Introduction/Meeting Description

Experts in the field of neuroblastoma have identified that the most pressing need to address in order to make progress through clinical trials in the treatment and outcome for children with neuroblastoma is to revise the International Neuroblastoma Response Criteria (INRC). The National Cancer Institute (NCI) Pediatric and Adolescent Solid Tumor Steering Committee (PASTSC) convened an international consensus meeting to revise the International Neuroblastoma Response Criteria (INRC) on April 12-13, 2012 in Washington, DC. The objectives of this meeting were:

- to establish consensus on methodology for measuring soft tissue disease response, quantification of metastatic disease (including $^{123}$I-MIBG), and for assessment of bone marrow disease;
- to propose revised criteria for complete and partial response to therapy based on such assessments;
- to assess response data and/or genetic data to define an ultra high risk neuroblastoma cohort;
- to evaluate whether appropriate data exists to incorporate FDG-PET imaging into response criteria;
to establish whether the same criteria for response assessment at diagnosis can be used in the setting of recurrent neuroblastoma.

In advance of the meeting, several working groups were organized in order to focus on individual objectives. Through a series of regular teleconferences, the Working Groups gathered available data and new data in order to support their recommendations. These recommendations were discussed at the meeting.

**Background/Importance of Research Topic/Disease/Limitations**

Neuroblastoma, a cancer of the sympathetic nervous system responsible for 12% deaths associated with cancer in children less than 15 years of age, is a heterogeneous disease with nearly 50% of patients having a high risk phenotype characterized by widespread dissemination of the cancer, and poor long term survival. Although current therapy consisting of aggressive multiagent chemotherapy, surgery, myeloablative therapy, autologous stem cell transplantation, external beam radiation, biologic agent and immunotherapy has resulted in an improved overall survival from high risk neuroblastoma, nearly 50% of children still succumb to disease. More than 20% of patients experience progressive disease or inadequate response to initial therapy while another 30% of patients develop recurrent disease, typically presenting as bone and bone marrow disease. New therapeutic approaches must build from prior randomized clinical trials and ideally utilize collaborative international clinical trials to efficiently advance therapy for patients classified as high risk.

The International Neuroblastoma Response Criteria (INRC) were last updated in 1993 and has significant limitations in accurately defining response at metastatic sites of disease specifically bone and bone marrow.\(^{(1-5)}\) It provides limited guidance in incorporating currently standard imaging modalities (\(^{123}\)I-MIBG imaging), no guidance for incorporation of FDG-PET or for evolving molecular markers(quantification of marrow disease).\(^{(6-9)}\) Current response criteria for recurrent solid tumors are based on cross sectional imaging of measurable disease. Because recurrence of neuroblastoma primarily occurs at metastatic disease sites that cannot be measured
by cross sectional imaging the ability to assess the activity of novel therapeutic agents in this population of patients is compromised. There is also a lack of consensus regarding the definition of high risk neuroblastoma treatment failure, further limiting international clinical trial collaboration.

Consensus & Recommendations

Important advances in imaging modalities have been made since the last major update to the INRC in 1993, namely the availability of high quality MIBG imaging at most treatment centers and the development of scoring systems (Curie and SIOPEN) for response assessment that permit within patient and across trial comparisons. A consensus on the use of such systems and their applicability to currently established response criteria is desirable. Moreover, technical advances in immunocytochemistry and RT-qPCR have improved the detection and quantification of bone marrow disease, yet a consensus on how to apply such measures uniformly is lacking.

Data were presented and analyzed from the Children’s Oncology Group, SIOPEN and GPOH contemporary clinical trials of treatment responses in both newly diagnosed neuroblastoma patients and recurrent disease patients. Revision of the INRC will address the following individual response criteria; primary tumor dimensions, metastatic disease assessment by \( ^{123} \text{I-MIBG} \) imaging and bone marrow morphologic assessment. \( ^{123} \text{I-MIBG} \) and PET scans (PET is recommended when MIBG of the primary site is negative) will replace bone scan for assessment of metastatic bone disease. Response criteria will be defined as complete response, partial response, minor response, stable disease, and progressive disease. Consistent criteria for eligibility and assessment of response across Phase 2 trials were proposed and agreed upon. Numerous proposals were presented to address common usage of MIBG and PET scans for soft tissue response and criteria for quantification of bone marrow disease. Finally, the meeting participants proposed a work plan to identify and characterize a cohort of patients that is non-responsive to current high risk therapy, tentatively defined as "ultra high risk". At present the only such measure to identify this group of patients is disease progression. The aim is to identify clinical and/or genetic determinants for the purpose of prospectively identifying such patients at
the time of diagnosis in order to redirect therapy. The agreed upon plan consists of an analysis of tumor samples from among the various international groups, collection of genetic and genomic data, and integration with bone marrow and imaging data.

This Executive Summary presents the consensus arising from the CTPM. These recommendations are not meant to address all clinical contexts, but rather represent priorities for publicly funded clinical research.

Anticipated Action(s)

Meeting participants will reconvene at the Advances in Neuroblastoma Research meeting (ANR, June 2012), with the aim of presenting the proposed revisions to INRC to the broader neuroblastoma research community. The final consensus criteria for overall response and measurement of soft tissue disease are anticipated to be completed and presented at the International Society for Pediatric Oncology meeting (SIOP, October 2012) and submitted for publication shortly thereafter. A timeline and strategy for data analyses of MIBG scoring systems and identification of markers for ultra high risk are expected to be finalized by December 2012. Numerous manuscripts are planned to describe the results of this meeting.

References