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Phase I Trial and Pharmacokinetics of Fenretinide in Children with Neuroblastoma

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Introduction

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- Neuroblastomas are the second most common malignant tumor in childhood

- Children with this disease have a poor prognosis with the 5 year survival rate being less than 50%

- Even with intense chemoradiotherapy children have a high fatal relapse rate and long term survival rate of merely 25%

Background

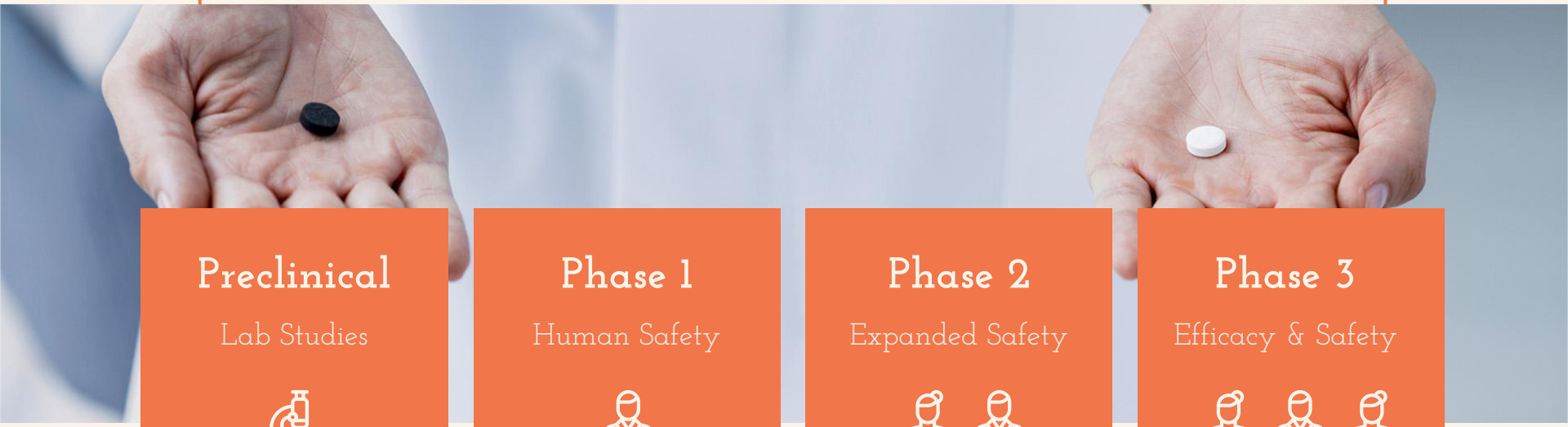
Fenretinide (4HPR)

N-(4-Hydroxyphenyl)- retinamide

Retinoids have been research extensively in vitro regarding neuroblastoma and under recent years have been used in clinical investigation.

In Vitro studies that have been conducted demonstrated that 4HPR can suppress malignant tumor growth associated with induced apoptosis. This includes Neuroblastomas and it is believed that administration of this drug over a long-term period may prevent relapse of the disease. This is essential in Neuroblastoma patients with a high rate of fatal relapse.

Clinical Trial



Preclinical

Lab Studies

Phase 1

Human Safety

Phase 2

Expanded Safety

Phase 3

Efficacy & Safety

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Methods

Patient Eligibility

Table 1 Patient's characteristics at enrollment in the trial

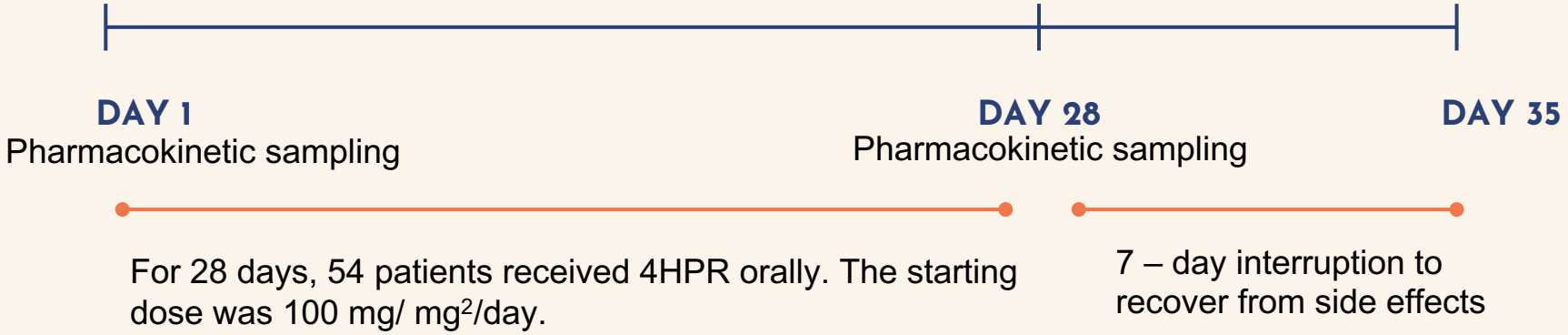
No. of enrolled patients	54
No. of assessable patients	53
No. of assessable courses	168
Median age (yr)	9
Range	2–22
Male/female	34/20
Stage	
3	4
4	50
Previous treatment	
Chemotherapy	54/54
MGT + PBSC[a]	37/54
MIBG therapy or RT	12/54
Status at entry	
First partial remission	20
Second or additional partial remission	20
Second or additional complete remission	5
Resistant disease	9

[a] MGT + PBSC, megatherapy plus peripheral blood stem cell rescue; RT, radiotherapy.

- **Patients older than 12 months with stage 3 or 4 neuroblastomas with a high risk of developing a progressive disease of relapsing**
  - Resistant disease
  - Partial remission at the end of treatment
  - Stage 4 in second or further complete remission

Trial Timeline

This timeline occurred for up to 6 courses, with three patients entering escalating 4HPR levels



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Results and Conclusion

Results

- Toxic effects observed in 34 of 53 patients and most commonly observed were skin xerosis and nyctalopia
- 12 patients showed early progression of the disease during the first course of treatment
- The disease remained stable 24 patients but died after disease progression
- 17 still living patients without disease progression

Conclusion

- It was determined that oral administration oce a day for 28 days followed by a 7 day discontinuation is better tolerated than continuous treatment

- This drug has no effect on patients with massive disease setting (advanced Neuroblastomas and those in relapse)

Patients who were treated with 4HPR in a PR phase showed prolonged stabilization of the disease, and some of them showed regression of some lesions.

Favorable effects occurred more frequently in patients who received doses of 4HPR of 1000 mg/ m2/day or higher and whose plasma levels where above 5 M after repeated treatment.

It can be said that a Phase II study testing 4HPR as possible maintenance therapy for the control of minimal disease in neuroblastoma would be warranted.

Results

Table 2 Toxicity of 4HPR in neuroblastoma patients

Dose level ($mg/m^2/day$)	No. of patients	No. of evaluable courses	Toxicity				
				No. of patients and grade			
			Type	n.a.[a]	1	2	3
100	6	12	Nyctalopia		1		
			Skin rash		1		
200	5	18					
300	4	10	Headache			1	
400	3	10	Nyctalopia			1	
			Headache		1		
500	6	14	Nyctalopia		2		
			Skin xerosis			2	
			Ungual dystrophy		1		
600	4	25	Nyctalopia		1		
			Cholelithiasis	1			
			Freckles	1			
700	3	14	HZV infection	1			
1000	6	21	Nyctalopia		1	2	1
			Skin xerosis		2		
1300	3	12	Nyctalopia		1		
			Skin xerosis		1		
			Ungual dystrophy		1		
1700	3	9	Skin xerosis		1	1	
			Conjunctivitis		1		
2300	3	6	Nyctalopia		1[b]		
			Skin xerosis		1[b]		
3000	3	8	Skin xerosis			3	
4000	4	9	Hepatic toxicity			1	
			Diarrhea		2	1	

[a] n.a., not applicable.
[b] The same patient complained of nyctalopia and skin xerosis.

Discussion Questions

- Do you believe Fenretinide is warranted to use in children with Neuroblastomas?
  - Should there be a Phase II trial as discussed in the conclusion?

- What do you think about drug trials involving children with progressive malignant tumor diseases?

- What do you think should be the next step in the trial, should it be continued?
- What do you think about using retinoids to treat cancer.
- Does the length of a drug trial have any impact on the validity of the results?

Citation

- Alberto Garaventa, Roberto Luksch, Maria Serena Lo Piccolo, Elena Cavadini, Paolo G. Montaldo, Maria Rosa Pizzitola, Luca Boni, Mirco Ponzoni, Andrea Decensi, Bruno De Bernardi, Franca Fossati Bellani, & Franca Formelli. (2003). Phase I Trial and Pharmacokinetics of Fenretinide in Children with Neuroblastoma. ***Clinical Cancer Research***, ***9***(6), 2032–2039.