Hepatic Perfusion (CHEMOSAT® or CS-PHP) of Melphalan vs. Best Alternative Care (BAC) in Patients with Hepatic Metastases from Melanoma: Update of a Randomized Phase 3 Study

H.R. Alexander Jr on behalf of Phase 3 Investigators, Department of Medicine, University of Maryland School of Medicine, Baltimore, MD, USA

Background
- The prognosis for patients with liver-dominant metastatic melanoma is grim.
- Recently introduced drugs, i.e. ipilimumab and vemurafenib, are limited by tolerability, long induction periods, and/or applicability to ocular melanoma patients.
- Regional therapies deliver high doses of chemotherapy to a cancer-burdened organ while limiting unwanted systemic toxicity.
- Regional therapy using isolated hepatic perfusion with melphalan has shown promising efficacy in patients with liver metastases from ocular melanoma, but requires an open surgical procedure and is not repeatable.

Chemosaturation-PHP*
- Isolates the liver from the systemic circulation using a system of arterial catheters introduced percutaneously.
- Infusion via the proper hepatic artery allows perfusion of the entire hepatic parenchyma.
- The procedure allows for considerable dose escalation to the affected organ and provides treatment for both established and microscopic disease.
- Hepatic versus extracorporeal is captured via a double-balloon catheter positioned in the retrohepatic vena cava, trained to remove chemotherapy agents, and then returned to the systemic circulation.*
- The procedure is minimally invasive and repeatable.

Case
- We performed an exploratory randomized phase 3 study (n=93) compared melphalan delivered via CS-PHP with BAC in patients with ocular or cutaneous metastases to the liver: Based on an intention-to-treat analysis by the investigators (April 2010, primary datalock), CS-PHP melphalan 6.4 months at the median, with a hazard ratio of 0.30 (95% CI 0.23–0.54, p<0.0001) versus BAC.†
- We performed an exploratory post-hoc analysis of BAC patients who crossed over to CS-PHP after disease progression: (BAC→CS-PHP crossover) vs. BAC only vs CS-PHP-randomized patients.

Purpose
- A randomized phase 3 study (n=93) compared melphalan delivered via CS-PHP with BAC in patients with ocular or cutaneous melanoma metastatic to the liver: Based on an intention-to-treat analysis by the investigators (April 2010, primary datalock), CS-PHP melphalan significantly improved hepatic progression-free survival by 6.4 months at the median, with a hazard ratio of 0.30 (95% CI 0.23–0.54, p<0.0001) versus BAC.†
- We performed an exploratory post-hoc analysis of BAC patients who crossed over to CS-PHP after disease progression: (BAC→CS-PHP crossover) vs. BAC only vs CS-PHP-randomized patients.

Study design
- Randomized, open-label, multicenter phase 3 study.
- Patients: Ocular or cutaneous metastatic melanoma predominantly in the liver parenchyma with limited extra-hepatic disease.
- Endpoints:
  - Primary: Hepatic progression-free survival (hPFS) by RECIST.
  - Secondary:
    - Hematologic objective response rate
    - Prolonged survival
    - Safety.

Study treatments
- CS-PHP with melphalan:
  - 3.0 mg/kg as a 30-minute intraarterial infusion
  - An additional 30 minutes of extracorporeal filtration at end of infusion (washout)
  - Under general anesthesia
  - Allowed up to 6 treatments, repeated every 4–8 weeks.
- Best alternative care (BAC):
  - Investigator’s choice of systemic, regional or other appropriate therapy.
  - Crossover to CS-PHP permitted after hepatic progression if patients still not eligible criteria.

Efficacy analysis

Conclusions
- CS-PHP significantly prolonged hPFS compared with BAC in patients with liver-dominant metastatic melanoma.
- The primary study objective was met:
  - Improved survival similar in both groups, as expected:
    - Confounded by crossover
    - Prolonged survival observed in BAC→CS-PHP crossover patients
    - Most long-term survivors received CS-PHP.
- Efficacy similar in BAC-crossover and CS-PHP-randomized patients.
- Hematological AEs managed effectively with supportive care.
- CS-PHP with melphalan is a new treatment option for unresectable metastatic melanoma in the liver.

References

Exploratory analysis: Overall survival

Exploratory analysis: hPFS

Patient flowchart

Baseline characteristics

Exploratory analysis

Most common (>10%) grade 3/4 AEs

Study investigators
- Maybeth Hughes, National Cancer Institute, Bethesda, MD.
- Charles W. Hilding, Swedish Medical Center, Englewood, CO.
- Jonathan S. Zagar, H.L. Moon MD Anderson Cancer Center & Research Institute, Tampa, FL.
- Mark Faris, John Wayne Cancer Institute, Santa Monica, CA.
- Gary Selin, Alaska Medical Center Hospital, Anchorage, AK.
- Sanjiv Agarwala, St. Luke’s Hospital and Health Network, Bethlehem, PA.
- Eric Weiner, Atlantic Melanoma Center, Montclair, NJ.
- Richard Byers, University of Texas, MD Anderson Cancer Center, Houston, TX.
- James Pogorzel, University of Pittsburgh, Hillman Cancer Center, Pittsburgh, PA.
- Jennifer Yoo, University of California, San Francisco, CA.

CS-PHP circuit

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