BACKGROUND

Approximately 50% of children with acute myeloid leukemia (AML) will become long-term survivors after treatment with chemotherapy. One drug, cytosine arabinoside (cytarabine or Ara-C), is a key element in achieving cure, and has been tested in serial clinical trials in combination with other drugs to achieve the successes seen with current therapy. Despite this progress, and despite the administration of uniform drug regimens in well-conducted national clinical trials, a proportion of children with AML still die from toxic side effects of therapy, and a larger number still relapse. Understanding the basis for this inter-individual variation in response to therapy will help extend cure to these groups of patients.

EXPERIMENTAL DESIGN

In this proposal, we have selected two complementary approaches to identify which inherited differences in our genes determine how a child responds to the drug cytarabine. In our first approach, we will test each child's DNA for variations in genes known to be important in how cytarabine is metabolized or utilized by our bodies. We know, however, that this small group of previously studied genes is not the only important factor in how this drug affects each person differently. Many unknown mechanisms in the body which are controlled by a variety of genes also play a role. That is why we are using a second approach as well. In this approach, we will use data from an already completed study that used a large database to examine all of the gene variations among humans to find those associated with response to cytarabine in a laboratory cell model. This study performed by our co-investigator and collaborator, Dr. Eileen Dolan, identified over 100 new inherited differences or gene variations. These gene variations discovered using this laboratory assay influenced the ability of the drug to kill the white blood cell lines (the cells from which AML cells are derived). Using this data, we will test each child for these newly discovered gene variants and be able to evaluate which of these may impact how a child may respond to the chemotherapeutic agent, cytarabine. We will use a new technology, OpenArray, which allows us to use a very small, previously collected and stored sample of DNA to determine which variations are present in each of the almost 500 children treated for AML. We will compare this information with each child's clinical outcome data to determine which gene variants from both approaches are important to chemotherapy response and cure. The combination of the two approaches described above allows for the potential development of the most comprehensive model that can predict responsiveness to cytarabine. If successful, these data will be used in future clinical studies to assign children to the appropriate drugs and doses.

SIGNIFICANCE

Progress in treating childhood cancer has been achieved with more than 30 years of clinical trials that have applied the discipline of giving uniform therapy to all children to allow progress to be made. To make further progress, such that all children with AML are cured, we now need to understand the variations in genetics in each child to allow us to individualize therapy for the children not cured with current regimens. Knowledge of genetic characteristics that predict either excessive side effects, or inadequate therapy (relapse) at the time of diagnose will allow better selection of therapy and will improve survival.