

## **Transdermal scrotal estrogens patches (TSEP) in the treatment of advanced prostate cancer.**

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GRUAS – Grupo Rosarino de Urología, Andrología y Sexología

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**Introduction:** Since 1941 estrogens has been used in the treatment (Tx) of prostate cancer (PC) patients (pts). In 2001 we presented “localized” PC Tx with TSEP and in 2003 TSEP intermittent Tx (ITx) in PC.

### **Methods:**

Thirty-five, age 68.9 years  $\pm 8,2$  (mean  $\pm$  sd) consenting advanced prostate cancer (APC) pts, 33 D3 and 2 D1, basal PSA range 8.3-4200 were treated with one 17-beta-estradiol long acting transdermal system loaded with 7.5 mg of E2 applied to the scrotum and changed twice per week. Ten D3 pts were surgically castrated. D3 basal testosterone (T)  $0.33 \pm 0.39$  and performance status (PS)  $1.71 \pm 1.31$ . Thirty-two D3 pts received continuous Tx (CTx), one D3 ITx and 2 DI pts ITx with “on” periods (p) lasting 9 months and “off” p 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 utilized when pain was irreducible or on last disease stages.

### **Results:**

The survival of 27 pts was  $271.1 \pm 181.1$  days, 5 pts survived more than 15 months (m), 14 pts between 6-15 m, 5 pts between 4-6 m and 3 pts 1m or less. Cause of death was PC related in 24 and unknown in 3. Eight pts are still alive, 2 DI ITx: 1, 79m; 1, 45m; 6 D3: 1, CTx 18m; 1, ITx 12m (9m “on”, 3 m “off”), 2 CTx: 1, 9m; 1, <1m and 1, abandoned Tx. Fourteen (40%) pts experienced a PSA decrease of more than 50%, 6 (17%) pts had PSA decrease of less than 50%, in 1 (3.3%) pt PSA remain stable and 9 (25.7%) pts experienced PSA progression, 3 (13%) pts 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 patients, TSEP seemed to have beneficial effects in pain control, PSA progression and possibly survival without CV side effects. In D1 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.

**Key words:** prostatic advanced neoplasm, estradiol, administration, cutaneous, scrotal

In 1941 it was observed by *Huggings and Hodges* that disseminated Prostate Cancer (PCa) responded favourably to bilateral orchiectomy. This finding and ulterior research led Huggins to be awarded with 1966 Nobel Prize in Medicine.<sup>1-3</sup>

The goal of orchiectomy, be it surgical or medical, is to make serum testosterone (T) go below castrate levels ( $<$  or  $=$  50 ng/dl). Nearly 90 to 95% of testosterone production in men comes from the testicles that produce 6 to 7 mg. daily with a half-life of 45 minutes. Castration level is achieved through surgical

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orchiectomy in about 8 hours; with estrogens (E) in about 38 days (21 to 60) and in approximately the same time with GnRh analogues.<sup>4</sup>

Estrogens have several mechanisms of action<sup>5</sup>: a) in the hypophysis, through the hypothalamus, they inhibit LH secretion and restrain the Leydig cells stimulation in the testes, b) in the liver they promote the SHBG (Sex Hormone Binding Globulin) synthesis, subsequently lowering the bioavailable T; c) in the prostate they inhibit 5 alpha-reductase and DNA polymerase<sup>6</sup>; d) in the androgen receptors (AR) they block T and DHT binding<sup>7</sup>; e) In 1966 Robertson observed that diethylstilbestrol (DES) and phosphate diethylstilbestrol (Ph DES) have a direct toxic action on the prostatic cell, with independence of estrogen receptor (ER), leading to an apoptotic cascade<sup>8</sup> and f) recently it's been observed that they produce a lowering of adrenal androgens and DHEA-S<sup>9-10</sup>.

This mechanism of action can explain the remarkable results obtained years ago by the empiric use at high doses of I.V. estrogens (1 to 3 mg daily), specially Ph DES, in terminal PCa patients (hemiplegia, paresthesia, multiple metastases)<sup>11-19</sup>.

Taking into consideration estrogen's results<sup>20-27</sup> and side effects, one may wonder: Why did they become out of use?

a) In 1967 the *Veterans Administration Cooperative Urological Research Group* (VACURG) informed that treating PCa with 5 mgs daily of oral DES was associated with an increased risk of cardiovascular death (CV)<sup>28-29</sup>. Later on, it was proved that either 1 or 5 mgs of DES have the same effect on stage D PCa, and although 1 mg does not achieve total suppression of serum T, regression or halting of metastases is achieved all the same<sup>30-31</sup>. After that, in a review of VACURG data methodological errors and failures were found<sup>24</sup>. It was nevertheless established that even despite its high toxicity, 5 mgs of oral DES is more effective than orchiectomy to retard tumour growth; that either 1 or 5 mg have a similar effect; that in men older than 75 years with stage D or C Prostate cancer, the treatment with 1 mg daily of DES achieves longer survival than no treatment and that in men older than 75, with any stage PCa, DES cardiovascular side effects of either 1 or 5 mgs are the same.

b) The introduction of LHRH analogues, and its effects on T, justified its use on Pca<sup>30-32</sup>. Castrated level is achieved in 60 days, with a previous testosterone flare up because of the LH stimulus. This situation, not observed neither with E or castration, contraindicates its use in the setting of large size tumours, ureteral obstruction, hyperazotemia or spinal metastases, given the possibility of spinal compression due to tumour growth. Because of this possibility, in the previous 10 days an antiandrogen must be administered (preferentially Flutamide, for its shorter half life). The rest of negative side effects, as a result of hypoandrogenism, are similar to those produced by E, except the hot flashes that are not frequently observed with estrogen therapy.

To imposed the analogues several arguments were used: that, unlike DES, they do not have CV side effects and that, unlike orchiectomy, they imply a non-definitive and surgical treatment, promoting a patient's choice for them.

c) Coincidentally with the introduction of LHRH analogues, DES patent expired in the USA, and the pharmaceutical industry lost interest in DES.

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### **Arguments for estrogen use in Prostate Cancer**

CV toxicity by the use of oral estrogens is explained because they first go into the liver, lowering fibrinolysis and altering coagulation in relation with plasminogen activator inhibitor-1 factor (PAI-1). This toxic effect can be diminished or eliminated by using a low dosage, by utilizing blood thinners or by using another path. Jazieh in 14 patients with hormone refractory PCa (CaPHR) associates Warferin to 3 mg daily of DES, obtaining in more than 75% of patients a PSA decline of more than 50%, without any thromboembolic event in 28 months(maximum survival)<sup>33</sup>. Smith treated 21 CaPHR with 1 daily mg of DES without blood thinners, observing a 63% survival at 2 years and one event (5%) of deep vein thrombosis<sup>34</sup>. Henriksson finds out that a monthly intramuscular injection of 320 mg of polyestradiol phosphate was not affecting coagulation factors, factor VII included, except for a significant antithrombin III decline<sup>35</sup>. Hedlund confirms the small cardiovascular repercussion<sup>36</sup>. Recently, Ockrim verifies a reduction in thrombophilic activity in transdermal E, and its protection against thrombosis risk.

The parenteral equivalence to Estrogens are: estradiol 50 ug, ethinyl estradiol 50 ug, mestranol 80 ug, DES and conjugated estrogens 5 mg<sup>37</sup>. In women, the effect of hormone replacement therapy (HRT) on coagulation depends on the type and way of administration of E<sup>38-39</sup>. The plasminogen activator inhibitor-1 (PAI-1) declines in the liver, and the serum high levels obtained with oral administration would be more effective than those obtained through the transdermal way. Rosenson in 23 menopausal women, with normal triglycerides level, treated for 12 weeks with estradiol (E2), found a 4% decline in blood viscosity, and a 20% decrease in death risk due to CV disease<sup>40</sup>.

In men, Estrogens have beneficial effects on the Cardiovascular System, the bones and the lipid metabolism. Blumenthal finds out that in men with known coronary disease, intravenous conjugated E increase the arterial flow by 32%<sup>41</sup>. Reis confirms that the action of Estrogens on the Coronary system is irrespective of sex and that the coronary flow increases by 54% when Estrogens are administered after vasoconstriction secondary to an increasing pressure due to the cold test<sup>42</sup>.

Osteoporosis in men is much less frequent than in women, and it begins about the fifth decade along with a slow decline of free Testosterone<sup>43</sup>. In men suffering PCa treated with GnRh analogues or antiandrogens, the testosterone decline accelerates the process, thereby increasing calcium loss inversely to what happens with Estrogens, which decrease bone resorption<sup>44</sup>. Should osteopenia exist previous to the Estrogen treatment, it can be sufficiently controlled with oral calcium and/or vitamin D intake, along with an adequate diet, thus rendering unnecessary the use of bisphosphonates or similar drugs.

### **Arguments for the use of intermittent hormonal treatment (IHT) in Prostate Cancer**

For a long time, the only method to hormonally treat Prostate Cancer was the definitive elimination of testicular androgens through orchiectomy or with continuous suppression with Estrogens, analogues or antiandrogens. In 1986, the first results of intermittent Testosterone suppression with DES were known<sup>45</sup>. Later, the effect produced by a new androgen stimulus on the surviving cells to the first suppression was recognized. This happens by helping to preserve or recuperate the altered differentiation characteristics due to long deprivation periods, which accelerate progression towards autonomous cellular growth<sup>46-49</sup>. It is so how subsequent cycles of androgenic hormonal suppression would retain its apoptotic potential and would retard tumour progression<sup>50</sup>.

In 1996, Umekita observes changes in estrogen receptors in HRPCa: they become androgen dependent and low T doses induce apoptosis<sup>19</sup>. On the other side, T administration in tumours absolutely refractory

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to androgen suppression could resensitize the androgens receptors, and hence allowing an alternation of E and T cycles, and disease remission<sup>8,51</sup>. These data are arguments in favour of the possibilities of IHT. IHT alternates periods of medication (on) with periods without medication (off)<sup>45-49</sup>. It is proposed the "On" period to last for nine months, because during that time: a) between 90% and 95% of patients achieve the PSA nadir; b) BCL2 (proto-oncogen, apoptosis inhibitor) reaches a minimum after an immediate initial increase when the androgen suppression is initiated and c) antiproliferative protein reaches its peak<sup>52</sup>. During the "on" period, and until the ninth month a periodic T and PSA control is performed. After that, the treatment is stopped and the "off" period begins until the PSA recovers up to the initial level or goes beyond 20ng/ml. At that moment, the new "on" period starts. During the "off" period, Testosterone increases and symptoms of hypoandrogenism partially or totally recede, the libido improves, morning erections come back, and there is a greater feeling of strength, well being and improvement in quality of life. T rise occurs quicker than PSA, which allows for "off" periods duration of 6 to 12 months, and sometimes longer.

Alternation would retard progression to hormone-independency<sup>49</sup>.

Sciarra compares figures of chromogranin A (CgA) (neuroendocrine differentiation marker for PCa) during continuous hormonal treatment and IHT, finding out in the latter figures significantly lower and highlights this effect in retarding tumour evolution towards hormone refractory status<sup>53</sup>.

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

### **Arguments in favour of treating Prostate Cancer with transdermal Estradiol (E2)**

(Measurement units used here for E2 are pg/ml and pmol/l.). Transdermal absorption of E2 varies according to the different parts of the body. In men, absorption through scrotal skin is 3 to 8 times superior to that on the forearm, the abdomen or the upper back. This is due to great number of hair and sebaceous follicles, to the permeability of alcoholic substances, to vascularity, temperature, skin thickness, and to the fact that there are no substances, as it is the case of androgens and 5-alpha reductase, that promote its metabolism<sup>54-55</sup>. In a pilot study, E2 absorption through forearm skin versus scrotal skin was compared. A patch was applied on a volunteer's left forearm, liberating 50 ug/day of 17 beta E2 LA, and on another volunteer one patch liberating 100 ug/day. E2 was measured using IRMA technology, yielding the following results: in the first one, basal, 24, 48, 72 and 120 hours, obtaining 20, 42, 55, 50 and 18 pg/ml, and in the second one, basal, 24, 48, 72 and 96 hours, obtaining 14, 70, 65, 180 and 60 pg/ml, respectively. Scrotal absorption was observed in 2 volunteers (the first one from the previous example), to whom a 17 beta E2 LA scrotal patch was applied, and were dosed with the same basal E2 technology every 24 hours. In the first one a patch that liberates 50 ug per day of E2 and the results obtained were: basal, 24, 48, 72, 96, 120, 144, 168 hours, 12, 220, 190, 140, 100, 105, 75, 65 pg/ml respectively; and in the second one a patch liberating 100 ug per day of E2 with the following results: basal, 24, 48, 72, 96, 120 and 192 hours; 27, 300, 500, 350, 250, 150 and 40 pg/ml respectively. (Table 1)<sup>56</sup>.

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**Table 1: TRANSDERMAL ABSORPTION OF ESTRADIOL ON SCROTUM AND FOREARM**

	Forearm			Scrotum	
	volunteer # 1	volunteer # 2		volunteer # 1	volunteer # 2
	50 ug E2	100 ug E2		50 ug E2	100 ug E2
	pg/ml-nmol/ml	pg/ml-nmol/ml		pg/ml-nmol/ml	pg/ml-nmol/ml
basal	20 - 73	14 - 51	basal	14 - 48	27 - 99
24 hrs.	42 - 154	70 - 256	24 hrs.	220 - 807	300 - 1101
48 hrs.	55 - 201	65 - 238	48 hrs.	190 - 697	500 - 1835
72 hrs.	50 - 183	180 - 660	72 hrs.	140 - 513	350 - 1284
96 hrs.	*	60 - 220	96 hrs.	100 - 367	200 - 734
120 hrs.	18 - 66	*	120 hrs.	105 - 385	150 - 550
			144 hrs.	75 - 275	*
			168 hrs.	65 - 238	*
			192 hrs.	*	40 - 146

In men, figures of E2 above 300-400 pg/ml (1100-1460 pmol.l) could be more effective in declining PAI-1, in comparison to women<sup>38-39</sup>, in whom, using a dose of 25 and 100 ug per day, 60 pg (220 pmol.l.) are achieved<sup>57-58</sup>.

Steg in 1979 used for the first time transdermal E2, via topic administration, in 21 men with PCa. In 3 to 6 months a decline in T and LH were achieved, without any changes either in triglycerides or LDL<sup>59</sup>.

In 2001, we presented the excellent results that we obtained with TSEP in the treatment of “localized” Pca<sup>60</sup>, and in 2003 the results with intermittent TSEP<sup>61</sup>.

Ockrim, in a pilot study, using E2 patches applied on body parts other than scrotum treats 20 patients with advanced PCa, 10 locally advanced and 10 with metastases, none hormone-refractory. He uses 6 patches, replaced daily, achieving in 20 days castrated levels for LH, FSH and T, and a mean PSA decline of 95,1% in six months (range 84,2%-99,8%), with a mean follow-up of 15 months (range 12 to 20 mos). He points out the lack of CV events, the improvement in the lipid profile, the beneficial effect on bones and the ten-fold reduction in treatment costs<sup>62</sup>. Bland treats 24 androgen independent patients with 6 patches of 0.1 mg, replaced every day, and he observes the lack of thromboembolic alterations or significant clinical changes, and in 3 patients he achieves a PSA decline greater than 50%, with a mean serum E2 value of 460.7 pg/ml<sup>63</sup>.

Ockrim confirms that transdermal E2 reduces thrombophilic activity and protects against thrombosis in men with advanced prostate cancer<sup>64</sup>. None of these communications used the scrotal path as a way of administration of E2, since they use 6 patches replaced every day and located outside the scrotum.

The list price for the medication habitually used in our country for the transdermal E2 patch is \$6.32 per day.

**Summary :**

In view of all the above, and taking into account: a) that the effect of E on T is at least similar to that of other non estrogenic hormonal treatments; b) the direct action of E on the prostatic cell; c) the beneficial effect on the Cardiovascular system, the lipids and the bones; d) the reduction or

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disappearance of toxic effects that occur when administered orally and e) the significant cost reduction in comparison with other androgenic blockers, it is evident that E administration through a different route than orally, easily applicable and acceptable, justifies its usage for the treatment of PCa.

### Treatment aim:

To verify the effect of TSEP on advanced PCa.

### Patients and method :

In January, 1997, we began to treat PCA patients with TSEP. A long lasting (LL) patch loaded with 7.5 mg of 17beta E2 was used that delivers 100 ug per day of E2, was located on the scrotal skin. The aim of this treatment, as in any hormonal treatment focused on decreasing T, is of no curative intent.

The treatment was applied to 35 patients with an age range of 52-82 years, approximately  $68.9 \pm 8.2$  (mean  $\pm$  standard deviation) with advanced PCa, 2 with D1 clinical stage and 33 D3; of which 10 D3 had previously undergone orchiectomy. Basal PSA range was 4,8 – 4,200 ng/ml, basal T in D3 was about  $0.33 \pm 0.39$  ng/ml, and the Performance Score, ECOG (65), was about  $1.71 \pm 1.31$  (Table 2).

33 D3 patients on Androgen Blockade with agents other than E, and T <50 ng/m, who experienced 3 consecutive PSA rises and/or bone metastases progression, and in whom androgen treatment was stopped, were given continuous TSEP treatment. The aim of this continuous treatment was intended to control tumor recurrence, decrease pain due to bone metastases and, eventually, prolong survival. In case of no objective response, continuous treatment could be stopped for short periods of time (2-3 months), in an attempt that non-surgically castrated patients may transiently recover their T.

In 2 D1 patients, one of them with positive pelvic lymph nodes detected in the course of an aborted radical prostatectomy, and the other one with positive pelvic lymph nodes detected with TAC/PET fusion test in 2002 at The Cleveland Clinic, after radiation therapy failure performed two years before in our country with normal T levels and PSA of 26 and 4.8 ng/ml respectively, intermittent TSEP was applied, with “On” periods of nine months, and “off” periods until PSA reached a basal level or above 20 ng/ml. Patches were permanently applied on the scrotum and were replaced two times per week (after 3 and 4 days).

Patients and relatives were informed about the treatment aim and its possibilities, and an instructive informed consent form was given to those who voluntarily may like to sign it.

**Table 2: TREATMENT OF ADVANCED PROSTATE CANCER UIT TRANSDERMAL SCROTAL ESTROGEN PATCHES (TSEP)- updated 07/30/05**

n	ag	diag	SG	orq	tHR	in tx	EC	EF	Tb	PSA bas	30d	60d	ult/d	TTT	EED	Evo	CO	otros Tx
01/01	82	12/91	6	si/91	5 <sup>a</sup>	03/97	D3	0	0.2	25	22		120	785	B	O	CP	paliat.
02/08	52	03/97	9	no	3m	06/97	D3	2	0.4	200				21	MB	O	CP	paliat.
03/10	71	07/91	7	si/91	4 <sup>a</sup>	06/97	D3	4	0.2	95		300	9000	180	MB	O	CP	paliat.
04/13	78	03/91	7	si/91	5 <sup>a</sup>	09/97	D3	2	0.6	500	34		750	462	MB	O	CP	paliat.

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05/15	66	09/97	8	no	3m	02/98	D3	3	0.3	8.3			300	188	MB	O	CP	paliat.	
06/17	74	10/95	7	si/95	2 <sup>a</sup>	02/98	D3	1	0.2	4200	500		500	450	Ex.	O	CP	paliat.	
07/18	57	01/95	9	no	1 <sup>a</sup>	02/98	D3	0	0.1	30	32		30	296	R	O	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	*	intermitente	
09/24	58	07/98	8	si/98	3m	01/99	D3	3	0.1	920	1500	1600	3000	130	R	O	CP	paliat.	
10/28	75	10/98	9	si/98	3m	06/99	D3	4	0.2	350	537			35	B	O	CP	paliat.	
11/31	82	12/97	7	no	1 <sup>a</sup>	08/99	D3	2	0.3	288	24	11	19	310	Ex	O	CP	paliat.	
12/34	58	05/99	8	si/99	4m	10/99	D3	0	0.4	65	14	1	289	545	Ex.	O	CP	paliat.	
13/35	71	07/97	7	no	1 <sup>a</sup>	12/99	D3	3	0.5	300				35	B	O	CP	paliat.	
14/36	78	01/99	7	no	1a	12/99	D3	2	0.5	23	6.7	2.4		365	MB	O	CP	paliat.	
15/37	74	07/97	7	si/97	1 <sup>a</sup>	12/99	D3	3	0.2	160	210	325	300	605	B	O	CP	paliat.	
16/39	75	06/98	7	no	1 <sup>a</sup>	12/99	D3	3	0.2	15	18.3			252	MB	O	CP	*	
17/40	68	01/00	8	si/00	4m	06/00	D3	2	0.2	637	520	230	480	325	MB	O	CP	paliat.	
18/41	61	08/00	10	no	3m	08/00	D3	3	0.2	320	271			305	B	O	CP	paliat.	
19/43	56	04/01	8	no	3m	04/01	D3	2	0.3	226	5	1	1.13	240	Ex	O	Des	*	
20/44	75	03/00	6	no	1 <sup>a</sup>	07/01	D3	3	0.4	135	100	124		120	B	O	Des	paliat.	
21/45	74	02/00	7	no	6m	07/01	D3	3	0.2	172	185			120	B	O	CP	*	
22/47	72	08/00	8	no	6m	10/01	D3	1	0.1	214	24	5.6		360	Ex	O	CP	paliat.	
23/48	72	04/98	7	no	3 <sup>a</sup>	09/02	D3	0	0.1	160	263	260	*	180	R	O	CP	paliat.	
24/49	64	03/99	8	si/00	2 <sup>a</sup>	09/02	D3	4	0.1	35	28	36	90	290	B	O	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	2 <sup>a</sup>	03/03	D3	1	0.2	88	75	66	*	180	Ex	O	Des	*	
27/53	64	04/98	7	no	3 <sup>a</sup>	06/03	D3	0	0.6	203	70	29	90	560	MB	B	*	paliat.	
28/54	63	01/00	9	no	2 <sup>a</sup>	09/03	D3	1	0.1	95			198	270	R	O	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	9 m	08/04	D3	1	0.1	99	62	64	99	150	B-R	O	CP	paliat	
31/60	58	12/03	10	si/03	5m	08/04	D3	2	0.3	264	48	93	*	120	B-R	O	CP	paliat.	
32/65	79	03/00	7	no	4 <sup>a</sup>	11/04	D3	1	0.2	37	26	20	48	250	B	B	*	paliat	
33/66	78	06/01	7	no	3 <sup>a</sup>	12/04	D3	0	0.1	39	7.5	6.6	9.9	234	Ex	Ex	*	*	
34/68	74	02/98	7	si/98	6 <sup>a</sup>	01/05	D3	2	0.4	98	*			20	*	AbT	*	*	
35/69	75	08/01	7	si/01	1 <sup>a</sup>	07/05	D3	0	0.2	344	*			30	B	B	*	*	

n°: n° CaP avanzado/n° serie ETE; ag: age; Dx: date of diagnosis CaP, SG: Score Gleason, orq: orchiectomie,  
tHR: time until hormono-refractory (a) years (m) months; in Tx, TSEP treatment start date  
EC: clinical stage, EF: physical status at TSEP start - (*Performance Status ECOG: Eastern Clinical Oncology Group*)  
Tb: basal testosterone, PSA, bas: basal, 30 d: 30 days, 60 d: 60 days, ult.d: ·last available  
TTT: Total TSEP treatment duration, EED: estradiol effect on pain, (Ex: excellent, MB:Very Good,  
B:Good, R: Fair, M:Poor. EVO: Final Evolution (Exc: excellent, B: good, R: Fair, O: decease, AbT: Treatment abandon)  
CO: Cause of death: CP, Prostate Cancer related, D: Unknown  
Otros Tx: other treatments, paliat: palliative (Rx, pain killers) interm: intermittent,

Note: case 8/23 last PSA july 05; 9,5 ng/ml; 240 days 4thtx. *Off period*

Note: case 25/50 last PSA july 05; 1,7 ng/ml; 30 days 3rd. *On period*

Note: case 29/58 radiotherapy on iliac and femoral mets. E2 is stopped every 2 months

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Exclusion criteria: a) absolute : known allergy to E2 or its derivatives, o current use of any drug containing estrogens (i.e.: estramustine phosphate); b) relative: big scrotal dermal lesions, severe hepatopathy in evolution and previous thromboembolic events, Deep Vein Thrombosis and phlebitis.

It was conventionally and tentatively assumed that  $\geq 300$  pg/ml to be the therapeutic values of serum E2, and the observation of lower figures, suggesting troubles in patches application, motivated a control of the methodology used for its placement.

Gynecomastia prophylaxis was offered, previous to treatment, in the form of breast radiation in low doses depending on the patient economic and clinical status. Patients taking CV medications and Acetyl Salicylic Acid (ASA) remained the same, and the rest were prescribed 325 mg of ASA per day. It was advised no to rub the scrotal region during the bath, and if the patch fell off incidentally, to replace it with a new one.

General measures were indicated in order to reduce the effects of the lack of T: physical exercise, a balanced diet, reduction or abolition of toxics like alcohol and cigarettes and, when possible, their counterparts were interviewed in order to know about sexual function and consider the possibility of vasoactive drugs use to facilitate erection. All patients were invited to periodically attend (every 15-20 days) group sessions, coordinated by the main author.

Treatment was evaluated in accordance to three parameters: changes in PSA, modification of symptoms produced by metastases (in bone, lymphatic system and organs), and urinary signs and symptoms. PSA was monthly or bimonthly checked and, depending on economic resources, T and E2. In non-castrated men, T castrated level was set at  $\leq 0.5$  ng/ml. During IHT, cycle duration, PSA nadir and T were measured.

PSA changes at 30/60 days from treatment start were established as: “marked decline”  $\geq 50\%$  from basal, “moderate decline” between 49% and 11%, “not significant” if  $\pm 10\%$  from basal figure (taking into account the variation coefficient and the method used for determinations)<sup>66</sup> and “rise”.

Performance status was evaluated according to the Eastern Clinical Oncology Group<sup>65</sup> scale, where the patient self evaluates the pain, and records the need for pain killers, and evolution of symptoms and neurological signs (paresis, paralysis) were watched over. Urinary frequency and flow quality were evaluated, spontaneous recovery of miction in patients with permanent urethral probe, and changes in the prostate evaluated by Digital Rectal Examination (DRE). Drugs to facilitate miction were administered if necessary.

During the first month, weight, blood pressure, edema, signs of venous alteration and changes in breasts and nipples (increase in size or sensibility) were checked weekly.

The blood used to perform tests was frozen and remains stored in the reference laboratory serum bank.

The medical association ethic committee of the second circumscription of the Santa Fe Province approved the realization of this study.

### **Results:**

Survival for 27 patients out of 35 (27%) was of  $271.1 \pm 181.1$  days(mean  $\pm$ SD); 5 (18.5%) survived for more than 15 mos, 14 (51.8%) between 6 and 15 mos, 5 (18.5%) between 4 and 6 mos and 3 (11.1%)

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≤month. Cause of death in 24 cases was PCa related, and unknown in 3. 8 patients (22.8%) remain alive: 2 D1 patients with intermittent treatment (one 79 months, the other 45 mos; 6 D3 patients: 1 of them for 18 months with continuous treatment, one for 12 months with intermittent treatment (9 months “on”, 3 months “off”); 2 patients for 9 months with continuous treatment; one with less than 1 month of treatment and one quitted treatment at 20 days.

PSA, at 30-60 days of treatment was: 14 (40%) patients with a decline ≥50%, 6 (17%) with a decline between 49% and 11%, in 1 (2.8%) no significant change was observed, in 9 (25.7%) an increase was observed, 1 (2.8%) has been less than a month on treatment, 3 (8.5%) died before control and 1 (2.8%) quitted treatment.

Basal E2 ranged between 12 and 43 pg/ml (44 and 157 nmol/l.), and oscillated during treatment within a range of 123 and 1200 pg/ml (451 and 4405 nmol/l.), with the majority of determinations around 500 pg/ml. (1835 pmol/l.). No hot flashes or excessive perspiration was observed.

In D3 patients, pain control was: excellent in 7 (21.2%), with no more need of pain killers before 30 days, very good in 8 (24.2%) with no more need of pain killers before 60 days, good-fair in 12 (36%) with a decrease in pain killers use, fair in 4 (12.1%) keeping or increasing pain killers use and in 2 (6%) no pain control was observed.

Treatment acceptance was excellent, and patch adherence very satisfactory because only in one case, a very obese patient, prostrated in bed, with a edematized scrotum for a recent orchiectomy, couldn't keep the patch in place, and despite the daily change, only in one occasion before passing away 30 days later could he reach over 100 pg/ml of E2. No cardiovascular events were registered, nor changes in clinical parameters, except in the period immediately previous to death.

In 2 D1 patients, intermittent TSEP treatment was used (Table 3). In the first case, the total “on” period was of 1,286 days, divided in 328, 339, 319 and 300 days, and 968 days of total “off” period, divided in 190, 328, 210 and 240 (currently) days, and the initial PSA of “on” periods was 26; 34; 19.7; 23.3 ng/ml and T was 3.34; 4.8; 3.6; 1.9 ng/ml and PSA at the start with “off” periods was 0.5; 1.2; 1; 1.5 ng/ml and T was 0.3; 0.2; 0.1; 0.1 ng/ml. In the second case, total “on” periods were 589 days divided in 3 periods of 285, 274 and 30 (currently) and 452 “off” days divided in 2 periods of 242 and 210 days. PSA at the start of “on” periods was 4.8; 6.5 and 10.9 ng/ml and T 3.4; 6 and 5.6 ng/ml, and at the start with “off” periods PSA was 0.3 and 0,6 ng/ml and T 0.1 and 0.1 ng/ml. Both patients underwent previous breast radiation, so no breast symptoms were observed, nor BP changes or body weight, and adhesion to treatment was excellent.

<b>Intermittent transermal escrotal patches in D1 Prostate Cancer</b>																								
	<b>First. on</b>			<b>First. off</b>			<b>2nd. on</b>			<b>2nd. off</b>			<b>3ird. on</b>			<b>3ird. off</b>			<b>4th. on</b>			<b>4th. off</b>		
	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	3.3	328	0.5	0.3	190	34	4.8	339	1.2	0.2	328	19.7	4	319	1	0.1	210	23.3	1.9	300	1.5	0.1	240
# 2	4.8	3.4	285	0.3	0.1	242	6.5	6	274	0.6	0.1	210	10.9	6	30									

note: case # 1: 240 days off PSA 9.5 ng/ml and T 2.6 ng/ml.

note: case # 2 : 3ird. on 30 days in course.

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The cost of intermittent TSEP is significantly lower than any other androgenic blockade, ranging about \$4 (July 2005) per day, accordingly to off treatment duration.

### **Discussion**

Despite the fact that many years have passed since the role of Estrogens in the treatment of PCa was discovered, they remain as a therapeutic option difficult to surpass. Its displacement by many subsequent therapeutic options was favoured by the many CV complications attributed to E. Yet, when those complications were avoided by using different types of parenteral estrogens, added to the observation of other beneficial effects for the CV system and bones, Estrogen use and indications have been “revived” and its role has been praised.

This communication is intended to take Estrogens back to the place that they should never have lost, regretting that if many of the resources that were employed in non estrogenic therapies would have been dedicated instead to the research in this field, most probably more effective treatments for PCa would have been reached.

Recent communications<sup>62-64</sup> are “officially” initiating a new approach in the treatment of PCa with transdermal estrogens outside the scrotum. E2 delivery through the scrotum that this article proposes, and which began more than 9 years ago and that, as far as we know, has no precedents, has yielded very satisfactory results. Despite the fact that no comparative studies exist, given the impossibility of performing control tests in the setting of HRPCa., the palliative results obtained with continuous TSEP can be evaluated as, at least, similar to those obtained with other therapies (chemotherapy and others), with less general impact, less side effects and with a positive analgesic effect on bone metastases. Taking into account that no treatment currently used achieves a long lasting and satisfactory response for this PCa stage, TSEP become a valid option.

Intermittent TSEP treatment highlights the need for further research to focus on hormonal receptors activity, in relation to changes produced by E administration and the possibility of using androgens in final stages of HRPCa, when TSEP are no longer effective. This hypothesis could make feasible to alternate cycles of E with androgens, and has been thought of as the last resort for the final stage but, for ethic implications, needs a careful selection, supervision and approval by the ethic committees of medical institutions.

To the unquestionable benefits of the use of Estrogens in PCa, it must be added a very important factor: the remarkable reduction in costs, a fact that is increased if they are used intermittently.

A paradoxical situation is the fact that some of the most important health organizations (HO) and pre-payments do not accept E2 patches as an oncology treatment and, hence, they do not cover it a 100%, but they do with analogues and antiandrogens, without taking into account treatment utility and cost difference. This has lead to a situation where patients with poor resources have difficulty to obtain the medication, as well as to control check-ups and to preventive breast radiation, that was only covered by some HO o pre-payments.

Taking into account that health costs reduction is a priority goal in the majority of countries, even in the highly developed ones, and that in our country this aspect acquires imperative characteristics, the use of parenteral E becomes a need; perhaps an inevitable one.

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Treatment compliance has been very good, as was made evident by patient concurrence to group meetings, coordinated by the main author, where they could exchange experiences.

Two studies are on their way: one is TSEP and bone densitometry whose preliminary results are yielding very good bone mineral density, and another one with anti-thrombin 3 medication (AT3) for patients treated with TSEP and for patients without prostatic disease in which, initially, no difference between populations is found.

This study was mainly financed by its main author, and the reference biochemistry laboratory, that made no charges for their tests, to a lesser extent by the social security, and many times by patients, most of them with poor resources. It must be highlighted the attitude of the E2 patches manufacturer company in our country, that for a long time provided us with that item and financed some biochemical determinations.

### **Conclusions:**

This communication is an attempt to restore Estrogens use, once the complications attributed to the oral administration have been resolved, to the place they deserve in the treatment of PCa in our present days. The transdermal scrotal way achieves high levels of E2, greater than those obtained on other dermal sites, which reduces the number of patches used and has a positive effect on PCa and its symptoms. The survival obtained with TSEP in HRPCa was acceptable, with a satisfactory effect on pain due to bone metastases. In D1 PCa, the intermittent treatment achieved a significant PSA decline and kept T castrated levels, which allowed for alternating “on” and “off” cycles, thus improving in the latter the quality of life.

No adverse CV effects were observed, nor hot flashes or perspiration, and gynecomastia was prevented with previous breast radiation, though it was not an important problem if not performed.

It must be taken in deep consideration the significant reduction in treatment costs with the use of TSEP, which is even more evident if they are used in intermittent form. Controlled randomised studies with a greater number of patients are necessary in order to certify this research and to confirm the role of transdermal estrogens in PCa.

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