antiandrogen therapy. Patients randomised to the continuous arm received CPA 200 mg/d plus monthly LHRH agonist, whereas those randomised to the IHT arm ceased treatment. Monotherapy with CPA 300 mg/d was restarted in the IHT arm if the PSA level rose to $\geq$20 ng/ml or if the patient experienced symptoms attributable to PCa.

Patients in both arms discontinued when there was evidence of objective progression (distant metastases or new metastatic sites) or subjective progression. Subjective progression was defined as the presence of at least two of the following three criteria: (1) biochemical progression, defined as an increase of the PSA level by 20% on two successive occasions at least 1 mo apart; (2) an increase in pain by two increments; or (3) worsening of performance status by two increments. QoL was assessed every 6 mo and in the intermittent arm when therapy was restarted, using the European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30 questionnaire and the Prostate Cancer Module.

2.3. Statistical analysis

The primary aim of the study was to demonstrate noninferiority of intermittent CPA therapy compared with continuous MAB in terms of OS. For continuous therapy, it was assumed that M0 and M1 patients had median survival of 5 yr and 2.9 yr, respectively. Assuming that approximately 65% and 35% of patients would have been M0 and M1, respectively, then the median survival time for the entire group of patients on continuous MAB was expected to be approximately 4.25 yr. Intermittent CPA therapy was considered to be noninferior to continuous MAB if median survival was no worse than 3.5 yr, which corresponds to an increase of 20% in the hazard ratio (HR; 1.21). Based on a one-sided log-rank test for noninferiority at error rates $\alpha = 0.05$ and $\beta = 0.20$, a total of 658 deaths were required for statistical analysis. With an entry rate of 150 patients per year and a follow-up period of 5 yr after the last patient had been entered, randomisation of 900 patients over 6 yr was planned.

Statistical analysis was carried out using R v.2.15 (R Foundation, Vienna, Austria). Chi-square tests were used to test the association between treatment and the percentage of patients with side effects. Kaplan-Meier curves were used to estimate the time to death and progression-free survival (PFS) and were compared using the two-sided log-rank test and a Cox proportional hazards model. Median survival was estimated from the Kaplan-Meier curve. HRs were expressed as intermittent therapy compared with continuous therapy, and a 95% confidence interval (CI) was used. The null hypothesis (HR: 1.21; specifying noninferiority) versus the alternative (HR: 1) was used for the main outcome of OS and a one-sided test. Cox regression models were used to account for the effect of prognostic factors. Cause-specific deaths were analysed by assessing competing risks [9,10] using the *cmprsk* library in R v.2.2-2 (R Foundation, Vienna, Austria). Mixed-effect regression models were used to investigate the trends in PSA and QoL scores during the course of the study. Results are reported at the 5% significance level, and 95% CIs are used for all estimated effects. The Benjamini and Hochberg procedure [16] was used to adjust for multiple testing of the subscores in the QoL analysis.

3. Results

In total, 1045 patients were recruited and 918 patients were randomised, 462 to IHT and 456 to continuous

Table 1 – Patient characteristics at randomisation

	Intermittent		Continuous	
	n	%	*n*	%
Total	462	–	456	–
Age group				
<65 yr	58	12.6	52	11.4
65–69 yr	72	15.6	83	18.2
70–74 yr	152	32.9	154	33.8
75–79 yr	157	34.0	149	32.7
≥80 yr	23	5.0	18	3.9
WHO performance status				
0	419	90.7	413	90.6
1	38	8.2	36	7.9
2	2	0.4	6	1.3
Tumour stage				
T2	15	3.2	20	4.4
T3	416	90.0	417	91.4
T4	31	6.7	19	4.2
Histology				
Biopsy	440	95.2	440	96.5
TUR	20	4.3	16	3.5
Not available	2	0.4	0	0
Tumour grade				
G1	23	5.0	25	5.5
G2	314	68.0	322	70.6
G3/X	125	27.1	109	23.9
Gleason score				
2–4	28	6.1	24	5.3
5–6	186	40.3	170	37.3
7–8	223	48.3	235	51.5
≥9	25	5.4	27	5.9
Bone scan				
Normal	355	76.8	343	75.2
1–6 hot spots	42	9.1	43	9.4
≥6 hot spots	7	1.5	2	0.4
Other abnormalities	39	8.4	46	10.1
Not carried out	19	4.1	22	4.8
Metastatic status				
M0	410	88.7	406	89
M1	52	11.3	50	11
Associated chronic disease*				
Any	122	28.4	121	28.4
MI	22	4.8	24	5.3
DVT	8	1.7	3	0.7
CVA	21	4.5	18	3.9
Respiratory	24	5.2	21	4.6
Other	2	0.4	2	0.4
OACD	70	15.2	70	15.4
PSA level				
<1 ng/ml	229	49.6	242	53.1
1–2 ng/ml	102	22.1	74	16.2
>2–4 ng/ml	131	28.4	140	30.7

CVA = cerebral vascular accident; DVT = deep vein thrombosis; MI = myocardial infarction; PSA = prostate-specific antigen; TUR = transurethral resection; WHO = World Health Organisation.

* Patients may have more than one chronic disease; two ineligible patients were randomised who had T2M0.

treatment. Patient and disease characteristics at randomisation are shown in Table 1. The patient distribution was similar in the two treatment groups (Table 1). The median PSA level at recruitment (before induction therapy) of patients that were subsequently randomised was 15 ng/ml and then 1.4 ng/ml after the induction period, with 31% having PSA ≤0.5 ng/ml. PSA level, Gleason score, and metastatic status at baseline were the only independent predictors of PSA level at randomisation; T stage, tumour grade, and age had no effect. PSA level at randomisation increased with higher baseline Gleason scores: Gleason score 2–4, median PSA level 0.6 ng/ml; Gleason score 5–6, median PSA level 0.7 ng/ml; Gleason score 7–8, median PSA level 1.2 ng/ml; Gleason score 9–10, median PSA level 1.6 ng/ml ($p < 0.001$).

The median follow-up time from randomisation was 66 mo (maximum: 12 yr), and 56% of patients were observed for >5 yr; 393 patients were alive at the last follow-up. Progression was reported in 299 patients, 168 in the IHT arm and 131 in the continuous arm (Table 2).

Table 2 – Patients alive, lost to follow-up, dead, with cause of death and progression by treatment arm

	Intermittent treatment		Continuous treatment		95% CI			*p*
	n	%	*n*	%	HR	Lower	Upper	–
Randomised	462	–	456	–	–	–	–	–
Alive at last contact	204	44.2	189	41.4	–	–	–	–
Lost to follow-up	11	2.4	11	2.4	–	–	–	–
Any progression	168	36.4	131	28.7	1.16	0.93	1.47	0.195
Dead	258	55.8	267	58.6	0.90	0.76	1.07	0.252
Cancer	103	22.3	96	21.1	1.00	0.76	1.32	0.995
Prostate cancer	82	17.7	82	18	0.93	0.69	1.26	0.648
Second primary	21	4.5	14	3.1	1.41	0.71	2.75	0.332
Cardiovascular death	107	23.2	122	26.8	0.83	0.64	1.07	0.152
Other/unknown	48	10.4	49	10.7	0.91	0.61	1.36	0.650

CI = confidence interval; HR = hazard ratio.
HRs for intermittent therapy compared with continuous therapy and 95% CIs from a Cox regression model.

Among patients with complete information on progression, there were slightly more progressions among those on IHT (HR: 1.16; 95% CI, 0.93–1.47; $p = 0.20$).

Overall, 525 patients died, 258 in the IHT arm and 267 in the continuous arm. There was no significant difference in OS on intermittent therapy (HR: 0.90; 95% CI, 0.76–1.07; $p = 0.99$ [one-sided test]) (Table 2, Fig. 1). The upper 95% confidence limit is less than the 1.21 limit specified in the design demonstrating noninferiority of IHT relative to continuous treatment. Both PSA and metastatic status at randomisation were independently associated with survival (Fig. 1), and there was evidence of a trend for an interaction of PSA with treatment ($p = 0.05$); intermittent therapy was more effective than continuous therapy among patients with PSA $\leq$1 ng/ml (HR: 0.79; 95% CI, 0.61–1.02, $p = 0.07$).

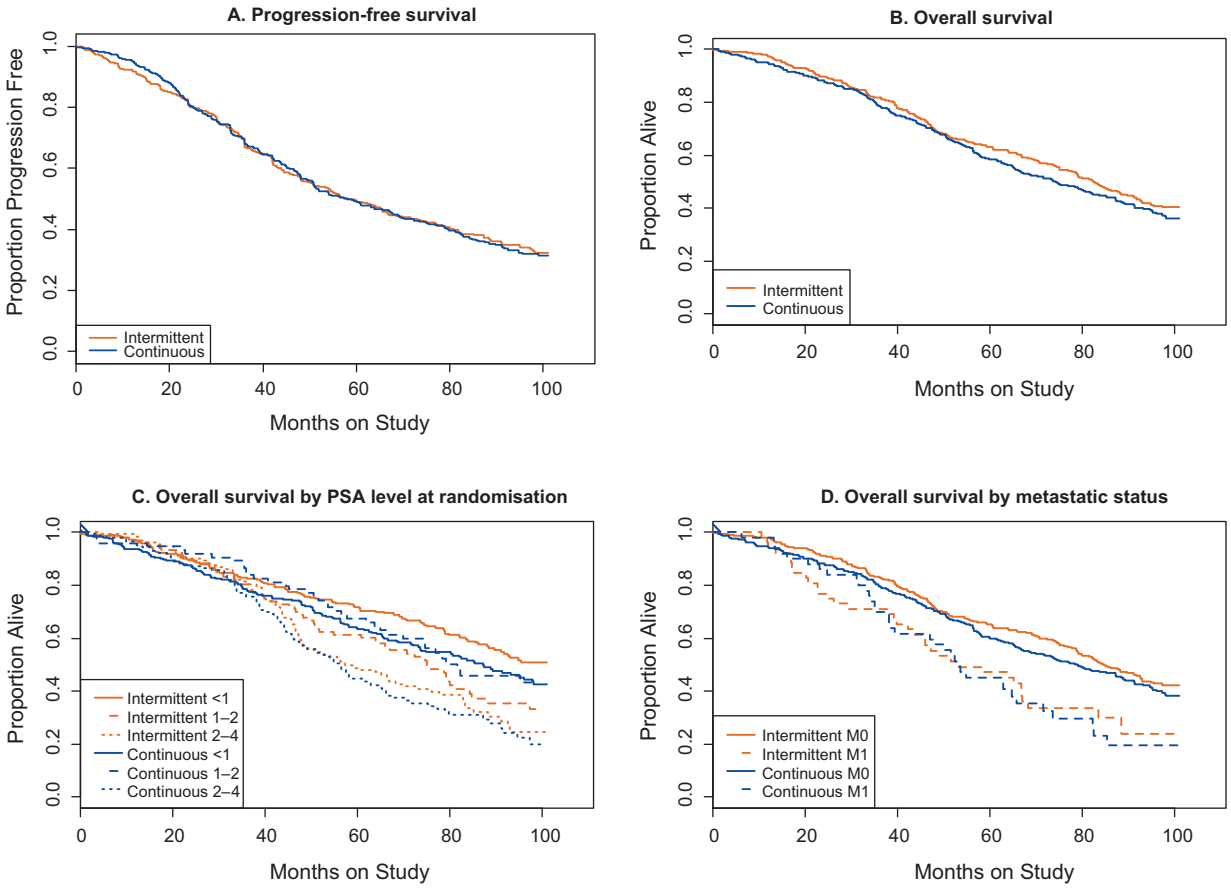

Fig. 1 – Kaplan-Meier curves for the time to any progression and time to death. The continuous arm is shown using green lines, and the intermittent arm is shown with black lines: (a) progression-free survival; (b) overall survival; (c) overall survival by prostate-specific antigen (PSA) level at randomisation; (d) overall survival by metastatic status.

Table 3 – Hazard ratios (HR) and 95% confidence intervals (lower and upper) from (a) the cox model for progression free survival and (b) the competing risks model for the cause of death

(a) Model for progression free survival

	HR	95% CI		p
		Lower	Upper	
Continuous	1.00			
Intermittent	1.02	0.87	1.20	0.8291
M0	1.00			
M1	1.66	1.29	2.12	0.0001
Age <60	1.00			
Age 60–69	0.74	0.49	1.10	0.1305
Age 70–74	0.88	0.60	1.31	0.5362
Age 75+	1.25	0.84	1.85	0.2702
PSA 0–0.5	1.00			
PSA 0.5–1	1.26	0.98	1.61	0.0703
PSA 1–2	1.41	1.11	1.80	0.0050
PSA 2–4	2.06	1.66	2.54	0.0000
Gleason 2–4	1.00			
Gleason 5–6	1.43	0.78	2.65	0.2478
Gleason 7–8	1.94	1.07	3.50	0.0285
Gleason 9+	1.83	0.88	3.81	0.1086

(b) Competing risks model for cause of death

	PCa			OMD			CVD			Other		
	HR	95% CI		HR	95% CI		HR	95% CI		HR	95% CI	
	–	Lower	Upper	–	Lower	Upper	–	Lower	Upper	–	Lower	Upper
Unadjusted												
Continuous	1	–	–	1	–	–	1	–	–	1	–	–
Intermittent	0.98	0.72	1.33	1.49	0.76	2.94	0.83	0.65	1.08	0.97	0.65	1.45
Adjusted												
Continuous	1	–	–	1	–	–	1	–	–	1	–	–
Intermittent	1.02	0.75	1.39	1.46	0.75	2.87	0.82	0.64	1.06	0.98	0.66	1.47
M0	1	–	–	–	–	–	–	–	–	–	–	–
M1	3.29	2.28	4.73	1.23	0.43	3.48	0.63	0.38	1.03	0.81	0.40	1.63
PSA <1 ng/ml	1	–	–	–	–	–	–	–	–	–	–	–
PSA 1–2 ng/ml	1.10	0.70	1.72	0.98	0.44	2.20	1.51	1.09	2.09	0.79	0.45	1.41
PSA >2–4 ng/ml	2.12	1.50	2.99	0.40	0.15	1.07	1.39	1.02	1.88	1.07	0.68	1.68

CI = confidence interval; CVD = cardiovascular disease; HR = hazard ratio; OMD = other metastatic disease (second primary); PCa = prostate cancer; PSA = prostate-specific antigen.

Another 69 patients, 25 on continuous therapy and 44 on IHT, progressed but were still alive at the time the analysis took place. There was no evidence of any difference between continuous therapy and IHT in terms of PFS (HR: 1.01; 95% CI, 0.86–1.19; $p = 0.89$). Metastatic status, age, PSA, and Gleason score were all independently associated with PFS (Table 3a).

The number of deaths due to any cancer, PCa, second primary cancer/other malignant disease (OMD), cardiovascular death (CVD), and other/unknown causes were similar between treatment arms (Table 2). The competing risks analysis showed that the slightly reduced hazard of dying in the group on IHT resulted primarily from fewer deaths from CVD balanced by an increased risk of death from a second primary cancer (Table 3b). None of these differences in HR was statistically significant (Table 3b).

Both metastatic status and PSA level at randomisation were associated with death from PCa but not with OMD or other causes of death (Table 3b). Adjusting for metastatic status and PSA at randomisation, the HR of dying from one of the four causes was similar to the unadjusted values.

3.1. *Safety and quality of life*

Side effects were generally reported more frequently among patients on continuous therapy (Table 4). Summary QLQ-C30 totals were similar between study arms (2.1 points

Table 4 – Patients reporting specified side effects at least once during follow-up by treatment arm

	Intermittent treatment	Continuous treatment	p*
No. of patients**	436	421	–
Side effect			
Hot flushes	8.3	24.9	<0.0001
Gynaecomastia	13.8	37.3	<0.0001
Headache	8.0	15.9	0.0005
Skin complaints	0.7	1.7	0.3124
Other	11.0	12.8	0.4741

* χ^2 test of the difference between the percentages.
** Number of patients with at least one follow-up form completed.

Table 5 – Patients and median times on and off therapy (weeks) in the intermittent arm according to prostate-specific antigen level at randomisation

	All patients		PSA <1 ng/ml		PSA 1–4 ng/ml	
	n	Time, median, wk	*n*	Time, median, wk	*n*	Time, median, wk
Randomisation to first time on therapy	454	132.0	224	162.0	230	110.0
Duration of time on first therapy	231	20.0	110	16.7	121	26.0
Duration of second off-therapy period	165	43.0	95	49.6	70	33.1
Duration of time on second therapy	121	19.6	75	18.1	46	21.1

PSA = prostate-specific antigen.

lower [worse QoL; standard error (SE): 1.27] in the continuous arm compared with the intermittent arm; $p = 0.11$) during 60 mo of follow-up. QLQ-C30 scores decreased in both arms, from 83.4 (SE: 1.96) at baseline to 70.5 (SE: 0.96) after 60 mo, and the gradient of the decline was similar in the two arms ($p = 0.94$). During follow-up, the only differences between the two groups of patients were in relation to the symptoms and sexual activity questions in the EORTC Prostate Cancer Module, with a significantly higher proportion of patients in the continuous arm reporting symptoms of hot flushes, gynaecomastia and swelling of the legs ($p = 0.0001$), and sexual problems ($p = 0.003$). Reported sexual activity decreased in both arms during the study, although sexual activity was significantly greater ($p < 0.0001$) in the IHT arm. Shortly after randomisation, with the majority of patients in the IHT arm off therapy, the level of sexual activity after 6 mo in this group was similar to pretreatment levels (31.3% and 32.7%, respectively); sexual activity then decreased as progressively more patients in the IHT arm received CPA therapy. However, at 30 mo after randomisation, the proportion of patients reporting sexual activity was significantly greater in the IHT arm than in the continuous arm (24.9% of 226 patients vs 6.4% of 145 patients, respectively; $p < 0.0001$).

Among the 462 patients randomised to IHT, 50% were off therapy for at least 2.5 yr following randomisation (Table 5) and 28% were off-therapy for >5 yr. The median time off therapy for patients whose PSA levels were ≤1 ng/ml and 1–4 ng/ml was 3.1 yr and 2.1 yr, respectively (Table 5). Patients returning to therapy had a median of 20 wk of treatment (16.7 wk and 26 wk for those with PSA levels <1 ng/ml and 1–4 ng/ml, respectively), which was followed by a second period off therapy (Table 5). Only 121 of patients on IHT had two returns to therapy postrandomisation, and this was for a median of 19.6 wk (Table 5).

4. Discussion

Two observations have considerable clinical importance: (1) a 3-mo period of induction therapy was used in this study, as in SEUG 9401 [2], and (2) patients in the intermittent arm who were on therapy received CPA 300 mg/d as monotherapy. This intermittent protocol is the first using antiandrogen monotherapy, and the study demonstrated that intermittent monotherapy with CPA 300 mg/d was noninferior to continuous therapy in terms of OS. Indeed, the hazard of dying on intermittent therapy was 20% lower than on continuous therapy in patients with a PSA level ≤1 ng/ml after induction therapy.

The study is reporting early in terms of numbers of deaths, as all randomised patients had been followed for at least 5 yr. The death rate was lower than anticipated, and the estimated proportion of patients surviving at 5 yr was 61%, with a median survival time of 6.6 yr compared with the anticipated 4.5 yr. By October 2012, there were 525 deaths and 106 deaths were accumulated over the last 2 yr follow-up. Thus a further 2 yr follow-up, at least, would be needed to accrue the additional 133 deaths required to reach the 658 deaths specified in the protocol. In addition, noninferiority of intermittent therapy compared with continuous therapy was demonstrated in terms of OS. There was also no evidence of any difference in terms of PFS, and with an HR of 1.01 (95% CI, 0.86–1.19), it is clear that noninferiority of IHT compared with continuous therapy can also be demonstrated for PFS. Metastatic status, PSA level at randomisation, Gleason score, and age were independent predictors of PFS, with age 60–74 yr, M0, low Gleason score, and low PSA associated with longer duration of PFS.

In this study, 50% of patients receiving IHT were off therapy for at least 2.5 yr following initial LHRH therapy, and 28% were off therapy for >5 yr. These findings support the work of Seruga and Tannock, with data collected from >1000 randomised patients indicating that IADT should be regarded as standard therapy [11] for specific patient groups. In 2007, Shaw et al. performed a meta-analysis of 1446 patients from international phase 2 studies and concluded that the duration of biochemical remission after a period of hormone therapy was a durable early indicator of how rapidly androgen-independent PCa and death would occur [12].

In our study, although not significant, more deaths from any cancer occurred in the IHT arm, but more deaths from CVD occurred in the continuous treatment arm. In contrast, although there were no differences between study arms in the domains of the QLQ-C30, side effects were generally less commonly reported in the intermittent arm. Patients on intermittent therapy experienced fewer sexual problems and reported greater sexual activity than patients on continuous therapy. During follow-up, although progressively more patients in the intermittent arm were on

therapy and sexual activity decreased, sexual activity was still significantly higher than among patients on continuous therapy. Similar results have been reported in SEUG 9401 [2] and in other studies [6,13–15].

In protocol S9346 from Hussein et al. [3], IADT was proven to be noninferior to continuous deprivation in patients with extensive disease; however, intermittent therapy was statistically inferior in patients with minimal disease, suggesting that continuous therapy would be the preferred treatment in this group. In contrast, there was no difference between minimal disease and extended disease in our trial.

5. Conclusions

From this study we can conclude that IHT should be considered as the standard therapy for patients who are not suitable for definitive therapy with advanced PCa because IHT is noninferior to continuous therapy with regard to OS. In addition, IHT is associated with better QoL (ie, sexual life) and lower costs for communities than continuous therapy. This study also showed that an induction period of 3 mo is adequate to sufficiently reduce PSA levels. Based on results from SEUG 9401 [2] and 9901, we can define an optimal candidate for intermittent therapy as a patient with (1) M0, (2) T3, and (3) PSA levels prior to induction therapy <100 ng/ml whose PSA decreases to <4 ng/ml (preferably <1 ng/ml) after 3 mo of induction therapy. Intermittent therapy is less likely to be beneficial for patients with metastasis and bone hot spots, with high initial PSA levels (>100 ng/ml), or with severe pain or extensive disease.

Author contributions: Fernando Calais da Silva had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: F. Calais da Silva.
Acquisition of data: F. Calais da Silva, F.M. Calais da Silva, Gonçalves, Santos, Kliment, Whelan, Oliver, Antoniou, Pastidis, Marques Queimadelos, Robertson.
Analysis and interpretation of data: F. Calais da Silva, Robertson.
Drafting of the manuscript: F. Calais da Silva.
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