Phase II Study of Oral Capsular 4-Hydroxyphenylretinamide (4-HPR/Fenretinide) in Pediatric Patients with Refractory or Recurrent Neuroblastoma: A Report from the Children's Oncology Group

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Abstract

**Purpose:** To determine the response rate to oral capsular fenretinide in children with recurrent or biopsy proven refractory high-risk neuroblastoma.

**Experimental Design:** Patients received 7 days of fenretinide: 2,475 mg/m²/d divided TID (<18 years) or 1,800 mg/m²/d divided BID (≥18 years) every 21 days for a maximum of 30 courses. Patients with stable or responding disease after course 30 could request additional compassionate courses. Best response by course 8 was evaluated in stratum 1 (measurable disease on CT/MRI ± bone marrow and/or MIBG avid sites) and stratum 2 (bone marrow and/or MIBG avid sites only).

**Results:** Sixty-two eligible patients, median age 5 years (range 0.6–19.9), were treated in stratum 1 (n = 38) and stratum 2 (n = 24). One partial response (PR) was seen in stratum 2 (n = 24 evaluable). No responses were seen in stratum 1 (n = 35 evaluable). Prolonged stable disease (SD) was seen in 7 patients in stratum 1 and 6 patients in stratum 2 for 4 to 45+ (median 15) courses. Median time to progression was 40 days (range 17–506) for stratum 1 and 48 days (range 17–892) for stratum 2. Mean 4-HPR steady-state trough plasma concentrations were 7.25 μmol/L (coefficient of variation 40–56%) at day 7 course 1. Toxicities were mild and reversible.

**Conclusions:** Although neither stratum met protocol criteria for efficacy, 1 PR + 13 prolonged SD occurred in 14/59 (24%) of evaluable patients. Low bioavailability may have limited fenretinide activity. Novel fenretinide formulations with improved bioavailability are currently in pediatric phase I studies. Clin Cancer Res; 17(21): 6858–66. ©2011 AACR.
resistant to standard neuroblastoma therapy. In contrast to the differentiating agent 13-cisRA, 4-HPR induces both apoptosis and nonapoptotic cell death (6, 9, 14). 4-HPR cytotoxic mechanisms may include increase of dihydrotachysterol and increased expression of matrix metalloproteinase-9. The CCG 09709 phase I trial determined the maximal-tolerated dose (MTD) of capsular fenretinide given for 7 days every 21 days to children with solid tumors was 2,475 mg/m²/d divided into 3 equal doses (25). The MTD achieved mean peak 4-HPR plasma levels [day 7, continuous steady state (Css)] of 9.9 μmol/L with minimal toxicity. Among 30 evaluable neuroblastoma patients, there was one complete response and 13 stable patients with disease for 8 or more courses. A phase I adult trial using an identical schedule of capsular fenretinide determined an MTD of 1,800 mg/m²/d divided into 2 equal doses (25). On the basis of these data, this phase II trial was designed to determine the response rate to capsular fenretinide (2,475 mg/m²/d for 18 years or younger of age or 1,800 mg/m²/d for more than 18 years of age) in children with recurrent/refractory neuroblastoma. Response was assessed in 2 strata: (i) disease measurable by CT/MRI, and (ii) disease evaluable by bone marrow morphology and/or iodine-131-MIBG uptake. Patients and Methods

Eligibility

Patients 21 years or older at diagnosis of high-risk neuroblastoma with recurrent or resistant/refractory disease were eligible after any number of prior therapies, including hematopoietic stem cell transplant and retinoids (excluding fenretinide). Patients were required to have at least one of the following: measurable soft tissue mass (>20 mm on MRI/CT scan; >10 mm on spiral CT); MIBG avid tumor; or bone marrow metastases by routine morphologic review. Patients with prior relapse were eligible if they had 5 or more tumor cells/μm² mononuclear cells by bone marrow immunocytochemistry (27) on 2 serial marrow samples. Patients without prior relapse were required to have histologic confirmation of tumor sites on CT/MRI, and/or MIBG scans if bone marrow morphology was negative. Normal hepatic and renal function was required. Hematologic criteria were hemoglobin 7.5 or more mg/dl (transfusion allowed). All patients and/or guardian(s) signed written informed consent approved at local Institutional Review Boards in accordance with an assurance filed with and approved by the U.S. Department of Health and Human Services.

Treatment

Fenretinide (provided by National Cancer Institute) was given as intact 4-HPR (100 mg) capsules by mouth at a dose of 2,475 mg/m²/d divided into 3 equal doses (≤18 years age) or 1,800 mg/m²/d divided into 2 equal doses (>18 years age) for 7 days followed by 2 weeks rest. Total dose administered (in milligrams) was reported for each course, and all doses and courses submitted were reviewed by investigators. Patients with stable or responding tumor could request additional compassionate access to fenretinide. Patients off protocol therapy were followed until entry onto another COG therapeutic study, loss to follow-up, or death.

Response criteria

Overall response was graded using a modification of the International Neuroblastoma Response Criteria using the Response Evaluation Criteria in Solid Tumors (RECIST) criteria (28) to evaluate CT/MRI response of measurable tumor (≥30% decrease in sum of longest diameters) and Curie score (29) for MIBG response (relative Curie score ≤0.5). A complete bone marrow response was defined as no tumor by morphology on 2 serial samplings 3 or more weeks apart. CT/MRI, MIBG scans, and bone marrow slides were centrally reviewed for patients with an overall response of stable disease for more than 3 courses or better. Radiology and bone marrow reports were reviewed to confirm tumor sites at entry.

Pharmacokinetics

Heparinized blood samples were collected during course 1 prior to the first dose and 6 hours later; prior to day 4 morning dose; and prior to day 7 morning dose at 6 hours later. Additional samples were collected before the day 1 morning dose of courses 2, 5, and 9; and before the day 7 morning dose of courses 4 and 8. Samples were wrapped in foil, immediately chilled in ice-water, and centrifuged.

Translational Relevance

This phase II study assessed the activity of a capsular formulation of fenretinide in refractory/recurrent neuroblastoma. A novel study design utilized two strata: (i) Response Evaluation Criteria in Solid Tumors (RECIST)–defined measurable disease by CT/MRI scans and (ii) disease evaluable by non-RECIST methods, that is, bone marrow morphology and semiquantitative scoring of I-131-MIBGavid disease. Other novel variables were identified that affected time to progression: history of prior relapse versus resistant tumor and tumor sites at study entry. Identification of variables affecting time to progression is critical for design of future studies using this endpoint. This study assessed the utility of a multistrata phase II trial evaluating agents with minimal systemic toxicity but also minimal activity against mass disease and showed sufficient activity of fenretinide at modest systemic exposures to justify ongoing trials of novel fenretinide formulations with higher bioavailability. Importantly, this study documents responses and time to progression in both strata for comparison with ongoing and future phase II clinical trials in recurrent neuroblastoma.
teins were precipitated by adding 900 μL albumin containing the internal standard. Plasma pro-

amounts of authentic compound to 500 μL standard curve samples were prepared by adding known

trifuge tubes were kept in the dark and cold. Retinol and retinol were measured by reverse phase high perfor-

cence liquid chromatography (HPLC) with UV absor-

mance detection using a modification of the assay of Formelli and colleagues (31) under indirect yellow light. Plasma samples prepared in silanized amber microcen-

tuge tubes were kept in the dark and cold. Retinol standard curve samples were prepared by adding known

amounts of authentic compound to 500 μL of 5% serum albumin containing the internal standard. Plasma pro-

teins were precipitated by adding 900 μL ice-cold acet-

onitrile and 100 μL ice-cold saturated potassium phosphate to each 500 μL plasma sample. After centri-

fugation, the supernatant was added to amber autosam-

er vials kept in the dark at room temperature until analyzed. HPLC separations were done on a Phenomenex Luna C18 (2) analytical column (100 mm × 4.6 mm i.d., 3 μL fitted with a Brownlee RP-18 precolumn (15 mm × 3.2 mm i.d., 7 μL) and eluted with a mobile phase composed of acetonitrile:water:glacial acetic acid (80:18:2) delivered at rate of 0.9 mL/min. The UV absorption wavelength and injection volume were 340 nm and 50 μL, respectively.

Statistical considerations

The primary trial aim was evaluation of the response rate to capsular fenretinide. Patients were eval-

uated for response if they completed 2 or more courses or had tumor progression any time before completing 2 courses. A responder was defined as a best overall response of complete (CR), very good partial (VGPR), or partial (PR) response after 8 or less courses. Response rates were assessed separately via a 1-stage rule within stratum 1: CT/MRI measurable tumor ± other sites; and stratum 2: MIBG avid tumor and/or tumor in bone marrow by morphol-

ogy without CT/MRI measurable tumor. Fenretinide would be deemed effective if there were 5 or more respon-

ders among 25 evaluable patients in a given stratum [power of 91% to detect a 20% difference (30% vs. 10%) at significance level of 0.098]. More than 25 patients were accrued to stratum 1 since not all patients were evaluable for response, and some patients were reassigned from stratum 2 after review of tumor sites at entry. Patients with tumor detectable only by bone marrow immunocytology at entry (stratum 3) were enrolled for descriptive analysis only until accrual was completed in other strata.

Toxicities were collected on patients who received at least 1 dose of fenretinide. The pharmacokinetics of fenretinide, metabolite 4-MPR, and plasma retinol levels were assessed via descriptive analyses of steady-state levels.

Progression-free survival (PFS) and OS were calculated using the method of Kaplan and Meier (32) with standard errors per Peto et al (33). Time to progression (TTP) was calculated from study enrollment date until the first occurrence of relapse/progression or death due to tumor, or last contact date if no progression occurred. OS was calculated from study enrollment date until death from any cause, or date of last contact. Survival curves were compared using a log-rank test.

TTP was calculated from study enrollment date until the first relapse/progression. Median times to progression were compared using a 2-sided Wilcoxon rank-sum test (34). P < 0.05 were considered statistically significant.

Results

Patient characteristics

Sixty-five patients enrolled from May 12, 2003 to December 17, 2004. Characteristics of the 62 eligible patients are shown in Table 1. Three patients were ineligible: (i) (stratum 3) enrolled, but failed to meet stratum 3 eligibility (stratum 2, for which the patient was eligible, was closed to accrual); (ii) (stratum 3) inadvertently enrolled prior to informed consent; (iii) (stratum 1) ineligible because oral etoposide was given the same day fenretinide was started; after one course went off protocol therapy due to progressive disease (PD).

The median age at enrollment was 5 years (range 0.6–19.9). Only 3 patients enrolled were less than 4 years of age. The median time from last prior retinoid use to study enrollment was 1.5 years (range 10 days–5.9 years). The median time from diagnosis to the start of fenretinide was 2.5 years (range 20 days–12.8 years). Three patients (2 in stratum 2; 1 in stratum 1) received more than 30 courses of fenretinide via compassionate release (Table 2).

Response

There were 38 eligible (35 evaluable) patients enrolled on stratum 1 and 24 eligible and evaluable patients on stratum 2. Three patients on stratum 1 were ineligible: 2 patients went off therapy prior to completion of 2 courses, and 1 patient was unable to swallow capsules. There was one partial response in stratum 2 and no responses in stratum 1. Both strata had less than the 5 responses required to meet protocol criteria for effectiveness of fenretinide. Thirteen patients (7 on stratum 1; 6 on stratum 2) had stable disease for 4 to 45+ (median 15) courses, and had a median Curie score of 6.5 (range 0–25, excluding 1 patient radiated at all MIBG sites); with a median longest dimension for mass disease of 4 (range 0–10.9) cm. Three patients with SD after course 30 remained alive at last follow-up (Table 2). One of these 3 patients, with a history of prior PD at study entry, maintained SD 13 months after completing 45 courses of fenretinide (30 per protocol plus 15 additional courses) without other therapy. The second patient, with refractory tumor at study entry, maintained SD after course 30. This patient achieved CR after 25 months of compassionate fenretinide therapy, and maintained a CR on fenretinide therapy with last follow-up 50 months after ending course 30. The third patient, with refractory tumor at study entry, had SD after 30 courses of fenretinide, then received 13-cisRA for 3 months, and was alive 57 months off fenretinide therapy.
Toxicity

Grade 3 and 4 toxicities are summarized in Table 3; there were no toxic deaths. For each patient, only the worst toxicity grade per type across all courses was counted. No unexpected toxicities occurred. There was one death in a 7-year-old female 10 days after completion of course 1 from hepatic failure presenting 6 days after the last dose of fenretinide. Autopsy found widespread tumor infiltration in the liver, which was felt to be the etiology of this event. No other predisposing factors were identified. No other patients had significant hepatic toxicity.

Pharmacokinetics

Twenty-eight patients submitted at least 1 specimen. Steady-state trough concentrations of 7.25 μmol/L 4-HPR were achieved by day 4 and maintained through day 7 of course 1. There was substantial interpatient variability (CV 40–56%) in 4-HPR plasma concentrations (Fig. 1A). The 4-HPR accumulation factor of 2.8, determined by comparing mean 6-hour plasma concentrations measured on day 1 (3.07 μmol/L) and day 7 (8.21 μmol/L), suggests the 4-HPR plasma half-life was 18 hours. Steady-state trough concentrations of 4.8 μmol/L 4-MPR were achieved on day 7 of course 1 (Fig. 1B). There was substantial interpatient variability (CV 44–61%) in 4-MPR plasma concentrations (Fig. 1B). The mean retinol plasma concentration before treatment with fenretinide was 4.64 μmol/L (range 0.58–9.12 μmol/L), decreased by 97.3% (range 87.8–100%) after 4 days of fenretinide, and returned to 52% (range 13–87%) of the initial value before course 2 and to 46% (range 20–61%) of the initial value before course 5 (not shown).

Survival analysis

For all eligible patients, the 3-year PFS was 6.1% ± 3.4% and OS was 19.1% ± 5.7% (n = 62; Table 1). There was no significant difference between stratum 1 and 2 for PFS (3-year PFS: 8.1% ± 5.5% vs. 4.2% ± 4.1%; Fig. 2A), OS (3-year OS: 16.0% ± 6.5% vs. 24.5% ± 10.6%; Fig. 2B), or median TTP (40 vs. 48 days). The median TTP for patients with bone marrow disease with or without other tumor sites at study entry (n = 37) was significantly shorter (P = 0.027) at 40 (range 17–892) days than for patients without bone marrow disease (n = 20), who had a median TTP of 73 (range 23–506) days. Four patients with tumor limited to the bone marrow only at study entry achieved on day 7 of course 1 (Fig. 1B). There was substantial interpatient variability (CV 44–61%) in 4-MPR plasma concentrations (Fig. 1B). The mean retinol plasma concentration before treatment with fenretinide was 4.64 μmol/L (range 0.58–9.12 μmol/L), decreased by 97.3% (range 87.8–100%) after 4 days of fenretinide, and returned to 52% (range 13–87%) of the initial value before course 2 and to 46% (range 20–61%) of the initial value before course 5 (not shown).
progressed after 1, 1, 2, and 11 courses, with only 1 survivor 3 years from study entry (Fig. 3A and B). There was no difference in median TTP for patients with MIBG avid sites at entry (\(n = 47\)) versus patients (\(n = 10\)) without MIBG avid sites (48 vs. 36.5 days, respectively).

Outcome for patients older versus younger than 18 years was not significantly different. Patients without a history of previous tumor progression/relapse had significantly longer PFS (\(P = 0.0005\)) and OS (\(P = 0.0026\)) than patients treated after relapse/progression. No prior retinoid therapy was also associated with a trend toward higher PFS and OS (\(P = 0.058\) and \(P = 0.168\), respectively).

Discussion

This phase II trial was designed to determine the response rate of capsular fenretinide in children with refractory/resistant high-risk neuroblastoma, based on activity observed against neuroblastoma in preclinical models (5–7, 35) and the phase I CCG 09709 study (25). The trial utilized a novel design evaluating response in 2 different cohorts based on tumor sites at entry. It was hypothesized that fenretinide activity may differ against mass disease (stratum 1) versus disease limited to MIBG avid sites and bone marrow metastases (stratum 2). Stratum 2 patients have traditionally not been eligible for phase II studies, which utilized the RECIST criteria (28). The RECIST criteria have not been shown to be associated with outcome, and may not be applicable to neuroblastoma, where bone and bone marrow are the most frequent and often only sites of relapse (36). In addition, agents with modest systemic toxicity are potentially suitable for treating minimal residual disease, nonmeasurable by RECIST criteria, that remains after completing front-line therapy. Responses in MIBG avid lesions were defined using the Curie scoring method (29), which has been validated for bone metastases and has shown prognostic value (37). Preliminary data from the COG A3973 trial for newly diagnosed high-risk neuroblastoma suggest that the Curie score at the end of induction chemotherapy is prognostic for EFS (38, 39). Bone marrow response is difficult to quantify, due to patchy involvement. Neuroblastoma patients may also have minimal residual marrow disease (<5% tumor) variably detected on serial sampling. This study defined only complete response, SD, or PD in bone marrow. An ongoing retrospective study in the New Approaches to Neuroblastoma Consortium (NANT) will evaluate if these response criteria correlate with PFS and OS.

Neither stratum had sufficient responses to meet protocol criteria for efficacy. One of 59 (1.7%) patients with MIBG avid bone sites had a partial response. However, 13/59 (22%) patients had prolonged SD for 4 or more (median: 15; range 4–45+) courses and one eventually achieved a CR on further compassionate fenretinide therapy. Among 13 patients with SD, the high median Curie score and large median longest dimension of 4 cm at study

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**Table 2. Summary of 14 patients with response SD or more (\(n = 59\) evaluable patients)**

<table>
<thead>
<tr>
<th>Stratum</th>
<th>MIBG score</th>
<th>CT longest dimension</th>
<th>Bone marrow</th>
<th>Overall response (site responses)</th>
<th># Courses response maintained</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>3</td>
<td>0</td>
<td>Negative</td>
<td>PR</td>
<td>11</td>
</tr>
<tr>
<td>2</td>
<td>11</td>
<td>0</td>
<td>Positive (&lt;5%)</td>
<td>SD (SD on MIBG; CR in BM)</td>
<td>15</td>
</tr>
<tr>
<td>2</td>
<td>15</td>
<td>0</td>
<td>Negative</td>
<td>SD</td>
<td>45+b</td>
</tr>
<tr>
<td>2</td>
<td>7 (all sites radiated C1)</td>
<td>0</td>
<td>Positive (&lt;5%)</td>
<td>SD (MIBG sites resolved, not evaluable since radiated)</td>
<td>35 (5 courses compassionate)</td>
</tr>
<tr>
<td>1</td>
<td>1</td>
<td>4 cm</td>
<td>Negative</td>
<td>SD</td>
<td>30+c</td>
</tr>
<tr>
<td>1</td>
<td>1</td>
<td>5 cm</td>
<td>Negative</td>
<td>SD</td>
<td>30+d</td>
</tr>
<tr>
<td>1</td>
<td>25</td>
<td>10.3 cm</td>
<td>Negative</td>
<td>SD</td>
<td>24</td>
</tr>
<tr>
<td>1</td>
<td>0</td>
<td>4 cm</td>
<td>Negative</td>
<td>SD</td>
<td>15</td>
</tr>
<tr>
<td>1</td>
<td>11</td>
<td>0</td>
<td>Negative</td>
<td>SD</td>
<td>9</td>
</tr>
<tr>
<td>1</td>
<td>15</td>
<td>10.9 cm</td>
<td>Negative</td>
<td>SD</td>
<td>7</td>
</tr>
<tr>
<td>2</td>
<td>1</td>
<td>0</td>
<td>Positive (&lt;5–10%)</td>
<td>SD (CR at MIBG avid bone site; not evaluable since radiated)</td>
<td>7</td>
</tr>
<tr>
<td>2</td>
<td>11</td>
<td>0</td>
<td>Positive (&lt;5%)</td>
<td>SD</td>
<td>7</td>
</tr>
<tr>
<td>1</td>
<td>1</td>
<td>6 cm</td>
<td>Negative</td>
<td>SD</td>
<td>5</td>
</tr>
<tr>
<td>1</td>
<td>2</td>
<td>8.5 cm</td>
<td>Negative</td>
<td>SD</td>
<td>4</td>
</tr>
</tbody>
</table>

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aBM slides not reviewed; reports were reviewed.
bCentrally reviewed C1–C20; 15 compassionate courses. Alive with SD and no further therapy 13 months off fenretinide.
cCompleted C30 with SD; achieved CR on compassionate fenretinide 25 months later; last confirmed 50 months post-C30; alive on fenretinide 53 months post-C30.
dPost-C30 given 13-cis-retinoic acid for 3 months. Alive 57 months post-C30. BM = bone marrow; C = course.
entry may indicate that prolonged SD was possible in patients with significant tumor burden. However, we cannot definitively conclude that the prolonged SD observed is any different from the natural history without any therapy in this diverse patient population.

The 2 strata design based on tumor sites at protocol entry may not be superior to a single strata design to determine efficacy based on response. Two other COG phase II studies (40, 41) using this same design found responses which met the statistical endpoint for efficacy in stratum 2 only. Additional studies are needed to resolve this issue. The 2 strata approach provides a framework for future clinical trials to better define the impact of disease burden on assessing drug activity in recurrent neuroblastoma.

The unplanned comparisons of survival by stratum, sites of tumor, or age were underpowered. However, marrow disease at entry was associated with significantly lower PFS and OS. The COG 09709 phase I study of fenretinide also found this association with shorter TTP in patients with bone marrow disease at entry (25). These data suggest that tumor sites may affect outcome after salvage therapy with novel agents. Patients with persistent refractory tumor (documented by histology) had significantly higher PFS and OS than patients with a history of prior relapse. Among patients with prolonged SD, 7 had prior relapse and 6 had refractory disease. The patient population on this study was heterogeneous in terms of sites of tumor, and whether they had recurrent PD after prior responses or were primarily

| Table 3. Toxicities of grade 3 or 4 in 62 eligible patients receiving at least 1 dose of fenretinide |
|--------------------------------------------------|---------------------------------|---------------------------------|
| Toxicity                                         | Number of patients | % patients | Number of patients | % patients |
| Rash*                                            | 1                  | 1.8        | 0                  | 0          |
| Diarrhea*                                        | 1                  | 1.8        | 0                  | 0          |
| Nausea*                                          | 2                  | 3.6        | 0                  | 0          |
| Vomiting*                                        | 1                  | 1.8        | 0                  | 0          |
| Bilirubin*                                       | 4                  | 7.1        | 0                  | 0          |
| AST (SGOT)*                                      | 2                  | 3.6        | 0                  | 0          |
| ALT (SGPT)*                                      | 2                  | 3.6        | 0                  | 0          |
| Nyctalopia*                                      | 0                  | 0          | 1                  | 16.7       |
| Abdominal pain*                                  | 3                  | 5.4        | 0                  | 0          |
| Catheter-related infection                       | 1                  | 1.8        | 0                  | 0          |
| Anorexia                                         | 1                  | 1.8        | 0                  | 0          |
| Muscle weakness                                  | 1                  | 1.8        | 0                  | 0          |
| Inner ear/hearing                                | 1                  | 1.8        | 0                  | 0          |
| Epistaxis                                        | 1                  | 1.8        | 0                  | 0          |
| Bone pain                                        | 8                  | 14.3       | 0                  | 0          |
| Hemoglobin                                       | 11                 | 19.6       | 1                  | 16.7       |
| Dyspnea (shortness of breath)                    | 1                  | 1.8        | 0                  | 0          |
| Infection without neutropenia                    | 2                  | 3.6        | 0                  | 0          |
| Hepatic enlargement                              | 1                  | 1.8        | 0                  | 0          |
| Liver dysfunction/failure (clinical)             | 1                  | 1.8        | 0                  | 0          |
| Leukocytes (total WBC)                           | 5                  | 8.9        | 0                  | 0          |
| Hypoxia                                          | 1                  | 1.8        | 0                  | 0          |
| Weight loss                                      | 2                  | 3.6        | 0                  | 0          |
| Pleural effusion (nonmalignant)                  | 1                  | 1.8        | 0                  | 0          |
| Lymphopenia                                      | 6                  | 10.7       | 0                  | 0          |
| Neutrophils/granulocytes (ANC/AGC)               | 5                  | 8.9        | 0                  | 0          |
| Platelets                                        | 9                  | 16.1       | 2                  | 33.3       |
| Hypokalemia                                      | 2                  | 3.6        | 0                  | 0          |
| Tumor pain                                       | 1                  | 1.8        | 0                  | 0          |
| Hyponatremia                                     | 2                  | 3.6        | 0                  | 0          |
| Transfusion: platelets                           | 5                  | 8.9        | 1                  | 16.7       |
| Transfusion: PRBCs                               | 9                  | 16.1       | 1                  | 16.7       |
| Pain—Other                                       | 1                  | 1.8        | 0                  | 0          |

NOTE: Only the worst toxicity grade per type per patient across all courses was counted. Also, targeted toxicities are indicated by asterisk.
refractory to therapy; these factors will be critical to consider in future phase II study design, because they potentially affect response rate and/or TTP endpoints. Further data with larger numbers of patients are required to test these hypotheses.

Fenretinide steady-state pharmacokinetics confirmed phase I CCG 09709 data (25) that steady state drug concentrations in the range associated with in vitro activity are achievable. However, intracellular biodistribution of fenretinide is complex, and much higher concentrations may be required in patient plasma than in cell culture to achieve cytotoxic intracellular drug concentrations. Although it was recommended that the drug be given with high fat meals known to increase fenretinide bioavailability (42), wide interpatient variability may be due to diet variations and/or incomplete disintegration of the gelatin capsules. Patients received 5 to 14 capsules per dose, which was challenging to administer to young children. Poor bioavailability of the capsular formulation may have limited efficacy.

Systemic toxicity was minimal. The death from hepatic failure was attributable to tumor progression. Although the phase I 09709 study reported 3 reversible cases of pseudotumor cerebri at 3 dose levels (25), none occurred on this study. Despite significant retinol depletion, only 1/6 patients older than 18 years reported nyctalopia. There were no cases in younger patients, which may be due to under-reporting.

Novel formulations of 4-HPR which optimize pharmacokinetics and feasibility of administration in children are currently being tested in pediatric and adult phase I trials. A 4-HPR formulation packaged in LYM-X-SORB (LXS; 43), a lipid matrix technology powder, was tolerated in doses up to 2,210 mg/m²/d without dose-limiting toxicity in an ongoing NANT trial (44). Mean peak plasma levels were 15 to 20 μmol/L versus 6 to 9 μmol/L with the capsular formulation. An absorption plateau was observed, as seen with the capsule formulation. An intravenous 4-HPR emulsion formulation is also being tested in ongoing adult cancer trials and a pediatric neuroblastoma (NANT) trial, with clinically tolerable peak plasma levels up to 50 μmol/L.
The cumulative data with fenretinide support activity of this agent against neuroblastoma. The capsule formulation utilized in this study was suboptimal due to poor bioavailability, and difficulty administering to children, and is not recommended for future trials. However, this study provides important clinical response data for comparison with data obtained in future trials of novel fenretinide formulations that can achieve higher drug exposures that will be necessary to define the role of fenretinide in therapy for high-risk neuroblastoma.

Disclosure of Potential Conflicts of Interest

Children’s Hospital Los Angeles (CHLA) holds patents and/or patent applications on anticancer therapies using the LYM-X-SORB (LXS) and intravenous emulsion fenretinide formulations. These formulations have been licensed to the company CerBi, Inc. founded by two of the inventors, Barry Maurer and C. Patrick Reynolds (Texas Tech University, Lubbock, Texas). CHLA may benefit financially from the development and future use of these formulations of fenretinide.

Acknowledgments

The authors thank Jeanette Vandergiessen (protocol data manager) and Sharon Bergeron (protocol research nurse) for their efforts during the conduct of this study and COG staff Dana Willis and Rinat Sared for their dedication and efforts in the data management of this study.

Grant Support

This work was supported by the NIH grants U10 CA98413 (COG SDC grant), U10 CA98543 (COG Chair’s grant), CA2820, and P30 CA15083, the Mayo Cancer Center support grant for the Pharmacology Shared Resource, T.J. Martell Foundation for Leukemia, Cancer and AIDS Research, The Bogart Pediatric Cancer Research Program, and by Cancer Prevention & Research Institute of Texas grant RP10072.

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Received April 15, 2011; revised August 10, 2011; accepted August 22, 2011; published OnlineFirst September 9, 2011.

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Clin Cancer Res 2011;17:6858-6866. Published OnlineFirst September 9, 2011.

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