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

Journal
Clinical Cancer Research, 19(2)

ISSN
1078-0432

Author
Matthay, Katherine K

Publication Date
2013-01-15

DOI
10.1158/1078-0432.ccr-12-3313

Peer reviewed

HHS Public Access

Author manuscript

Clin Cancer Res. Author manuscript; available in PMC 2018 April 10.

Published in final edited form as:

Clin Cancer Res. 2013 January 15; 19(2): 311–313. doi:10.1158/1078-0432.CCR-12-3313.

Targeted isotretinoin in neuroblastoma: Kinetics, Genetics or Absorption

Katherine K. Matthay, MD

Department of Pediatrics and Helen Diller Family Comprehensive Cancer Center, University of California San Francisco School of Medicine and UCSF Benioff Children's Hospital, San Francisco, CA

SUMMARY

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.

In this issue of *Clinical Cancer Research*, Veal et al use pharmacokinetically-guided dose adjustments to try to achieve peak plasma levels of isotretinoin (13-cisRA) ≥2 μM 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 et al, 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 co-variates 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 5–10 micromolar 13-cisRA (4). A phase I trial then demonstrated mean peak serum levels of 7.2 ±5.3 with doses of 160 mg/m^2/day, 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).

Based on these data, a Children's Cancer Group randomized trial of maintenance therapy with 13-cisRA used pulsed dosing at 160 mg/m^2/day in two 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 to no maintenance therapy after myeloablative therapy (2, 8). A European randomized trial initiated in 1989, before the North American results were

Corresponding Author: Katherine K. Matthay, MD, UCSF School of Medicine, 505 Parnassus Avenue, M647, San Francisco, CA 94143-0106, Telephone: 415-476-3831, Facsimile: 415-502-4372, matthayk@peds.ucsf.edu.

I have no conflicts of interest

available, used a much lower continuous dosing of 13-cisRA (0.75 mg/kg/day ≈ 22 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 et al 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 (Figure). Specific details related to mode of administration included swallowing intact capsules vs. extracting capsule contents, nasogastric tube versus oral administration, type of food co-administered, and possible drug-drug interactions. Only two of these covariates significantly affected pharmacokinetics of the 13-cisRA. As noted in a prior publication by this group (11), swallowing intact capsules compared to extraction of contents was significantly associated with a higher proportion of patients achieving $C_{max} \geq 2$ μM. Also, the use of weight-based dosing used in infants <12 kg resulted in failure to achieve target levels.

The target C_{max} for this study was modest, at ≥ 2 μM, compared to the 5–10 μM range established as effective in pre-clinical studies, and the mean of 7 μM 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 μM, and had their dose increased by 25–50%. 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_{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 two of the six SNPs with putative relevance to 13-cisRA disposition, but there was not a significant relationship between any of the variants and the13-cisRA $AUC_{0–6h}$. 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 inter-patient 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 the 103 patients took the drug after extraction of the contents from the capsular formulation. The target C_{max} was achieved by 25/27 patients who were able to swallow the capsules, compared to only 42/76 (55%) of those who extracted the drug and mixed it with food or gave it via NG 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 $C_{max} \geq 2\mu M$ until their doses were increased by 25–50%. 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 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 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 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 <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 demonstrates that the majority of children with neuroblastoma would benefit from a liquid formulation of 13-cisRA in order to achieve effective plasma levels of this agent with proven efficacy.

Acknowledgments

This work was supported in part by National Cancer Institute P01 81403 and the Dougherty and Campini Foundation.

References

1. Veal GJ, Errington J, Rowbotham SE, Illingworth NA, Malik G, Cole M, et al. Adaptive dosing approaches to the individualization of 13-cis-retinoic acid (isotretinoin) treatment for children with high-risk neuroblastoma. Clinical Cancer Research. 2012 in press.
2. Matthay KK, Villablanca JG, Seeger RC, Stram DO, Harris RE, Ramsay NK, et al. Treatment of high-risk neuroblastoma with intensive chemotherapy, radiotherapy, autologous bone marrow transplantation, and 13-cis- retinoic acid. Children's Cancer Group. N Engl J Med. 1999; 341:1165–73. [PubMed: 10519894]
3. Yu AL, Gilman AL, Ozkaynak MF, London WB, Kreissman SG, Chen HX, et al. Anti-GD2 antibody with GM-CSF, interleukin-2, and isotretinoin for neuroblastoma. N Engl J Med. 2010; 363:1324–34. [PubMed: 20879881]
4. Reynolds CP, Kane DJ, Einhorn PA, Matthay KK, Crouse VL, Wilbur JR, et al. Response of neuroblastoma to retinoic acid in vitro and in vivo. Prog Clin Biol Res. 1991; 366:203–11. [PubMed: 2068138]
5. Khan AA, Villablanca JG, Reynolds CP, Avramis VI. Pharmacokinetic studies of 13-cis-retinoic acid in pediatric patients with neuroblastoma following bone marrow transplantation. Cancer Chemother Pharmacol. 1996; 39:34–41. [PubMed: 8995497]

6. Villablanca JG, Khan AA, Avramis VI, Seeger RC, Matthay KK, Ramsay NK, et al. Phase I trial of 13-cis-retinoic acid in children with neuroblastoma following bone marrow transplantation. J Clin Oncol. 1995; 13:894–901. [PubMed: 7707116]

7. Finklestein JZ, Krailo MD, Lenarsky C, Ladisch S, Blair GK, Reynolds CP, et al. 13-cis-retinoic acid (NSC 122758) in the treatment of children with metastatic neuroblastoma unresponsive to conventional chemotherapy: report from the Childrens Cancer Study Group. Med Pediatr Oncol. 1992; 20:307–11. [PubMed: 1608352]

8. Matthay KK, Reynolds CP, Seeger RC, Shimada H, Adkins ES, Haas-Kogan D, et al. Long-term results for children with high-risk neuroblastoma treated on a randomized trial of myeloablative therapy followed by 13-cis-retinoic acid: A Children's Oncology Group study. Journal of Clinical Oncology. 2009; 27:1007–13. [PubMed: 19171716]

9. Kohler JA, Imeson J, Ellershaw C, Lie SO. A randomized trial of 13-Cis retinoic acid in children with advanced neuroblastoma after high-dose therapy. Br J Cancer. 2000; 83:1124–7. [PubMed: 11027423]

10. Matthay KK, Reynolds CP. Is there a role for retinoids to treat minimal residual disease in neuroblastoma? [In Process Citation]. Br J Cancer. 2000; 83:1121–3. [PubMed: 11027422]

11. Veal GJ, Cole M, Errington J, Pearson AD, Foot AB, Whyman G, et al. Pharmacokinetics and metabolism of 13-cis-retinoic acid (isotretinoin) in children with high-risk neuroblastoma - a study of the United Kingdom Children's Cancer Study Group. British journal of cancer. 2007; 96:424–31. [PubMed: 17224928]

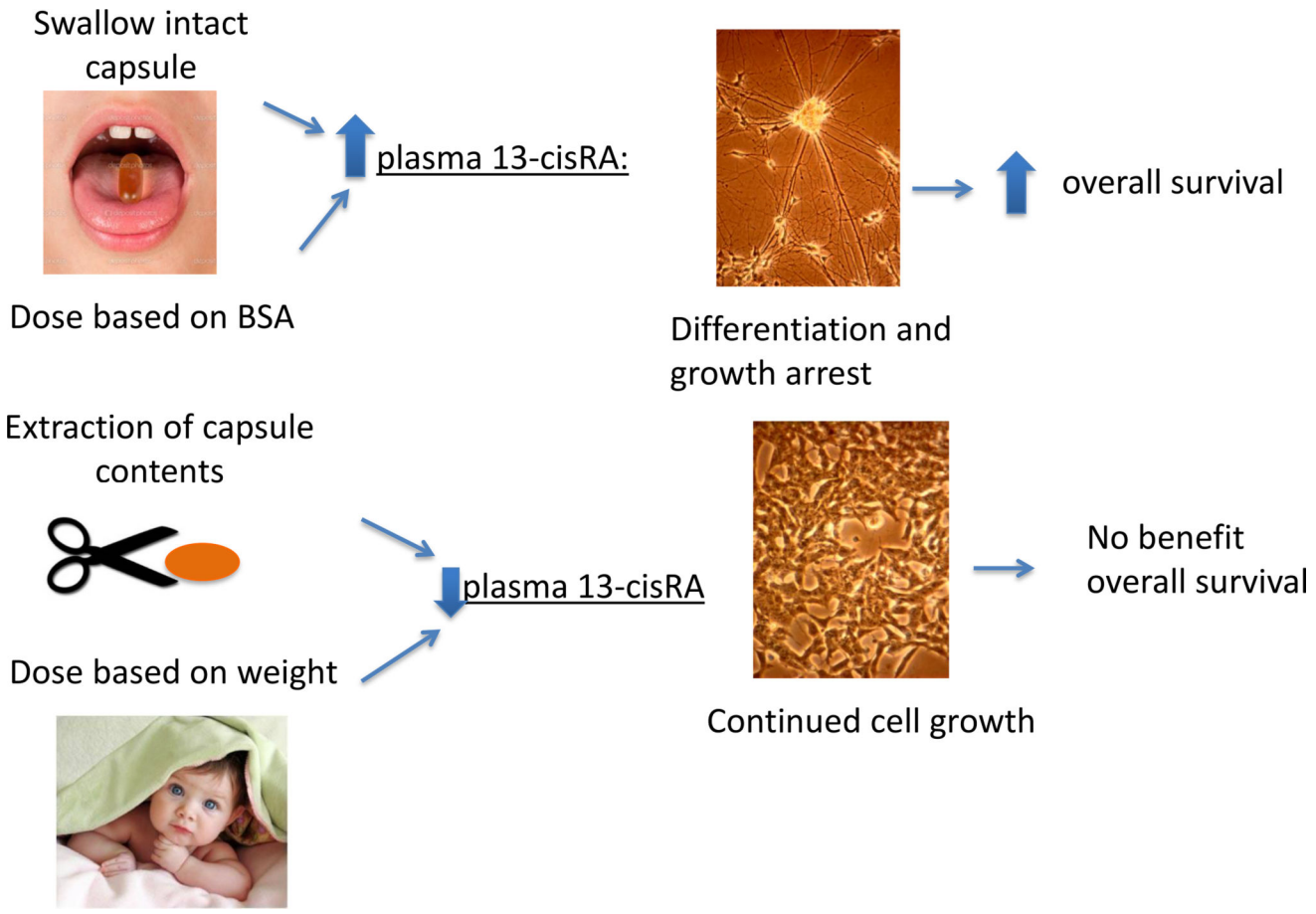

Figure.

Postulated effect of increasing 13-cisRA plasma levels on outcome for children with neuroblastoma. The significant factors for raising Cmax plasma levels ≥ 2 μM 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, ALT, bilirubin, GFR, creatinine, type of food mixed with capsule contents, use of NG tube, or the pharmacogenetics examined.