

Title: Treatment of Children with All Stages of Hepatoblastoma - A Groupwide Phase III Study (AHEP0731)

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Synopsis:

Hepatoblastoma is the most common malignant liver neoplasm in children. This study builds on the results of the last 20 years of hepatoblastoma clinical trials and seeks to diminish toxicity in the approximately 30% of low-risk patients, increase survival in intermediate-risk patients and identify new agents(s) that may be used in high-risk and recurrent patients.

Patients will be staged for risk classification and treatment at diagnosis using COG staging guidelines. Study enrollment for patients with Stage I and II tumors is contingent on rapid central pathologic review of tumor specimens. All patients with Stage I pure fetal histology (PFH) hepatoblastoma will be classified as very low-risk and will be treated with surgery only. Patients with Stage I non-PFH, non-small cell undifferentiated (SCU) hepatoblastoma or with Stage II non-SCU hepatoblastoma will be classified as low-risk and will be treated on Regimen T with 2 adjuvant cycles of cisplatin, 5-fluorouracil, and vincristine (C5V), a reduction from the standard 4 cycles of chemotherapy used in previous COG trials. Patients with Stage I SCU, Stage II SCU, or any Stage III hepatoblastoma will be classified as intermediate-risk and will be treated with Regimen F. This treatment regimen is based on previous COG trials which administered 6 cycles of C5V therapy plus surgical resection of the tumor. However, to improve resection and survival rates, doxorubicin, an agent with proven efficacy will be added to the C5V therapy (C5VD). Surgical resection is necessary for cure and surgical resection whether by primary resection or orthotopic liver transplant (OLT) is intended after 4 cycles of intermediate-risk therapy.

This trial will assess the feasibility in a cooperative group setting of timely referral (by the completion of Cycle 2) for OLT in children with hepatoblastoma designated as potentially unresectable following central surgical review and staging according to the PRETEXT (Pretreatment Extent of Disease) grouping system. AHEP0731 also aims to determine if PRETEXT grouping can predict tumor resectability and to assess if institutional assessment of PRETEXT grouping is reliable by comparing to PRETEXT grouping as performed by central review.

All patients with any Stage IV hepatoblastoma as well as patients with any stage of hepatoblastoma and initial AFP <100 ng/mL will be classified as high-risk and will be treated with a novel agent (irinotecan) in Regimen W in order to improve survival. This regimen includes 2 cycles of "up-front" vincristine and irinotecan window therapy. Patients who respond to vincristine/irinotecan will continue to receive this combination. Responder patients will receive a total of 6 cycles of C5VD therapy with 2 more cycles of VI (total of 4). Non-responder patients will only receive the 6 cycles of C5VD following the "up-front" window therapy.

The primary goal of AHEP0731 is to show that a risk-based treatment approach will maintain or improve EFS, decrease acute and long-term chemotherapy toxicity, and identify new agents for the treatment of children with hepatoblastoma.