

IMPROVING THE EFFECTIVENESS OF TUMOR TARGETED MIBG THERAPY FOR PATIENTS WITH NEUROBLASTOMA

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The New Approaches to Neuroblastoma Therapy Consortium (NANT; www.nant.org) is a group of 15 university children's cancer centers dedicated to improving the survival of children with neuroblastoma. We conduct clinical trials to test new therapies that are active in the laboratory and shown to be targeted to the tumor or its environment. We are requesting funding for our new study, "NANT07-03, Vorinostat with ¹³¹I-MIBG Therapy for Resistant or Relapsed Neuroblastoma".

MIBG contains radioactive iodine-131 and when given by vein is taken up by neuroblastoma but not by normal cells and so provides a way to administer radiation therapy to tumor sites throughout the body with minimal side effects upon normal tissues. We know that MIBG therapy is one of the most effective agents for patients with relapsed or resistant neuroblastoma as we have shown that 37% of patients treated with MIBG respond to this therapy with tumors that get smaller or disappear. We are now working to improve upon this therapy by adding a new drug named vorinostat that we believe will make MIBG work better against tumor cells.

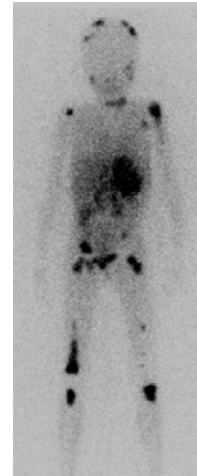
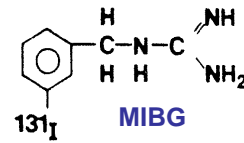
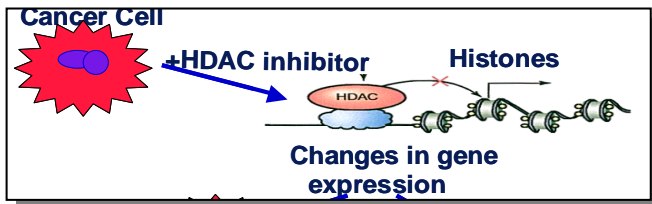
In this study, we will evaluate whether vorinostat will improve the effectiveness of the MIBG therapy without increasing side effects. Vorinostat is a drug that is taken by mouth that is approved for some adult cancers and has been tested in children to determine the safe dose. Vorinostat is a histone deacetylase inhibitor, and therefore affects the way the DNA that carries our genes is folded into cells; hence whether genes are sending their message or are silent. Vorinostat slows the growth of neuroblastoma tumors in the laboratory and has also been shown to make neuroblastoma more sensitive to the effects of radiation therapy. Vorinostat also causes neuroblastoma cells to make more of the "transporter" that MIBG uses to get into the cells. We therefore believe that vorinostat will make MIBG more effective in two different ways: 1) by making the neuroblastoma cells more likely to die when exposed to the radiation delivered by MIBG and 2) by making the neuroblastoma cells accumulate more of the MIBG. The ideas behind this study and a scan of a child whose neuroblastoma tumors have taken up MIBG is shown in the accompanying figure.

Summary. This NANT Study 07-03 is the first to combine MIBG with vorinostat to attempt to improve upon the efficacy of MIBG therapy. We expect to treat approximately 24 to 36 patients over a period of two years. If this new treatment combination is successful, it will make one of our best neuroblastoma therapies even more effective.

Donations:

**New Approaches to Neuroblastoma Therapy (NANT) Consortium
c/o Claudia Looney, Sr Vice President Foundation
Children's Hospital Los Angeles
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NANT 07-03: ^{131}I -MIBG + Vorinostat



MIBG scan of child with widespread tumors in bones and abdomen, shown by the dark spots.

- **Neuroblastoma** - tumor of sympathetic nervous system with poor survival
- **^{131}I -MIBG** - radioactive chemical that is taken up specifically into neuroblastoma via the norepinephrine transporter (NET)
- **Vorinostat** – histone deacetylase (HDAC) inhibitor that slows neuroblastoma tumor growth, sensitizes tumor to radiation and increases uptake of MIBG by increasing the NET transporter
- **N07-03** will test the hypothesis that vorinostat with MIBG will improve tumor response for neuroblastoma by increasing uptake and enhancing radiation effect of MIBG