Clinical development of fenretinide as an antineoplastic drug: Pharmacology perspectives

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Impact statement

One of the critical components in drug development is understanding pharmacology (especially pharmacokinetics) of the drugs being developed. Often the pharmacokinetic properties, such as poor solubility leading to poor bioavailability, of the drug can limit further development of the drug. The development of numerous drugs has often halted at clinical testing stages, and several of them were due to the pharmacological properties of the agents, resulting in increased drug development cost. The current review provides an example of how improved clinical activity can be achieved by changing the formulations of a drug with poor bioavailability. Thus, it emphasizes the importance of understanding pharmacologic characteristics of the drug in drug development.

Abstract

Fenretinide (4-HPR) is a synthetic retinoid that has cytotoxic activity against cancer cells. Despite substantial *in vitro* cytotoxicity, response rates in early clinical trials with 4-HPR have been less than anticipated, likely due to the low bioavailability of the initial oral capsule formulation. Several clinical studies have shown that the oral capsule formulation at maximum tolerated dose (MTD) achieved $<10\,\mu$mol/L concentrations in patients. To improve bioavailability of 4-HPR, new oral powder (LYM-X-SORB®, LXS) and intravenous lipid emulsion (ILE) formulations are being tested in early-phase clinical trials. ILE 4-HPR administered as five-day continuous infusion achieved over $50\,\mu$mol/L at MTD with minimal systemic toxicities; multiple complete and partial responses were observed in peripheral T cell lymphomas. The LXS oral powder 4-HPR formulation increased plasma levels approximately two-fold at MTD in children without dose-limiting toxicities and demonstrated multiple complete responses in recurrent neuroblastoma. The clinical activity observed with new 4-HPR formulations is attributed to increased bioavailability. Phase I and II clinical trials of both LXS 4-HPR and ILE 4-HPR are in progress as a single agent or in combination with other drugs.

Keywords: Fenretinide, LYM-X-SORB®, fenretinide/LYM-X-SORB®, fenretinide–LYM-X-SORB®, drug formulation development, pharmacokinetics

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Background

Fenretinide (*N*-(4-hydroxyphenyl)retinamide; also known as 4-HPR) is an analog of all-*trans* retinoic acid (ATRA) first synthesized in the late 1960s by R.W. Johnson Pharmaceuticals.[1] At the time, chemists were searching for alternatives to natural retinoids which, while known to be efficacious treatments for skin diseases, effects on cancer cells have largely been to act as differentiating inducers but not as cytotoxic agents, with oncology clinical activity seen in only limited settings.[2–4] 4-HPR generated interest in initial screening experiments because it exhibited lower toxicity and better tissue distribution than both its natural congeners and other synthetics such as retinyl acetate.[5,6] Subsequent preclinical studies have shown that 4-HPR has chemopreventative activity in several animal models,[7–10] as well as cytotoxic activity in a variety of human cancer cell lines *in vitro,* including head and neck, non-small cell lung cancer, small cell lung cancer, breast cancer, ovarian cancer, prostate cancer, neuroblastoma, Ewing's family of tumor, leukemia, multiple myeloma, and pancreatic cancer at concentrations of $1–10\,\mu$mol/L.[11–15] In neuroblastoma and leukemia cell lines that are resistant to ATRA or 13-cis retinoic acid, 4-HPR has shown activity as well.[11,16] 4-HPR has also been tested clinically both as a chemoprevention agent

in breast,[17] bladder,[18,19] oral mucosal,[20–22] and prostate cancers;[23] and more recently as a chemotherapeutic agent in pediatric[24–27] and adult malignancies.[28–32]

As clinical testing of 4-HPR has progressed, its low toxicity from initial oral capsule formulation has allowed dose levels to be steadily increased in an effort to improve outcomes.[26,33–36] The daily doses for current chemotherapy trials in adult and pediatric solid tumors are 20- to 25-fold higher than those utilized in early chemoprevention trials.[17,24,25,37] Until recently, all trials have employed an oral gelatin capsule containing 4-HPR (100 mg) suspended in corn oil and polysorbate 80; and despite the increasing dose levels, patient plasma drug concentrations and tumor response rates have not increased as expected. This has led investigators to suggest that the low bioavailability of the capsule may be limiting the clinical activity of 4-HPR. We have estimated a mean oral bioavailability of only 16% in beagle dogs given a single 10 mg/kg oral dose of 4-HPR capsules (equivalent to a human dose of about 200 mg/m^2).[38] Thus, to address the problem of low systemic 4-HPR exposure with an aim to improve clinical outcomes, new oral, and intravenous formulations with improved bioavailability have been developed.[38,39]

While its use in chemoprevention has been covered previously,[1,40,41] we review the development of 4-HPR as cytotoxic chemotherapy for existing malignancies with emphasis on formulation improvements that have led to improved pharmacokinetics. Clinical trials utilizing 4-HPR as single agent chemotherapy are listed in Table 1, and our discussion of selected trial results that follows is organized by formulation and malignancy type.

Clinical studies with oral capsule 4-HPR formulation

Adult cancers

In their early phase II study evaluating oral 4-HPR capsules at 300–400 mg/day, Modiano *et al*. did not observe any responses in 15 patients with metastatic melanoma or breast cancer.[42] A later phase I trial tested oral 4-HPR capsules at doses from 500 to 4800 mg/m^2 (divided twice or thrice daily) in 31 patients with advanced solid tumors.[43] While toxicities were minimal at all doses, a dose of 1800 mg/m^2 divided twice daily gave the highest achievable 4-HPR plasma concentration. Two minimal responses were observed; one in a patient with breast cancer after 12 cycles and the other in a patient with renal cancer after nine cycles. The authors attributed the ''ceiling'' on 4-HPR plasma concentrations to saturated intestinal absorption.[43]

A subsequent phase II study was performed in patients with renal cell carcinoma at a 4-HPR dose of 1800 mg/m^2 (divided twice daily). Again, 4-HPR was well tolerated but

Table 1 Pediatric and adult cancer trials for existing malignancies employing 4-HPR as a single agent

Indication	Sponsor	Phase	Formulation	Daily dose	Enrollment/ evaluable	Plasma levels[a] (μmol/L)	Response	Ref
Prostate cancer	CTRG	II	Capsule	1800 mg	27	[b]	≥50% reduction in PSA in 1/27	31
Prostate cancer	CCC	II	Capsule	1800 mg	23	[b]	No objective response	45
Brain tumors	NABTC	II	Capsule	1600–1800 mg	45	2 ± 0.9	No activity	28
Ascitic ovarian cancer	EIO	I–II	Capsule	400–800 mg	22	1.4	No activity	46
Ovarian cancer	CCC	II	Capsule	1800 mg	31	12.5	OS at 18 mo 66% in >9 μmol/L	30
Solid tumors	BAKCI	I	Capsule	500–4800 mg/m^2	31	Unknown	No activity	43
Renal cell carcinoma	BAKCI	II	Capsule	1800 mg/m^2	19	[b]	No activity	29
Small cell lung cancer	UMCC	II	Capsule	1800 mg/m^2	19	7 ± 4	No objective responses	32
Pediatric neuroblastoma	IG & INT	I	Capsule	100–4000 mg/m^2	54	13 ± 6[c]	No CR/PR, 41 SD	24
Pediatric solid tumors	COG	I	Capsule	350–3300 mg/m^2	54	10 ± 3	1 CR, 13 SD	25
Pediatric neuroblastoma	COG	II	Capsule	2475/1800 mg/m^2 fixed	58	8 ± 3	1 PR, 7 SD	26
Pediatric neuroblastoma	NANT	I	4-HPR/LXS	352–2210 mg/m^2	32	16 ± 3	4 CR, 6 SD	27
Pediatric neuroblastoma	NANT	I	4-HPR/LXS + ketoconazole	1500 mg/m^2 fixed		18 ± 4	On-going	49
Hematologic malignancies	NCI	I	4-HPR-ILE	80–1810 mg/m^2	19	>50 μmol/L	36% CR + PR	35

IG: Istituto Gaslini; INT: Istituto Nazionale Tumori; COG: Children's Oncology Group; BAKCI: Barbara Ann Karmanos Cancer Institute; UMCC: University of Michigan Cancer Center; NCI: National Cancer Institute; EIO: European Institute of Oncology; CCC, California Cancer Consortium; CTRG: Cancer Therapeutics Research Group; NABTC: North American Brain Tumor Consortium; NANT: New Approaches to Neuroblastoma Therapy Consortium; 4-HPR/LXS: oral formulation of 4-HPR in an organized lipid matix (LYM-X-SORB); 4-HPR-ILE: intravenous formulation of 4-HPR in an intralipid emulsion; PSA: prostate specific antigen; OS: overall survival; SD: stable disease; CR: complete response; PR: partial response.

[a]Average C_{max} achieved at the highest dose administered.

[b]No plasma PK is assessed.

[c]The PK values are for day 28 of continuous 28-day dosing.

only minimally active in 18 evaluable patients.[29] 4-HPR concentrations of 3.6–7.9 μmol/L were measured in post-treatment tumor biopsy samples from four patients. Based on the lack of responses during the study and the fact that preclinical testing in solid tumor cell lines required exposure to 4-HPR concentrations of 10 μmol/L for at least 72 h to elicit 50–90% cell growth inhibition and apoptosis, the authors concluded that intratumoral levels were too low for 4-HPR to show biological activity.

A phase I/II study by Cowan *et al*. used 4-HPR oral capsule formulation (dose escalated to 1800 mg/m^2/day divided twice daily) in the phase I ($n = 7$) and combined rituximab in the phase II ($n = 25$) of the trial in B-cell lymphoma and mantle cell lymphoma patients.[44] The median peak and trough plasma 4-HPR levels were assessed regardless of the phase of the study and were 12.9 and 2.6 μmol/L, respectively. The trough bone marrow levels of 4-HPR were also measured and showed to be achieving efficacious levels of inducing apoptosis. No objective responses were seen and the toxicities were tolerable and reversible in patients treated with 4-HPR alone.

Small cell lung cancer. A phase II study evaluating oral 4-HPR capsules in patients with small cell lung cancer using a dose of 1800 mg/m^2 (divided twice daily) for days 1–7 of each 21-day cycle.[32] Toxicities were mild and reversible with cessation of treatment. No objective responses were observed in 17 response-evaluable patients, but four experienced stable disease after 2–17 cycles. Overall, the median survival was 25 weeks after start of treatment and the one-year survival rate was 29%. In 14 patients, the mean 4-HPR plasma concentration was 7.4 μmol/L (range: 0–14.9 μmol/L) prior to treatment on day 7 of cycle 1.

Prostate cancer. Two phase II studies tested the oral 4-HPR capsule in patients with prostate cancer.[31,45] Both trials utilized a dose of 1800 mg/m^2 (divided twice daily) for seven days every three weeks and found that although it was well tolerated, 4-HPR had limited activity against existing disease. The trial conducted by the Cancer Therapeutics Research Group had only one of 27 evaluable patients achieve the primary trial endpoint of a 50% decrease in pretreatment plasma prostate specific antigen level (PSA).[31] In a trial by the California Cancer Consortium (CCC) testing 4-HPR oral capsules in patients with asymptomatic rising PSA levels, no responses were observed but seven of 22 evaluable patients achieved biochemically stable disease (plasma PSA stabilization) after 17.7 months of follow-up.[46] Due to the lack of objective responses, the CCC study was terminated early.

Brain tumors. A phase II study was conducted in 45 patients with recurrent malignant glioma: 22 with astrocytic glioma (AG arm) and 23 with glioblastoma multiforme (GBM arm).[28] Oral 4-HPR capsules were given at doses of 1200 or 1800 mg/m^2 (divided twice or thrice daily) for days 1–7 and 22–28 of six-week cycles. All but four patients in the trial received the lower dose. In general, 4-HPR was well-tolerated at both dose levels but the trial was stopped after the first stage due to inadequate 4-HPR activity: median progression-free survival (PFS) was six weeks in both arms, and the PFS at six months was 10% for the AG arm and 0% for the GBM arm. The study authors concluded that 4-HPR was inactive against recurrent malignant gliomas at the trial doses and schedule and suggested the use of higher doses in future trials given the lack of toxicity and the fact that one of the four patients treated at 1800 mg/m^2 showed a durable radiologic response and remained progression free, with no substantial toxicity after 13 cycles of therapy. The authors also stated that the high number of capsules per administration was perceived as inconvenient by several patients. Data on achievable levels of 4-HPR in the CNS were not obtained.

Ovarian cancer. An early phase I–II trial by the European Institute of Oncology of oral 4-HPR capsules at 400–800 mg/day in patients with ascitic ovarian cancer for up to four weeks prior to surgery found no evidence of activity, even at the highest dose.[47] A mean 4-HPR plasma concentration of 1.4 μmol/L was measured in patients at the 800 mg/day dose, and while 4-HPR concentrations in malignant ascitic cells and tumor tissue samples were higher than those in plasma, the intracellular levels were lower than those measured in human ovarian carcinoma cell lines treated *in vitro* with 4-HPR at a concentration of 1 μmol/L.[46]

A phase II study of oral 4-HPR capsules at 1800 mg/m^2 (divided twice daily) was carried out in patients with recurrent ovarian cancer.[30] Out of 28 evaluable patients, no objective responses were observed but 42% experienced stable disease for a median duration of 7.2 months. The PFS at six months was 26%. In 24 pharmacokinetics-evaluable patients, 4-HPR plasma concentrations ranged from 3.1 to 12.5 μmol/L. Interestingly, when outcome was analyzed in the context of achieved 4-HPR plasma concentrations PFS at six months was 42% for patients achieving $\geq$9 μmol/L versus 17% for patients with <9 μmol/L and overall survival (OS) at 18 months was 66% at $\geq$9 μmol/L versus 13% at <9 μmol/L.

Pediatric cancers

A phase I trial at the Istituto Gaslini and Istituto Nazionale Tumori was conducted in patients with stage 3 or 4 neuroblastoma using oral 4-HPR capsules at doses from 100 to 4000 mg/m^2 (single daily dose) for 28 days followed by a seven-day drug holiday.[24] Reported toxicities were mild and reversible with only one patient experiencing a dose-limiting toxicity (DLT) of grade 3 nyctalopia. Testing at the highest dose of 4000 mg/m^2/day was discontinued due to poor compliance in taking the required number of capsules. Overall, no complete or partial responses were observed, but 41 of 53 evaluable patients experienced stable disease for a median of 23 months. 4-HPR plasma concentrations measured in 42 patients on day 28 of cycle 1 ranged from 1.3 to 12.9 μmol/L, with wide inter-patient variability in attained plasma concentrations—particularly at the higher dosing levels.

The Children's Oncology Group conducted a phase I study in 54 children with solid tumors (39 with neuroblastoma) administered oral 4-HPR capsules at doses from 350 to 3,300 mg/m^2 (divided twice or thrice daily) for days 1 to 7 every three weeks.[25] The toxicities were more severe than in the study by Garaventa *et al*.,[24] and included DLTs of grade 4 alanine aminotransferase elevation in one patient, grade 4 bilirubin elevation in one patient, and pseudotumor cerebri in one patient. The mean 4-HPR plasma concentration was 9.9 μmol/L on day 7 of cycle 1 at the maximum tolerated dose (MTD) of 2475 mg/m^2. As in the study by Garaventa *et al*., inter-patient variability in attained plasma concentrations was increased at higher dosing levels. Out of 30 evaluable neuroblastoma patients who completed at least eight cycles, one complete response occurred and 13 others experienced stable disease. In addition, one child with melanoma completed 26 cycles at the 3300 mg/m^2/day dose with stable lung metastasis before progression. The study authors noted that some patients had difficulty swallowing the required number of 4-HPR capsules and that their pharmacokinetic data suggested that an intestinal absorption plateau occurred at single doses above 900 mg/m^2. A phase II study of 4-HPR capsules achieved one partial response and seven stable disease, of which one achieved a durable (>10 years) complete response when continued on 4-HPR by compassionate access post-study.[26] These early-phase studies of capsule 4-HPR were not able to determine true maximal tolerated dose due to the bioavailability issue, suggesting that improvement in formulation of 4-HPR could be used to enhance clinically achievable levels and anti-tumor activity.

Development of oral powder and intravenous 4-HPR formulations

The oral 4-HPR capsule formulation was well tolerated, with dosing limited as ''maximal practical dose'' (due to numbers of capsules) rather than an MTD based on systemic toxicities. Both preclinical data and clinical study results suggested that increased 4-HPR exposures would result in higher levels of biological activity (i.e. growth inhibition and/or apoptosis) and tumor response. More specifically, data in solid tumors suggested that steady-state 4-HPR plasma and tumor tissue concentrations needed to approach or exceed 10 μmol/L. However, patient compliance in taking the required number of capsules was already challenging, especially for children. In addition, studies in both adults and children suggested that intestinal absorption of the capsule contents might be limited. For these reasons, new oral and intravenous formulations were developed to enhance bioavailability and increase systemic drug exposure.

A novel oral formulation delivers 4-HPR in an organized lipid matrix called LYM-X-SORB^{TM} (LXS^{TM}, 4-HPR/LXS^{TM}) to improve intestinal lymphatic absorption.[39] The LXS matrix is composed of a mixture of lysophosphatidylcholine, monoglycerides, and free fatty acids at a molar ratio of 1:4:2 to optimize 4-HPR incorporation. When compared to the capsule in mice *in vivo*, 4-HPR/LXS increased 4-HPR levels up to four-fold in plasma and seven-fold in tissues (liver, lung, kidney, and brain were analyzed) over levels achieved with the capsule. In addition, the *in vivo* activity of 4-HPR/LXS has been confirmed in human neuroblastoma murine xenograft models where it increased survival.[48] As a neat formulation, the LXS matrix has a bitter taste and is the consistency of candle wax at room temperature. Therefore, to make the delivery more patient-friendly (especially to children), 4-HPR/LXS can be combined with sugar and flour to form a coarse, free-flowing powder with the consistency of brown sugar and taste of raw cookie dough that is then suitable for mixing with solid foods or liquids for consumption.

The intravenous formulation delivers 4-HPR in a lipid emulsion (4-HPR-ILE) composed of a mixture of egg phospholipids, glycerin, alcohol, and soybean oil.[38] When compared in beagle dogs *in vivo*, an oral dose of 70 mg/kg/day (divided thrice daily) 4-HPR capsules for seven days attained a mean 4-HPR plasma concentration of 13.3 μmol/L at day seven; while with 4-HPR-ILE administered as a continuous intravenous infusion (c.i.v.) of 25 or 50 mg 4-HPR/kg/day for seven days, mean 4-HPR plasma concentrations at day seven were three-fold higher at 25 mg 4-HPR/kg/day and 10-fold higher at 50 mg 4-HPR/kg/day. Peak 4-HPR tissue concentrations in the dogs (kidney, liver, adrenal gland, lung, and lymph nodes were analyzed) after a 22-day c.i.v. of 4-HPR-ILE were 16.8 to 35.2 μg/g for the 25 and 50 mg 4-HPR/kg/day doses, respectively. Toxicity was also minimal with 4-HPR-ILE, even at the 50 mg 4-HPR/kg/day dose.

Clinical trials employing 4-HPR/LXS or 4-HPR-ILE

Pediatric neuroblastoma. The New Approaches to Neuroblastoma Therapy Consortium conducted a phase I study using the 4-HPR/LXS formulation in 30 evaluable patients with relapsed or refractory neuroblastoma.[27] 4-HPR doses ranged from 352 to 2,210 mg/m^2 (divided twice daily) for seven days (days 0–6) every three weeks. The administered 4-HPR/LXS oral powder was composed of (by weight) 3% 4-HPR, 55% wheat flour, 22% LXS lipid matrix, and 20% sucrose, and doses were mixed into Slim-Fast® liquid nutritional supplement drinks to ensure uniform delivery to patients. No MTD was identified and major toxicities included alkaline phosphatase elevation (grades 3 and 4, one patient each) and grade 3 alanine aminotransferase/aspartate aminotransferase elevation in one patient. Overall, the 4-HPR plasma levels attained with 4-HPR/LXS were over two-fold higher than those achieved previously with the capsule at similar doses; at a dose of 1700 mg/m^2/day, the mean peak 4-HPR plasma concentration on day 6 of cycle 1 was 21 μmol/L. However, the inter-patient variability in attained plasma levels that was previously noted for the capsule was also observed for the 4-HPR/LXS. Out of 29 evaluable patients, four had complete responses after 10–30+ cycles and six had stable disease after 4–27 cycles. All responses were at doses ≥774 mg/m^2/day. The study authors also observed an intestinal absorption plateau at doses above 1700 mg/m^2/day.

The feasibility studies of co-administration of low-dose ketoconazole using liver microsomes and in mice demonstrated that ketoconazole can inhibit the metabolism of 4-HPR and significantly increase 4-HPR levels in those models.[48] The increased 4-HPR exposures achieved using 4-HPR/LXS + ketoconazole was associated with both enhanced 4-HPR activity against neuroblastoma murine xenografts.[48] Based on these data, the phase I study of 4-HPR/LXS[27] was amended to add a cohort of 4-HPR and ketoconazole. Concurrent ketoconazole + 4-HPR/LXS 1500 mg/m^2 was well-tolerated, increased mean 4-HPR peak plasma levels ~50% relative to 4-HPR/LSX alone give at 1500 mg/m^2 (12 vs. 18 μmol/L), and demonstrated clinical activity, including two complete responses and a PFS.[49] A phase I study combining 4-HPR/LXS + ketoconazole was developed based on preclinical data in neuroblastoma xenografts[50] and is currently accruing patients (NCT02163356).

Intravenous 4-HPR in hematologic malignancies. The first phase I study evaluating the new 4-HPR-ILE formulation in patients with refractory hematologic malignancies has been presented.[35] At a dose range of 80–1810 mg/m^2/day administered as a continuous intravenous infusion for five days every three weeks, five responses (partial + complete) have been observed in 10 T-cell lymphoma patients at doses ≥905 mg/m^2/day. Steady-state 4-HPR plasma concentrations have been measured as high as 62 μmol/L at the 1810 mg/m^2/day dose, which are six- to seven-fold higher that plasma concentrations attainable with the oral capsule at the same dose. In addition, five of the six DLTs encountered thus far have been hypertriglyceridemia that is reversible upon discontinuation of the infusion, which the authors attributed to the lipid emulsion vehicle and not to the 4-HPR. In a case study, a dramatic response in cutaneous T cell lymphoma to ILE formulation was seen in patient achieving ~40–60 μmol/L plasma levels.[51] A phase II study of intravenous 4-HPR in peripheral T cell lymphoma is currently accruing patients (NCT0249515).

Conclusions

4-HPR has consistently been well tolerated in clinical studies for adult and pediatric cancers, and trials employing the oral capsule as a chemotherapeutic agent yielded some encouraging results at high doses. However, the corn oil suspension capsules limited achievable plasma drug concentrations, due to the low bioavailability of the capsule and/or to poor patient compliance in taking the required number of capsules. Novel oral and intravenous formulations that increase 4-HPR bioavailability and ease delivery to patients are now being clinically evaluated. The initial phase I clinical trials of these novel formulations have reported durable patient responses with systemic toxicity that, thus far, is comparable to experiences with the capsule. 4-HPR plasma concentrations attained with the new formulations were also two- to seven-fold higher than those seen previously with the capsule. The final report from the first phase I study with 4-HPR/LXS has just been released and the report from the first phase I trial employing 4-HPR-ILE has been published. Given that the clinical responses are moderate with new formulations despite achieving much higher plasma levels, studies to identify biomarkers to select patients for 4-HPR treatment are warranted to further improve clinical outcome. Several clinical trials of 4-HPR with new formulations as a single agent or in combination with additional agents (NCT02075177, NCT02163356, NCT01535157, NCT01553071, NCT02495415) are now in progress. If the new formulations continue to show improved clinical activity, malignancy types in which 4-HPR has shown effective *in vitro* activity but where current therapy has failed are candidates for further clinical investigations.

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The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: Certain intellectual property rights to 4-HPR/LXS^{TM} oral powder and intravenous fenretinide intralipid emulsion as cited here may be retained by The Children's Hospital Los Angeles. CPR is one of the inventors of this intellectual property and may potentially benefit financially from said intellectual property. MHK is a consultant for CerRx, Inc.

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