ORIGINAL ARTICLE

Taylor&Francis
healthsciences

A Phase I/II Study of High-Dose Tamoxifen in Combination with Vinblastine in Patients with Androgen-Independent Prostate Cancer

Michael Hamilton, William Dahut, Otis Brawley, Patricia Davis, Toni Wells-Jones, David Kohler, Paul Duray, David J. Liewehr, Nehal Lakhani, Seth M. Steinberg, William D. Figg and Eddie Reed

From the Medicine Branch, Center for Cancer Research, National Cancer Institute, Bethesda, MD, USA

Correspondence to: William D. Figg, Molecular Pharmacology Section, National Cancer Institute, National Institutes of Health, 9000 Rockville Pike, Building 10, Room 5A01, MSC 1910, Bethesda, MD 20892, USA. Tel: +1 301 4023 622. Fax: +1 301 4028 606. E-mail: wdfigg@helix.nih.gov

Acta Oncologica Vol. 42, No. 3, pp. 195–201, 2003

In this phase I/II clinical trial the antitumor activity of high-dose tamoxifen when administered in combination with vinblastine was assessed and the toxicity profile of this combination characterized. All 25 patients enrolled in this study were required to have androgen-independent prostate cancer and to maintain androgen ablation during treatment. Vinblastine was given by continuous infusion over 5 days. Doses were increased from 0.9 mg/m^2/day to 1.5 mg/m^2/day in successive cohorts of at least 3 patients, with no further escalation even in the absence of dose-limiting toxicity. Intra-patient dose escalation was permitted. Tamoxifen was administered at a dose of 200 mg/kg on day 1, then 120 mg/kg/day on day 2. Standard response criteria were utilized to assess antitumor activity and CTC toxicity criteria were used. Quality of life (QOL) pain assessments were evaluated at each visit to the clinic. Most patients tolerated the highest dose of vinblastine at 1.5 mg/m^2/day by continuous infusion over 5 days with 200 mg/kg/day of tamoxifen on day 1 and day 2. One patient had a greater than 50% decline in prostate-specific antigen that lasted for 170 days. Two patients received dose reductions because of toxicity. The most common serious toxicities included neutropenia, and fatigue. Reversible neurosensory, neuromotor, neurocortical and neurocerebellar toxicities were reported. Six of the 25 patients enrolled in the study (24%) experienced reversible neurologic toxicity of at least grade III. No statistically significant differences between precycle assessment of QOL and subsequent cycles were observed. It is concluded that vinblastine at 1.5 mg/m^2/day continuous IV infusion combined with tamoxifen 200 mg/kg/day on day 1 and day 2 is inactive, and not without toxicity in the treatment of advanced metastatic androgen-independent prostate cancer.

Received 5 June 2002
Accepted 20 December 2002

Prostate cancer is the most prevalent visceral malignancy and the second most common cause of cancer-related mortality in males in the USA (1, 2). This year it is estimated that 170 000 men will be diagnosed and that 30 200 will die of prostate cancer (3). Testicular suppression is the cornerstone of treatment for metastatic prostate cancer (4). Although hormonal ablation is extremely effective, androgen-independent disease will ultimately intervene in most patients (4, 5). Treatment options for androgen-independent prostate cancer are extremely limiting, with no regimen showing a survival advantage (6–8). Cytotoxic chemotherapy has traditionally been felt to have a minimal place in the treatment of prostate cancer after a series of trials in the pre-PSA (prostate-specific antigen) era failed to demonstrate significant clinical activity. More recently, however, several agents are showing promise (i.e., docetaxel, mitoxantrone) (6–8). Nonetheless, there is a tremendous need for more active treatment options that are more clearly targeted towards prostate-specific endpoints.

TGF-β plays an important role in regulating prostate cell growth (9). TGF-β directly inhibits the growth of prostatic carcinoma cells in vitro (10) and appears to have the same effect in vivo (11). Loss of TGF-β responsiveness is an early step in neoplastic transformation. Tamoxifen has been shown to alter prostate cancer cell growth via a non-estrogenic process similar to TGF-β (12). Tamoxifen inhibits protein kinase C (PKC) and alters the TGF-β transduction pathway by inducing p21. p21 induction is associated with a decrease in the phosphorylation of Rb and cell cycle arrest at the G1/S phase interface (12). Based on those observations, we initiated a phase II trial of high-dose tamoxifen in patients with androgen-independent metastatic prostate cancer (34). Thirty patients were treated with 160 mg/m^2/day tamoxifen. Steady-state plasma concentrations

 ISSN 0284-186X
DOI: 10.1080/02841860310010718

of 2.9 ± 1.3 μM were reached. One patient had an 80% decline in PSA and disease stabilization was observed in six patients.

Vinblastine is a semi-synthetic, nitrogen-containing alkaloid (13, 14). It inhibits mitosis in the metaphase and blocks transition at the G2/M phase interface (15). This blockage is associated with alterations of the fine structure of the spindle. Vinblastine has some activity as a single agent, with one report suggesting a response rate of 21% (16). At the time of developing this protocol, vinblastine was showing promise when combined with estramustine (17). Furthermore, the side effect profile of high-dose tamoxifen (cerebellar) was considerably different from that of vinblastine (i.e. myelosuppression). Furthermore, Trump et al. had recently conducted a phase-I trial of high-dose tamoxifen plus vinblastine (18). In that study, vinblastine as administered at 1.5 mg/m^2/day over 5 days and patients received up to 520 mg/m^2/day tamoxifen for 13 days. The maximum tolerated dose as determined in that study was 300 mg/m^2/day tamoxifen and the regimen was well tolerated with no unusual side effects reported. Based on these data, plus in vitro evidence of synergy in several prostate cancer cell lines (19), we conducted a phase-I/II trial in patients with androgen-independent metastatic prostate cancer.

MATERIAL AND METHODS

Patient enrolment

All patients had androgen-independent metastatic prostate cancer. All patients had failed testicular suppression with either surgical or medical castration (medical castration was continued throughout the duration of this study) and antiandrogen withdrawal if an androgen receptor antagonist had been initiated. Clinically progressive disease was characterized by two conditions: 1) PSA of at least 20 ng/ml for those with intact prostates, or 10 ng/ml for those having their prostate removed, ablated with radiation or cryosurgery, and 2) a documented 50% increase in PSA (2 measurements separated by at least one week). Patients were required to have an ECOG performance status of 2 or better and a life expectancy of more than 4 months. Patients were excluded if they were on active therapy for their cancer, or did not have progressive disease since their last treatment. Patients were excluded from the trial if they had received prior cytotoxic chemotherapy or an injectable radioisotope. This trial was conducted prior to the publication of the PSA Consensus Guidelines for Eligibility and Response in this population (20).

All patients were staged within 4 weeks prior to beginning therapy by bone scan, CT scan of the abdomen and pelvis, and chest x-ray. Baseline laboratory studies and bone marrow core biopsy/aspirates were collected within 4 weeks prior to starting therapy. Follow-up laboratory studies were obtained at each visit to the clinic. PSA was obtained at baseline, then monthly. Bone scans, x-rays of bone lesions and CT scans were repeated after every three cycles. A complete response was defined as complete disappearance of all small tissue tumor masses for at least two measurement periods separated by 4 or more weeks, normal PSA for a 4-week period, recalcification of osteolytic lesions, disappearance of osteoblastic lesions, and absence of disease-related decline. Objective partial response was defined as a decrease of 50% or greater in the sum of the bidimensional products of all measurable soft lesions, a greater than 50% decrease in the number of areas on bone scans showing increased uptake, a greater than 50% recalcification of osteolytic lesions and the resolution of pleural effusion and/or lymphangitic spread. Progressive disease was defined as an increase of greater than 25% of the sum of the products of all measurable lesions, appearance of any new lesion, a greater than 50% increase in PSA. Stable disease was defined as neither responding nor progressing. Declines in PSA were reported similarly to those of the consensus conference guidelines (20). Patients were removed from the study for progressive disease or unacceptable toxicity. Toxicity was graded by the National Cancer Institute's Common Toxicity Criteria, version 1.0. Dose-limiting toxicity (DLT) was defined as any grade 3 or greater non-hematological toxicity within the first 28 days of daily dosing, or absolute neutrophil concentration (ANC) < 50 for more than 5 days or ANC < 500 of any duration with fever, occurring in at least 2 out of 6 patients. Maximum tolerated dose (MTD) was defined as one dose level below that dose level at which DLT was seen.

This study was approved by the NCI's Institutional Review Board and all patients signed an informed consent prior to participating in the trial.

Study design

Patients received tamoxifen for one week before starting on vinblastine. The first cycle of vinblastine and tamoxifen was 28 days while all other cycles were 21 days in duration. The first cohort of 3 patients was started on 0.9 mg/m^2/day $\times$ 5 days CIV of vinblastine. If the doses were well tolerated for one cycle, the dose was increased to 1.2 mg/m^2/day $\times$ 5 days, if this dose was tolerated for 1 cycle, the dose was increased to 1.5 mg/m^2/day $\times$ 5 days. If 3 patients completed a dose level and had not experienced DLT, then this level of dosing was complete. Patients whose doses were escalated to a new dose level could be counted as one of the three necessary patients at both dose levels. If DLT was observed, an MTD below 1.5 mg/m^2/day $\times$ 5 days was defined and this dosage was used in the phase-2 portion of the trial. If one patient experienced DLT, three additional patients were accrued at that dose level. If no other patient experienced DLT, then accrual continued in groups of 3. If one additional patient experienced DLT, then the next lower dosage level was the MTD for the phase 2 portion of this trial. Even if DLT was

not reached at 1.5 mg/m^2/day × 5 days, no further dose escalation was allowed (Table 1).

Drug administration

Tamoxifen (Nolvadex®) was provided by Zeneca Pharmaceuticals (Wilmington, DE) and vinblastine was purchased by the NIH pharmacy as a generic commercial product. Patients were administered a loading dose of 200 mg tamoxifen on day 1. Approximately one week after starting the daily dosing of 120 mg of tamoxifen, vinblastine was given as a continuous infusion for 5 days.

Statistics

Statistical evaluation of results from pain/quality of life survey. Seventeen of the 25 (68%) patients enrolled in this trial provided at least one response to a survey focusing on quality of life and pain while on treatment. We concentrated on the results from five questions that were to be answered prior to each of cycles 1 through 4 of therapy. From among these 17 patients, based on 5 questions and up to 4 potential time points, only 65.5% of the potential survey responses were completed. Thus, the results obtained may not reflect those of the entire set of treated subjects.

For each survey question, we cross-tabulated the pre-cycle 1 response with the response for pre-cycles 2, 3 and 4. Among the resulting contingency tables that had sufficient data for statistical evaluation (at least 5 subjects addressing both a pre-cycle 1 question and the same question at a later cycle), we performed an exact marginal homogeneity test of agreement between the two cycles (21). This test is a generalization to tables larger than 2 × 2 of the McNemar test for differences in paired categorical data. In the case of perfect agreement, indicating no change between pre-cycle 1 and each subsequent cycle, all of the counts would occur on the main diagonal. The difference between pre-cycles 2, 3 and 4 values, and pre-cycle 1 values for each survey question was calculated, using negative differences indicating that the later cycle value was less than the pre-cycle 1 value, and a positive value indicating the opposite. For the four questions in which a larger value corresponded to more pain, a negative difference indicated a decrease in pain; for 'question 19', the opposite was true.

Table 1

Dosage levels

Dosage level	Vinblastine dose (mg/m^2/day)	No. of patients
1	0.9	3
2	1.2	11
3	1.5	13

RESULTS

Patient characteristics

Twenty-five patients with androgen-independent prostate cancer were enrolled in this study (see Table 2). The average age was 67 years (range 53–78) and the median performance status was 2 (96%). Seventeen out of 25 (68%) patients had bone lesions at the start of treatment and 16 out of 25 (64%) had positive CT scans. Five of 25 (20%) patients had received external beam radiation for pain control. All 25 patients had failed hormonal ablation prior to enrolling. The median time from diagnosis of prostate cancer to the start of the clinical trial was 59 months (range, 6 to 143 months). At the time of initial diagnoses, 62% of patients had an initial Gleason score between 5 and 7, while 38% of patients had scores between 8 and 10. Five patients were receiving narcotics for pain control at the time of start of treatment.

Clinical outcomes

Eighteen patients were removed from study owing to progressive disease, 2 were removed because of toxicity, 3 came off treatment for other reasons and 2 patients refused further treatment. Five patients were taken off-study within 30 days, while 3 patients were taken off-study between 31 and 60 days. One patient withdrew from study prior to receiving vinblastine, 5 patients withdrew after receiving one dose of vinblastine (1.2 mg/m^2/day). Two patients had a $\leq$ 25% increase in PSA for 131 days and 239 days, respectively. One patient had a decline in PSA $>$ 50% that lasted for 170 days (210 to 70.6 ng/ml).

Toxicities

Two patients required dose reductions because of toxicity. Both patients had their treatment reduced from 1.2 mg/m^2/

Table 2

Demographics of patients

No. of patients	25		
Age: median	67 years	(Range 53–78 years)	
Performance status			
Median	2		
	0	0	0%
	1	1	4%
	2	22	96%
Gleason at diagnosis (mean)	8		
	5–6	3	12%
	7	11	44%
	8–10	10	40%
No. of patients with bone lesions at start	17/25 (68%)		
No. of patients with positive CT scans	16/25 (64%)		
Date from diagnosis to on study (months)	Avg. 59 months	(Range 6–143 months)	

day to 0.9 mg/m^2/day for grade IV neutropenia, and 1.5 mg/m^2/day to 1.2 mg/m^2/day, respectively, for grade IV neutropenia.

The most common grade III toxicities were fatigue and neurologic symptoms. Five patients experienced grade III or greater fatigue. Six patients developed reversible grade III neurologic symptoms including neurocortical, neurocerebellar, neuro-motor and neuro-sensory symptoms. Pain, weakness, thrombosis, nausea and vomiting were also reported (Table 3).

Quality of life analysis

The full set of results for pain as reported at various time-points is reported in Table 4A–E. As an example, for question 1, pre-cycle 1, 7/15 (47%) of patients reported pain 'once in a while', with 4/15 (27%) reporting that they almost never had pain, and the same fraction reporting pain several times a week, or almost constantly. When pain is initially reported (question 2), it is generally either very mild (8/15; 54%) or only mildly distressing (5/15; 33%). The magnitude of individual changes through time is better illustrated in Table 5, which presents the frequency of differences between the indicated pre-survey responses for each of the 5 relevant questions. For the first 4 questions, a positive change corresponds to an increase in pain, while the reverse is true for the last question. The number of subjects who responded to each question at both of the indicated time-points and the p-value for the marginal homogeneity test are shown in the table; no statistically significant differences were found at the 0.05 level. However, the sample sizes were often quite small, and because only 17 of the 25 patients completed any part of the survey, and from that group of patients, over one-third of the questions were not answered across the time-points, these results are not necessarily representative of the results that would be obtained from all participants in the trial.

Table 3

Highest achieved

Patient no.	Dose level	Days on HDT/VBN	Off-study reason
1.	1	118	PD
2.	3	69	PD
3.	2	72	PD
4.	3	146	PD
5.	3	78	O
6.	2	21	O
7.	2	31	PD
8.	2	96	O
9.	3	70	PD
10.	1	129	PD
11.	NO VBN	3	T
12.	2	174	PD
13.	2	195	R
14.	2	55	R
15.	2	14	PD
16.	2	12	T
17.	3	146	PD
18.	3	203	PD
19.	1	98	PD
20.	2	11	PD
21.	2	47	PD
22.	3	74	PD
23.	1	53	PD
24.	1	67	PD
25.	3	223	PD

Abbreviations: HDT = High-dose tamoxifen; VBN = vinblastine; PD = progressive disease; T = toxicity; O = other; R = refused.

DISCUSSION

Despite the increasing use of chemotherapy for patients with androgen-independent prostate cancer, no agent or combination of agents has been shown to have an impact on disease survival (6). Factors that regulate the growth of prostate cancer cells are not well understood. A deeper understanding of prostate cancer regulatory pathways is imperative to the development of new therapeutic agents in the treatment of this disease. One approach towards developing new therapeutic agents has been to use agents that modulate the negative regulatory factors of prostate cancer. Transforming growth factor-β (TGF-β), a cytokine that controls cell proliferation, differentiation and death, is capable of inhibiting prostate cell growth in vitro (22–24). The TGF-β family includes many related factors that have diverse functions during embryonic development and adult tissue homeostasis (25,26). They bind to membrane receptors that have a cytoplasmic serine/threonine kinase/protein kinase C (PKC) domain. PKC is a signaling enzyme in regulating the growth and/or differentiation of a variety of cell types and inhibition of PKC activity is associated with the loss of regulatory function (27). Binding of the ligand causes the assembly of a receptor complex that phosphorylates proteins that bind DNA and recruit transcriptional co-activators or co-repressors (25, 26). Phosphorylation causes SMAD proteins to move into the nucleus, where they assemble complexes that directly control gene expression.

Down-regulation of the TGF-β receptor has been associated with prostatic carcinogenesis (28). Loss of responsiveness to TGF-β has been associated with clinical progression of prostate cancer (11), and there is also some speculation that it might be responsible for androgen-independent disease. Tamoxifen (1-[p dimethylaminoethoxyphenyl]-1,2-diphenyl-1-butene) has been shown to up-regulate TGF-β production and activation by many cell types including human prostate cancer cell lines (29) and human breast cancer cell lines (30). Tamoxifen has also been shown to inhibit prostate cancer cell growth by its PKC inhibitory activity (31) and induction of p21$^{wafl/cip\ 1}$ (12). Hence, Tamoxifen has been shown to reverse the early molecular and cellular events leading to prostate carcinogenesis (32).

Table 4

Response frequencies for each survey question, by cycle. Percentages of each frequency within a cycle are shown in parentheses

A. Question 1: Pain (1–5)

Cycle	1. I almost never have pain	2. I have pain once in a while	3. I frequently have pain several times a week	4. I am usually in some degree of pain	5. I am in some degree of pain almost constantly
1	4 (26.7%)	7 (46.7%)	2 (13.3%)	2 (13.3%)	0
2	8 (66.7%)	2 (16.7%)	1 (8.3%)	1 (8.3%)	0
3	8 (53.3%)	4 (26.7%)	0	3 (20.0%)	0
4	8 (53.3%)	4 (26.7%)	1 (6.7%)	2 (13.3%)	0

B. Question 2: Pain (1–5)

Cycle	1. When I do have pain, it is very mild	2. When I do have pain, it is mildly distressing	3. The pain I do have is usually fairly intense	4. The pain I have is usually very intense	5. The pain I have is almost unbearable
1	8 (53.5%)	5 (33.3%)	2 (13.3%)	0	0
2	8 (80.0%)	1 (10.0%)	1 (10.0%)	0	0
3	10 (71.4%)	2 (14.3%)	2 (14.3%)	0	0
4	9 (69.2%)	4 (30.8%)	0	0	0

C. Question 11 (1–7): How uncomfortable do you feel today?

Cycle	1. Not at all	2	3	4	5	6	7. Very uncomfortable
1	7 (43.7%)	5 (31.3%)	1 (6.3%)	3 (18.7%)	0	0	0
2	1 (33.3%)	0	1 (33.3%)	0	1 (33.3%)	0	0
3	1 (50.0%)	0	1 (50.0%)	0	0	0	0
4	6 (40.0%)	5 (13.3%)	0	2 (13.3%)	2 (13.3%)	0	0

D. Question 13 (1–7): How much is pain or discomfort interfering with your daily activities?

Cycle	1. Not at all	2	3	4	5	6	7. A great deal
1	6 (37.5%)	4 (25.0%)	4 (25.0%)	1 (6.3%)	1 (6.3%)	0	0
2	0	1 (33.3%)	1 (33.3%)	0	0	1 (33.3%)	0
3	0	0	1 (50.0%)	0	1 (50.0%)	0	0
4	8 (53.3%)	4 (26.7%)	1 (6.7%)	1 (6.7%)	1 (6.7%)	0	0

E. Question 19 (1–7): Rate how willing you were to see and spend time with friends in the past two weeks.

Cycle	1. Unwilling	2	3	4	5	6	7. Very willing
1	5 (31.3%)	6 (37.5%)	1 (6.3%)	0	2 (12.5%)	1 (6.3%)	1 (6.3%)
2	0	0	2 (66.7%)	0	0	0	1 (33.3%)
3	0	0	0	0	1 (50.0%)	0	1 (50.0%)
4	8 (57.1%)	2 (14.3%)	0	1 (7.1%)	1 (7.1%)	0	2 (14.3%)

This clinical trial was designed to expand on the preclinical observation that high-dose tamoxifen increases the sensitivity of prostate cancer cells to growth inhibition by TGF-β, induces stromal cell production of TGF-β and induces cell-cycle blockade at the G_1/S-phase interphase (12, 29). Vinblastine, is known to bind directly to tubulin, causing disruption of microtubules composing the mitotic spindle (33) and thus blocking the cell in the G_2/M-phase interphase. Co-administration of vinblastine and tamoxifen provides simultaneous blockade at two points within the cell cycle. Preclinically, this combination leads to the synergistic growth inhibition of prostate cancer cells (19). The toxicity of each agent differs from the other. Thus, the goal of this trial was to achieve clinical efficacy in the setting of acceptable toxicity.

Our trial, which used standard phase-II eligibility criteria, enrolled a population of patients with advanced, rapidly progressing disease. Ninety-six percent of the patients had an ECOG performance status of 2, 64% had soft tissue disease, and 38% had a Gleason score greater than or equal to 8. Five of the 25 patients (20%) were removed from the study within the first 30 days owing to rapid tumor

Table 5

Frequency of differences between the indicated pre-survey responses for each of the five questions. Samples sizes (n), and p-values for the marginal homogeneity test are shown, as well

Survey question (response range)	Cycles compared	Difference between pre-cycle survey responses[1]										n	p[2]
		−5	−4	−3	−2	−1	0	1	2	3	4		
1 (1 to 5)	C1 vs. C2				1	4	5	1				11	0.19
	C1 vs. C3				1	5	5	2				13	0.23
	C1 vs. C4				1	4	8					13	0.063
2 (1 to 5)	C1 vs. C2					2	7					9	0.50
	C1 vs. C3					2	10					12	0.50
	C1 vs. C4					4	7					11	0.13
11 (1 to 7)	C1 vs. C2					1		2				3	–[3]
	C1 vs. C3					2						2	–
	C1 vs. C4				2	2	6	2	1			14	0.87
13 (1 to 7)	C1 vs. C2					2		1				3	–
	C1 vs. C3						2					2	–
	C1 vs. C4				3	3	7	1				14	0.078
19 (1 to 7)	C1 vs. C2				2		1					3	–
	C1 vs. C3						2					2	–
	C1 vs. C4				1	3	5	1	2			13	0.60

[1] For survey questions 1, 2, 11 and 13, positive differences indicate more pain was experienced in subsequent cycles; for question 19, negative differences indicate that more pain was experienced in subsequent cycles.
[2] Two tailed p-value for exact marginal homogeneity test.
[3] Insufficient data to perform test.

progression. In retrospect, this is not the population one would expect to benefit from a high-dose tamoxifen regimen (34).

High-dose tamoxifen alone, standard-dose tamoxifen plus intermittent vinblastine, or vinblastine alone have had no significant activity in androgen-independent prostate cancer. We cannot rule out that this regimen would have activity in early-stage prostate cancer patients, although in this advanced population the combination of high-dose tamoxifen and continuous infusion vinblastine is inactive. In addition, the neurologic toxicity is not trivial and any further trials with this combination should proceed with caution.

REFERENCES

1. Pirtskhalaishvili G, Hrebinko RL, Nelson JB. The treatment of prostate cancer: an overview of current options. Cancer Pract 2001; 9: 295–306.
2. Rini BI, Small EJ. An update on prostate cancer. Curr Opin Oncol 2001; 13: 204–11.
3. Jemal A, Thomas A, Murray T, Thun M. Cancer statistics, 2002. CA Cancer J Clin 2002; 52: 23–47.
4. Figg WD, Feuer J, Bauer KS. Management of hormone-sensitive metastatic prostate cancer. Cancer Pract 1997; 5: 258–63.
5. Goktos S, Crawford ED. Optimal hormonal therapy for advanced prostatic carcinoma. Semin Oncol 1999; 26: 162–73.
6. Beedassy A, Cardi G. Chemotherapy in advanced prostate cancer. Semin Oncol 1999; 26: 428–38.
7. Figg WD, Arlen P, Gulley J, et al. A randomized phase II trial of docetaxel (taxotere) plus thalidomide in androgen-independent prostate cancer. Semin Oncol 2001; 28(Suppl 15): 62–6 (Aug).
8. Oh WK. Chemotherapy for patients with advanced prostate carcinoma: a new option for therapy. Cancer 2000; 88(Suppl 12): 3015–21.
9. Wikstrom P, Damber J, Bergh A. Role of transforming growth factor–beta in prostate cancer. Microsc Res Tech 2001; 52: 411–9.
10. Barrack ER. TGF beta in prostate cancer: a growth inhibitor that can enhance tumorigenicity. Prostate 1997; 31: 61–70.
11. Kim IY, Ahn HJ, Zelner DJ, et al. Loss of expression of transforming growth factor beta type I and type II receptors correlates with tumor grade in human prostate cancer tissues. Clin Cancer Res 1996; 2: 1255–61.
12. Rohlff C, Blagoskonny MV, Kyle E, et al. Prostate cancer cell growth inhibition by tamoxifen is associated with inhibition of protein kinase C and induction of $p21^{waf1/cip1}$. Prostate 1998; 37: 51–9.
13. Ritchie GL. Current therapeutics. 218. Vinblastine in malignant disease. Practitioner 1966; 196: 310–5.
14. Navarro M, Bellmunt J, Balana C, Colomer R, Jolis L, del Campo JM. Mitomycin-C and vinblastine in advanced breast cancer. Oncology 1989; 46: 137–42.
15. Downing KH. Structural basis for the interaction of tubulin with proteins and drugs that affect microtubule dynamics. Annu Rev Cell Dev Biol 2000; 16: 89–111.
16. Murphy GP. Review of phase II hormone refractory prostate cancer trials. Urology 1999; 54(Suppl 6A): 19–21.
17. Hudes GR, Greenberg R, Krigel RL, et al. Phase II study of estramustine and vinblastine, two microtubule inhibitors, in hormone-refractory prostate cacner. J Clin Oncol 1992; 10: 1754–61.
18. Trump DL, Smith DC, Ellis PG, et al. High-dose oral tamoxifen, a potential multidrug-resistance-reversal agent:

phase I trial in combination with vinblastine. J Natl Cancer Inst 1999; 84: 1811–6.
19. Pienta KJ, Replogle T, Lehr JE. Inhibition of prostate cancer growth by vinblastine and tamoxifen. Prostate 1995; 26: 270–4.
20. Bubley GJ, Carducci M, Dahut W, et al. Eligibility and response guidelines for phase II clnical trials in androgen-independent prostate cancer: recommendations from the Prostate-Specific Antigen Working Group. J Clin Oncol 1999; 17: 3461–7.
21. Agresti A. Categorical data analysis. New York: John Wiley and Sons, 1990.
22. Wilding G, Zugmeier G, Knabbe C, Flanders K, Gelmann E. Differential effects of transforming growth factor beta on human prostate cancer cells in vitro. Mol Cell Endocrinol 1989; 62: 79–87.
23. Knabbe C, Klein H, Zugmaier G, Voigt KD. Hormonal regulation of transforming growth factor beta-2 expression in human prostate cancer. J Steroid Biochem Mol Biol 1993; 47: 137–42.
24. Robertson KM, Penland SN, Padilla GM, et al. Fenretinide: induction of apoptosis and endogenous transforming growth factor beta in PC-3 prostate cancer cells. Cell Growth Differ 1997; 8: 101–11.
25. Massague J. How cells read TGF-β signals. Nature 2000; 1: 169–78.
26. Massague J. TGF-β signal transduction. Annu Rev Biochem 1998; 67: 753–91.
27. Goodnight J, Mischak H, Mushinski JF. Selective involvement of protein kinase C isozymes in differentiation and neoplastic transformation. Adv Cancer Res 1994; 64: 159–209.
28. Wilding G. Response of prostate cancer cells to peptide growth factors: transforming growth factor-beta. Cancer Surv 1991; 11: 147–63.
29. Muir GH, Butta A, Shearer RJ, et al. Induction of transforming growth factor beta in hormonally treated human prostate cancer. Br J Cancer 1994; 69: 130–4.
30. Koli KM, Ramsey TT, Ko Y, Dugger TC, Brattain MG, Arteaga CL. Blockade of transforming growth factor β signaling does not abrogate antiestrogen-induced growth inhibition of human breast carcinoma cells. J Biol Chem 1997; 272: 8296–302.
31. O'Brian CA, Liskamp RM, Solomon DH, Weinstein IB. Inhibition of protein kinase C by tamoxifen. Cancer Res 1985; 45: 2462–5.
32. Sporn MB. New agents for chemoprevention of prostate cancer. Eur Urol 1999; 35: 420–3.
33. Jordan MA, Margolis RL, Himes RH. Identification of a distinct class of vinblastine binding site on microtubules. J Mol Biol 1986; 187: 61–73.
34. Bergan RC, Reed E, Myers CE, et al. A Phase II study of high-dose tamoxifen in patients with hormone-refractory prostate cancer. Clin Cancer Res 1999; 5: 2366–73.