Targeted Isotretinoin in Neuroblastoma: Kinetics, Genetics, or Absorption

Katherine K. Matthay

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 used pharmacokinetically guided dose adjustments to try to achieve peak plasma levels of isotretinoin (13-cisRA) 2 μmol/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 Cmax 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 μmol/L 13-cisRA (4). A phase I trial then showed mean peak serum levels of 7.2 ± 5.3 with doses of 160 mg/m2/d, the maximum-tolerated dose (5, 6). Not surprisingly, a previous study that used lower continuous dosing also showed mean peak serum levels of 13-cisRA (4). A phase I trial then showed mean peak serum levels of 7.2 ± 5.3 with doses of 160 mg/m2/d, the maximum-tolerated dose (5, 6). Not surprisingly, a previous study that used lower continuous dosing also showed mean peak serum levels of 13-cisRA (4). A phase I trial then showed mean peak serum levels of 7.2 ± 5.3 with doses of 160 mg/m2/d, the maximum-tolerated dose (5, 6). Not surprisingly, a previous study that used lower continuous dosing also showed mean peak serum levels of 13-cisRA (4). A phase I trial then showed mean peak serum levels of 7.2 ± 5.3 with doses of 160 mg/m2/d, the maximum-tolerated dose (5, 6).

The target Cmax for this study was modest, at 2 μmol/L or more, compared with the 5 to 10 μmol/L range established as effective in preclinical studies, and the mean of 7 μmol/L achieved in the phase I study at the same dose of 160 mg/m2. At the end of course 1, 20 (34%) patients failed to achieve the target Cmax of 2 μmol/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.
Next, the investigators studied whether metabolism or pharmacogenetic variation accounted for the variation in $C_{\text{max}}$. 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 $C_{\text{max}}$ 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 $C_{\text{max}}$ 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 $C_{\text{max}}$ 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 $C_{\text{max}}$. Eight of 11 infants dosed by weight did not achieve $C_{\text{max}} \geq 2 \mu\text{mol/L}$ 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 $C_{\text{max}}$ with outcome, determination of the lowest acceptable effective $C_{\text{max}}$ 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.

References
Targeted Isotretinoin in Neuroblastoma: Kinetics, Genetics, or Absorption

Katherine K. Matthay


Updated version
Access the most recent version of this article at:
doi:10.1158/1078-0432.CCR-12-3313

Cited articles
This article cites 11 articles, 3 of which you can access for free at:
http://clincancerres.aacrjournals.org/content/19/2/311.full.html#ref-list-1

E-mail alerts
Sign up to receive free email-alerts related to this article or journal.

Reprints and Subscriptions
To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.

Permissions
To request permission to re-use all or part of this article, contact the AACR Publications Department at permissions@aacr.org.