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Percutaneous Hepatic Perfusion (PHP) with Melphalan versus Best Alternative Care (BAC) in Patients with Unresectable Hepatic Metastases from Melanoma: A *Post-hoc* Analysis of PHP-randomized vs BAC-to-PHP Crossover vs BAC-only Patients

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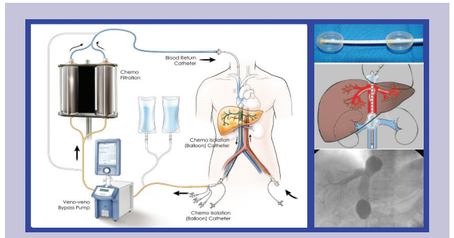
Background

- The prognosis for patients with liver-dominant metastatic melanoma is dismal with a survival time of approximately 2 months.[1]
- Recently introduced drugs are limited by toxicity, long induction periods (e.g., ipilimumab) or applicability (e.g., vemurafenib):
  - vemurafenib is an inhibitor of BRAF mutations, but these mutations do not occur in ocular melanoma and are evident in only a subset of patients with cutaneous melanomas (40% to 60%).[2]
- There are no agents that meaningfully alter the natural history of metastatic melanoma.
- Regional therapies deliver high-dose chemotherapy to the whole organ while limiting unwanted systemic toxicity.

Chemosaturation-PHP*

- Isolates the liver from the systemic circulation using a system of special 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 cancer-burdened organ and provides treatment for both established and micrometastatic disease.
- Hepatic venous effluent is captured via a double-balloon catheter positioned in the retrohepatic vena cava, filtered to remove chemotherapeutic agents, and then returned to the systemic circulation.[3]
- The procedure is minimally invasive and repeatable.

*Delcath Systems, Inc., NY, NY



Purpose

- A prospective randomized multicenter study compared melphalan PHP versus BAC in patients with unresectable hepatic metastases from ocular or cutaneous melanoma and showed a highly significant advantage for PHP in terms of the primary endpoint, hepatic PFS, and multiple secondary endpoints.[4]
- We present an exploratory *post-hoc* analysis of patients assigned to BAC who crossed over to PHP after disease progression (BAC-to-PHP crossover) versus those who did not (BAC-only) versus PHP-randomized patients.

Patient population

- Proven ocular or cutaneous metastatic melanoma predominantly in the liver parenchyma.
- Limited extra-hepatic disease.
- Adequate liver function:
  - total serum bilirubin <3.0 mg/dL
  - prothrombin time within 2 seconds of ULN
  - liver function tests ≤10 x ULN.
- No portal hypertension.

Study treatments

- Melphalan PHP:
  - 3.0 mg/kg as a 30-minute intra-arterial infusion[3]
  - 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 PHP permitted after hepatic progression (if patients still met eligibility criteria).

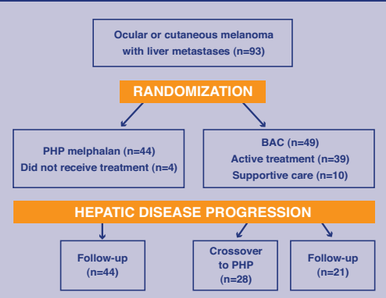
Study design and endpoints

- Randomized, open-label, multicenter phase 3 study.
- Study endpoints:

Primary
- hepatic progression-free survival (hPFS) (RECIST)
- defined as time from randomization to hepatic disease progression or death.

Secondary
- hepatic objective response rate
- overall survival
- safety.

Patient flowchart



Baseline characteristics

Characteristic	PHP-randomized (n=44)	BAC (n=49) Total (n=49)	BAC-to-PHP crossover (n=28)	BAC only (n=21)
Median age, years	55	56	56	57
Primary tumor site, %				
Ocular	89	88	82	95
Cutaneous	11	12	18	5
Hepatic tumor burden, %				
<50%	77	78	86	67
≥50%	18	22	14	33
Unknown	5	0	0	0
Extrahepatic sites, %	27	33	36	29
Previous treatment, %				
Radiation therapy	52	53	54	52
Surgery/procedure	55	65	64	67
Chemotherapy	16	14	14	14

Intent-to-treat population

BAC treatments

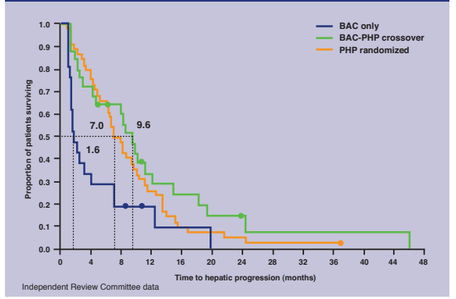
- BAC constituted:
  - active treatment (n=39)
  - supportive care/watchful waiting (n=10).
- Active treatments:
  - Temozolomide (n=20)
  - Chemoembolization (n=10)
  - Yttrium microspheres (n=3)
  - Systemic chemotherapy (n=6).

Exploratory analysis

Endpoint	PHP-randomized (n=44)	BAC only (n=21)	BAC-to-PHP crossover (n=28)
Median hPFS (investigator), months	8.0	1.6	8.8
HR (crossover vs BAC-only)		0.32	
Median hPFS (IRC), months	7.0	1.6	9.6
HR (crossover vs BAC-only)		0.44	
Median overall survival, months	9.8	4.1	15.3
HR (crossover vs BAC-only)		0.33	
Still alive as of 31 March 2011 Follow-up: 9.7–53.5 months	4	3*	7

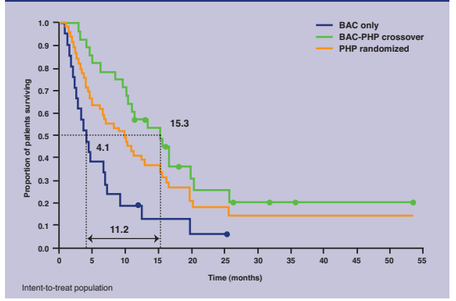
*1 patient crossed over but never received PHP; Intent-to-treat population; Data as of 31 March 2011
IRC, independent review committee

Exploratory analysis: hPFS



Independent Review Committee data

Exploratory analysis: Overall survival



Intent-to-treat population

Most common peri-procedural* grade 3/4 AEs

Percentage of patients	PHP-randomized (n=40)	BAC-to-PHP crossover (n=25)
Platelet count decreased	73	80
Hemoglobin decreased	63	60
aPTT prolonged	30	16
AST increased	30	8
Blood calcium decreased	20	8
ALT increased	10	8
Blood bilirubin increased	10	8
Back pain	10	0

*Day of treatment through to day 3 post-treatment; Safety population

Most common in-cycle* grade 3/4 AEs

Percentage of patients	PHP-randomized (n=40)	BAC-to-PHP crossover (n=25)
Neutrophil count decreased	93	92
Platelet count decreased	83	84
White blood cell count decreased	58	32
Hemoglobin decreased	55	60
Blood bilirubin increased	18	8
Febrile neutropenia	15	8
AST increased	13	12
Blood alkaline phosphatase increased	13	0
ALT increased	10	8
Blood albumin decreased	8	8

*Day 4 post-treatment through to end of treatment cycle; Safety population

Conclusions

- Efficacy of melphalan PHP in BAC-to-PHP crossover patients was consistent with that seen in PHP-randomized patients with hepatic metastases from melanoma.
- Crossover from BAC to PHP after hepatic disease progression led to a median 11-month survival advantage vs BAC alone.
- The safety profile of melphalan PHP in BAC-to-PHP crossover patients was similar to that seen in PHP-randomized patients.
- PHP delivery of melphalan is a new treatment option for unresectable metastatic melanoma in the liver.

Study investigators

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