Therapy Insight: parenteral estrogen treatment for prostate cancer—a new dawn for an old therapy

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SUMMARY

Oral estrogens were the treatment of choice for carcinoma of the prostate for over four decades, but were abandoned because of an excess of cardiovascular and thromboembolic toxicity. It is now recognized that most of this toxicity is related to the first pass portal circulation, which upregulates the hepatic metabolism of hormones, lipids and coagulation proteins. Most of this toxicity can be avoided by parenteral (intramuscular or transdermal) estrogen administration, which avoids hepatic enzyme induction. It also seems that a short-term but modest increase in cardiovascular morbidity (but not mortality) is compensated for by a long-term cardioprotective benefit, which accrues progressively as vascular remodeling develops over time. Parenteral estrogen therapy has the advantage of giving protection against the effects of andropause (similar to the female menopause), which are induced by conventional androgen suppression and include osteoporotic fracture, hot flashes, asthenia and cognitive dysfunction. In addition, parenteral estrogen therapy is significantly cheaper than contemporary endocrine therapy, with substantive economic implications for health providers.

KEYWORDS administration routes, estradiol, estrogen, prostate cancer, treatment

REVIEW CRITERIA

Data for this review were identified by searching the PubMed and MEDLINE databases. The search terms used alone or in combination were "prostate cancer", "estrogen", "estradiol", "treatment", "prognosis", "administration route", "transdermal administration", "cutaneous administration", "administration and dosage", "toxicity", "side effects", "adverse effects", "complications", "thromboembolism", "fibrinolysis", "blood coagulation factors", "blood vessels", "blood flow velocity", "bone metastases", "osteoporosis", "bone fracture", "hot flashes", "castration", "andropause", and "quality of life". The search was limited to articles published in English and indexed up until December 2005.

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Received 11 November 2005 **Accepted** 14 June 2006
www.nature.com/clinicalpractice
doi:10.1038/ncponc0602

INTRODUCTION—A HISTORICAL PERSPECTIVE

In 1941, Huggins and Hodges published the first description of a clinical response to estrogen therapy in patients with advanced carcinoma of the prostate (CaP).[1] Over the next four decades, estrogens (and orchiectomy) were the primary management for all patients with CaP, their unfettered use propagated by two large pooled, but retrospective analyses concluding that estrogens improved survival for all stages of the disease.[2,3] The recognition of the hormonal influences on CaP and the potential to manipulate the natural history of the disease by androgen suppression led to Charles Huggins being awarded the Nobel Prize in 1966, thereby becoming the only urologist ever to receive such an honor.

It was not until the publication of the first controlled studies by The Veterans Administration Cooperative Urological Research Group (VACURG) that the discrepancy between disease-specific survival and overall survival was recognized.[4–6] In these studies, estrogen therapy achieved clinical responses in up to 80% of patients, and delayed disease progression; however, there was little evidence that any type of hormone manipulation improved overall survival. These studies also revealed a significantly increased risk of cardiovascular toxicity in up to 35% of patients receiving estrogen therapy; thromboembolism was experienced by 15%. The VACURG studies concluded that estrogen therapy should be reserved for those with advanced and symptomatic disease.[6] Following the development of luteinizing hormone-releasing hormone (LHRH) agonists and subsequently nonsteroidal anti-androgens (NSAAs) with equivalent oncological effect and lesser cardiovascular toxicity, the use of and research into estrogen therapy rapidly declined.

Contemporary first-line androgen suppression therapy worldwide is based on the use of LHRH agonists, NSAAs or orchiectomy. Whilst these treatments have a lower incidence of cardiovascular toxicity compared with oral estrogen,

they are still associated with significant morbidity. Hypogonadism, as a result of androgen suppression therapy, causes accelerated osteoporosis and a significant increase in the risk of osteoporotic fracture.[7,8] Androgen suppression therapy also induces an andropausal state (castration syndrome) characterized by hot flushes, loss of libido, reduced energy levels and cognitive dysfunction.[9,10] As evidence accumulates that initiation of androgen suppression during early-stage disease may improve outcome,[11–13] there is increasing concern that long-term androgen deprivation may paradoxically be the cause of complications that it was hoped to avoid. By contrast, estrogen therapy in the form of hormone replacement therapy (HRT) is an established treatment for the equivalent condition (menopause) in women.[14] An estrogenic formulation with similar oncological benefits to oral estrogen and the advantages inherent to the estrogenic milieu, but with reduced cardiovascular toxicity, would therefore appear an attractive proposition in the treatment of CaP.

MECHANISMS OF ESTROGEN TOXICITY

Toxicity (and clinical response) is related to dose

The accepted dose of oral estrogen, 3 mg diethylstilbestrol (DES), was based on historical studies to establish equivalence to castrate levels of testosterone.[15] This dose was established as the 'standard' even though the VACURG studies demonstrated that a lower 1 mg dose of DES had equivalent oncological effect, as well as a reduced cardiovascular toxicity.[5] The non-cancer-related mortality rate in the 3 mg (and 5 mg) DES arms of the VACURG studies was 29.6%, compared with 21.6% for the non-estrogen treatments (relative risk of estrogen-related mortality 1.45). Almost all of this difference in mortality was due to an excess of cardiovascular mortality (17.0% versus 11.7%) for the higher dose estrogen arms, manifest within the first months after treatment was initiated. By contrast, the 1 mg dose of DES was associated with a significantly lower level of cardiovascular toxicity; the overall non-cancer-related mortality was 21%, similar to that observed in the non-estrogen arms.[5] Subsequent studies have established that the risk of serious cardiovascular morbidity with a 3 mg dose of DES ranges between 30 and 35%.[16–19]

In 1995, the European Organisation for Research and Treatment of Cancer (EORTC) published its study comparing orchiectomy, orchiectomy plus cyproterone acetate (which causes maximum androgen blockade; MAB), and low-dose 1 mg DES in patients with metastatic disease.[20] This study provided the first opportunity to evaluate the efficacy and toxicity of low-dose DES since the publication of the VACURG studies. No differences were seen in time to progression or overall survival between the three treatment arms; however, the cardiovascular toxicity and mortality rate (14.8%) with the 1 mg dose of DES approached twice that with orchiectomy alone (8.3%). This difference was most marked in patients with a prior history of cardiovascular disease. In a smaller, single-institution study, 106 patients with advanced CaP were initially treated with a 1 mg daily dose of DES, which was subsequently titrated depending on hormonal and prostate-specific antigen (PSA) responses.[21] Although only 27% of the patients achieved castrate levels of testosterone with 1 mg DES, 66% achieved a sustained PSA response. A secondary response occurred in 33% of the patients with biochemical (PSA) failure once the DES dose was doubled. Cardiovascular toxicity was noted in 7.5% of patients, but only one life-threatening (thromboembolic) event occurred. Bishop and co-workers[21] suggested that low-dose estrogen titrated to levels that produced hormonal and clinical responses could achieve efficacy with acceptable toxicity levels. It is evident, however, that the cardiovascular risk encountered with oral estrogen therapy, even at low doses, compares unfavorably to rates of 3–6% cardiovascular mortality, and 8–20% cardiovascular morbidity expected during treatment with orchiectomy or LHRH agonists.[22] As such, dose modulation for oral estrogen therapy has not been pursued.

The relationship between dose response and cardiovascular toxicity for parenteral estrogen therapy is less well defined. The dose of intramuscular estrogen depot, polyestradiol phosphate (PEP), utilized in Scandinavia as first-line hormone therapy, was established by a sequence of pilot studies that compared four doses (80 mg, 160 mg, 240 mg and 320 mg) and different depot scheduling (induction and maintenance regimes) to achieve rapid castration and thereafter maintain castrate levels of testosterone.[23–25] The patient numbers in these pilot studies were small (Table 1) and the methodologies simplistic—although the dosing regimens were predicted using statistical computer modeling, the dose adjustments were based on retrospective testosterone assay, rather than, ideally, prospective dose-response

Table 1 Studies using parenteral estrogens for the treatment of men with advanced prostate cancer.

Study and reference	Study type	Patient number	Median follow-up (months)	Cardiovascular risk and complications
Finnprostate studies				
PEP versus orchidectomy Haapiainen *et al*. (1990)[69]	Comparative	200	24	Mortality 1.6% PEP versus 1.3% orchiectomy (morbidity not reported)
PEP versus orchidectomy Aro (1991)[44]	Epidemiological	477	72	Relative cardiovascular risk 0.17 PEP versus 0.78 orchiectomy
PEP versus LHRH agonist Aro *et al*. (1993)[70]	Comparative	147	36	Morbidity 7.1% PEP versus 7.8% LHRH agonist Mortality 5.7% PEP versus 5.2% LHRH agonist
PEP versus LHRH agonist Lukkarinen and Kontturi (1994)[71]	Comparative	236	23	Morbidity 19.6% PEP versus 9.3% LHRH agonist Mortality 6.5% PEP versus 6.2% LHRH agonist
PEP versus orchidectomy Mikkola *et al*. (1998)[36]; (2005)[43]	Randomized	444	24	Overall morbidity 6.0% PEP versus 1.4% orchiectomy, first year Overall morbidity 6% PEP versus 4% orchiectomy, second year (difference not significant) T3–4 M0 years 1–3 PEP (4.8%, 6.3%, 6.7%) versus orchiectomy (0.8%, 2.7%, 1.9%) T1–4 M1 years 1–3 PEP (8.8%, 4.7%, 0%) versus orchiectomy (2.0%, 6.3%, 2.9%)
SPCG studies				
PEP Henriksson *et al.* (1988)[23]	Pilot	38	14.1	0%
PEP Stege *et al.* (1988)[24]	Pilot	27	6	0%
PEP Stege *et al.* (1989)[25]	Pilot	17	12	0%
Oral, PEP and orchidectomy Carlstrom *et al.* (1989)[27]	Pilot	48	12	0%
PEP versus orchidectomy Henriksson *et al*. (1999)[45]	Randomized	33	24	6% PEP versus 24% orchidectomy (statistical analysis not provided)
PEP versus MAB Hedlund and Henriksson (2000)[35]; Hedlund *et al*. (2002)[46]	Randomized	917	18.5	Overall mortality 16% PEP versus 14% MAB (difference not significant) Cardiovascular mortality 3.5% PEP versus 3.1% MAB (difference not significant) Cardiovascular morbidity 12.5% PEP versus 7.9% MAB
Other studies				
PEP versus orchidectomy Bishop *et al*. (1989)[21]	Comparative	117	Not recorded	Morbidity 13.1% PEP versus 7.1% orchiectomy
Transdermal estradiol Ockrim *et al*. (2003)[26]	Pilot	20	12	Morbidity 5%

LHRH, luteinizing hormone-releasing hormone; MAB, maximum androgen blockade; PEP, polyestradiol phosphate; SPCG, Scandinavian Prostate Cancer Group

pharmacokinetic profiling. Nevertheless, the dose and schedule established (and utilized in larger studies) achieved castrate levels of testosterone in all patients and are, therefore, presumed to be bioequivalent to the 3 mg dose of oral DES. Cardiovascular toxicity was not observed in these pilot studies.[23–25] In the single pilot study of transdermal estradiol,[26] dose was also titrated to

castrate testosterone (due to clinical necessity in symptomatic patients). Rapid induction using six patches per week of 7.8 mg Progynova® TS forte (Schering Aktiengesellschaft Berlin, Germany) was used for symptomatic disease control before the dose was titrated downwards according to the predicted pharmacokinetic requirements and the testosterone assays. Dose modulation was easily achieved by using between two and three patches per week (washout occurs within 24 hours) according to monthly testosterone levels. As such, the serum estradiol levels achieved (Figure 1) are also assumed to be equivalent to a 3 mg DES dose. Whilst bioequivalence between oral and parenteral estrogen administration is still not completely resolved (and pharmacokinetic work is still required), the parenteral doses of estrogen in use have equivalent oncological effect to other hormone therapies and can be taken as valid clinical comparators when evaluating relative toxicities.

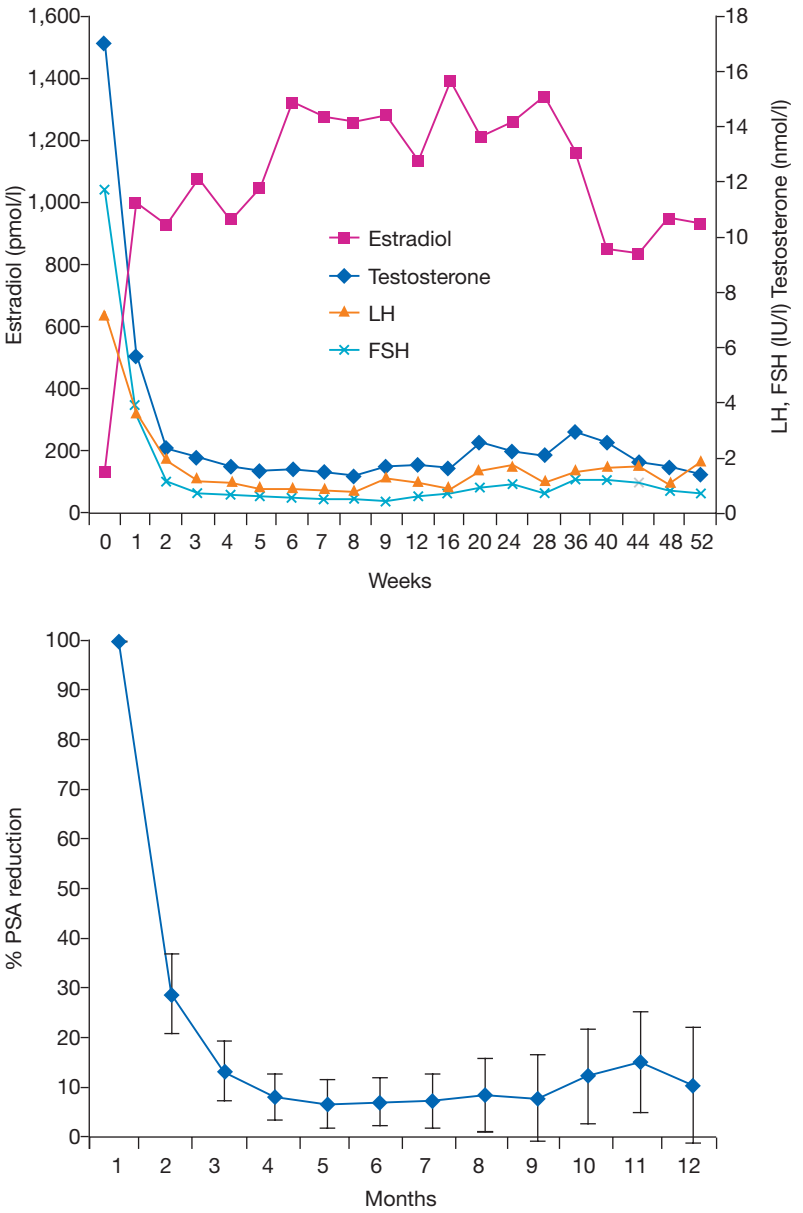

Figure 1 Pituitary–testicular response to transdermal estradiol therapy and the PSA response (mean and standard error mean) over 12 months. Abbreviations: FSH, follicle-stimulating hormone; LH, luteinizing hormone; PSA, prostate-specific antigen. Permission obtained from Lippincott, Williams & Wilkins © Ockrim JL *et al.* (2003) *J Urol* **169:** 1735–1737.

Toxicity is related to route of administration

Much of the adverse cardiovascular toxicity of oral estrogen therapy is now recognized to be related to the route of administration. The direct exposure of the liver to high doses of estrogen, via the portal circulation, upregulates the metabolism of hormones, lipids and coagulation proteins, all contributing to the changes thought to be responsible for short-term and long-term cardiovascular events.[26–29] Avoidance of enteric absorption using parenteral routes of administration (intravenous, intramuscular and transdermal) significantly reduces this metabolic upregulation. While oral estrogens cause multi-fold increases in the ratio of estradiol and its metabolites (particularly estrone), the physiological ratios of sex hormones and their binding globulins are not affected by equivalent doses of parenteral estrogen.[26,27] Similarly, the physiological ratios of HDLs and LDLs and other lipids are reversed with oral estrogens, but the cardioprotective ratios are preserved with parenteral estrogen administration.[30] Clinically, the most apparent adverse effect of oral estrogens is venous and arterial thromboembolism, which is manifest as transient ischemic attack, cerebrovascular accident and myocardial infarction. These thromboembolic events are associated with a marked increase in activated coagulation proteins (including factors VII, VIII, IX, and X and fibrinogen), decreases in inhibitors of coagulation (antithrombin III, protein S and tissue factor pathway inhibitor) and increased levels of fibrinolytic factors (plasminogen, tissue plasminogen activator and D-dimer).[29]

Parenteral estrogens do not cause such changes, and have been shown to reduce the levels of thrombophilic activation, particularly prothrombin fragments F1 and F2, fibrinogen and D-dimer, which are often associated with advanced CaP (Figure 2).[31] The thrombophilic data seem to be well supported by the clinical studies (discussed

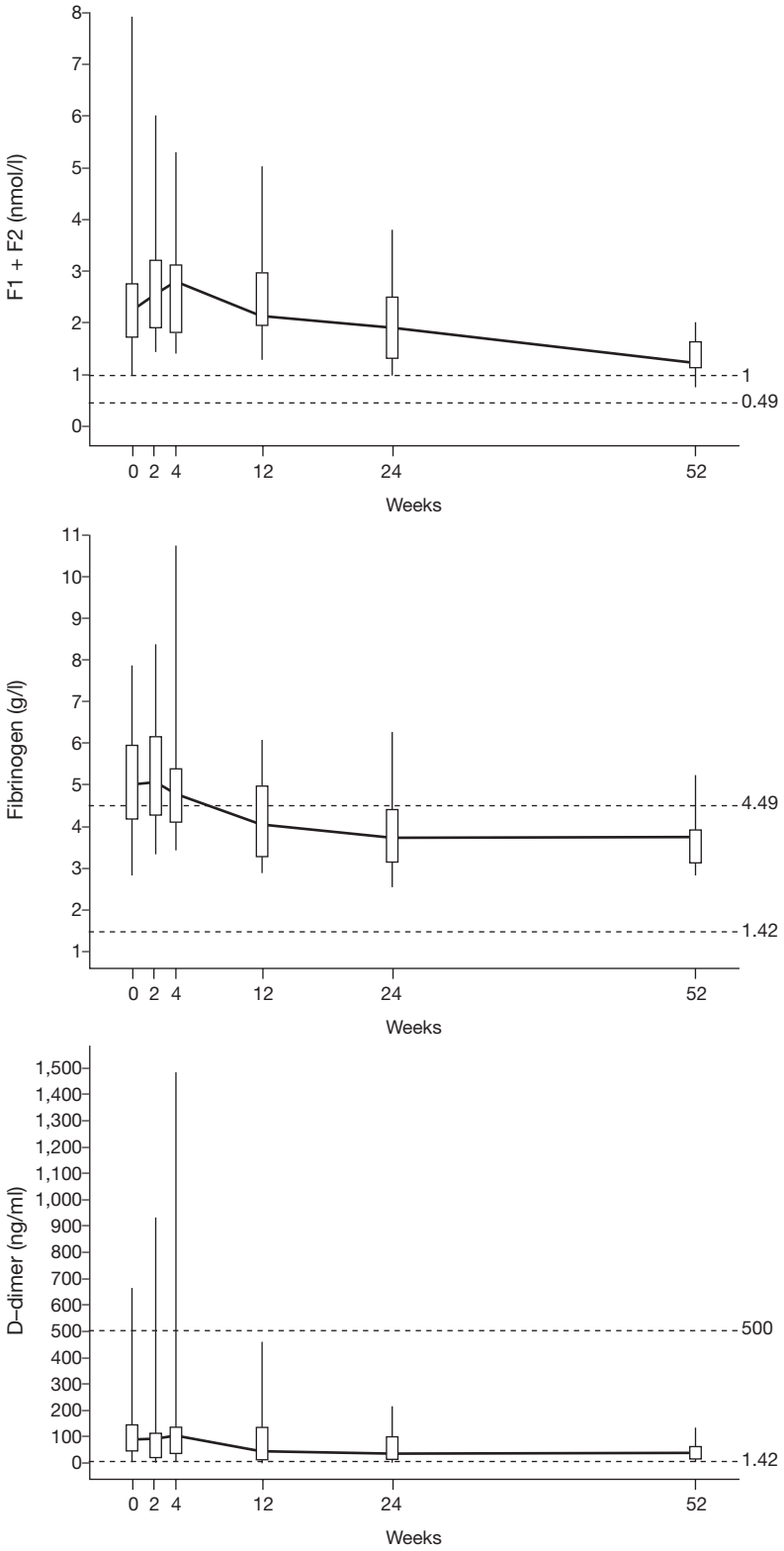

Figure 2 Improved levels of prothrombin fragments F1 and F2, fibrinogen and D-dimer during transdermal estradiol therapy. The column whiskers represent minimum and maximum values, the boxes delineate the first and third quartiles, the heavy lines connect the medians, and the dashed lines mark the normal ranges. Permission obtained from Lippincott, Williams & Wilkins © Ockrim JL *et al.* (2005) *J Urol* **174:** 527–533.

below), but also by studies of patients undergoing gender reassignment, in whom a 20-fold increase in the incidence of thromboembolism was negated by conversion from oral to transdermal estradiol preparations.[32]

Toxicity is related to changes in vascular flow over time

The other major determinant of estrogen toxicity appears to be related to the vascular changes incurred on the arterial circulation over time. Estrogens initially cause arterial dilatation (but less venous effect) and an associated reduction in arterial compliance (stiff arteries). In addition, cardiac demands and capillary filtration increase, resulting in an increased incidence of peripheral and pulmonary edema and cardiac decompensation.[33,34] It is now apparent that this effect is time-dependent, and most of this risk is manifest within the first months (over 75% within the first 6 months) of estrogen therapy.[17,35,36] Over time the arterial compliance improves (Figure 3), possibly as a result of estrogen-driven vascular remodeling leading to improved cardiovascular dynamics.[37,38] Time dependency may be explained by the dual mode of action that estrogen has on the vasculature.[33,34,36–38] Immediate changes in vascular compliance are mediated by the release of endothelial-derived vasodilatory factors (endothelium-dependent vasodilatation). Long-term modulation of vascular compliance is a consequence of vascular wall remodeling, a gradual response to estrogen-stimulated transcriptional (genomic) activation. The cardiovascular benefit only emerges once the vascular adaptation is sufficient to reduce the overall cardiac workload.[37,38]

The time-dependent aspect of the cardioprotective effect of HRT has only recently been recognized in postmenopausal women. Epidemiological studies have repeatedly suggested a cardioprotective effect of estrogen, with an overall risk reduction of around 30–50%.[14,39] Until recently, it was assumed that this vascular benefit was immediate, but the results of the first prospective study of the Heart and Estrogen/progestin Replacement Study (HERS) established otherwise.[40] The HERS unexpectedly demonstrated an increase in cardiovascular events in the first year. The favorable cardiovascular effect was not established until 2 years after treatment initiation; however, the cardioprotective benefit increased consistently for the 3 years thereafter. This time trend has also been supported by

data from the Nurses' Health Study,[41] in which patients initially excluded from analyses because of baseline coronary artery disease also showed a temporary increase in cardiovascular risk in the first year (relative risk 1.25), followed by a later decrease in cardiovascular toxicity such that long-term users, up to 20 years, had a significant reduction in cardiac events (relative risk 0.65). These data would suggest that parenteral estrogen therapy for CaP may be best reserved for patients with a predicted prognosis longer than 2 years, where long-term cardiovascular protection would compensate for an early increase in the risk of cardiovascular morbidity. In addition, parenteral estrogen therapy seems suitable as a second-line hormone escape therapy, where an initially increased (but substantially lower than oral estrogen) risk of cardiovascular complication might be deemed more acceptable. Given the gradual dynamic of vascular remodeling, with the cardiovascular toxicity loaded 'up front', it is unlikely that parenteral estrogen will be judged acceptable for intermittent use. Vascular changes after estrogen treatment is withdrawn are unknown.

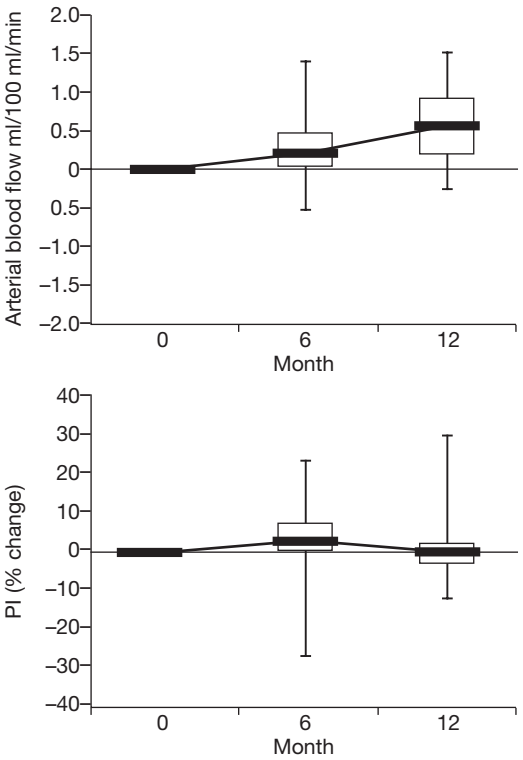

Figure 3 Arterial blood and capillary filtration increase during transdermal estradiol therapy, a possible explanation for increased risk of edema and cardiac decompensation. The arterial compliance (an inverse of the pulsatility index, shown here) initially reduces, but improves over the second 6 months of therapy. This improvement explains the improved vascular dynamics and cardioprotective benefits that accrue subsequently. Abbreviation: PI, pulsatility index. Permission obtained from Blackwell Publishing © Ockrim JL *et al.* (2006) *BJU Int* **97:** 498–504.

TOXICITY IN CLINICAL STUDIES OF PARENTERAL ESTROGEN

Are the findings discussed above supported by clinical data of parenteral estrogen treatment in men with CaP? To date, only 13 studies have been published on the use of parenteral estrogens in CaP (Table 1). The quality of the limited data available and particularly the problems of inclusion criteria, dose variability and outcome assessment, is the subject of a recent systematic review.[42] Pooled data analysis proved impossible, but this review and historical comparisons of oral estrogen and LHRH agonists suggest that cancer-specific efficacy is essentially equivalent between the two treatments. Most of the data pertaining to toxicity come from the two Scandinavian groups who use intramuscular PEP to treat patients with CaP.[35,36,43–46] In the Finnprostate studies comparing PEP to orchiectomy there was an increased cardiovascular morbidity in the first 2 years of therapy (11% with PEP versus 5% with orchiectomy), although the disparity was only statistically significant within the first year.[36] Data on the breakdown of cardiovascular toxicity over 3 years of PEP treatment were recently published.[43] For patients with metastatic disease, PEP-related cardiovascular toxicity (9%) was higher than orchiectomy-related cardiovascular toxicity(2%) in the first year, but not in the subsequent 2 years (PEP 5% at year 2 and 0% at year 3 versus orchiectomy 6% at year 2 and 3% at year 3). The cardiovascular toxicity for patients with locally advanced but nonmetastatic disease, however, remained consistently higher over three years of treatment for the PEP-treated patients (5%, 6%, and 7%) than for those treated by orchiectomy (1%, 3%, and 2%). The discrepancy between the two groups is not explained. Based on these (unique) data, the authors suggest that PEP should be avoided as a first-line therapy in locally advanced disease, but make no recommendation for treatment of metastatic patients. By contrast, a longitudinal risk analysis of 477 Finnprostate patients projected over 10 years suggested that the long-term cardiovascular trend was subsequently reversed; the relative cardiovascular risk was

calculated at 1.51 for those using oral estrogens, 0.78 for those treated by orchiectomy and only 0.17 for those using PEP.[44] The Finnprostate findings are supported by those of the Scandinavian Prostatic Cancer Group (SPCG) consisting of four pilot studies, which together contain over 1,000 patients (Table 1).[23,25,27,45] The SPCG-5 study randomized 917 men to treatment with either PEP or MAB.[35] The PEP cardiovascular morbidity was substantially reduced compared with that expected from the equivalent dose of oral estrogen (expected oral estrogen toxicity up to 35.0% versus 12.5% for PEP and 7.9% for MAB). Notably, the PEP group had a higher prevalence of cardiovascular disease prior to study. The overall cardiovascular mortality was equivalent (3.5% PEP versus 3.1% MAB) after 27 months.[35,46] Further analysis of the cardiovascular toxicity is pending. These results are encouraging, but clearly need further validation and longitudinal follow-up.

ADVANTAGES OF PARENTERAL ESTROGEN THERAPY

The traditional concerns of clinicians treating CaP have been disease-specific and overall survival. Following the findings of the VACURG studies,[4–6] endocrine therapy was limited to those with advanced and mostly symptomatic disease, in which the palliative treatment effect was most marked and the anticipated length of therapy short. In this setting, the benefits of therapy more easily prevail over any long-term side effects. In recent times, the management protocols for CaP have become more complex. The earlier diagnosis of CaP caused by PSA screening, the greater number of available endocrine treatment options, and the increased expectations of effective therapy by patients, have all stimulated a renewed interest in the timing and nature of hormonal interventions. The best evidence at present suggests that early hormonal therapy may provide a survival benefit for CaP patients with nodal metastases or biochemical failure after radical prostatectomy (and as adjuvant to radical radiotherapy).[11,13] Equally important is the recognition that early hormonal therapy for these patients, and also patients with early asymptomatic (high-grade) metastatic disease, might delay progression and reduce both symptoms and complication rates.[12] On this basis, many urologists now offer androgen suppression therapy to patients much earlier in the natural history of the disease. Thus, the duration many patients are exposed to hormonal therapy has significantly increased,[47] and consequently the disparity between palliative benefit and the accumulation of toxicity has become less distinct. In settings in which long-duration endocrine therapy is anticipated, issues pertaining to the impact on overall quality of life (QOL), patients' ability to function normally and treatment-related side effects have now become as important parameters as disease outcome. Parenteral estradiol therapy might offer significant QOL advantages over contemporary hormone therapies.

Parenteral estrogen therapy and osteoporosis

Bone loss from protracted androgen suppression is of increasing concern amongst urologists and the wider medical community. Contemporary hormone therapies are all associated with significant reduction in bone mass, with reported reductions of between 2.4% and 10.0% during the first year of treatment, and further losses of between 1.4% and 2.6% observed annually for up to 10 years following initiation of androgen suppression therapy.[7,8,48,49] These losses exceed those reported in untreated menopausal women, and are associated with high risk of osteoporotic fracture.[50] The accumulated incidence of osteoporotic fracture after androgen suppression is 28% after 7 years and 40–50% after 9 years, compared with a 1% incidence for men with untreated CaP observed during the same time period.[8] The overall fracture risk is increased by 3.5-fold for those using conventional hormone therapies.[51] It is not surprising that such numbers have encouraged pharmaceutical companies to include adjuvant drug therapy to protect bone density during routine patient care. Bisphosphonate therapy (currently used as monthly intravenous infusions) adds a significant burden to patients and a major additional cost to health providers. Whilst the role of oral bisphosphonate therapy has yet to be fully established, intravenous therapy remains invasive and limited to those with the most severe disease.[49]

By contrast, estrogens (HRT) have a long established role in osteoprotection for postmenopausal women. We have recently published preliminary evidence to demonstrate that osteoprotection is also conferred to patients with advanced CaP treated with transdermal estradiol.[52] Bone density in our series improved by 1.9–3.6% at 1 year (Figure 4) and improved the classification of patients with bone densities in the 'at risk' range. These improvements in bone density have an inherent advantage to a

population already susceptible to significant skeletal morbidity (i.e. osteoporotic fracture).

Parenteral estrogen therapy and hot flashes

Hot flashes are the most commonly reported side effect of conventional hormonal therapy, with up to 80% of men experiencing persistent flashes after orchiectomy, LHRH agonists or MAB.[53,54] Flashes severe enough for palliation are documented in one-third of patients and cause disabling distress in over 10%.[53,54] The incidence of flashes and severity of the symptoms caused by estrogen therapy are far less than that caused by conventional hormonal therapies. In the SPCG-5 study, distressing hot flashes were documented in 36.7% of patients treated by MAB but only 5.4% of those treated by intramuscular PEP. In addition, the flashes resolved in over half the PEP-treated patients after 1 year of therapy.[54] Transdermal estrogens induce complete or partial relief in up to 90% of patients with CaP who suffered symptomatic flashes after taking conventional hormone therapy.[55]

Parenteral estrogen therapy and gynecomastia

Gynecomastia is a well-recognized effect of oral and also parenteral estrogen therapy. The reported incidence (and severity) of this event varies from 40% to 77%.[19,20,35] In our study, transdermal estradiol caused mild discomfort in 63% of the patients and modest discomfort in the remaining 37%.[26] The distress was worst in the first 6 months of therapy; thereafter, the gynecomastia stabilized, and the distress decreased for most patients. These findings are consistent with the level of painful gynecomastia reported for 3 mg DES therapy.[19] Gynecomastia can be effectively prevented by the use of pretreatment radiotherapy given as a single or fractionated therapy. The side effects of this therapy are minimal, and consist mostly of temporary skin discoloration.[56] Treatment after gynecomastia has developed is more problematic. After several months, glandular proliferation, stromal expansion and periductal edema (the cause of initial discomfort) are replaced by fibrosis. At this time discomfort is reduced, but the gynecomastia is irreversible. Radiation therapy at this stage has minimal impact on breast size. It is important to note that gynecomastia also occurs in those treated by other hormonal modalities, especially NSAAs; increased circulating testosterone induced by NSAA therapy is converted to estrogens within the peripheral adipose tissues.[57]

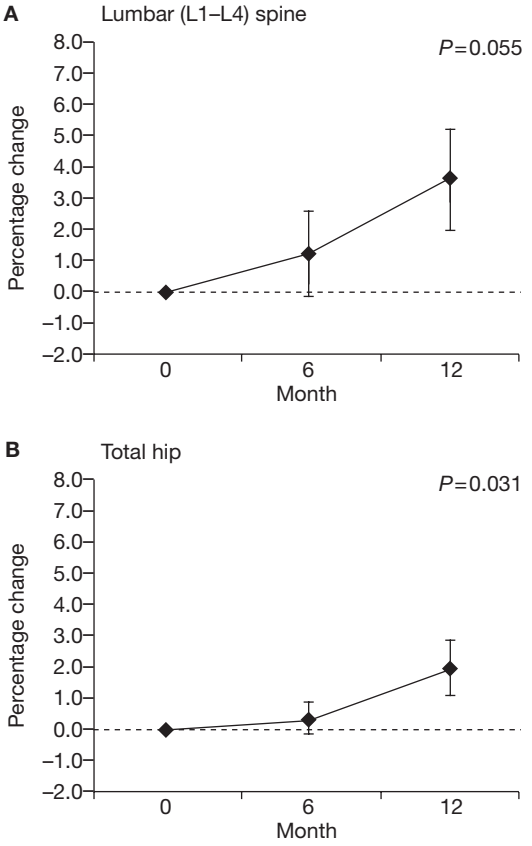

Figure 4 Changes in bone mineral density in men treated with transdermal estradiol patches over 1 year. (**A**) Changes in bone mineral density in the lumbar spine and (**B**) in total hip. Bars represent the mean and standard error of the mean. Permission obtained from Lippincott, Williams & Wilkins © Ockrim JL (2004) *J Urol* **172:** 2203–2207.

Prophylactic radiotherapy or adjuvant tamoxifen is now commonly employed alongside NSAA therapy to reduce gynecomastia,[58] and could be equally applied to parenteral estrogen therapy.

Parenteral estrogen therapy and the andropause

The abrupt suppression of androgens in men treated by current endocrine therapies results in a male version of the 'climacteric' similar to that experienced by women during menopause, sometimes termed andropause or castration syndrome. The best-recognized sequelae are loss of libido and erectile dysfunction. While sexual function in younger patients is intimately related to testosterone levels, in the elderly, mental and psychological factors are more important. Thus, the distress caused in these groups may be quite different. Castration syndrome also causes

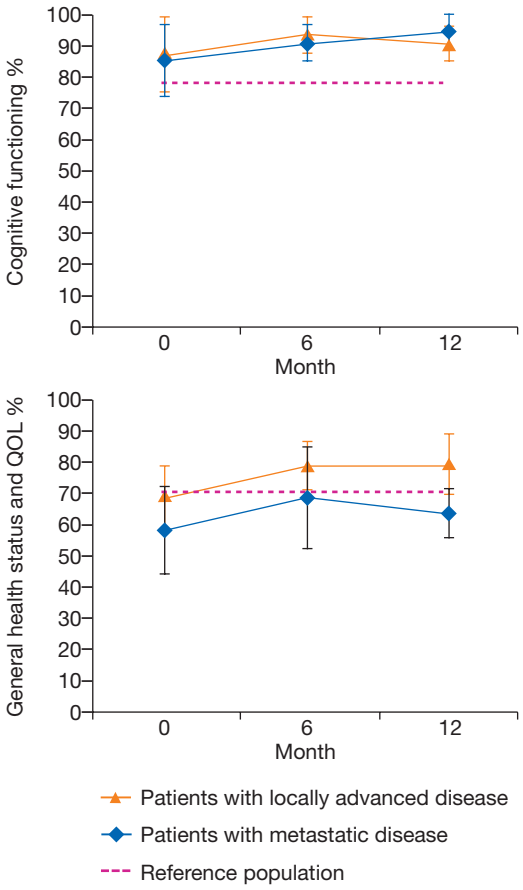

Figure 5 Change in cognitive function and overall quality of life during 12 months of transdermal estradiol therapy as measured by EORTC QLQ-C30 and PR25 CaP-specific QOL questionnaires. The vertical lines represent means and 95% confidence intervals.

cognitive dysfunction, and complex psychological changes often associated with depression. These symptoms may be far more important to patients (and their relationships) than the sexual changes or hot flashes commonly emphasized in counseling by urologists.

Evidence to demonstrate the deleterious effect of andropause on patients' QOL is now accumulating. While patients with symptomatic metastases generally show improvement or stabilization of QOL parameters with short-term (i.e. up to 1 year) endocrine therapy,[59,60] patients with non-symptomatic metastastic disease are adversely affected by androgen suppression. Decreases in physical, cognitive and emotional function as well as fatigue, lethargy and depression, have been widely recognized.[9,61,62] These adverse effects are most marked with LHRH agonists, especially when combined with an NSAA as MAB.[63,64] For those with early-stage disease committed to long-term therapy the detrimental effects are even more apparent. The progressive deterioration in QOL scores is independent of the disease status, and worsens over time.[10]

In these aspects, parenteral estrogen therapy might have significant advantages over other endocrine therapies. Epidemiological and experimental data suggest that estrogen therapy may protect against age-related decline in cognitive function and dementia.[14] Our own data seem to support this hypothesis at least in the shorter term. Patients treated with transdermal estradiol had an improved overall QOL during the first year of therapy, because of stabilized or improved functional and emotional status, reduced disease-related symptoms and minimal andropause scores.[65] The scores compared favorably with those expected from the reference population (Figure 5). This benefit is accrued whether the patients presented with symptomatic or asymptomatic disease. It is not yet clear whether the apparent benefits of transdermal estradiol therapy continue with longer duration therapy.

ECONOMIC BENEFITS OF PARENTERAL ESTROGEN THERAPY

The rising cost of endocrine therapy for CaP has been an issue of increasing concern amongst health-care providers throughout the world. In the US, Medicare expenditure on LHRH agonists increased from US$477 million in 1994 to over $800 million in 1999, and approaches $2 billion annually worldwide.[66,67] Analysis of cost-effectiveness and quality-adjusted life years (QALY) is now a topic of serious debate. A cost: QALY ratio of less than $20,000/QALY is universally considered to represent a reasonable use of health-care resource (i.e. good value). In a meta-analysis,[66] the historical use of oral estrogens was compared to current endocrine therapy by orchiectomy, LHRH agonists, NSAAs and MAB. The cardiovascular toxicity of oral estrogens was adjusted for within the analysis. The analysis demonstrated a QALY of 4.64 for oral estrogen therapy, 5.03 for NSAAs, 5.03 for MAB, and 5.10 for LHRH agonists and orchiectomy. This small QALY benefit of current therapies over oral estrogens (i.e. a maximum improvement of 0.46 QALY) was achieved at an astounding cost. Oral estrogens cost $8,100/QALY less than orchiectomy, whilst LHRH agonists or NSAAs cost over

$100,000/QALY, and MAB $1,110,000/QALY, more than orchiectomy.[66]

Transdermal estradiol monotherapy costs approximately one-tenth the price of LHRH agonist therapy alone, and the disparity increases further when compared with LHRH and NSAA combination therapy and/or bisphosphonates. A crude estimate of the cost saving for endocrine therapy alone would amount to approximately £100,000,000 in the UK and $900,000,000 in the US each year.[68] A substantial disparity remains even once the possibility of reduced LHRH agonist cost following patent expiration is considered. Additional savings accrue if the potential of parenteral estradiol therapy to confer long-term cardioprotective and osteoporotic benefit is also considered. Even if estrogen therapy resulted in a small reduction in the incidence of these complications, the cost savings would be considerable.

CONCLUSIONS AND FUTURE DIRECTIONS

The recognition of oral estrogen toxicity and the introduction of new hormone therapies led to the rapid demise of estrogen use in CaP. The mechanisms of toxicity and the potential to circumnavigate these problems were given scant regard, and the benefits of an estrogenic milieu received little consideration. The morbidity of contemporary hormone therapies has only recently been addressed, and the established health industry has embraced this new awareness by promoting adjuvant therapies to protect against osteoporosis and andropause, but sees little incentive in developing old treatments. With the new and expanding indications for androgen deprivation, the long-term toxicities of current hormone therapies are no longer acceptable. As such, it is incumbent upon clinicians and health economies to re-evaluate the old and validate the new data presented.

The future of estrogen in the management of CaP remains contemporary, evolving and exciting. Parenteral estrogen delivery may offer the benefits of oral estrogens with a substantially reduced cardiovascular risk. With parenteral delivery, this risk seems to be equivalent to that associated with orchiectomy, LHRH agonists and NSAAs for patients with metastatic disease. For patients with locally-advanced disease the risk may be more than with current therapies, but substantially lower than that of oral estrogens used historically. Over the longer term, this increase in cardiovascular morbidity could be converted into a substantial cardiovascular benefit. As such, clinicians and patients might choose to accept an initially higher risk in exchange for protection against osteoporosis, andropause and a better QOL.

Transdermal patches are easy to apply, dose modulate, and withdraw in the advent of toxicity developing. The development of selective estrogen (and androgen) receptor modulators might provide targeted hormonal benefits in the future, and the opportunities for translational research appear considerable. Parenteral estrogens should be considered as first-line therapy, a second-line treatment (to reduce the toxicity of oral estrogens) of locally advanced and metastatic CaP, an alternative adjuvant to radiotherapy, and a high-dose treatment for men with androgen-independent disease, as part of the multimodal armamentarium available to clinicians.

A phase II randomized controlled trial of transdermal estradiol compared with LHRH agonists began recruitment in April 2006 in collaboration with the Clinical Trials Unit of the Medical Research Council supported by the National Cancer Research Network Prostate Cancer UK studies group and funded by Cancer Research UK. The prospects of a new estrogen dawn look promising.

KEY POINTS

- Oral estrogens were abandoned as first-line hormone therapy for CaP because of their cardiovascular and thromboembolic toxicity
- Thromboembolic toxicity during first pass absorption of estrogens from the gut necessitates the need for parenteral routes of administration, which reduce thromboembolic risk
- Cardiovascular toxicity is related to estrogen-mediated vascular effects, which are both dose-dependent and time-dependent. Whilst short-term estrogen therapy has an increased risk of cardiovascular toxicity, long-term estrogen therapy may be associated with a cardiovascular benefit
- Current conventional androgen deprivation therapy is associated with considerable morbidity (castration syndrome/andropause) resulting in osteoporosis, hot flashes, cognitive dysfunction, asthenia and anemia
- Estrogen therapy is protective against the andropausal side effects of current hormone therapies
- Estrogen therapy is cheap with substantial health-care economic implications

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Competing interests
P Abel is the principal investigator on a Cancer Research UK grant for a phase II randomized controlled trial of estrogen patches versus luteinizing hormone-releasing hormone. The other authors declared they have no competing interests.