

Targeted Isotretinoin in Neuroblastoma: Kinetics, Genetics, or Absorption

Katherine K. Matthay^{1,2}

Isotretinoin (13-cis-retinoic acid; 13-cisRA) has been shown to significantly improve survival for children with high-risk neuroblastoma. Pharmacokinetics of isotretinoin may be negatively affected by the mode of drug administration and the dosing formula. *Clin Cancer Res*; 19(2); 311–3. ©2012 AACR.

In this issue of *Clinical Cancer Research*, Veal and colleagues use pharmacokinetically guided dose adjustments to try to achieve peak plasma levels of isotretinoin (13-cisRA) 2 $\mu\text{mol/L}$ or more in children with neuroblastoma (1). Children with high-risk neuroblastoma have a long-term survival of less than 50%, despite the use of intensive multimodality therapy. One component of this therapy is treatment of minimal residual disease with 13-cisRA and monoclonal chimeric anti-GD2 antibody, both of which have been shown to improve outcomes in randomized trials (2, 3). 13-cisRA has been shown to induce differentiation and growth arrest of neuroblastoma cells (4). One hypothesis to explain tumor resistance in patients who relapse after such treatment may be insufficient exposure to 13-cisRA plasma levels to induce these effects. In this study by Veal and colleagues, the ability to adjust plasma levels based on the first course C_{max} to achieve a minimum target level is assessed, with investigation of the effect of clinical and genetic covariates on pharmacokinetics.

Preclinical and clinical studies have suggested that maintenance of adequate 13-cisRA plasma levels is crucial to drug activity. *In vitro* studies in neuroblastoma cell lines showed that sustained growth arrest was obtained by pulse dosing of 5 to 10 $\mu\text{mol/L}$ 13-cisRA (4). A phase I trial then showed mean peak serum levels of 7.2 ± 5.3 with doses of 160 $\text{mg/m}^2/\text{d}$, the maximum-tolerated dose (5, 6). Not surprisingly, a previous study that used lower continuous dosing with 100 mg/m^2 showed little clinical activity (7).

On the basis of these data, a Children's Cancer Group randomized trial of maintenance therapy with 13-cisRA used pulsed dosing at 160 $\text{mg/m}^2/\text{d}$ in 2 divided doses for 14 out of every 28 days. This trial showed a significant improvement in overall survival for children treated with

13-cisRA compared with no maintenance therapy after myeloablative therapy (2, 8). A European randomized trial initiated in 1989, before the North American results were available, used a much lower continuous dosing of 13-cisRA (0.75 $\text{mg/kg/d} \approx 22 \text{ mg/m}^2$) in a double-blind randomized trial (9). This trial showed no benefit, giving further credence to the hypothesis that achieving significant plasma levels was important for efficacy (10).

Veal and colleagues' report in this issue the effect of adaptive dosing on plasma levels of 13-cisRA using adjustment in the second course based on day 14 pharmacokinetics in course 1. The study also attempted to examine potential factors that might affect the plasma level of the 13-cisRA, including clinical features, dose regimen, metabolism, pharmacogenetics, and mode of administration (Fig. 1). Specific details related to mode of administration included swallowing intact capsules versus extracting capsule contents, nasogastric tube versus oral administration, type of food coadministered, and possible drug–drug interactions. Only 2 of these covariates significantly affected pharmacokinetics of the 13-cisRA. As noted in a prior publication by this group (11), swallowing intact capsules compared with extraction of contents was significantly associated with a higher proportion of patients achieving $C_{\text{max}} \geq 2 \mu\text{mol/L}$. Also, the use of weight-based dosing used in infants less than 12 kg resulted in failure to achieve target levels.

The target C_{max} for this study was modest, at 2 $\mu\text{mol/L}$ or more, compared with the 5 to 10 $\mu\text{mol/L}$ range established as effective in preclinical studies, and the mean of 7 $\mu\text{mol/L}$ achieved in the phase I study at the same dose of 160 mg/m^2 . At the end of course 1, 20 (34%) patients failed to achieve the target C_{max} of 2 $\mu\text{mol/L}$ or more, and had their dose increased by 25% to 50%. Of these 20 patients, 12 achieved the target level at the end of course 2, 6 patients required further adjustments in courses 3 and 4, and 2 patients never achieved the target. Grade 3- and 4-related toxicities were rare, and there were no cases of hypercalcemia, a previously reported toxicity with 13-cisRA (6). The lack of toxicity may be related to the low-target dose. There was no correlation with event-free or overall survival to determine any relation of dose to disease outcome, no doubt due to the relatively small sample size.

Author's Affiliations: ¹Department of Pediatrics and Helen Diller Family Comprehensive Cancer Center, University of California San Francisco School of Medicine; and ²UCSF Benioff Children's Hospital, San Francisco, California

Corresponding Author: Katherine K. Matthay, UCSF School of Medicine, 505 Parnassus Avenue, M647, San Francisco, CA 94143. Phone: 415-476-3831; Fax: 415-502-4372; E-mail: matthayk@peds.ucsf.edu

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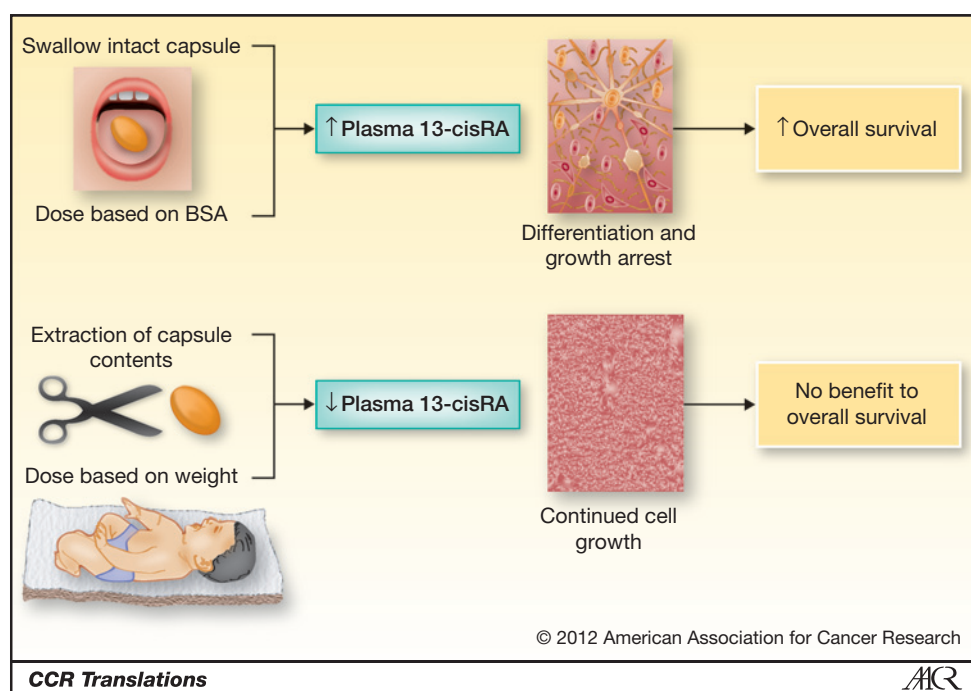


Figure 1. Postulated effect of increasing 13-cisRA plasma levels on outcome for children with neuroblastoma. The significant factors for raising C_{max} plasma levels ≥ 2 $\mu\text{mol/L}$ were the ability to swallow the capsules whole rather than extraction of the contents, and the dosing by body surface area rather than conversion to weight based dosing. No significance was found to age, gender, weight, BSA, alanine aminotransferase (ALT), bilirubin, glomerular filtration rate, creatinine, type of food mixed with capsule contents, use of nasogastric tube, or the pharmacogenetics examined.

Next, the investigators studied whether metabolism or pharmacogenetic variation accounted for the variation in C_{max} . All patients accumulated the 4-oxo-13-cisRA metabolite, with peak levels higher than 13-cisRA by day 14. There was a significant correlation with the day 14 4-oxo-13-cisRA C_{max} for 2 of 6 single-nucleotide polymorphisms with putative relevance to 13-cisRA disposition, but there was not a significant relationship between any of the variants and the 13-cisRA area under the curve (AUC)_{0-6 h}. These data are inconclusive, given the small number of patients and the fact that not all possible genomic variations were tested. More investigation will be necessary to determine whether pharmacogenetics play a significant role in the metabolism of 13-cisRA.

The take-home observations from this study relate to the very wide 20-fold interpatient variability observed in C_{max} without significant relation to either body surface area (BSA) or to weight. However, due to the young age of this population (median 4.3 years), 76 of 103 patients took the drug after extraction of the contents from the capsular formulation. The target C_{max} was achieved by 25 of 27 patients who were able to swallow the capsules, compared with only 42 of 76 (55%) of those who extracted the drug and mixed it with food or gave it via nasogastric tube. Thus, the lack of a child-friendly formulation clearly had a detrimental effect on the attainable plasma levels of 13-cisRA. Furthermore, infants who were dosed by weight rather than BSA also had lower C_{max} . Eight of 11 infants dosed by weight did not achieve $C_{max} \geq 2$ $\mu\text{mol/L}$ until their doses were increased by 25% to 50%. These data strongly suggest that all children should be dosed by BSA regardless of size although the fact that they also had to

extract the drug from the capsules may have confounded this observation.

The Best Pharmaceuticals for Children Act provides a potential remedy to this lack of a pediatric formulation. The National Institute of Child Health and Human Development (NICHD) submitted a draft request, which the U.S. Food and Drug Administration (FDA) issued as a "Written Request" to the pharmaceutical industry to provide data in support of a new indication for isotretinoin for neuroblastoma, and to develop a pediatric formulation. The request was declined by industry and sent to the NICHD. NICHD and National Cancer Institute (NCI) are in the process of submitting the requested efficacy and safety data from NCI/COG trials to the FDA in support of new pediatric labeling for neuroblastoma. The NIH is exploring the development of a pediatric formulation, with support from the Pediatric Subcommittee of the Oncologic Drugs Advisory Committee.

The report by Veal and colleagues makes a number of important contributions relevant to the use of 13-cisRA for children with neuroblastoma, including documentation of the problem of under-dosing infants less than 12 kg by prescribing on a weight basis; confirming previous pharmacokinetic results showing large interpatient variation; and showing that adaptive dosing can safely achieve higher levels through dose escalation. Remaining issues to be resolved with further study are the question of correlating C_{max} with outcome, determination of the lowest acceptable effective C_{max} , and further study of the impact of pharmacogenetics. Most importantly, this study shows that the majority of children with neuroblastoma would benefit from a liquid formulation of 13-cisRA to

achieve effective plasma levels of this agent with proven efficacy.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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