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## COG UPDATE ON PEDIATRIC CANCER RESEARCH

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In children less than 15 years of age, cancer differs considerably from cancer in adults. These differences include the kinds of cancer, the incidence rates, the symptoms that children experience and the ways in which they respond to treatment. When it comes to cancer, children are not miniature adults, and they need to be treated in centers that have expertise in pediatric malignancies.

Fortunately, the overwhelming majority of children are treated in comprehensive pediatric cancer centers that are active participants in the Children's Oncology Group (COG), which is an NCI-sponsored cooperative group for the treatment of all types of pediatric cancer. Formed in 2000, COG's mission is to cure and prevent childhood and adolescent cancer through scientific discovery and compassionate care. COG presents pediatric cancer specialists with a consolidated, unified, North-America-based clinical trials consortium focused on the treatment of all pediatric malignancies. COG also actively participates with centers in Australia, New Zealand and Europe, because with the rare nature of some pediatric cancers, this is the most effective way to conduct clinical trials and improve the outcome of all children with cancer.

Overall, adults get cancer more often than children. In pediatric cancer, the specific types of cancer are related to the age of the child. In general, pediatric malignancies tend to be associated with shorter latency periods, grow rapidly and are often widespread at the time of presentation.

In the last several decades, enormous progress has been made in understanding the biology of pediatric cancers and developing improved methods of treating many of these tumors. Largely through the efforts of COG, the overall prognosis for pediatric cancers has improved from a nearly uniformly fatal disease for all tumor types in 1955 to one in which more than 78% of children are expected to achieve a disease survival of five years. Since the mid 1970's, there has been a 25% decrease in mortality.

That progress continues today. The Children's Oncology Group continues to make substantial research progress, to improve treatments and find more cures for children

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diagnosed with cancer. Current research focuses on discovering new and better treatments for difficult to treat cancers with five-year survival rates of less than 50%. Researchers in COG also seek to expand risk-adjusted therapy approaches to disease, explore opportunities for targeted therapy, increase survivorship and cancer control research, increase translational studies (from the lab to the bedside) and support more investigation into rare cancers.

One area of significant improvement over the last 20 years has been in the therapy for standard and high-risk Acute Lymphocytic Leukemia (ALL). Advances include better genetic classification of leukemia sub-types, evaluation of minimal residual disease (MRD) and intensified therapy post-induction. COG has proven the value of escalating dose methotrexate for interim maintenance in standard risk patients, has validated the use of augmented therapy for initial poor response to therapy in ALL and has utilized MRD in blood and bone marrow to identify and treat these patients.

The study of the biology of ALL by COG investigators has also identified genetic expression signatures that predict early response and survival in the context of current chemotherapy. In patients with Ph+ chromosome ALL, the use of targeted biologic therapy has produced significant improvement in disease free survival for a type of leukemia that has been resistant to conventional chemotherapy. Perhaps the most significant development in the classification of the risk categories in ALL, which builds on all of the recent studies, has been the ability to identify a group of patients that with minimal therapy have cure rates exceeding 95%.

In acute myelogenous leukemia (AML), targeted therapy with monoclonal antibody has pushed survival rates over 50%. New biologic markers are also being identified to further improve survival.

In neuroblastoma, traditionally a difficult tumor to treat, immunotherapy and retinoic acid have increased disease-free survival by 20% following stem cell transplant in high risk patients. This study was built on previous findings of the benefit of retinoic acid treatments in the minimal disease setting post autologous transplant. There is an international collaboration to improve classification and predictors for outcome in neuroblastoma that will allow patients to be treated effectively.

In localized Ewing's sarcoma, intensified timing has not only decreased the timeline for therapy but improved the outcome. Novel targeted therapies are now under consideration or study for infant leukemia, rhabdomyosarcoma and acute myelogenous leukemia. Patients with Hodgkin's lymphoma are receiving therapy with dose dense regimens, short duration and based on early response.

In the future, COG plans to continue its research into the genetic component of pediatric tumors and leukemias. To do this, we will utilize the pediatric cancer bio-specimen repository to identify specific gene defects which could be used for targeted therapies. The TARGET project, in collaboration with the NCI, is planning studies in ALL, neuroblastoma, sarcomas and brain tumors that will help predict outcome at

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diagnosis and hopefully allow clinicians to tailor therapy to prevent relapse.

With our improvement in overall survival, we now have a large group of survivors who face a broad range of long-term effects of their disease and treatment. To address the particular and unique medical needs of these young patients, the COG has provided the medical community with evidence-based, comprehensive long-term follow-up guidelines for childhood cancer survivors.

Lastly, given that most children with cancer will be treated at institutions that are members of the COG, the new initiative – the North American Childhood Cancer Research Network (CCRN) – represents an opportunity for pediatric cancer research. The CCRN will provide the potential for integrated research into genetic alterations that influence treatment outcomes, clinical trials based on tumor profiling of individual patients or groups of patients and epidemiologic studies that identify patterns of pediatric malignancy across the member institutions. The CCRN was initiated in January 2008 in the COG and all of its North American institutions.

Clearly, continued progress in improving the outcome of childhood cancer requires the coordinated integration of correlative biology studies with well controlled clinical trials, the translation of basic molecular genetics into refinement of risk groups, development of risk-adjusted therapy, and ultimately, therapy targeted to specific molecular lesions. With successful therapy, we have long-term survivors, and will continue to provide them with guidelines for their future medical care through the COG's long term follow-up program.

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