

## Phase III Prevention Trial of Fenretinide in Patients with Resected Non – Muscle-Invasive Bladder Cancer

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**Abstract Purpose:** The study aims to evaluate the efficacy and toxicity of fenretinide in preventing tumor recurrence in patients with transitional cell carcinoma (TCC) of the bladder.

**Experimental Design:** We conducted a multicenter phase III, randomized, placebo-controlled trial of fenretinide (200 mg/day orally for 12 months) in patients with non – muscle-invasive bladder TCC (stages Ta, Tis, or T1) after transurethral resection with or without adjuvant intravesical Bacillus Calmette-Guerin (BCG). Patients received cystoscopic evaluation and bladder cytology every 3 months during the 1-year on study drug and a final evaluation at 15 months. The primary endpoint was time to recurrence.

**Results:** A total of 149 patients were enrolled; 137 were evaluable for recurrence. The risk of recurrence was considered to be “low” in 72% (no prior BCG) and intermediate or high in 32% (prior BCG) of the evaluable patients. Of the lower-risk group, 68% had solitary tumors and 32% had multifocal, low-grade papillary (Ta, grade 1 or grade 2) tumors. The 1-year recurrence rates by Kaplan-Meier estimate were 32.3% (placebo) versus 31.5% (fenretinide;  $P = 0.88$  log-rank test). Fenretinide was well tolerated and had no unexpected toxic effects; only elevated serum triglyceride levels were significantly more frequent on fenretinide (versus placebo). The Data Safety and Monitoring Board recommended study closure at 149 patients (before reaching the accrual goal of 160 patients) because an interim review of the data showed a low likelihood of detecting a difference between the two arms, even if the original accrual goal was met.

**Conclusions:** Although well tolerated, fenretinide did not reduce the time-to-recurrence in patients with Ta, T1, or Tis TCC of the bladder.

An estimate of over 61,000 new cases of bladder cancer occurred in the United States in 2006 (1). According to the National Cancer Institute, the U.S. prevalence of bladder cancer (~ 500,000 cases) has surpassed that of lung cancer (2). As

many as 70% of newly diagnosed bladder cancers are non-muscle-invasive (superficial) transitional cell carcinoma (TCC), which is confined to the mucosa [Ta and Tis (carcinoma *in situ*)] or lamina propria (T1). Standard treatment of superficial TCC is transurethral resection of the bladder tumor with or without adjuvant intravesical chemotherapy or Bacillus Calmette-Guerin (BCG). Although BCG is the most effective available adjuvant treatment, 60% to 70% of bladder TCCs recur within 5 years after BCG therapy. Risk factors for tumor recurrence after initial diagnosis and treatment include multifocality and the diameter, grade, and stage of tumor (3–7). Approximately, 50% of patients diagnosed with a solitary bladder tumor will experience disease recurrence within 4 years, and 70% of patients with multiple bladder tumors will recur within 1 year. Despite the high risk of recurrence for non-muscle-invasive TCC patients, the risk of disease progression is comparatively modest — 15% overall and highest in patients with grade 3 T1 tumors.

Cancer chemoprevention is a promising approach for improving the long-term control of non-muscle-invasive bladder cancer (8, 9). This disease setting is ideal for testing chemoprevention strategies because of its high recurrence rates and relatively easy access to monitoring via cystoscopy and urine biomarkers. Animal bladder cancer models have produced promising results with several classes of potential

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chemopreventive agents, including retinoids (10). The synthetic retinoid fenretinide has been widely studied in rat and mouse bladder carcinogenesis models, wherein it has shown the highest therapeutic index among >20 retinoids (11–14). Fenretinide also preferentially accumulates in bladder tissue (10-fold to 20-fold greater than in plasma) and in breast tissue (4-fold greater than in plasma; ref. 15). Fenretinide is a potent apoptosis inducer: it induced apoptosis more potently than did all-*trans*-retinoic acid or 9-*cis*-retinoic acid in cancers of the bladder, head and neck, lung, and other sites and induced apoptosis in all-*trans*-retinoic acid-resistant leukemia cells (16–20). Randomized clinical trials in contralateral breast cancer, ovarian cancer, and oral premalignancy suggested that fenretinide has preventive activity (21–23). Furthermore, preclinical data in the bladder indicated that fenretinide potentially was more potent and less toxic than is the retinoid etretinate (10–14, 24), which was active in preventing superficial bladder cancer recurrence in randomized clinical trials (25, 26). Subsequent long-term phase III clinical data have shown the low toxicity and high tolerability of fenretinide (21, 24, 27, 28).

These promising data on fenretinide in bladder tumorigenesis led us to conduct a multicenter phase III clinical trial to test the hypothesis that fenretinide would significantly reduce the high incidence of non-muscle-invasive bladder TCC recurrence.

## Patients and Methods

**Patients.** Led by M. D. Anderson Cancer Center (MDACC), the trial began recruiting eligible lower-risk patients (Ta grades 1 and 2 TCC previously treated with transurethral resection but no prior BCG) at MDACC, MDACC Community Clinical Oncology Program affiliates, Baylor College of Medicine, and Veterans Affairs Puget Sound Healthcare System (affiliate of University of Washington). The protocol was amended during the course of the trial to expand eligibility to include intermediate- and higher-risk patients (with stage Ta, T1, or Tis TCC treated with transurethral resection plus BCG). This expanded eligibility allowed the trial to absorb BCG-treated patients from a similar trial in the Southwest Oncology Group (SWOG; SWOG-9460) that had been closed earlier than planned (October 1999) because of slow accrual. The same dose and schedule of fenretinide, BCG schedule, and randomization to drug or placebo were used in the MDACC and SWOG studies. SWOG meticulously collected all clinical data (including recurrences) on the SWOG-9460 subjects. Because our study was powered to detect recurrence rates, joint discussions between SWOG, MDACC, and National Cancer Institute statisticians determined that SWOG patient data could be incorporated into the MDACC study without jeopardizing the primary clinical end point.

Study eligibility criteria included histologically confirmed Ta, T1, or Tis TCC of the urinary bladder. Tumors could be solitary or multifocal and primary (first diagnosis) or recurrent (with a minimum preceding 12-month disease-free interval). Complete transurethral resection of all visible papillary disease and an assessment (IVP, retrograde pyelogram, or CT scan) that was negative for upper urinary tract tumor within 12 months before registration were required. Other criteria included a Zubrod performance status of 0 to 2, complete history (including tobacco-use history) and physical examination, and serum chemistry and hematology values within normal limits within 6 weeks before registration. Patients who had taken "megadose" vitamin A (>25,000 IU),  $\beta$ -carotene (30 mg/day), or retinoids within 3 months before registration were excluded. For women patients of childbearing potential, a negative urine or serum pregnancy test within 7 days

before registration was required and other rigorous measures were taken to protect against pregnancy during treatment because of the known teratogenic effects of fenretinide. All patients were required to sign an informed consent before registration. Patients meeting all other eligibility criteria were required to be registered and randomized within 30 days of transurethral resection of the bladder tumor (if not treated with BCG) or no sooner than 3 weeks and no later than 6 weeks after the last dose of maintenance BCG (if treated with BCG, which was given using a 6-plus-3 schedule: 6 weekly intravesical doses of induction BCG started within 21 days of transurethral resection of the bladder tumor; 3 weekly intravesical doses of maintenance BCG started 6 to 10 weeks after induction in BCG patients with negative cystoscopy and bladder cytology; if a maximum tolerated BCG dose had been reached in induction, one maintenance dose was allowed).

**Study design.** We designed a double-blind, placebo-controlled multicenter phase III trial to test fenretinide (200 mg/day for 12 months) for preventing recurrence of non-muscle-invasive bladder TCC. The primary trial end point was biopsy-confirmed TCC recurrence (including carcinoma *in situ*). Study treatment was daily oral ingestion of two capsules containing either drug (each capsule contained 100 mg of fenretinide) or placebo for 12 months. Drug and placebo appeared identical and were supplied by R.W. Johnson Pharmaceutical Research Institute. All patients were given a 3-day "drug holiday" during every 28-day period to avoid the known fenretinide toxicity of night blindness. Patients had a history, physical exam, and comprehensive cystoscopic bladder evaluation at baseline (study entry) and every 3 months for 15 months (including the 12-month treatment period). Diagnostic urine cytology and blood tests including fasting serum triglyceride, serum creatinine, and SGPT or SGOT were obtained at each visit.

Cystoscopic examination included the entire bladder and urethra. Any visually suspicious areas of the bladder mucosa were biopsied at the discretion of the urologist, and biopsy tissue was sent for routine pathologic assessment. The urologist documented the location and measurement of all lesions and sites of biopsies and abnormalities. Patients with positive cytology and negative biopsy remained on study drug and continued follow-up until biopsy confirmation of recurrence was obtained. Biopsy-confirmed TCC required discontinuation of the study drug and taking the patient off study.

Endpoint reviews were done independently by two or three reviewers (A.L.S., H.B.G., S.P.L.) for each recurring study participant. Reviewed items were the baseline cystoscopy and pathology reports, bladder cancer history, last protocol follow-up date, cystoscopy findings at the time an abnormality or recurrence was detected, date of the examination under anesthesia and biopsy, and the resulting biopsy pathology and any additional diagnostic exams when recurrence was detected. These reviews generated a report that included a summary of the current disease status and treatment plan (reported by the treating investigator). Each reviewer recorded a final end point review summary. In cases of disagreement, the reviewers discussed the case at the monthly protocol meeting and reviewed it again for consensus. If questions persisted, the reviewers obtained further documentation and repeated the process of disagreement resolution. A final summary of the end point review was then sent to the treating physician.

**Statistical analysis.** The statistical design was based on the primary end point of time to TCC recurrence. Patients were stratified by the following categories: solitary tumor resection without adjuvant BCG treatment, multifocal tumor resection without adjuvant BCG treatment, and tumor resection with adjuvant BCG treatment. A random block-restricted randomization was done within each stratum. The overall anticipated event rate at 1 year was 44.5%, which we predicted would be reduced to 25% by fenretinide. We calculated that a sample size of 160 patients (80 per arm) would be adequate to provide a power of 80% when using a two-sided test with  $\alpha = 0.05$  for detecting a significant reduction in recurrence at 1 year from 44.5% (placebo) to 25% (fenretinide). We anticipated a 10% drop-out rate and so

**Table 1.** Accrual of all randomized patients by study site

Site	Randomized
Independent	
Baylor College of Medicine	40
University of Washington/VA Puget Sound Healthcare System	32
MDACC	15
(Subtotal)	(88)
SWOG	
East Virginia - UCOP	8
University of Oklahoma - UCOP	7
University of Michigan	6
LSU Shreveport - UCOP	6
Central Illinois - CCOP	3
Oregon Health Science - UCOP	3
Tulane University - UCOP	2
Upstate Carolina	2
University of Colorado - UCOP	1
Birmingham, AL - UCOP	1
Henry Ford - UCOP	1
(Subtotal)	(40)
MDACC CCOPs	
Virginia Mason	13
Atlanta Regional	6
Grand Rapids	1
Greenville	1
Metro Minnesota	1
(Subtotal)	(22)
Total	149

Abbreviations: CCOP, Community Clinical Oncology Program; LSU, Louisiana State University; UCOP, Urologic Cancer Outreach Program; VA, Veterans Affairs.

planned to accrue 178 patients (89 per arm) to achieve the sample size of 160 evaluable patients. Interim analyses used the  $\alpha$  spending method of Lan and DeMets (29). Time-to-recurrence curves were calculated using the method of Kaplan and Meier; fenretinide and placebo were compared for effect on time to recurrence using the log-rank and Wilcoxon tests.

## Results

**Patients.** The Internal Review Boards of MDACC and all other participating centers approved the study protocol, and all patients signed an informed consent. One hundred forty-nine patients were randomized between September 1998 and November 2003, when the trial was closed early to accrual by recommendation of the Data Safety and Monitoring Board (DSMB), which determined that, based on interim data, the study had met the primary end point because of a low likelihood of detecting a difference between the treatment arms even if the original accrual goal was met. The 149 randomized patients were enrolled in the following centers: MDACC, MDACC Community Clinical Oncology Program sites, Baylor College of Medicine, University of Washington/Veterans Affairs Puget Sound Healthcare System, and SWOG (Table 1). The two study arms were similar with respect to important baseline patient characteristics (Table 2). Twelve of the 149 patients were not included in the final analysis because of ineligibility (9), withdrawn consent before first follow-up (1), or study closure before starting study drug (2). This left 137 eligible and

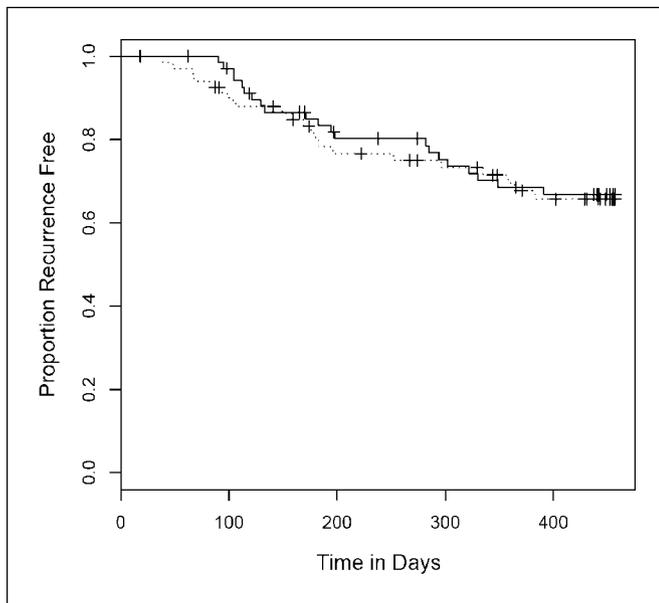
evaluable patients who have been included in this intent-to-treat analysis. Seventy patients were randomized to fenretinide and 67 to placebo. Seventy of the 137 evaluable patients did not complete treatment for the following reasons: recurrence (36 patients), toxicity (11), study ended (8), withdrew consent (8), refused treatment (4), lost to follow-up (2), and adverse events not related to study agent (1). The risk of recurrence was considered to be "low" in 72% of the evaluable patients who, thus, received no prior BCG, and intermediate or high in 32% who, thus, had prior BCG. Of the lower-risk group, 68% had solitary tumors and 32% had multifocal, low-grade papillary (Ta, grade 1 or grade 2) tumors.

**Recurrence.** The 1-year recurrence rates by Kaplan-Meier estimate were 31.5% (fenretinide) and 32.3% (placebo;  $P = 0.88$ , log rank test;  $P = 0.67$ , Wilcoxon test; Fig. 1). The proportions of patients recurring within 1 year by stratum in the fenretinide and placebo arms were as follows: solitary, no BCG (24% placebo, 30% fenretinide); multifocal, no BCG (45% placebo, 58% fenretinide); and BCG (39% placebo, 13% fenretinide). A proportional hazards model analysis that allowed for the effect of strata on time-to-recurrence and included treatment arm and strata as predictors indicates that strata had a statistically significant effect ( $P < 0.005$ ), whereas treatment arm still did not ( $P = 0.99$ ). Smoking had no significant effect on recurrence, either within or across intervention arms (Table 3). However, the interactive effect of smoking and fenretinide on superficial TCC recurrence cannot be determined definitively because of the low patient numbers in each smoking category.

**Toxicity.** Fenretinide was relatively well-tolerated at the study dose and schedule of 200 mg/day with a 3-day drug holiday every 28 days (Table 4). Fenretinide was associated with the expected toxicities included in Table 4, which shows that only serum triglyceride was significantly increased

**Table 2.** Baseline characteristics of evaluable patients ( $n = 137$ )

Characteristic	Placebo ( $n = 67$ )	Fenretinide ( $n = 70$ )
Age (y) mean, median, range	69.2, 70.9, 43.4-84.7	64.5, 64.0, 39.8-87.5
Gender		
Male	55	58
Female	12	12
Race		
Black	2	1
Hispanic	3	0
Asian	1	0
White	59	66
Other	2	3
TCC characteristics		
Ta grade 1, grade 2 (no prior BCG)		
Solitary	34	33
Multifocal	15	17
Intermediate-risk, high-risk (prior BCG)	18	20
Smoking status		
Current	16	16
Former	37	39
Never	14	15



**Fig. 1.** Recurrence by treatment arm ( $n = 137$ ). Proportion of subjects who were recurrence-free in the fenretinide arm (solid line;  $n = 70$ ) and placebo arm (dotted line;  $n = 67$ ) during the trial. Recurrences did not differ overall between the placebo and fenretinide arms ( $P = 0.88$ , log-rank test;  $P = 0.67$ , Wilcoxon test).

(versus placebo). Other statistically nonsignificant and less frequent side effects included infection, nausea, flatulence and other gastrointestinal events, headache, and stomatitis. There were no unexpected toxicities. Toxicities by maximum grade for the fenretinide arm ( $n = 74$ ) versus the placebo arm ( $n = 75$ ) included the following respective data: no toxicity in 29 versus 41 patients, grades 1 to 2 toxicity in 29 versus 22 patients, and grades 3 to 4 toxicity in 11 versus 11 patients. Capsule counts indicated that median compliance was 98.5% in the fenretinide arm.

## Discussion

This phase III trial established that fenretinide (200 mg/day for 12 months) did not prevent recurrence in a mixed population of lower-risk patients (no BCG treatment) and intermediate-risk and higher-risk patients (treated with adjuvant intravesical BCG). There was no significant difference between the fenretinide and placebo arms in the proportion of patients who recurred within 1 year. The trial was closed early (and before full accrual) by recommendation of the DSMB,

**Table 3.** Recurrence by smoking status and treatment arm (evaluable patients)

Smoking Status	Placebo	Fenretinide
	Recurred/total (%)	Recurred/total (%)
Never smoker	6/14 (43%)	5/15 (33%)
Former smoker	8/37 (22%)	10/39 (26%)
Current smoker	3/16 (19%)	4/16 (25%)
Unknown	0/0 (0%)	0/0 (0%)
Total	17/67 (25%)	19/70 (27%)

**Table 4.** Most frequent toxicity events by study arm

Toxicity	Placebo	Fenretinide	$P^*$
Pruritis/itching	9	14	0.265
Diarrhea	10	7	0.608
Ocular/visual	6	7	0.780
Nyctalopia	5	7	0.563
High serum triglyceride	1	10	0.005
Conjunctivitis	6	5	1.00

\*Fisher's exact test.

which determined that, based on interim data and a futility analysis, the study had met the primary end point because of a low likelihood of detecting a difference between the treatment arms even if the original accrual goal was met. One hundred forty-nine of the planned 160 patients were accrued. Adverse events were nonstatistically significantly increased in the fenretinide arm (versus placebo).

In a subgroup analysis, recurrence among highest-risk (BCG) patients was thrice more likely in the placebo than fenretinide arm. This increase was not statistically significant, however, because of the small size of this subgroup. Data from a murine bladder tumor model have indicated that simultaneous administration of retinoids and BCG is more active than of retinoids alone or BCG alone (30). Therefore, it is plausible that BCG potentiates fenretinide activity against bladder TCC through nonspecific immunostimulation, a hypothesis that could be tested in a randomized controlled trial.

Smoking, the major risk factor for bladder cancer, did not seem to influence the outcome of patients taking fenretinide. The small patient numbers within each smoking status category, however, did not allow a definitive assessment of the interaction of smoking and fenretinide within this study. Previous reports indicate that cigarette smoking can interact with chemopreventive agents including  $\beta$ -carotene and certain retinoids (31, 32). The  $\alpha$ -Tocopherol and  $\beta$ -Carotene Study and  $\beta$ -Carotene and Retinol Efficacy Trial indicated that  $\beta$ -carotene alone ( $\alpha$ -Tocopherol and  $\beta$ -Carotene Study) or combined with retinol ( $\beta$ -Carotene and Retinol Efficacy Trial) had a harmful effect in current smokers with no lung cancer history (increased incidence of lung cancer; refs. 33, 34). The Lung Intergroup Trial indicated that effects of the retinoid 13-*cis*-retinoic acid were beneficial in never smokers but harmful (increased recurrence, reduced survival) in current smokers who had definitively treated early-stage lung cancer (35).

Decensi and colleagues reported two previous trials of fenretinide at the same dose as, and in similar patients to, those of the present study (36, 37). One trial was single arm, the other was randomized, and the primary end point of both was aneuploidy in exfoliated bladder epithelial cells (measured by DNA flow cytometry). The single-arm trial suggested that fenretinide had the favorable effect of reducing aneuploidy in patients previously treated with transurethral resection of the bladder tumor and BCG. The randomized trial (fenretinide versus no intervention) enrolled 99 patients but did not confirm the first trial's promising ploidy results (although insulin-like growth factor-I levels were reduced in the fenretinide arm) and was negative with respect to recurrence, which

was a secondary end point (37, 38). The randomized trial, however, had biomarkers of aneuploidy as primary and secondary end points and lacked a placebo control or histologic confirmation of recurrence. In contrast to the randomized trial design of the Decensi group, our present trial design included a clinical primary end point (histologically confirmed recurrence), a placebo control arm, and a larger sample size for testing the hypothesis, which was based on strong preclinical and intriguing clinical data (10–17, 24–28). These and other clinical trial data (21–23, 39–42) substantiate the tolerability and safety of fenretinide at the dose used in the present trial and at even higher doses.

The lack of fenretinide efficacy in the current or previous trials could be due to a fenretinide dose (43) that was too low to induce apoptosis, the major hypothesized mechanism based on data from bladder TCC and other cultured cells (44). Fenretinide induces apoptosis in cells that are resistant to the retinoid all-*trans*-retinoic acid, the primary biologically active form of vitamin A, suggesting that fenretinide-induced apoptosis may involve retinoic acid receptor-independent mechanism(s) (45–49), such as increased generation of reactive oxygen species and activation of stress kinases (50, 51). Retinoic acid receptor-independent apoptosis, however, depends on high fenretinide concentrations (49). In an earlier chemoprevention trial conducted in the setting of oral intra-epithelial neoplasia, we showed that the same dose/schedule of fenretinide as used in the present study had possible retinoic acid receptor-mediated differentiation activity but not retinoic acid receptor-independent proapoptotic activity (42). Fenreti-

nide serum levels in that study were ~10-fold below the 3 to 5  $\mu\text{mol/L}$  levels shown by our group and other groups to be necessary for inducing apoptosis *in vitro* (42, 51). A major factor in selecting 200 mg/day of fenretinide was that the only strong safety data available when the trial was designed and activated were on this relatively low dose (21–23). Clinical data since that time, however, support the safety of substantially higher fenretinide doses (41).

In conclusion, our results indicate that fenretinide at the dose and schedule used in this study is inactive against bladder TCC recurrence. This result, along with the inactivity of another promising chemoprevention agent (difluoromethylornithine) in a recent randomized trial (52), highlights the need for new approaches for reducing recurrence and progression of bladder TCC. The management of bladder cancer, particularly surveillance for and treatment of eventual recurrences, results in major clinical and economic burdens that include the highest cost per cancer case in the United States (53, 54). Future preclinical and/or clinical studies could examine promising new approaches, including fenretinide combined with the cyclooxygenase-2 inhibitor celecoxib (ref. 55, a report on a recently completed trial of celecoxib alone in this setting is being prepared for publication), *N*-(4-methoxyphenyl)retinamide, which is the primary fenretinide metabolite (49), *N*-(3-hydroxyphenyl)retinamide, and other members of a group of novel structurally related phenylretinamides (44), and epidermal growth factor receptor tyrosine kinase inhibitors (56) for the chemoprevention of recurrence of bladder TCC and its serious health and economic burdens.

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