Premoli et al. (2005) - Tratamiento del Cáncer de Próstata Avanzado con Estrógenos Transdérmicos Escrotales [Transdermal Scrotal Estrogen Patches in the Treatment of Advanced Prostate Cancer]

- Premoli, F., Re, I., Asenjo, G., Maximino, G., & Micheletti, L. (2005). Tratamiento del Cáncer de Próstata Avanzado con Estrógenos Transdérmicos Escrotales (ETE). [Transdermal Scrotal Estrogen Patches (TSEP) in the Treatment of Advanced Prostate Cancer.] *Revista Argentina de Urología* [*Rev Arg de Urol*], *70*(4), 231–241. [Google Scholar] [URL] [PDF]

English Translated

Abstract

Introduction: Since 1941 estrogens have been used in the treatment (Tx) of prostate cancer (PC) patients. In 2001 we presented "localized" PC Tx with transdermal scrotal estrogen patches (TSEP) and in 2003 TSEP intermittent Tx (ITx) in PC.

Patients and Method: Thirty-five, age 68.9 years ± 8.2 (mean ± SD) consenting advanced prostate cancer (APC) patients, 33 D3 stage, and two D1 stage, basal PSA range 8.3–4200 ng/mL were treated with one 17β-estradiol long acting transdermal system loaded with 7.5 mg of E2 applied to the scrotum and changed twice per week. Ten D3-stage patients were surgically castrated. Stage D3 basal testosterone (T) was 33 ± 39 ng/dL and performance status (PS) was 1.71 ± 1.31. Thirty-two D3 patients received continuous Tx (CTx), one D3-stage ITx, and two D1-stage patients ITx with "on" periods lasting 9 months and "off" periods until PSA reach basal levels. All cases received 325 mg of aspirin daily. PSA and T values were determined on days 30/60 after inclusion and bimonthly thereafter. Clinical parameters, CV-related events, and pain score were assessed on weekly and monthly basis. Palliation was used when pain was irreducible or on last disease stages.

Results: The survival of 27 patients was 271.1 days ± 181.1, five patients survived more than 15 months, 14 patients between 6–15 months, five patients between 4–6 months, and three patients 1 month or less. Cause of death was PC related in 24 and unknown in three. Eight patients were still alive, two D1-stage ITx: one, 79 months; 1.45 months; six D3-stage: one, CTx 18 months; 1, ITx 12 months (9 months "on", 3 months "off"), two CTx: one, 9 months; one, <1 month, and one, abandoned Tx. Fourteen (40%) patients experienced a PSA decrease of more than 50%, six (17%) patients had PSA decrease of less than 50%, in one (3.3%) patient PSA remain stable, and 9 (25.7%) patients experienced PSA progression, three (13%) patients died prior to testing for PSA. Pain score was excellent in 7, very good in 8, good in 11, fair in 4, poor in 2, not registered in 1, and pain free in 2. No CV events or clinical parameters changes except occasional slight gynecomastia were registered.

Conclusions: Although palliation remains as the mainstream Tx for D3-stage patients, TSEP seemed to have beneficial effects in pain control, PSA progression and possibly survival without CV side effects. In D1-stage cases intermittent TSEP kept disease under control. Controlled randomized studies comparing TSEP with other treatment alternatives are necessary to prove benefit with a larger cohort of men.

Keywords: Prostatic advanced neoplasm; Estradiol; Administration; Cutaneous; Scrotal

Introduction

In 1941 *Huggins* and *Hodges* showed that disseminated prostate cancer (PCa) responded favorably to bilateral orchiectomy. This finding and subsequent research earned *Huggins* the 1966 Nobel Prize in Medicine.[1–3]

The goal of orchiectomy, surgical or hormonal, is to lower plasma testosterone (T) below the castration level (≤50 ng/dL). Ninety-percent to 95% of a man's T comes from the testicles that secrete approximately 6 to 7 mg daily and the half-life is 45 minutes. The level of castration is reached with surgical orchiectomy in about 8 hours; with estrogen (E) in about 38 days (21 to 60) and approximately the same time with GnRH analogues.[4]

E acts by several mechanisms:[5] a) in the pituitary, through the hypothalamus, inhibit the secretion of LH and slow the stimulation on the testicular Leydig cells; b) in the liver they promote the synthesis of SHBG and consequent decrease of bioavailable T; c) in the prostate they inhibit 5α-reductase and DNA polymerase,[6] d) at the androgen receptor (AR) block the binding of T and DHT;[7] e) *Robertson* in 1996 showed that diethylstilbestrol (DES) and diethylstilbestrol phosphate (DESDP) have a direct toxic action on the prostate cell, independently of the estrogen receptor (ER), causing a cascade of apoptosis;[8] and f) recently it was found that they produce a decrease in adrenal androgens with a decrease in DHEA-S.[9–10]

This mechanism of action can explain the remarkable results that were obtained years ago with the empirical use of high doses of intravenous E (1 to 3 g daily), especially DESDP, in patients with terminal PCa (paraplegia, paresis, multiple metastases).[11–19]

Considering the effects and results of E,[20–27] it is worth asking: Why did they stop being used?

A. In 1967 the *Veterans Administration Cooperative Urological Research Group* (VACURG) reported that the treatment of PCa with 5 mg daily of oral DES was associated with increased risk of death from cardiovascular (CV) disease.[28–29] Later it was shown that 1 or 5 mg of DES have the same effect on stage D PCa and despite the fact that 1 mg does not completely suppress plasma T, it also achieves regression or arrest of metastases.[30–31] Subsequently, the review of the VACURG data found errors and methodological flaws.[24] However, it was established that even with high toxicity, 5 mg of oral DES is more effective than orchiectomy in delaying tumor growth; that 1 or 5 mg of DES have a similar effect; that in men younger than 75 years with stage C and D PCa treatment with 1 mg of DES achieved greater survival than the lack of treatment, and that in men older than 75 years with PCa at any stage the CV effects of 1 or 5 mg of DES are the same.
B. The appearance of GnRH analogues and its effect on T justified its use in the PCa.[30–32] The level of castration is achieved in about 60 days previously observing the "flare up" (increase in T) by stimulation of LH. This situation, not observable with E or castration, contraindicates its use as a single treatment in the case of large tumors, ureteral obstruction, hyperazoemia, or vertebral metastasis to the possibility of spinal cord compression due to its growth. Given this possibility, it is necessary to previously administer an antiandrogen (preferably flutamide for having a shorter half-life) for 10 days. The other negative effects, product of hypoandrogenism, are similar to those caused by E that are frequently associated with non-observed hot flashes with estrogen therapy.

Several arguments were used to impose GnRH analogues, namely that, unlike DES, they have no CV effect and that, unlike orchiectomy, they mean a non-surgical and non-definitive treatment, inducing the patient at their choice.

C. Coincident with the appearance of GnRH analogues, the expiration of the DES patent and the loss of interest of the pharmaceutical industry occurred in the USA.

Arguments for the use of estrogens in prostate cancer: The CV toxicity of oral E is due to the primary passage through the liver with decreased fibrinolysis and alterations in coagulation related to the inhibition of plasminogen-activating factor type 1 (PAI-1). This toxic effect can be reduced or eliminated using low doses, combining anticoagulants, or using another route.[32] *Jazieh* in 14 patients with hormone-refractory PCa (HRPCa) combined warfarin with 3 mg daily of DES obtaining in more than 75%, decrease in PSA higher than 50%, without any thromboembolic event in 28 months (maximum survival).[33] *Smith* treated 21 HRPCa patients with 1 mg of DES daily without anticoagulants, confirming 63% survival at 2 years and one case (5%) of deep thrombosis.[34] *Henriksson* found that a monthly intramuscular injection of 320 mg of polyestradiol phosphate does not affect coagulation factors, including factor VII, except for a significant decrease in antithrombin III.[35] *Hedlund* confirmed the low CV repercussion.[36] Recently *Ockrim* verified the reduction of the thrombophilic activity of transdermal E and the protection against the risk of thrombosis.[62]

The equivalence of parenteral E is: estradiol 50 μg, ethinyl estradiol 50 μg, mestranol 80 μg, and DES and conjugated estrogens 5 mg.[37]

In women, the effect of hormone replacement therapy (HRT) on coagulation depends on the type and route of administration of E.[38–39] In the liver the inhibition of plasminogen activator type 1 (PAI-1) decreases and high levels plasma levels obtained with oral administration would be more effective than those achieved with the transdermal route. *Rosenson* in 23 menopausal women with normal triglycerides treated 12 weeks with estradiol (E2) found low of 4% in blood viscosity and 20% less risk of death from CV disease.[40]

In men, E has beneficial effects on the CV system, bone system, and lipid metabolism. *Blumenthal* found that in men with known coronary heart disease, intravenous conjugated E increases blood flow by 32%.[41] *Reis* confirmed that the action of E on the coronary arteries is independent of sex and that the coronary flow increases 54% with its administration after the vasoconstriction caused by the increase in pressure by the cold test.[42]

Male osteoporosis is much less frequent than female osteoporosis and begins around 40 years of age, accompanying the slow decrease in free T.[43] In men with PCa treated with GnRH analogues or antiandrogens, the decrease in T accelerates the process by increasing calcium loss, in contrast to what happens with E that reduce bone resorption.[44] When there is osteopenia prior to treatment with E the addition of oral calcium and/or vitamin D with a suitable diet are sufficient for its control, the use of bisphosphonates or the like being unnecessary.

Arguments for intermittent hormonal therapy (IHT) in prostate cancer: For a long time the only way to perform hormonal treatment of PCa was the definitive elimination of testicular androgens through orchiectomy or continuous suppression with E, GnRH analogues, or antiandrogens. In 1986, the first results of intermittent suppression of T with DES were known.[45] Subsequently, the effect produced by a new androgenic stimulation on the cells surviving the suppression was known to help preserve or

recover altered differentiation characteristics for long periods of deprivation, which accelerate the progression towards autonomous cell growth.[46–49] as well as successive cycles of androgen suppression would maintain the potential for apoptosis and delay tumor progression.[50]

In 1996, *Umekita* found changes in ERs in HRPCa that became androgen-dependent and in which small doses of T produced apoptosis.[19] On the other hand, the administration of T in tumors absolutely refractory to androgen suppression could sensitize ERs again allowing alternation of cycles of E and T with remissions of the disease.[8,51] These data are arguments in favor of the possibilities of IHT.

IHT alternates periods with medication ("on") and periods without medication ("off").[45–49] It is proposed that the “on” period lasts nine months because at that time: a) between 90% and 95% of patients arrive at the nadir of PSA; b) BCL2 (proto-oncogene, inhibitor of apoptosis) reaches the minimum after the immediate rise at the start of androgen suppression; and c) the antiproliferative protein reaches its maximum.[52] Periodic monitoring is carried out during the “on” period up to the ninth month of T and PSA to then interrupt the treatment and start the “off” period that extends until PSA reaches the initial level or exceeds 20 ng/mL and starts a new period on. In the “off” period T rises and the symptoms of hyperandrogenism regress partially or totally with improvement of libido, recovery of morning erections, more strength and feeling of well-being, and improvement in quality of life. The rise of T occurs faster than PSA, which allows the “off” cycles to be 6 to 12 months and sometimes longer. The alternation would retard the evolution towards hormone-independence.[49] *Sciarra* compares the figures of chromogranin A (CgA) (marker of neuroendocrine differentiation of PCa) during continuous hormonal treatment and IHT, finding significantly lower figures in this and emphasizing this effect in the delay of evolution towards the hormone-refractory tumor.[53]

Taking into account the favorable effects of transdermal E in women, the low rate of complications, and the response of PCa to oral or parenteral E, the transdermal route can be an effective therapeutic option for men.

Arguments for the treatment of prostate cancer with estradiol (E2) transdermal: (In this communication, it is used as a unit of measurement of E2 pg/mL and pmol/L.) The transdermal absorption of E2 varies according to the different parts of the body. In men, the absorption through the skin of the scrotum is 3 to 8 times greater than in the forearm, abdomen, or back, and this is due to the large number of hair and sebaceous follicles, to the permeability to alcoholic substances, to vascularity, temperature, and thickness of the skin, not allowing substances, as occurs with androgens with 5α-reductase, which facilitates their metabolism.[54–55] In a pilot study E2 absorption by forearm skin and scrotal skin was compared. One volunteer applied a patch on the skin of the left forearm that releases 50 µg/day of 17β-E2 and another one that releases 100 µg/day and measured E2 with IRMA technology with the following results: in the first, basal, 24, 48, 72, and 120 hours, obtaining 20, 42, 55, 50, and 18 pg/mL, and in the second, basal, 24, 48, 72, and 96 hours, registering 14, 70, 65, 180, and 60 pg/mL, respectively.

The scrotal absorption was checked in two volunteers (one, the first of the previous example), to which a patch of 17β-E2 was applied to the skin of the scrotum and dosed with the same baseline E2 technology and every 24 hours. In the first one a patch that releases 50 µg of E2 daily, obtaining the following values: basal, 24, 48, 72, 96, 120, 144, and 168 hours: 12, 220, 190, 140, 100, 105, 75, and 65 pg/mL, respectively, and in the second a patch that releases 100 µg E2 daily with the following result: baseline, 24, 48, 72, 96, 120, and 192 hours; 27, 300, 500, 350, 200, 150, and 40 pg/mL, respectively. (Table 1.)[56]

Forearm			Scrotum		
Time	**Volunteer # 1 50 µg E2 pg/mL (pmol/L)**	**Volunteer # 2 100 µg E2 pg/mL (pmol/L)**	**Time**	**Volunteer # 1 50 µg E2 pg/ml (pmol/L)**	**Volunteer # 2 50 µg E2 pg/ml (pmol/L)**
Baseline	20 (73)	14 (51)	Baseline	14 (48)	27 (99)
24 hours	42 (154)	70 (256)	24 hours	220 (807)	300 (1101)
48 hours	55 (201)	65 (238)	48 hours	190 (697)	500 (1835)
72 hours	50 (183)	180 (660)	72 hours	140 (513)	350 (1284)
96 hours	*	60 (220)	96 hours	100 (367)	200 (734)
120 hours	18 (66)	*	120 hours	105 (385)	150 (550)
			144 hours	75 (275)	*
			168 hours	65 (238)	*
			192 hours	*	40 (146)

Table 1. *Transdermal absorption of estradiol in forearm and scrotum.*

In men, E2 values greater than 300–400 pg/mL (1100–1460 pmol/L) could be more effective in lowering PAI-1 compared with women,[38–39] in which with doses of 25 and 100 µg per day reaches around 60 pg/mL (220 pmol/L).[57–58]

Steg in 1979 first used transdermal E2 in topical form in 21 men with PCa. Between 3 and 6 months, they lost T and LH, without changes in triglycerides or LDL.[59]

In 2001, we presented the excellent results obtained with TSEP in the treatment of "localized" prostate cancer,[60] and in 2003 the results with TSEP intermittently.[61]

Ockrim in a pilot study dealt with E2 patches located in areas of the body other than the scrotum, 20 patients with advanced PCa, 10 locally, and 10 with metastasis, none of them hormone-refractory. They used six patches changed every day achieving castration levels in 21 days for LH, FSH, and T with average PSA decrease of 95.1% at 6 months (range 84.2–99.8%) with an average follow-up of 15 months (range 12 to 20 months). It indicates the lack of CV events, the improvement of the lipid profile, the beneficial effect on bones, and the ten-fold reduction in treatment costs.[62] *Bland* treated 24 androgen-independent patients with six patches of 100 µg/day changed every day and showed absence of thromboembolic alterations or important clinical changes, and in three of patients achieved a decrease in PSA ≥50% with a mean plasma E2 value of 460.7 pg/mL.[63] *Ockrim* confirmed that transdermal E2 reduces thrombophilic activity and protects against thrombosis in men with advanced prostate cancer.[64] These three communications in no case used the scrotal passage as the gateway for E2, since they used six patches changed daily located outside the scrotum.

The list price of the medication usually used in our country for the transdermal E2 patch has a cost of $6.32 daily.

In summary: For everything expressed and taken into account: a) the effect of E on T is at least similar to that of other non-estrogenic hormonal therapies; b) the direct action of E on the prostate cell; c) the beneficial action on the CV apparatus, lipids, and bone system; d) the reduction or disappearance of the toxic effects produced by the oral route; and e) the significant decrease in cost compared with other variants of androgen blockade, it is evident that the administration of E by another route, not oral, easy to apply and accept, justifies its use for the treatment of PCa.

In this communication, the terms HRPCa (hormone-refractory prostate cancer) and androgen-independent prostate cancer will be used as synonyms.

Objective

Check the effect that the TSEP have on the advanced PCa.

Patients and Method

In January 1997, patients with PCa were treated with TSEP. A patch loaded with 7.5 mg of long-acting 17β-E2 that releases 100 μg of E2 per day located on the skin of the scrotum was used. The purpose of this treatment, like that of all hormonal treatments aimed at lowering T, is not curative.

We treated 35 patients between 52 to 82 years – 68.9 ± 8.2 (mean ± SD) of age with advanced PCa, two clinical stage D1, and 33 D3 stage, 10 D3 stage orchiectomized previously. The baseline PSA in the range between 4.8 and 4200 ng/mL, the baseline T in stage D3 – 33 ± 39 ng/dL, the physical state (*Performance Score* ECOG)[65] – 1.71 ± 1.31 (Table 2).

n	ed	diag	SG	orq	tHR	in tx	EC	EF	PSA Tb	PSA bas	PSA 30 d	PSA 60 d	PSA ult/d	TTT	EED	Evo	CO	otros Tx
01/01	82	12/91	6	sí/91	5a	03/97	D3	0	0,2	25	22		120	785	B	0	CP	paliat.
02/08	52	03/97	9	no	3m	06/97	D3	2	0,4	200				21	MB	0	CP	paliat.
03/10	71	07/91	7	sí/91	4a	06/97	D3	4	0,2	95		300	9000	180	MB	0	CP	paliat.
04/13	78	03/91	7	sí/91	5a	09/97	D3	2	0,6	500	34		750	462	MB	0	CP	paliat.
05/15	66	09/97	8	no	3m	02/98	D3	3	0,3	8,3			300	188	MB	0	CP	paliat.
06/17	74	10/95	7	sí/95	2a	02/98	D3	1	0,2	4200	500		500	450	Ex	0	CP	paliat.
07/18	57	01/95	9	no	1a	02/98	D3	0	0,1	30	32		30	296	R	0	CP	paliat.
08/23	60	10/98	8	no	NO	01/99	D1	0	2,3	26	3,5	0,5	9,5	2380	*	Ex	*	paliat.
09/24	58	07/98	8	sí/98	3m	01/99	D3	3	0,1	920	1500	1600	3000	130	R	0	CP	paliat.
10/28	75	10/98	9	sí/98	3m	06/99	D3	4	0,2	350	537			35	B	0	CP	paliat.
11/31	82	12/97	7	no	1a	08/99	D3	2	0,3	288	24	11	19	310	Ex	0	CP	paliat.
12/34	58	05/99	8	sí/99	4m	10/99	D3	0	0,4	65	14	1	289	545	Ex	0	CP	paliat.
13/35	71	07/97	7	no	1a	12/99	D3	3	0,5	300				35	B	0	CP	paliat.
14/36	78	01/99	7	no	1a	12/99	D3	2	0,5	23	6,7	2,4		365	MB	0	CP	paliat.
15/37	74	07/97	7	sí/97	1a	12/99	D3	3	0,2	160	210	325	300	605	B	0	CP	paliat.
16/39	75	06/98	7	no	1a	12/99	D3	3	0,2	15	18,3			252	MB	0	CP	*
17/40	68	01/00	8	sí/00	4m	06/00	D3	2	0,2	637	520	230	480	325	MB	0	CP	paliat.
18/41	61	08/00	10	no	3m	08/00	D3	3	0,2	320	271			305	B	0	CP	paliat.
19/43	56	04/01	8	no	3m	04/01	D3	2	0,3	226	5	1	1,13	240	Ex	0	Des	*
20/44	75	03/00	6	no	1a	07/01	D3	3	0,4	135	100	124		120	B	0	Des	paliat.
21/45	74	02/00	7	no	6m	07/01	D3	3	0,2	172	185			120	B	0	CP	*
22/47	72	08/00	8	no	6m	10/01	D3	1	0,1	214	24	5,6		360	Ex	0	CP	paliat.
23/48	72	04/98	7	no	3a	09/02	D3	0	0,1	160	263	260	*	180	R	0	CP	paliat.
24/49	64	03/91	8	sí/00	2a	09/02	D3	4	0,1	35	28	36	90	290	B	0	CP	paliat.
25/50	58	12/98	6	no	NO	11/02	D1	0	3,4	4,8	1,5	0,7	10	1345	*	Ex	*	interm.
26/51	73	12/00	8	no	2a	03/03	D3	1	0,2	88	75	66	*	180	Ex	0	Des	*
27/53	64	04/98	7	no	3a	06/03	D3	0	0,6	203	70	29	90	560	MB	B	*	paliat.
28/54	63	01/00	9	no	2a	09/03	D3	1	0,1	95			198	270	R	0	CP	paliat.
29/58	67	12/99	8	no	4a	07/04	D3	2	0,9	208	47	50	98	365	B	B	*	Rx, interm.
30/59	71	07/03	8	no	9m	08/04	D3	1	0,1	99	62	64	99	150	B-R	0	CP	paliat.
31/60	58	12/03	10	sí/03	5m	08/04	D3	2	0,3	264	48	93	*	120	B-R	0	CP	paliat.
32/65	79	03/00	7	no	4a	11/04	D3	1	0,2	37	26	20	48	250	B	B	*	paliat.
33/66	78	06/01	7	no	3a	12/04	D3	0	0,1	39	7,5	6,6	9,9	234	Ex	Ex	*	*
34/68	74	02/98	7	sí/98	6a	01/05	D3	2	0,4	98	*			20	*	AbT	*	*
35/69	75	08/01	7	sí/01	1a	07/05	D3	0	0,2	344	*			30	B	B	*	*

Table 2. *Treatment of advanced prostate cancer with transdermal scrotal estrogen patches (TSEP).*

Abbreviations: nº: nº PCa advanced / serial nº. TSEP; ed: age; Dx: PCa diagnosis date; SG: Gleason Score; Orq: orchiectomy; tHR: time to hormone-refractory (a) years, (m) months; in Tx: TSEP procedure start date; EC: clinical stage; EF: physical state at the

beginning of TSEP - (ECOG *Performance Status*: *Eastern Clinical Oncology Group*); **Tb: basal testosterone (ng/*mL*)**; PSA, bas: basal; 30 d: 30 days; 60 d: 60 days; ult/d: last available; TTT: total time with TSEP treatment; EED: estradiol effect on pain, (ex: excellent, MB: very good, B: good, R: regular, M: bad, Evo: final evolution (Exc: excellent, B: good, R: regular, O: death, AbT: abandonment treatment, CO: cause death, CP: related to prostate cancer, D: unknown, AbT: abandonment Tx, Other Tx: other treatments, palliative (Rx, analgesic), interm: intermittent.

Note: case 8/23 last PSA July '05 "9.5" 240 days, 4th period "off".
Note: case 25/50 last PSA July '05, 1.7 ng/mL, 30 days 3rd period "on".
Note: case 29/58 radiotherapy in met. femur and iliac, suspended E2 every two months.

To 33 D3-stage patients with androgen blockade with agents other than E and T <50 ng/dL that presented three consecutive increases in PSA and/or increased bone metastases and after interruption of the blocking medication, continuous treatment with TSEP was applied. The purpose of the continuous treatment was to try to control the tumor recurrence, to diminish the pain of the bone metastases and eventually to prolong the survival. If no obvious response was obtained, the continuous treatment could be interrupted for short periods (2–3 months) by attempting in patients not surgically castrated to recover transiently from T.

In two stage D1 patients, one with positive pelvic nodes detected during an aborted radical prostatectomy and one with positive pelvic nodes detected by PET fusion plus CT in 2002 at the *Cleveland Clinic* in the USA after the failure of radiant therapy 2 years earlier in our country, with normal T and PSA levels of 260 ng/dL and 4.8 ng/mL, respectively, intermittent treatment with TSEP was applied with “on” periods of 9 months duration and “off” until PSA reached the baseline level or exceeded 20 ng/mL.

The patches were applied permanently on the scrotum and were changed twice a week (every 3 or 4 days).

The purpose and possibilities of the treatment were informed to patients and/or relatives and an instructive and informed consent was given to those who voluntarily wanted to sign it.

The criteria for non-inclusion were: a) absolute: known allergy to E2 or its derivatives or receiving a preparation with estrogens (e.g. estramustine phosphate); b) relative: large scrotal lesions of the skin, severe liver disease in evolution, and history of thromboembolism, deep thrombosis, and phlebitis.

In a conventional and tentative way, therapeutic values of plasma E2 were established in ≥300 pg/mL and the verification of smaller figures, suggesting difficulties in the application of the patches, motivated controls on the methodology used in their placement.

As prophylaxis of gynecomastia, low-dose mammary radiation therapy was offered prior to treatment, depending on the practice of the patient's clinical status and financial resources. The patients with CV disease and aspirin medication continued the same, and the remaining 325 mg of daily aspirin were indicated. It was recommended not to scrub the scrotal region during the bath and for the case that at some point the patch was removed replace it with a new one.

General measures aimed at reducing the effects of lack of T: physical exercise, adequate diet, reduction or elimination of toxins such as alcohol and cigarettes were indicated and, when possible, their partners were interviewed to inquire about genital function and consider the possibility of using vasoactive drugs or sildenafil to facilitate erection. All the patients were invited to attend periodically (every 15–20 days) to group meetings coordinated by the main author.

The treatment was evaluated according to three parameters: changes in PSA, modification of the symptoms produced by metastasis (bone, lymphatic, and visceral), and symptoms and urinary signs.

PSA was determined on a monthly or bimonthly basis and when economic possibilities allowed T and E2. In non-castrated men, the castration T level was set at ≤50 ng/dL. During the IHT the duration of the cycles, the nadir of PSA, and the relation with T.

Changes in PSA at 30/60 days of initiation were established as: "marked decrease" ≥50% of the baseline, "moderate decrease" between 11 and 49%, "not significant" ± 10% of the baseline (taking into account the coefficient of variation of the method used for the determinations),[66] and "ascent".

Physical status (Performance Status) was evaluated with the qualification of the *Eastern Clinical Oncology Group*,[65] pain with a scale in which the patient self-evaluates the symptom and records the need for analgesics, and monitored the evolution of neurological symptoms and signs (paresis, paralysis). We evaluated urinary frequency and jet quality, resumed spontaneous urination in patients with permanent urethral catheter, and prostate changes checked by rectal examination. If necessary, medication aimed at facilitating urination was added.

During the first month, weight, TA, edema, or signs of venous alteration, and changes in breasts and nipples (sensitivity and/or size increase) were monitored weekly.

The blood from which the material used for the determinations was extracted was frozen and kept in the laboratory of the reference laboratory.

The Ethics Committee of the Medical Association of the 2nd Circumscription of the Province of Santa Fe approved the completion of this study.

Results

Survival for 27 (77.2%) of the 35 patients was 271.1 ± 181.1 days (mean ± SD), five (18.5%) survived more than 15 months, 14 (51.8%) between 6 and 15 months, five (18.5%) between 4 and 6 months, and three (11.1%) ≤1 month. The cause of death in 24 cases was related to PCa and in three it could not be determined. There were alive 8 (22.8%) patients, two D1 stage with intermittent treatment: one, 79 months, and one, 45 months; six D3-stage: one, 18 months with continuous treatment, one, 12 months with intermittent treatment (9 months “on”, 3 months “off”), one, 9 months with continuous treatment, one, <1 month of treatment, and one, abandoned at 20 days.

PSA in 30/60 days of treatment registered: 14 (40%) patients with decrease ≥50%, six (17%) with decrease between 11 and 49%, in one (2.8%) there was no significant variation, in 9 (25.7%) increased, one (2.8%) had less than 1 month of treatment, three (8.5%) died before control, and one (2.8%) left treatment.

The baseline E2 varied between 12 and 43 pg/mL (44 and 157 pmol/L) and during treatment ranged between 123 and 1200 pg/mL (451 and 4405 pmol/L), most of the determinations being found around 500 pg/mL (1835 pmol/L). In no case were hot flashes or excessive sweating observed.

In D3-stage patients pain control was: excellent in 7 (21.2%) with elimination of analgesics before 30 days, very good in 8 (24.2%) with elimination of analgesics before 60 days, good–regular in 12 (36.3%) with analgesic decrease, regular in four (12.1%) maintaining or increasing analgesics, and in two (6%) without effect. The acceptance of the treatment was excellent and the adhesion of the patch very satisfactory since in only one case, an enormously obese and bedridden patient with scrotum edematized by recent orchiectomy, it was not possible to keep it attached and despite the daily change in only one occasion before of dying at 30 days exceeded 100 pg/mL of E2. In no case were there CV events or changes in clinical parameters, except in the period immediately after death.

In two D1-stage patients, treatment with intermittent TSEP was performed (Table 3). In the first case it covered 1286 days “on” in four periods of 328, 339, 319, and 300 days, and 968 days “off” in four periods of 190, 328, 210, and 240 (in progress) days, PSA at the beginning of the “on” periods was 26, 3.4, 19, 7, and 23.3 ng/mL and T 334, 480, 360, and 190 ng/dL, and PSA at the beginning of the “off” periods was 0.5, 1.2, 1.0, and 1.5 ng/mL and T 30, 20, 10, and 10 ng/dL. In the second case it covered 589 days “on” in three periods of 285, 274, and 30 (ongoing) days and 452 days “off” in two periods 242 and 210 days, PSA at the beginning of the “on” periods was 4.8, 6.5, and 10.9 ng/mL and T 340, 600, and 560 ng/dL and at the beginning of the “off” periods PSA was 0.3 and 0.6 ng/mL and T 10 and 10 ng/dL. Both patients received previous mammary radiotherapy, so they did not experience breast symptoms, there were no changes in BP or body weight, and the adherence to the treatment was excellent.

	1° “on”			1° “off”			2° “on”			2° “off”			3° “on”			3° “off”			4° “on”			4° “off”		
	PSA	**T**	**Days**	**PSA**	**T**	**Days**	**PSA**	**T**	**Days**	**PSA**	**T**	**Days**	**PSA**	**T**	**Days**	**PSA**	**T**	**Days**	**PSA**	**T**	**Days**	**PSA**	**T**	**Days**
#1	26	330	328	0.5	30	190	34	480	339	1.2	20	328	19.7	400	319	1	10	210	23	190	300	1.5	10	240
#2	4.8	340	285	0.3	10	242	6.5	600	274	0.6	10	210	10.9	600	30									

Table 3. *Intermittent Transdermal Estrogens in Stage D1 Prostate Cancer.*

Note: case #1: 240 days "off" PSA 9.5 ng/mL and T 260 ng/dL.
Note: case #2: 3rd "on" 30 days in progress.

The cost of intermittent TSEP treatment is significantly lower than any other androgen blocker, ranging from $4 (July 2005) per day, varying according to the duration of the “off” periods.

Discussion

Despite the fact that more than 60 years have passed since the role of E in the treatment of PCa was discovered, they have not lost their validity and remain a difficult therapeutic option to overcome. Their displacement due to the numerous therapeutic attempts that happened to them was facilitated due to the CV complications attributed to them. However, the elimination of CV complications observed with parenteral use of different types of E, coupled with the verification of other beneficial effects on the CV and bone systems, has produced in recent years a "greening" in its indications, and has weighted its role.

This communication tries to contribute to position E again in the role that should never have been lost, lamenting that if many of the resources that were used in non-estrogenic therapies had been dedicated to research in this field, it would probably have been possible to reach treatments more effective for PCa.

Recent communications[62–64] officially "initiate" a new approach in the treatment of PCa with transdermal E outside the scrotum.

The administration of E2 through the scrotum proposed in this work started more than 9 years ago and that in our knowledge does not record antecedents has provided very satisfactory results. Although there are no comparative studies, given the impossibility of carrying out controls in HRPCa, the palliative results obtained with TSEP in a continuous manner can be estimated as at least similar to those obtained with other therapeutics (chemotherapy, and others) with less general repercussion, fewer undesirable effects, and positive analgesic effect on bone metastases. Taking into account that no treatment currently used achieves a satisfactory and lasting response to this stage of PCa, TSEP are a valid option.

Intermittent treatment with TSEP indicates the need to direct investigations into the activity of hormonal receptors in relation to the changes produced by the administration of E and the possibility of androgen administration in the final stages of HRPCa when the TSEP cease to have an effect. This hypothesis could make feasible the alternation of cycles with E and androgens and has been thought of as a last resort for the final stage but, given the ethical implications, it needs careful selection, supervision, and approval of the Ethics Committees of Medical Institutions.

To the undoubted clinical benefits of the use of E in PCa is added a very important factor that is the remarkable reduction of costs, a circumstance that increases if they are used intermittently.

A paradoxical situation occurs with the fact that some of the most important social works (SW) and prepaid do not recognize E2 patches as oncological treatment and therefore do not give 100% coverage, but they do with GnRH analogues and antiandrogens, without considering the usefulness of the treatment and the difference in costs. This made patients of modest resources have difficulty accessing the medication, as well as the performance of control analysis or preventive mammary radiation therapy that was only covered by some SW or prepayments.

Bearing in mind that the decrease in health expenditures is a priority goal in most countries, even in highly developed countries, and that in our country this eventuality acquires imperative characteristics, the use of parenteral E becomes necessary and perhaps inescapable.

The adherence to the treatment has been very good, being evidenced by the concurrence of the patients to the group meetings coordinated by the main author where they exchange experiences.

Two studies are underway: one TSEP and bone densitometry whose preliminary result shows very good density of bone mass, and another, with measurement of antithrombin 3 (AT3) in people treated with TSEP and in people without prostatic pathology who initially can not find difference between both populations.

The financing of this study was mostly covered by the main author and the reference biochemical laboratory, who did their work free of charge, to a lesser extent for social security and often for patients, most of them with modest resources. It is worth noting the attitude of the pharmaceutical company of our country that produces the E2 patches that for a certain time provided material and financed the performance of some biochemical determinations.

Conclusions

This communication is aimed at trying to replace E, overcome the complications attributed to oral administration, in the role that corresponds to the treatment of PCa at present.

The transdermal scrotal route obtains high levels of E2, higher than those obtained with other dermal locations, which decreases the number of patches used and exerts a positive effect on PCa and its symptoms. The survival obtained with TSEP in the HRPCa was acceptable, the effect on pain being a result of bone metastasis being satisfactory. In the PCa D1 stage the intermittent treatment achieved a significant decrease in PSA and maintained castration levels of T, allowing alternating cycles with and without treatment, improving the quality of life in the latter.

There were no undesirable CV effects, hot flashes, or sweating, and gynecomastia was prevented with previous irradiation of the gland. In those who did not do it, it was not an important problem.

The significant decrease in the costs of TSEP treatment that becomes even more evident when used intermittently must be taken into account.

Randomized controlled studies with a larger number of patients are necessary to certify the results obtained in this research and confirm the role of transdermal E in PCa.

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