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Chemosaturation with Percutaneous Hepatic Perfusions: Vasopressor, Nitroglycerin, and Pre-Embolization Requirements

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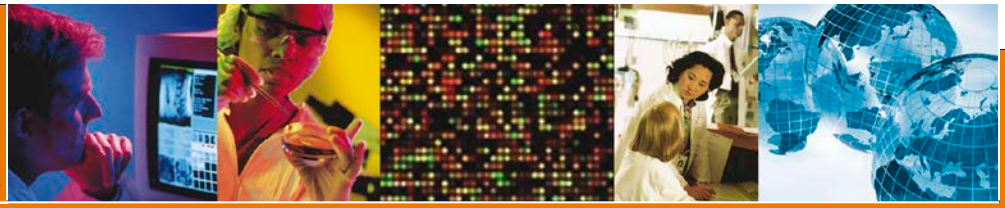
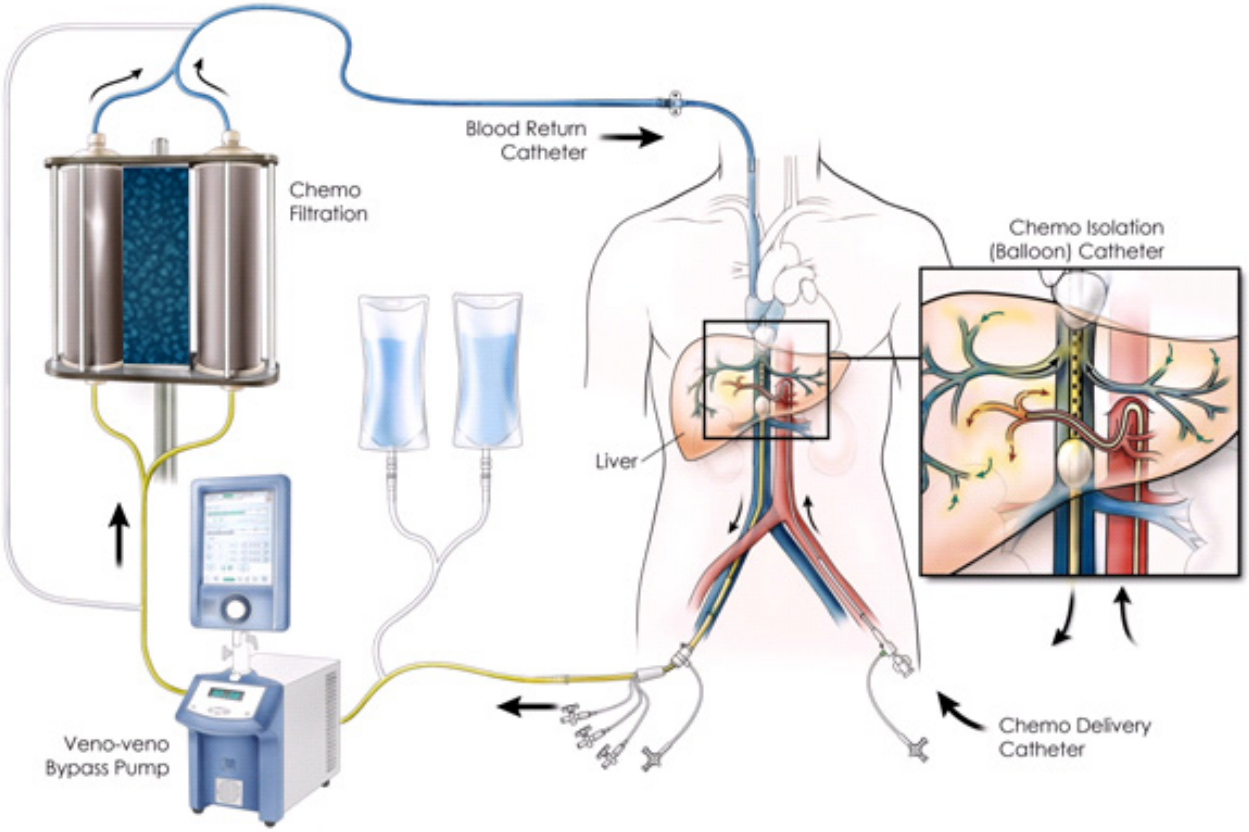


Background

- Chemosaturation with percutaneous hepatic perfusions (CS-PHP; CHEMOSAT®; Delcath Systems, Inc, NY, USA) is a novel regional therapy for unresectable hepatic tumors
- A randomized phase 3 study (n=93) compared CS-PHP using high-dose melphalan with best alternative care (BAC) in patients with ocular or cutaneous melanoma metastatic to the liver[1]
  - Based on an intention-to-treat analysis by the investigators (April 2010), 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 0.18-0.50; p<0.0001) versus BAC[1]

1. Pingpank JF, et al. JCO 2010;28:18s (abstr LBA8512)

CS-PHP circuit



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CS-PHP procedure

- Prior to the first cycle of CS-PHP, a compete visceral angiogram is performed to map the hepatic arterial anatomy
- Embolization of gastrointestinal arterial branches arising from the hepatic arteries is required in most patients to prevent non-target delivery of chemotherapy ("vascular optimization")
- During CS-PHP, hypotension occurs when
  - Occlusion balloons are inflated in the IVC, reducing cardiac output
  - Filters remove endogenous catecholamines[2]
- Hypotension requires intra-procedural vasopressor support
- Vasopressor administration may lead to hepatic arterial spasm, which should be managed with intra-arterial nitroglycerin

2. Ravikumar TS, et al. JCO 1994;12:2723-36

Methods

- An analysis of blood pressure changes and need for pre-procedural embolization and intra-procedural nitroglycerin was performed in patients who received CS-PHP from the phase 3 study
- Patients from two subgroups were considered in the present analysis:
  - CS-PHP-randomized patients (n=42)
  - BAC-randomized patients who subsequently crossed over to CS-PHP after hepatic disease progression (n=28)*
- Data were collected prospectively
- All data were summarized using descriptive statistics

* Crossover after hepatic disease progression was permitted in the study protocol provided that patients continued to meet the eligibility criteria

Pre-procedure embolization

n (%)	CS-PHP (n=42)	BAC-crossover (n=28)	Total (n=70)
Embolization performed, n	34 (81)	17 (61)	51 (73)
Artery embolized, n			
Gastroduodenal	27 (64)	15 (54)	42 (60)
Right gastric	5 (12)	1 (4)	6 (9)
Left gastric	2 (5)	1 (4)	3 (4)
Other*	4 (10)	1 (4)	5 (7)

*phrenic + middle hepatic, supraduodenal branch of R hepatic , gastrohepatic , L gastric/hepatic branch, L hepatic caudal branch

Likely reasons for lack of embolization were

- Origin of gastroduodenal artery sufficiently proximal to eliminate risk of perfusing GI tract
- Prior embolization for loco-regional therapy
- Vascular anatomy precluded CS-PHP

In total, 48 embolizations were performed in cycle 1 and most of the remainder in cycle 2 (11 patients)

Intra-arterial nitroglycerin use

	CS-PHP (n=42)	BAC-crossover (n=28)	Total (n=70)
Hepatic artery spasm, n (%)	30 (71)	17 (61)	47 (67)
Nitroglycerin use, n (%)	29 (69)	18 (64)	47 (67)
Nitroglycerin dose,* µg			
Median	200	315	230
Range	50–1200	100–720	50–1200

*Nitroglycerin was given in aliquots (usually 100 µg) as needed during the procedure

Safety population

Peri-procedure BP reductions

	CS-PHP (n=42)	BAC-crossover (n=28)	Total (n=70)
BP decrease, n (%)	38 (91)	17 (61)	59 (84)
Systolic BP			
Median nadir, mmHg	60	71	65
Median time to nadir, hr	1.5	1.6	1.6
Diastolic BP			
Median nadir, mmHg	38	40	40
Median time to nadir, hr	1.7	1.4	1.5

Peri-procedure = day of treatment to day 3 post-treatment

Vasopressor use

Vasopressor*, n(%)	CS-PHP (n=42)	BAC-crossover (n=28)	Total (n=70)
Norepinephrine	22 (52)	12 (43)	34 (49)
Phenylephrine	19 (45)	9 (32)	28 (40)
Ephedrine	7 (17)	6 (21)	13 (19)
Epinephrine	6 (14)	4 (14)	10 (14)
Vasopressin	7 (17)	1 (4)	8 (11)
Atropine	2 (5)	0	2 (3)
Vasopressor not specified	2 (5)	0	2 (3)
Dopamine	1 (2)	0	1 (1)

* Patients may have received more than one vasopressor

Safety population

Conclusions

- Arterial mapping and embolization is an important preparatory step for CS-PHP to avoid infusion of non-target vessels leading to GI side-effects
- Embolization was performed in 71% of patients, and usually of the gastroduodenal artery
- Transient blood pressure reductions occurred in 84% of patients as expected at the time of isolation-aspiration catheter balloon inflation and when the filters were first brought on line
- Blood pressure management with vasopressors and fluid support is essential to minimize hemodynamic fluctuations during CS-PHP
- Hepatic arterial spasm requiring nitroglycerin occurred in 67% of patients
- Intra-arterial vasodilator therapy (nitroglycerin) is essential to manage hepatic arterial spasm and avoid inadvertent retrograde reflux into non-target vessels

With these key preventive measures, CS-PHP can be safely administered for treatment of liver metastases