Cancer Chemother Pharmacol (2010) 66:845–850
DOI 10.1007/s00280-009-1228-x

ORIGINAL ARTICLE

A phase II study of fenretinide in patients with hormone refractory prostate cancer: a trial of the Cancer Therapeutics Research Group

M. M. Moore · M. Stockler · R. Lim · T. S. K. Mok · M. Millward · M. J. Boyer

Received: 23 July 2009 / Accepted: 20 December 2009 / Published online: 16 January 2010

Abstract
Purpose Fenretinide is a synthetic retinoid with activity in prostate cancer and other cell lines. The aim of this study was to assess the efficacy and tolerability of fenretinide in chemotherapy-naïve men with hormone refractory prostate cancer.
Methods Eligibility criteria included hormone refractory prostate cancer with a rising PSA at least 6 weeks after peripheral anti-androgen withdrawal, ECOG performance status (PS) 0–1, and no prior chemotherapy. Fenretinide was administered orally at 900 mg m^{-2} twice daily for 7 of every 21 days. PSA was measured before each cycle. The primary endpoint was a $\geq$50% reduction in PSA maintained for at least 3 weeks; secondary endpoints included duration of PSA response, time to treatment failure (TTF: treatment stopped for progression or toxicity) and adverse events (AE).
Results Twenty seven pts were recruited from 7 centres over 27 months. Median age was 74 (range 49–86), median baseline PSA was 129 (range 19–1,000), and 70% had a PS of 0. The median number of cycles received was 2 (range 0–11) and 20 pts completed at least 1 cycle. One pt (4%) achieved a 50% reduction in PSA lasting 39 days and 15 pts (56%) had not progressed within 6 weeks of starting fenretinide. The median TTF was 54 days (IQR 19–73): 22 (81%) failed with tumour progression, 3 (11%) failed with toxicity and 2 (7%) never commenced the drug. Grade 3 rash occurred in 1 patient, all other AE were grade 1 or 2. The most common AE were nausea (40%), hot flushes (36%), constipation (32%) and nyctalopia (32%).
Conclusion High-dose fenretinide had limited anti-tumour activity in patients with advanced hormone refractory prostate cancer: further evaluation in this setting is not warranted.

Keywords Prostate cancer · Hormone refractory · Fenretinide

M. M. Moore (✉)
Sydney Cancer Centre, Hospital Rd, Concord,
NSW 2139, Australia
e-mail: mmm@med.usyd.edu.au

M. Stockler
Sydney Cancer Centre and NHMRC Clinical Trials Centre,
University of Sydney, Missenden Rd, Camperdown,
NSW 2050, Australia
e-mail: stockler@med.usyd.edu.au

R. Lim
Department of Hematology-Oncology,
National University Hospital, 5 Lower Kent Ridge Road,
Singapore 119074, Republic of Singapore

T. S. K. Mok
Department of Clinical Oncology,
Chinese University of Hong Kong,
Prince of Wales Hospital, Shatin, Hong Kong

M. Millward
Sir Charles Gairdner Hospital, Hospital Avenue,
Nedlands, WA 6009, Australia

M. J. Boyer
Sydney Cancer Centre, Missenden Rd,
Camperdown, NSW 2050, Australia

Introduction

Prostate cancer is the most common male malignancy in most Western countries, and the second most common cause of cancer death. Worldwide, approximately 500,000 new cases of the disease are diagnosed each year, and it

results in the death of 200,000 men [1]. It is predominantly a disease of elderly men, with a median age at diagnosis of approximately 72 years.

Metastatic prostate cancer causes substantial morbidity. Many patients develop widespread bony metastatic disease, with associated pain, and complications such as spinal cord compression, and pathological fracture. Although specific therapies are available for such complications, the most effective way of preventing and treating them is to control the underlying malignancy.

Androgen ablation is highly effective in the initial treatment of metastatic prostate cancer. However, in men who live long enough, first-line hormonal therapy for advanced prostate cancer inevitably fails. Subsequent hormonal therapy is effective in controlling disease in some of these patients, although responses to second or third-line hormonal treatments are usually short-lived. Ultimately, the tumor becomes androgen independent (also referred to as hormone refractory prostate cancer, HRPC), and is able to progress despite hormonal manipulations.

There are currently limited systemic therapy options for HRPC. Chemotherapy with mitoxantrone has been shown to produce palliative responses in patients with symptomatic HRPC [2, 3] and docetaxel has resulted in improvements in survival [4]. There is a need for more effective therapies for HRPC.

The retinoids are a large group of compounds that include vitamin A and its derivatives. Retinoids, including fenretinide, have both anti-proliferative and apoptosis-inducing activities [5]. They seem to exert their effects by altering gene activity. Upon cellular entry, they bind to cellular receptors, and are conveyed to nuclear receptors, including the retinoic acid receptors and the retinoid X receptors [6].

Fenretinide [N-(4-hydroxyphenyl)retinamide], a synthetic retinoid, is a derivative of all-*trans*-retinoic acid (ATRA). In pre-clinical studies, the compound has activity against a range of cell lines in vitro including prostate, breast, ovarian and leukemia cell lines [7–9]. In animal models, fenretinide has demonstrated efficacy in the prevention or treatment of mammary, prostate, colon, and ovarian cancers, as well as leukemia [7, 10–12].

Previous human studies using relatively low doses of fenretinide (200–400 mg day^{-1}) demonstrated little activity in the prevention or treatment of breast cancer, prostate cancer, bladder cancer or melanoma [13–18]. Pre-clinical data suggest that higher doses of the drug, administered on an intermittent schedule may be effective against tumors, and phase I studies have demonstrated the feasibility of administering high dose fenretinide to humans [19]. The aim of this phase II study was to assess the efficacy and tolerability of high-dose fenretinide in men with advanced or metastatic hormone refractory prostate cancer.

Patients and methods

This was a multicentre, open-label, phase II study of orally administered fenretinide. The ethics committees of all participating institutions approved the study protocol and all patients provided signed informed consent before study entry. Fenretinide was supplied by the National Cancer Institute who also approved the study (NCI protocol number 6062).

Patients

Patients with histologically or cytologically confirmed adenocarcinoma of the prostate with castrate levels of serum testosterone and a serum PSA concentration that was rising and greater than 10 ng ml^{-1} were eligible for the study. Patients were able to have measurable or non-measurable disease. Other eligibility criteria included: age >18 years; life expectancy of greater than 12 weeks; ECOG performance status 0–1; adequate bone marrow function (neutrophils $>1.5 \times 10^9\ l^{-1}$, platelet count $>100 \times 10^9\ l^{-1}$); adequate renal (creatinine within normal institutional limits) and liver function (serum bilirubin within normal institutional limits, AST/ALT $\leq$2.5 times institutional upper limit of normal) and ability to tolerate oral medication. Prior anti-androgen therapy with cyproterone, flutamide, bicalutamide or nilutamide must have been ceased at least 6 weeks prior to study entry.

Exclusion criteria included: previous cytotoxic chemotherapy; radiotherapy within 4 weeks of study entry; other investigational agent within 4 weeks of study entry; presence of brain metastases; history of allergic reactions attributed to compounds of similar chemical or biologic composition to fenretinide; concurrent anti-oxidant, vitamin A or beta carotene supplementation; and uncontrolled inter-current illness.

Drug dosage and administration

Patients received 900 mg m^{-2} of fenretinide orally twice daily for the first 7 days of a 21-day cycle, with doses rounded to the nearest 100 mg. The 100 mg tablets were to be taken with high protein, fatty foods to maximize bioavailability. Treatment was to continue for 12 months or until the patient experienced disease progression or unacceptable adverse events. Responding patients were able to continue treatment beyond 12 months at the discretion of the investigator.

Patients were able to receive routine supportive care for symptoms and problems caused by their prostate cancer. This included the use of analgesics, anti-emetics and bisphosphonates. Patients who were receiving corticosteroids at the time of study entry were able to continue with the

medication, however, once enrolled in the study, corticosteroids were not permitted to commence.

Dose modifications

Treatment was interrupted for grade 3 or 4 hypertriglyceridemia, nyctalopia or liver function abnormalities or any grade 2 toxicity until resolved. Treatment was recommenced at the same dose but duration was reduced to 5 days of a 21-day cycle. Medication to control hypertriglyceridemia was permitted. Patients were removed from the study for grade 3 or 4 toxicities other than hypertriglyceridemia, nyctalopia or liver function abnormalities.

Treatment was allowed to be withheld for up to 21 days to allow for resolution of toxicity. Patients were removed from the study if there was any recurrence of a grade 2 toxicity after dose reduction.

Assessment of efficacy and safety

Patient assessments, including measurement of serum PSA, were performed every 3 weeks except for CT/MRI (performed every 6 weeks in patients who had abnormalities at baseline) and radionucleotide bone scan (performed every 12 weeks in patients who had abnormalities at baseline). Following the first documentation of a response, a confirmatory PSA level and, if appropriate, CT or MRI scan was obtained at least 4 weeks following initial documentation of objective response.

PSA response was the primary endpoint for the trial. Secondary endpoints included: duration of PSA response, PSA-progression-free survival and adverse events. Measurable lesions were defined as those that could be accurately measured in at least one dimension as $\geq$20 mm with conventional techniques (CT, MRI, X-ray) or as $\geq$10 mm with spiral CT scan. Bone lesions were not considered measurable.

A PSA response was defined as a 50% or greater decrease in serum PSA compared to the last value assessed prior to initiation of the trial medication, documented on at least two consecutive occasions at least 4 weeks apart. PSA progression was defined as an increase in PSA by 25% over the baseline or nadir PSA (whichever was lower) confirmed by a second PSA at least 4 weeks later. The date on which the PSA response or progression was first observed was considered to be the date of response/progression.

For those patients with measurable disease, tumour response and progression were also evaluated by the Response Evaluation Criteria in Solid Tumors (RECIST) [19].

Statistical methods

A Simon two-stage optimal design was used to distinguish between a PSA response rate of 10% or less versus 25% or more. Stage 1 was to include 21 patients who completed at least 1 cycle of fenretinide. The trial was to be closed and fenretinide judged not to be worthy of further assessment if there were 2 or fewer responses in stage 1, because this would indicate a probability of less than 10% that the true response rate was 25% or more. The trial was to accrue a total of 50 patients if there were 3 or more responses in stage 1. Fenretinide was to be judged worthy of further assessment if there were 8 or more responses in the 50 patients.

All study results are reported for the intent-to-treat population. Response rate was calculated as the percentage of patients who experienced a complete or partial response (if measurable disease) or PSA response. Duration of PSA response was the number of days from the date of first documented response to the earlier of either: death, PSA or radiological progression, last on-study PSA. Progression-free survival was the number of days from the day of first treatment to the earlier of: death, rising PSA or radiological progression or last on-study PSA assessment.

Results

Patient characteristics

Between August 2003 and June 2006, 7 centers in Australia and South-East Asia enrolled 27 patients with advanced or metastatic hormone refractory prostate cancer. Patient characteristics are summarized in Table 1. The median age was 74 (range 49–86) and most patients had an ECOG performance status of zero. Eighty percent of patients had bone metastases and 31% of patients had soft-tissue metastases. Most patients had 0–1 co-morbidities.

Treatment compliance

Patients received a median of two cycles (range 0–11). Four patients withdrew from the study before completing the first cycle of treatment. One of these patients was enrolled on the study and then no further information was collected. One patient was dispensed the medication for cycle one and did not commence due to pre-existing nausea and vomiting. Two patients decided to stop taking the study medication after 2 and 4 days respectively. A total of 76 treatment cycles was commenced.

Efficacy

All 27 patients enrolled on the study were included in the intention-to-treat analyses. There was a single PSA response which lasted 39 days (PSA response rate 4%). 14 patients (52%) had not progressed within 6 weeks of

Table 1 Patient characteristics

Characteristics	Number of patients $n = 27$ (%, rounded to nearest percent)
Median age (range)	74 years (49–86)
Median baseline PSA (range)	129 ng ml^{-1} (19–1,000)
ECOG performance status[a]	
0	19 (70)
1	7 (26)
Missing	1 (4)
Androgen ablation type	
Goserelin	12 (44)
Leuprorelin acetate	7 (26)
Orchidectomy	6 (22)
Missing	1 (4)
Bone metastases[b]	
Yes	20 (74)
No	5 (19)
Missing	2 (7)
Soft tissue metastases[c]	
Yes	8 (30)
No	18 (67)
Missing	1 (4)
Number of co-morbidities	
0	7 (26)
1	10 (37)
2	6 (22)
3	1 (4)
4	2 (7)
Missing	1 (4)
Median number of cycles (range)	2 (0–11)

[a] $n = 26$, performance status not recorded for one patient

[b] $n = 25$, details of bone metastases not recorded for two patients

[c] $n = 26$, details of soft tissue metastases not recorded for one patient

starting fenretinide. The median time to treatment failure was 54 days . Failure was due to tumor progression in 22 patients, treatment toxicity in 3 patients, and 2 patients never started study drug.

Safety

Table 2 lists the most frequently occurring adverse events, all but one of which were grade one or two. One patient experienced a grade three skin rash that necessitated cessation of the study drug after cycle one. Nausea, hot flushes, nyctalopia (night blindness) and lethargy were the most common adverse events. Four patients required dose modifications or treatment delay due to adverse events.

Table 2 Adverse events occurring in >5% patients ($n = 25$)

Adverse event	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)
Nausea	8 (32)	2 (8)	0
Hot flushes	8 (32)	1 (4)	0
Constipation	6 (24)	2 (8)	0
Nyctalopia	6 (24)	2 (8)	0
Lethargy	5 (20)	2 (8)	0
Diarrhea	3 (12)	4 (16)	0
Anorexia	4 (16)	1(4)	0
Abdominal discomfort	4 (16)	1 (4)	0
Vomiting	2 (8)	2 (8)	0
Back pain	3 (12)	1 (4)	0
Dyspnea	3 (12)	1 (4)	0
Dry mouth	4 (16)	0	0
Rash/pruritis	4 (16)	0	1 (4)
Myalgia	3 (12)	0	0
Yellowing of lights	3 (12)	0	0
Arthralgia	3 (12)	0	0
Edema	0	2 (8)	0
Hypertriglyceridemia	1 (4)	1 (4)	0

There were no adverse events of grade 4 or 5

Adverse events not recorded for one patient and one patient never commenced study medications

Discussion

This study has demonstrated that high-dose fenretinide has limited anti-tumor activity in patients with metastatic or advanced hormone refractory prostate cancer. Only one of 27 patients achieved a PSA response indicating a low probability that the true response rate was 25% or more. The median time to treatment failure was short at only 54 days. Treatment with fenretinide was well tolerated with only one patient experiencing a grade three toxicity (rash), and only 3 patients ceasing treatment as a result of toxicity.

To our knowledge, this is the first published data of high-dose fenretinide for the treatment of hormone refractory prostate cancer. The lack of efficacy mirrors results from phase II trials in recurrent glioma [20] and advanced renal cell carcinoma [21]. Both of these trials used fenretinide at similar doses to the present study. Only 1 of 45 patients with recurrent glioma and none of the 19 patients with renal cell carcinoma had objective responses. A role for fenretinide in the prevention of prostate cancer has been suggested, but not fully tested [16]. A phase II trial did not show a benefit but drawing conclusions was difficult given small patient numbers (22 patients) and the fact that determining tolerability was the main aim of the study.

Trials of fenretinide as a chemopreventive for other types of cancer have also been disappointing. Phase III trials of fenretinide to prevent bladder cancer [22] and second breast cancers [18] have been negative although both used a lower dose of fenretinide (200 mg m^{-2}) than our trial. However, a hypothesis-generating post-hoc subgroup analysis of the breast cancer trial suggested a reduction in second breast cancers among premenopausal women after 15 years of follow-up [23]. The authors speculated that this might be due to the differing modulation of fenretinide on IGF-1 levels in pre-menopausal versus post-menopausal women.

The reason for fenretinide's lack of efficacy in this trial is unclear. Fenretinide is thought to exert its effects through a number of mechanisms including decreasing levels of IGF-1, increasing levels of IGF binding protein 3, promoting apoptosis by generation of reactive oxygen species, and activation of nuclear factor kappa B (NFκB). Despite promising results in pre-clinical studies, it may be that in the complex milieu of advanced human cancers, fenretinide is unable to overcome the multiple pathways involved in tumour progression.

Oral administration may reduce the efficacy of fenretinide. Kokate et al. [24] postulated that the poor oral bioavailability of fenretinide was due to accumulation in the cell membrane of the gut lumen. This has led to the development of novel ways to deliver fenretinide which are yet to be tested in the clinical setting [25].

Conventional phase 2 trials in advanced cancer are a suitable strategy for selecting cytotoxics drugs that warrant further evaluation as treatments for advanced cancer. However, the optimal strategy for selecting possible preventive therapies for further evaluation is a dilemma. A positive result in this trial would have supported further evaluation of fenretinide in range of settings. However, the observed negative result does little to resolve whether whether fenretinide is worthy of evaluation as a preventive therapy. A succession of recent negative trials of cancer prevention suggest that better methods are needed for selecting suitable candidates for chemoprevention.

The present study demonstrates that further evaluation of high-dose fenretinide in hormone refractory prostate cancer is not warranted. The role of fenretinide in prevention of prostate cancer is yet to be answered.

References

1. Ferlay JBF, Pisani P, Parkin DM (2001) GLOBOCAN 2000: cancer incidence, mortality and prevalence worldwide. IARC Press, Lyon
2. Kantoff PW et al (1999) Hydrocortisone with or without mitoxantrone in men with hormone-refractory prostate cancer: results of the cancer and leukemia group B 9182 study [see comment]. J Clin Oncol 17(8):2506–2513
3. Tannock IF et al (1996) Chemotherapy with mitoxantrone plus prednisone or prednisone alone for symptomatic hormone-resistant prostate cancer: a Canadian randomized trial with palliative end points. [see comment] J Clin Oncol 14(6):1756–1764
4. Tannock IF et al (2004) Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer [see comment]. N Engl J Med 351(15):1502–1512
5. Martin SJ, Bradley JG, Cotter TG (1990) HL-60 cells induced to differentiate towards neutrophils subsequently die via apoptosis. Clin Exp Immunol 79(3):448–453
6. Tallman MS, Wiernik PH (1992) Retinoids in cancer treatment. J Clin Pharmacol 32(10):868–888
7. Chan LN et al (1997) N-(4-hydroxyphenyl)retinamide induces apoptosis in T lymphoma and T lymphoblastoid leukemia cells. Leuk Lymphoma 25(3–4):271–280
8. Roberson KM et al (1997) Fenretinide: induction of apoptosis and endogenous transforming growth factor beta in PC-3 prostate cancer cells. Cell Growth Differ 8(1):101–111
9. Sabichi AL et al (1998) Retinoic acid receptor beta expression and growth inhibition of gynecologic cancer cells by the synthetic retinoid N-(4-hydroxyphenyl) retinamide. J Natl Cancer Inst 90(8):597–605
10. Moon RC et al (1992) Chemoprevention of MNU-induced mammary tumors in the mature rat by 4-HPR and tamoxifen. Anticancer Res 12(4):1147–1153
11. Slawin K et al (1993) Dietary fenretinide, a synthetic retinoid, decreases the tumor incidence and the tumor mass of ras + myc-induced carcinomas in the mouse prostate reconstitution model system. Cancer Res 53(19):4461–4465
12. Zheng Y et al (1999) Effect of retinoids on AOM-induced colon cancer in rats: modulation of cell proliferation, apoptosis and aberrant crypt foci. Carcinogenesis 20(2):255–260
13. Cobleigh MA et al (1993) Phase I/II trial of tamoxifen with or without fenretinide, an analog of vitamin A, in women with metastatic breast cancer. J Clin Oncol 11(3):474–477
14. Cobleigh MA, Gray R, Graham M (2000) Fenretinide versus placebo in the postmenopausal breast cancer patients receiving adjuvant tamoxifen. An Eastern Cooperative Oncology Group Phase III intergroup trial (EB193,INT-0151) 19 Abstract 328. In: Proc American society of clinical oncology
15. Modiano MR et al (1990) Phase II study of fenretinide (N-[4-hydroxyphenyl]retinamide) in advanced breast cancer and melanoma. Invest New Drugs 8(3):317–319
16. Pienta KJ et al (1997) Phase II chemoprevention trial of oral fenretinide in patients at risk for adenocarcinoma of the prostate. Am J Clin Oncol 20(1):36–39
17. Urban D et al (1999) Evaluation of biomarker modulation by fenretinide in prostate cancer patients. Eur Urol 35(5–6):429–438
18. Veronesi U et al (1999) Randomized trial of fenretinide to prevent second breast malignancy in women with early breast cancer. [see comment]. J Natl Cancer Inst 91(21):1847–1856
19. Therasse P et al (2000) New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada [see comment]. J Natl Cancer Inst 92(3):205–216
20. Puduvalli VK et al (2004) Phase II study of fenretinide (NSC 374551) in adults with recurrent malignant gliomas: A North American Brain Tumor Consortium study. J Clin Oncol 22(21):4282–4289
21. Vaishampayan U et al (2005) Phase II trial of fenretinide in advanced renal carcinoma. Invest New Drugs 23(2):179–185
22. Sabichi AL et al (2008) Phase III prevention trial of fenretinide in patients with resected non-muscle-invasive bladder cancer [see comment]. Clin Cancer Res 14(1):224–229

23. Veronesi U et al (2006) Fifteen-year results of a randomized phase III trial of fenretinide to prevent second breast cancer [see comment]. Ann Oncol 17(7):1065–1071
24. Kokate A, Li X, Jasti B (2007) Transport of a novel anti-cancer agent, fenretinide across Caco-2 monolayers. Invest New Drugs 25(3):197–203
25. Okuda T et al (2009) Enhanced in vivo antitumor efficacy of fenretinide encapsulated in polymeric micelles. Int J Pharm 373(1–2):100–106