

First International Choroid Plexus Tumor Research Meeting

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In a joint meeting of COG and SIOP members, 35 choroid plexus tumor specialists from five countries, three continents and six specialties presented the data and planned for the next choroid plexus tumor studies.

Website Development: Stephen Fulcher presented his work and the group provided input. It is important to keep the efforts for remote data entry of the clinical study and the parent registration separate.

CPT SIOP 2000 Study: Dr. Wrede presented an update of the data. Unchanged from before, there was good response, good overall survival, sharp separation between those patients requiring treatment following our algorithm as opposed to those on only watch and wait.

The surprising finding in the most recent interim analysis was the reduced role of complete resection among patients with choroid plexus carcinoma. In the past all analysis has shown significantly better survival for choroid plexus carcinoma patients after complete surgical resection. With intensive chemotherapy, the significant influence of surgery has now disappeared. The finding needs to be updated. However, a hypothesis of why this might be the case is that physicians typically do not stop treatment after the prescribed six cycles of chemotherapy if there is still a residual tumor visible on MRI. If the finding remains stable and the hypothesis can be confirmed, this would be an argument for extending treatment in the future.

Literature Analysis: Dr Berrak presented a literature analysis comparing different drugs. In her analysis

etoposide is the most effective drug for choroid plexus carcinoma.

Radiation Oncology: Dr. Mahajan presented a literature analysis which allow more precise radiation, spare more normal tissue and therefore allow us to go below the typical age limit.

Intrathecal Therapy: The previous committee meeting ended with a vote to use intrathecally. Since then specialists had been contacted, a detailed procedure written and regulatory issues have been addressed. Dr. Rytting presented the progress in this point of the discussion. It appears that intrathecal etoposide will only be possible if an IND (investigational drug number) exempt letter is issued. It remains uncertain whether such a letter will come into existence. The possibilities of returning to the original plan with cytarabine or switching to thiotepa were discussed. In conclusion, a recommendation was made to try to obtain the letter for etoposide, in case that fails to use cytarabine.

Neurosurgery: Dr. Weinberg presented the modern technology of intra-operative MRI and various guiding systems and the local experience at M. D. Anderson with such a system. A recent literature review confirms that in other histological diagnoses the most benefit was obtained with total resection.

Standard Treatment Algorithm: The present version of the preliminary next international CPT protocol, (Version 93) has an elaborate algorithm – how to treat different patients – depending on patient age, tumor location,

tumor staging, histology, response to first line treatment. This algorithm was reviewed and a number of modifications were made. Final algorithm was agreed in consensus and may serve not just as a part of the protocol but also as a standard of care recommendation.

Case Presentations and Institutional Experience: Institutional experience from Istanbul University (R Kebudi), Marmara University (S Berrak), Los Angeles Children's Hospital (S Khatua) and Sick Kids Hospital (U Tabori) in Toronto were presented and numerous interesting details discussed. Prominent findings were a.) The high relevance of focusing on a detailed family history, b.) The uncertainty of how "complete resection" is defined. It became obvious that centralized radio diagnostic review would be significantly beneficial for the group, and c.) P53 Mutation: In both blood (germline) and tumor should be evaluated respectively.

Biological Models: Dr. Miller presented the SV11 mouse, which has S40 integrated and develops choroid plexus carcinoma. Dr. Slopis described the development of brain tumors as the spontaneous tumors in dogs. The first of those models could be used as a standardized laboratory model. Frozen embryos are available. Reactivation will require a grant. The second model can be used in a way very similar to clinical trials in treating pet animals. A comparative neurooncology program has been started with this aim.

Statistical Design: The preliminary (version 93) protocol for the coming international CPT study outlines the first phase of the study with four different treatment protocols which will then be evaluated for event free survival and toxicity. This evaluation will then result in reducing the number of treatment protocols to two. A significant point of critique in the past discussions was "how many patients are necessary for such design?" A number of innovative study elements have since been created. One of those is the endpoint of the study combining event-free survival and toxicity as one two dimensional measure. Another is the co-variant adjustment. The required patient numbers were calculated by simulation for a minimal power 0.80. A four-treatment arm will require 153 patients, an equivalent of approximately seven years of study duration. Starting with three arms requires a maximum of 111 patients equivalent to five years of study. The study design is presented in detail for the first time and finds

numerous comments critiques and questions such as: lumping various histological diagnoses such as atypical choroid plexus pathaloma and choroid plexus carcinoma together in one design with an uncertainty, if drugs working in one histological diagnosis will also work in the other. Dr. Thall will adjust this statistical design for that point. The heated discussion ended with a plan to recalculate the patient numbers taking this into consideration and then return to the group to grow closer to a decision.

Chemotherapy of the Future Protocol: The present protocol proposes the use of a standard treatment which is a synthesis of the two arms of the present well running protocol. It proposes a comparison to three experimental arms, one of which is anthracycline based regimen and is successful in atypical teratoid-rhabdoid tumors. The second is high-dose methotrexate and the third is temozolomide/irinotecan. Various treatment details are discussed. Overall, all of the treatment approaches find support with small adjustments still needed.

Administrative Structure: The present administrative structure of the international group was described. International enrollment, Reference Neuropathology, Reference Radiation Oncology, Reference Neurosurgery and Biostatistics support at M. D. Anderson are functioning. The most important alterations recommended after discussion are: We want to explore implementing a radio-diagnostic review process. For Europe, Dr. Warmuth-Metz will be approached for North America. One of the radiologists active in COG will be approached. Further, a basic biology committee is suggested. Agreeable names are: Martin Hasselblatt, Yuri Tabouri, Douglas Miller. Details are to be worked out during the next few days.

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