CHILDREN'S ONCOLOGY GROUP

The world's childhood cancer experts

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CCG-3891 Long Term Outcome for Children with High Risk Neuroblastoma
Additional Information on Corrected Overall Survival Results

April 10, 2014

The Children's Oncology Group (COG) has discovered two analytical errors in our 2009 publication (J Clin Oncol 27:1007-1013, 2009) describing the long-term outcome for children with high-risk neuroblastoma enrolled on CCG-3891, *Conventional Dose Chemoradiotherapy vs Ablative Chemoradiotherapy With Autologous BMT for High-Risk Neuroblastoma*. These errors were in the calculation of statistical test results related to overall 5-year survival for children enrolled on this study. A letter correcting these has been submitted for publication to the *Journal of Clinical Oncology*.

The following questions and answers relate to the correction, ongoing clinical trials, and current standard therapy for children with high-risk neuroblastoma.

What were the findings for CCG-3891 as originally published in 1999?

The primary study question for Children's Cancer Group (CCG) study 3891 was to determine whether autologous bone marrow transplant (ABMT) improved event-free survival (EFS) at three years from diagnosis for children with high-risk neuroblastoma. A second study question was whether maintenance therapy with isotretinoin, also known as 13-cis-retinoic acid or Accutane®, was more effective than observation after consolidation therapy. In 1999, the results of this study were published in the *New England Journal of Medicine (N Engl J Med* 1999:341(16):1165-1173).

For the comparison of ABMT versus continuation chemotherapy, EFS at three years was significantly improved with the use of ABMT (34 ± 4% vs. 22 ± 4%, P=0.034). For the evaluation of isotretinoin versus observation as maintenance therapy, the EFS rate at three years was significantly higher for patients receiving isotretinoin compared to no further therapy (46 ± 6% vs. 29 ± 5%, P=0.027). These results, which were important in establishing ABMT and isotretinoin as components of standard therapy for children with high-risk neuroblastoma, were confirmed by recent independent statistical review of the trial data and are not in question.

Why was event free survival (EFS) used as the endpoint for this study?

Similar to almost all phase 3 clinical trials conducted in children with cancer, CCG-3891 was designed to define a meaningful improvement in EFS (disease progression, relapse, or death from toxicity), but was not designed to detect a statistically significant improvement in overall survival (OS).

In phase 3 trials for children with cancer, EFS (or the related progression free survival, PFS) is used as an endpoint because for certain diseases, children can survive for an extended period of time after the initial event (relapse), usually receiving additional types of treatment. If OS were used as the primary endpoint, these additional treatments could impact on our ability to know the true effect of the original treatment; this does not occur when using EFS as the primary endpoint. In addition, EFS is considered an excellent predictor for the effects of treatment intervention because for many cancers, including high risk neuroblastoma, few children who experience disease progression/relapse (an event) ultimately survive. Importantly, if OS were used as the

primary endpoint for a study, many more children would have to be enrolled onto the clinical trial and followed for significantly longer periods of time, potentially delaying determining whether the new treatment was of benefit. For children with high risk neuroblastoma, nearly a decade would be required for a clinical trial to assess OS given the low incidence of neuroblastoma.

What were the two analytical errors made in the 2009 publication of CCG-3891 and what do the corrected analyses show?

The analytical errors in the 2009 publication (J Clin Oncol 27:1007-1013, 2009) were in the calculation of p-values related to overall survival estimates at the 5-year time point:

- For the comparison of overall survival (OS) at 5-years for isotretinoin *versus* no isotretinoin, the correct p-value is p=0.11 and not p=0.0006.
- For the comparison of OS at 5-years for autologous bone marrow transplant (ABMT) *versus* continuing chemotherapy (CC), the correct p-value is p=0.08 and not p<0.0001.

The survival curves and all other statistical analyses published in this manuscript have been independently reviewed and confirmed.

How were the analytical errors discovered?

In 2008, FDA released a Pediatric Study Request for the development of an isotretinoin liquid formulation that additionally included a request for submission of CCG-3891 data to FDA. NICHD, working through the Best Pharmaceuticals for Children Act (BPCA), had a contractor collect data from COG for patients enrolled on CCG-3891 so that a Clinical Study Report (CSR) could be prepared to submit to FDA. It was in the process of preparing the CSR that the contractor identified the discrepancy between their test of significance for the isotretinoin overall survival results and those published by COG in the 2009 article. Upon evaluation of this discrepancy by COG statisticians, in consultation with NCI statisticians, the error in the isotretinoin overall survival calculation was confirmed and the error in the ABMT overall survival calculation was discovered.

What is COG doing to prevent similar mistakes in the future?

The COG Statistics and Data Center (SDC) has determined that the primary cause of these two analytical errors relate to the use of custom programming code (for an analytical method previously unused by COG) that had not been subjected to COG's standard validation procedures. A corrective action plan is being implemented to minimize the likelihood of such errors occurring again.

Who has reviewed the corrected analyses to evaluate their impact on ongoing COG clinical trials?

In April 2014, the COG *Neuroblastoma Steering Committee* reviewed all data from CCG-3891, alongside other relevant data related to the administration of isotretinoin or ABMT for children with high risk neuroblastoma, and developed recommendations that were reviewed and approved by COG leadership.

In April 2014, the COG Data and Safety Monitoring Committee (DSMC) also reviewed and discussed the CCG-3891 corrected analyses. The study was discussed in the context of new information relevant to ongoing COG neuroblastoma clinical trials that utilize isotretinoin or ABMT:

- ANBL0032: *Isotretinoin With or Without Monoclonal Antibody Ch14.18, Aldesleukin, and Sargramostim Following Stem Cell Transplant in Treating Patients With Neuroblastoma*.
- ANBL09P1: *Induction Therapy Including 131 I-MIBG and Chemotherapy in Treating Patients With Newly Diagnosed High-Risk Neuroblastoma Undergoing Stem Cell Transplant, Radiation Therapy, and Maintenance Therapy With Isotretinoin.*
- ANBL12P1: *Busulfan, Melphalan, and Stem Cell Transplant After Chemotherapy in Treating Patients With Newly Diagnosed High-Risk Neuroblastoma.*

The recommendation of the DSMC was that the risk-benefit ratio for these three trials was unchanged by the corrected analytical results and that no modifications in the clinical trials were required.

The NCI has reviewed the recommendations of the COG committees as described above and will work with COG on implementation of a corrective action plan to minimize the likelihood that analytical errors occur in the future.

What is the current standard of care for patients with newly diagnosed high-risk neuroblastoma in 2014?

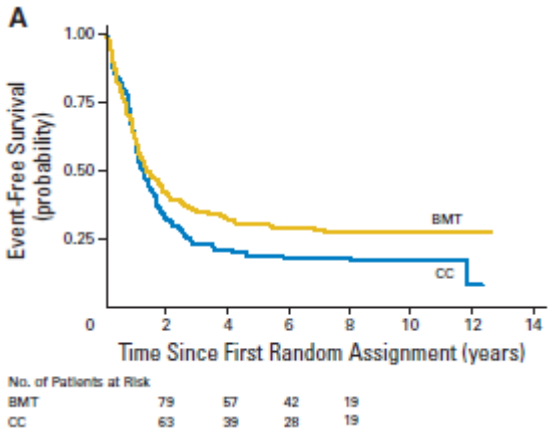
The current standard of care for children with newly diagnosed neuroblastoma begins with an assessment of the risk of treatment failure, an assessment currently based on clinical characteristics (e.g., age and extent of disease), pathological characteristics, and biological characteristics of the cancer cells (e.g., extra copies of the MYCN gene).

The standard treatment approach in the US and Canada for children with high risk neuroblastoma is based on results from prior COG clinical trials, including CCG-3891, and on three other randomized clinical trials in patients with high risk neuroblastoma. Treatment (i) begins with an induction phase of multi-agent chemotherapy, (ii) is followed by a consolidation phase that includes ABMT and radiation to the primary tumor area, and (iii) is then followed with a regimen that includes ch14.18, an anti-GD2 monoclonal antibody, and isotretinoin.

What is the impact of the corrected statistical analysis in defining for the role of ABMT in the treatment of children with high-risk neuroblastoma?

The COG DSMC, the COG Neuroblastoma Committee and COG leadership independently determined that the corrected analyses of OS for CCG-3891 should not change the standard of care recommendations for high risk neuroblastoma and do not impact ongoing clinical trials. The primary objective of the CCG-3891 clinical trial was to evaluate the effect of ABMT on EFS, and both published manuscripts confirm the clinical benefit of ABMT.

The figure below shows the Kaplan-Meier curve for EFS for patients randomized to ABMT versus conventional chemotherapy as correctly published in the 2009 and illustrates the approximately 11% higher EFS at 5 years for children receiving ABMT on CCG-3891 (30 ± 4% versus 19 ± 3%, p = 0.04). The corrected statistical analysis for OS is consistent with a potential trend toward improvement in OS at 5 years for children receiving ABMT on CCG-3891 (39 ± 4% versus 30 ± 4%, p = 0.08).



The CCG-3891 study is not the only randomized clinical trial data supporting a benefit for ABMT for children with high-risk neuroblastoma. Other clinical trials that support a benefit for transplant are listed below:

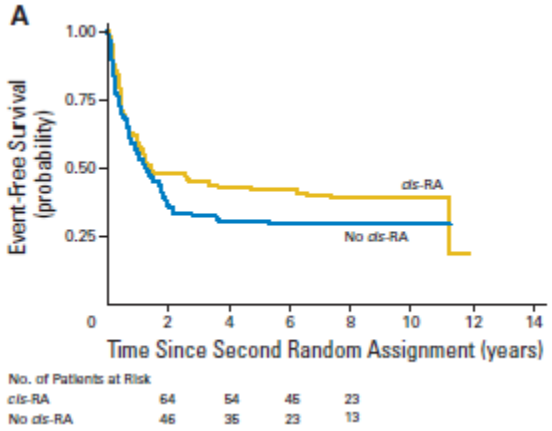
- The ENSG1 study compared high-dose melphalan to no further treatment. This small study (approximately 30 patients per arm) conducted in the 1980s showed evidence for benefit with long-term follow-up, particularly for patients with age > 1 year and Stage IV disease [Pritchard J, et al. Pediatr Blood Cancer 2005:44(4):348-357].

- A German study conducted between 1997 and 2002 randomized high-risk neuroblastoma patients to ABMT versus maintenance chemotherapy [Berthold F, et al. Lancet Oncol 2005:6(9):649-658]. The primary endpoint was EFS, and a significant difference in EFS was observed using an intent to treat analysis.

- A SIOPEN study that was reported at the Plenary Session at ASCO in 2011 compared two different preparative regimens [Busulfan and melphalan (Bu-Mel) versus carboplatin, etoposide, and melphalan (CEM)]. The latter regimen is the standard preparative regimen used in recent COG clinical trials. The Bu-Mel regimen had a significantly superior EFS in comparison to the CEM regimen, implying that therapeutic interventions associated with ABMT can improve outcome [Ladenstein RL, et al. J Clin Oncol 2011:29:(suppl; abstr 2)].

What is the impact of the corrected statistical analysis in defining the role of isotretinoin (13-cis-retinoic acid) for children with high risk neuroblastoma?

Isotretinoin has been a component of standard therapy for high-risk neuroblastoma for over a decade, based on the intended primary analysis of the CCG-3891 results. The long-term analysis results, while not meeting statistical significance as defined by a p value of < 0.05, may be consistent with a trend toward improvement in EFS for those children receiving isotretinoin, but no statistically significant improvement in OS has been observed. The figure below shows the Kaplan-Meier curve for EFS in children receiving maintenance therapy with isotretinoin versus those proceeding to observation as correctly published in 2009 and illustrates the approximately 11% higher EFS rate at 5 years for those receiving isotretinoin (42 ± 5% versus 31 ± 5%, p=0.08).



Neither the COG DSMC or the COG Neuroblastoma Committee believe that changes to ongoing clinical trials that include isotretinoin are required. Several factors contributed to this decision, including:

- The initial results published in NEJM in 1999 showed a benefit for use of isotretinoin with regards to 3-year EFS rates.
- With longer term follow-up, the possibility remains that there is an improvement in EFS, though there is less certainty about this conclusion.
- The acute and long-term toxicities associated with isotretinoin administration in young children are relatively modest.

What is the impact of the corrected statistical analysis on the ability of the FDA to include treatment of children with high risk neuroblastoma in the isotretinoin product label and to have a new isotretinoin liquid formulation developed and approved?

COG, NICHD and NCI have notified FDA staff of the two analytical errors that were made in the 2009 publication. It is not yet known what impact these findings will have on the ability of the FDA to include treatment of children with high risk neuroblastoma in the isotretinoin product label and to have a new isotretinoin liquid formulation developed and approved. Discussion between NCI, NICHD, COG, and FDA will be required to determine what future actions will be taken.