Hepatic arterial chemotherapy (HAC) for colorectal liver metastases (CRLM)

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Disclosure

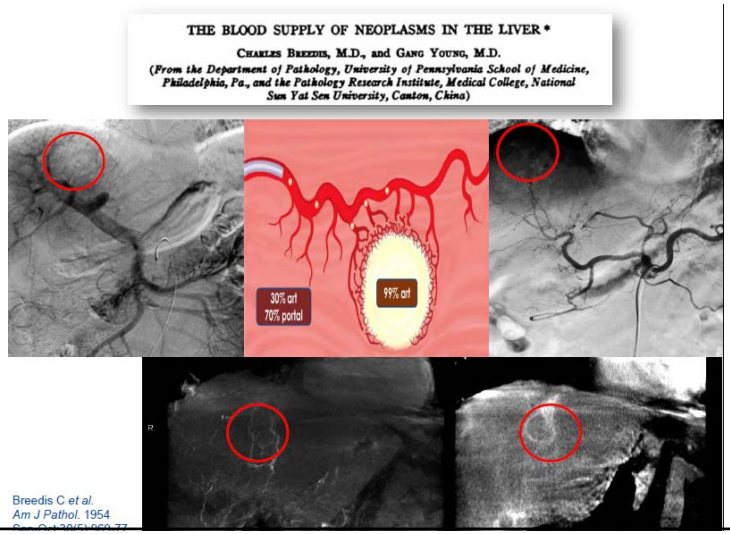
Amgen
Bayer
Celgene
Ipsen
Keocyt
Lilly
Merck Serono
MSD
Novartis
Roche
Sanofi-Aventis
Teva

HAC: rationale

- **The therapeutic armamentarium for metastatic colorectal cancer (mCRC) is evolving slowly**
  - ➔ Only 1 new cytotoxic agent since mid-90's (TAS-102)
  - ➔ Only 1 new targeted agent class since mid-00's (regorafenib)

- ▶ **HAC**
  - Allows optimizing available anticancer drugs

HAC: rationale



Breedis C *et al.*
Am J Pathol. 1954

HAC: rationale

- **Colorectal liver metastases (CRLM)**
  - ➔ Preferential arterial blood supply (notably when > 3 cm)

▶ **HAC**
- Allows optimizing available anticancer drugs
- Logical in case of CRLM

HAC: rationale

- **Surgery for CRLM**
  - ➔ Mostly concerns patient with liver-only or liver-dominant disease
  - ➔ Notably when conversion to resectability is necessary

▶ **HAC**
- Allows optimizing available anticancer drugs
- Logical in case of CRLM
- Logical in case of potentially resectable CRLM

HAC: rationale

- **Strong liver extraction**
  - ↗ local concentrations
  - ↘ systemic concentrations

Agent	½-life	↗ exposure by HAC (fold)
Floxuridine (FUDR)	< 10 mn	100-400
5-fluorouracil (5FU)	10 mn	5-10
Oxaliplatin	15-19 h	4-5
Mitomycin C	≤ 10 mn	6-8

▶ **HAC**
- Allows optimizing available anticancer drugs
- Logical in case of CRLM
- Logical in case of potentially resectable CRLM
- Allows chemotherapy intensification

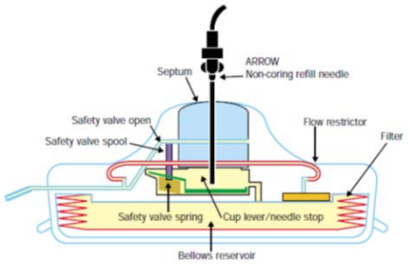
HAC: Fact #1

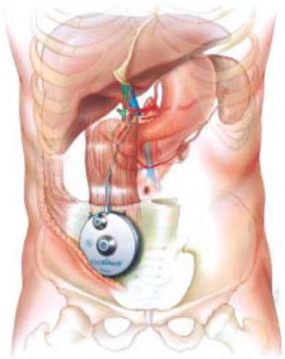
A logical approach in case of exclusive/dominant CRLM (notably potentially resectable) that allows optimizing the available drugs and intensifying chemotherapy

HAC: fact #2

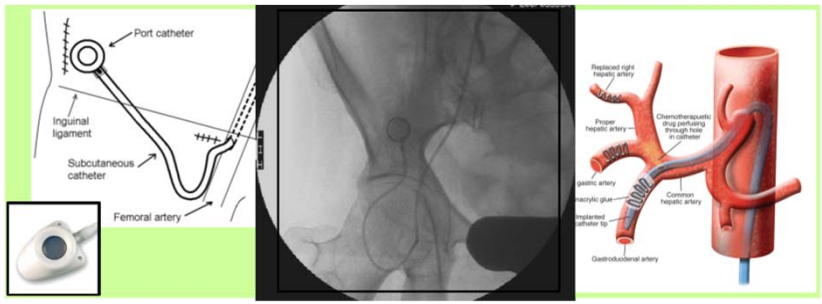
Easier (except for the interventional radiologist!) since the advent of subcutaneously implantable HA catheters and ports

HA pumps





HA catheters



HAC: Fact #3

More effective than systemic CTx (at least for FUDR)

HAC: palliative setting

Randomized trials (n = 10)							
First Author	Treatment Arms	N	Response Rate (%)	p	Median survival (mo)	p	Design flaws
Kemeny[30]	HAI FUDR SYS FUDR	48 51	53 21	.001	17 12	NS	Cross-over allowed (60% crossed over)
Chang[28]	HAI FUDR SYS FUDR	32 32	62 17	.003	17 12	NS	Extrahepatic disease, dose of HAI FUDR
Hohn[29]	HAI FUDR SYS FUDR	67 76	42 9	.001	16.5 15.8	NS	Extrahepatic disease, cross-over allowed
Martin[34]	HAI FUDR SYS 5-FU	39 35	48 21	.02	12.6 1.5	NS	Extrahepatic disease, dose of HAI FUDR
Wagman[36]	HAI FUDR SYS FUDR	31 10	55 20	NR	13.8 11.6	NS	Cross-over allowed
Rougier[35]	HAI FUDR SYS 5-FU or BSC	81 82	41 9	NR	15 11	<.02	Dose of HAI FUDR
Allen-Mersh[27]	HAI FUDR SYS 5-FU or BSC	51 49	NR NR	NR	13.5 7.5	.03	
Lorenz[33]	HAI FUDR HAI 5-FU + LV	54 57	43 45	.019	12.7 18.7	NS	Ports used, cross-over allowed, dose adjustment of HAI FUDR
Kerr[32]	SYS 5-FU + LV HAI 5-FU + LV SYS 5-FU + LV	57 145 145	27 22 19	NS	17.6 14.7 14.8	NS	Ports used, FUDR not used for HAI
Kemeny[31]	HAI FUDR + Dex SYS 5-FU + LV	68 67	47 24	.02	24.4 20	.003	

HAI, hepatic artery infusion; SYS, systemic infusion; 5-FU, 5-fluorouracil; FUDR, floxuridine; BSC, bischlorethylnitrosurea; NS, not significant; NR, not reported.

→ HA FU/FUDR: ↗ ORR (HA, 41-62%; i.v., 9-27%) – ↗ OS?

HAC: Fact #4

It is possible to intensify associated systemic CTx

Palliative HAC

JOURNAL OF CLINICAL ONCOLOGY — ORIGINAL REPORT

Conversion to Resectability Using Hepatic Artery Infusion Plus Systemic Chemotherapy for the Treatment of Unresectable Liver Metastases From Colorectal Carcinoma

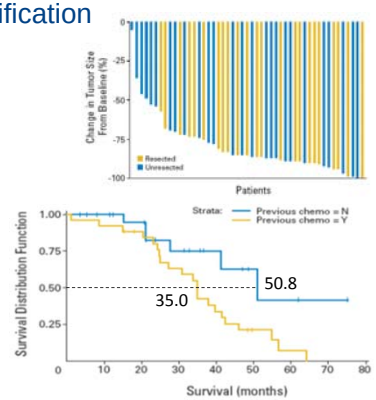
Nancy E. Kemeny, Fidel D. Huitzil Melendez, Marinela Capanu, Philip B. Paty, Yuman Fong, Lawrence H. Schwartz, William R. Jarnagin, Dina Patel, and Michael D'Angelica

Kemeny NE, et al. J Clin Oncol 2009;27:3465-71

Palliative HAC

i.v. intensification

- 49 patients
  - Non-resectable CRLM
  - pretreated: 53%
- Treatment
  - HAI: FUDR + dexamethasone
  - IV: oxaliplatin + irinotecan
- ORR: 92% (CR: 8%)
  - 1st-line: 100%
  - pretreated: 85%
- 2ary resection: 23/49 (47%)
  - 1st-line: 57%
  - pretreated: 38%
  - R0: 19/49 (39%)
  - pRC: n = 3



Kemeny NE, et al. J Clin Oncol 2009;27:3465-71

HAC: Fact #4

It is possible to intensify HAC

Palliative HAC

HA oxaliplatin + i.v. LV5FU2 1st-2nd line

JOURNAL OF CLINICAL ONCOLOGY | ORIGINAL REPORT

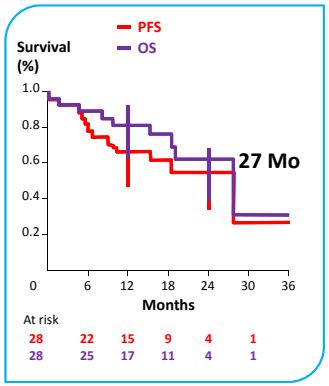
Hepatic Arterial Oxaliplatin Infusion Plus Intravenous Chemotherapy in Colorectal Cancer With Inoperable Hepatic Metastases: A Trial of the Gastrointestinal Group of the Fédération Nationale des Centres de Lutte Contre le Cancer

Michel Ducreux, Marc Ychou, Agnès Laplanche, Erick Gamelin, Philippe Lasser, Fares Husseini, François Quenet, Frédéric Viret, Jacques-Henri Jacob, Valérie Boige, Dominique Elias, Jean-Robert Delperro, and Monique Luboinski

Palliative HAC

HA oxaliplatin + i.v. LV5FU2 1st-2nd line

- **Phase II FNCLCC (1999-2001, 6 centers)**
- **28 patients**
  - Prior 1L CTx (without oxaliplatin) : 21/28 (75%)
  - Non-resectable CRLM
  - No extrahepatic disease
- **No biliary toxicity (≠ FUDR)**
- **ORR: 64% (CR: 7%)**
- **DCR: 75% (100% ≤8 cycles)**
- **2ary resection: 18%**



Palliative HAC

HA oxaliplatin + i.v. LV5FU2 ≥2nd line

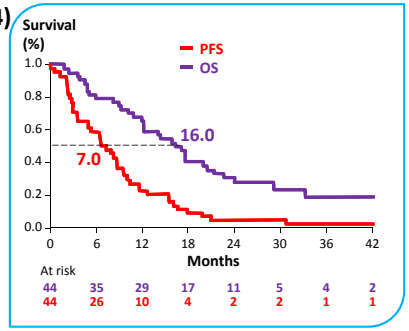
Hepatic Arterial Infusion of Oxaliplatin and Intravenous LV5FU2 in Unresectable Liver Metastases from Colorectal Cancer after Systemic Chemotherapy Failure

Valérie Boige, MD,[1] David Malka, MD, PhD,[1] Dominique Elias, MD, PhD,[2] Marine Castaing, MS,[3] Thierry De Baere, MD,[4] Diane Goere, MD,[2] Clarisse Dromain, MD,[4] Marc Pocard, MD, PhD,[2] and Michel Ducreux, MD, PhD[1]

Palliative HAC

HA oxaliplatin + i.v. LV5FU2 ≥2nd line

- Retrospective series, GR (2000-04)
- 44 pretreated patients
  - 21/28 (66%) : ≥ 2 prior lines
    - FOLFOX or FOLFIRI: 43/44 (98%)
    - Both: 28/44 (64%)
- ORR: 62% (CR: 0%)
- DCR: 87%
- 2ary resection: 18%



HA oxaliplatin: effective after failure of systemic CTx, including i.v. oxaliplatin

HAC: Fact #5

The activity of HA oxaliplatin after failure of i.v. oxaliplatin is by itself a proof-of-concept of HAC

(that of HA mitomycin C, ineffective by i.v. route, is another one!)

HAC: Fact #6

It is possible to intensify both HAC and systemic CTx

Palliative HAC

HA oxaliplatin + 5FU + irinotecan + i.v. cetuximab ≥2nd line

OPTILIV: multicenter, international, Phase II trial

- 64 patients with KRAS WT, non-resectable CRLM
- Médian: 10 CRLM, involving 6 segments
- 41%: 1-3 extrahepatic mets (< 1 cm)

Prior chemotherapy drugs	n of patients (%)
5-FU	61 (95%)
Irinotecan	50 (78%)
Oxaliplatin	40 (63%)
Both Irinotecan and Oxaliplatin	26 (41%)
Cetuximab	21 (33%)
Bevacizumab	40 (63%)
Both Cetuximab and Bevazucimab	12 (19%)

Palliative HAC

HA oxaliplatin + 5FU + irinotecan + i.v. cetuximab ≥2nd line

Endpoints	Prior chemotherapy protocols			
	All (n=64)	1 line (n=28)	2-3 lines (n=36)	p
CR	1 (2%)	1 (4%)	0	
PR	25 (39%)	9 (32%)	16 (44%)	
SD	28 (44%)	12 (43%)	16 (44%)	
PD	3 (5%)	1 (4%)	2 (6%)	
NE	7 (11%)	5 (18%)	2 (6%)	
ORR	41%	36%	44%	ns
DCR	84%	79%	89%	ns
R0-R1 resection	30%	46%	17%	0.014
PFS (mo) [95% CI]	9.3 [7.8-10.9]	10.1 [7.8-12.3]	8.5 [5.8 -11.2]	0.088
OS (mo) [95% CI]	25.5 [18.8-32.1]	31.8 [26.0-37.6]	15.7 [10.1-21.2]	0.001

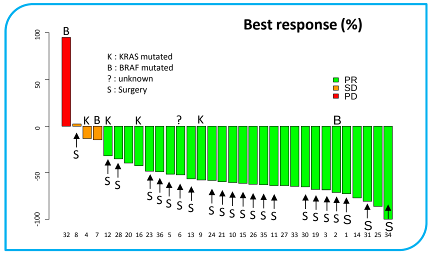
HAC: Fact #7

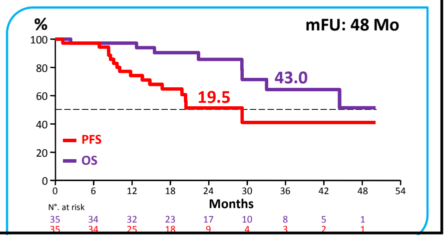
It is possible to administer it in 1st-line

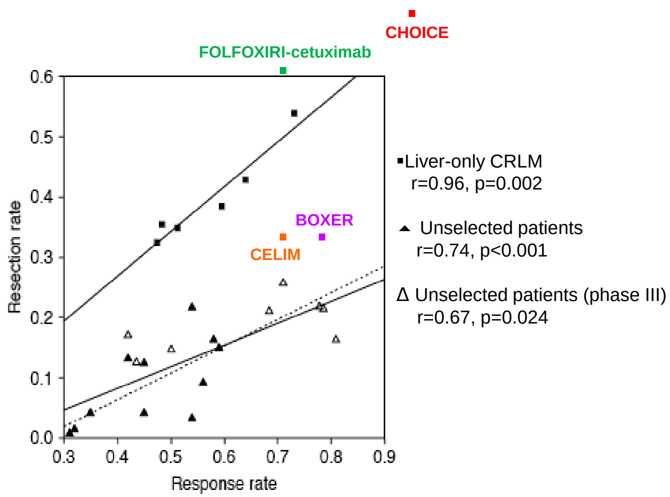
Palliative HAC

HA oxaliplatin + i.v. LV5FU2 and cetuximab, 1st line

- **Phase II CHOICE (8 centers)**
- **35 patients, 1st line**
  - Non-resectable CRLM
  - *KRAS*WT: 30/35 (86%)
- **ORR: 88% (CR: 3%)**
  - *KRAS*/BRAF WT: 96%
- **DCR: 97%**
  - *KRAS*/BRAF WT: 100%
- **2ary resection: 66% (23/35)**
  - *KRAS*/BRAF WT: 74%







HAC: Fact #8

Liver-only/dominant CRLM should be considered as potentially resectable until clear demonstration of the contrary

HAC: Fact #9

It is possible to administer it in the 'adjuvant', post-hepatectomy setting

Adjuvant HAC

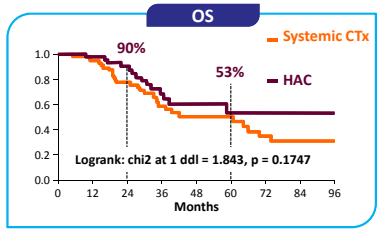
Méta-analysis, Cochrane 2009 (n=7)

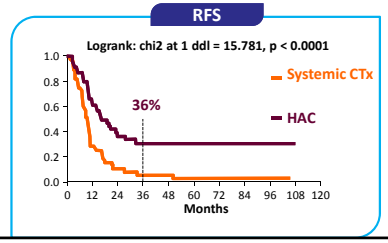
Authors	N	HAC	Control arm	Hepatic DFS	DFS	OS
Wagman 1990	91	FUDR	-	-	p = 0.03	NS
Lygidakis 1995	40	Carboplatin, 5FU, MMC, IFN	-	p < 0.001	p ≤ 0.001	11 vs 2 mo P ≤ 0.001
Lorenz 1998	226	5FU (+ 5FU IV)	-	21.6 vs 24.0 mo NS	14.2 vs 13.7 mo NS	34.5 vs 40.8 mo NS
Kemeny N 1999	156	FUDR (+ 5FU IV)	5FU IV	90% vs 60% at 2 years p < 0.001	57% vs 42% at 2 years p = 0.07	86% vs 72% at 2 years 72.2 vs 62.2 mo p = 0.03
Tono 2000	19	5FU	-	-	78% vs 30% at 2 years p = 0.045	78% vs 50% at 5 years NS
Rudroff 1999	42	5FU + MMC	-	-	15% vs 23% at 5 years NS	25% vs 31% at 5 years NS
Kemeny M 2002	75	FUDR (+ 5FU IV)	-	67% vs 43% at 4 years p = 0.03	46% vs 25% at 4 years p = 0.04	64 vs 49 mo NS

Adjuvant HAC

HA oxaliplatin

- **Prospective database GR (2000-09)**
- **98 patients**
  - → OR/SD after preop CTx
  - → **≥ 4 resected** CRLM
  - → ≥ 1 cycle of adjuvant CTx
- **Treatment**
  - → HA oxaliplatin: n = 44
  - → i.v. FOLFOX or FOLFIRI : n = 54
- **Median follow-up: 45 mo**





Adjuvant HAC: PACHA-01

Postoperative hepatic Arterial Chemotherapy in High-risk patients as Adjuvant treatment after resection of colorectal liver metastases

Sponsor: Gustave Roussy - PI: D Goéré – co-PI: D Malka

Multicenter, randomized Phase 2-3 trial (PHRC 2013)

≥ 4 resected Liver-only CRLM
PS 0-1
≥ 18 years

Stratification factors
- Preop oxaliplatin (Y/N)
- Preop CTx duration (≤ 3 vs > 3 mo)
- Response to preop CTx (OR vs SD)
- Nb of CRLM (4-8 vs > 8)
- Center

R

n = 114

FOLFOX 4

Oxaliplatine IAH + LV5FU2 IV

Endpoints
- primary: hepatic RFS at 18 mo (30% → 50%)
  - Phase 3
    - RFS at 3 years (15% → 30%; HR : 0,63)
    - 220 patients (+106)
- Secondary: feasibility (≥ 4 cycles), toxicity, RFS, OS

HAC: Fact #10

and why not in the adjuvant, post-colectomy setting?

Adjuvant HAC

Design

- **Phase III**
- **18-75 yrs**
- **Stage II-III**
- N = 688

HAC → Surgery → ***folfox***

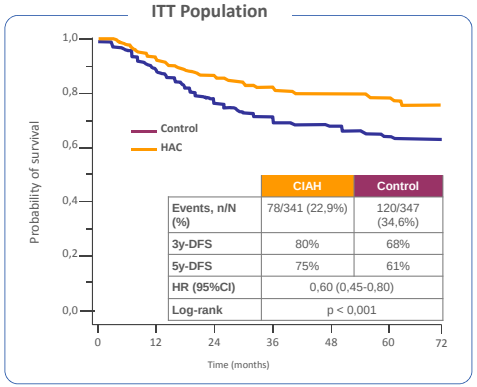
Surgery → ***folfox***

HAC
- 7 days before resection of the primary
- FUDR 650 mg/m², oxaliplatin 75 mg/m², mitomycin C 8 mg/m²

- Primary endpoint: RFS
- Secondary endpoints
  - Hepatic RFS, OS
  - Toxicity

Adjuvant HAC

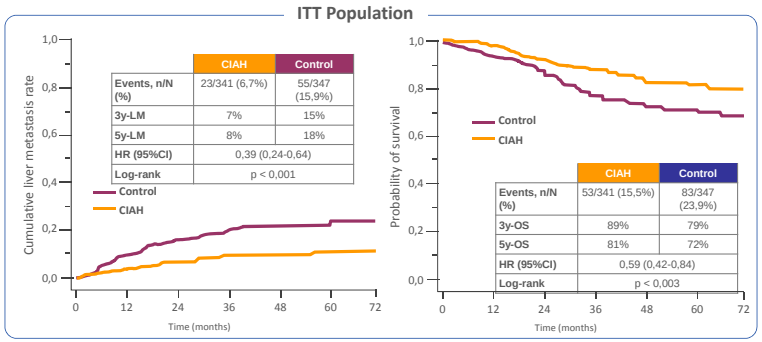
- Primary endpoint: 5-yr RFS
  - 75% HAC+CT *versus* 61% CT (HR 0.60 ; p<0.001)



	CIAH	Control
Events, n/N (%)	78/341 (22,9%)	120/347 (34,6%)
3y-DFS	80%	68%
5y-DFS	75%	61%
HR (95%CI)	0,60 (0,45-0,80)	
Log-rank	p < 0,001	

Adjuvant CT

- 5-yr liver recurrence rate
  - 8% HAC + CT *versus* 18% CT (HR 0.39 ; p<0.001)
- 5-yr OS
  - 81% HAC + CT *versus* 72% CT (HR 0.59 ; p=0.003)



	CIAH	Control
Events, n/N (%)	23/341 (6,7%)	55/347 (15,9%)
3y-LM	7%	15%
5y-LM	8%	18%
HR (95%CI)	0,39 (0,24-0,64)	
Log-rank	p < 0,001	

	CIAH	Control
Events, n/N (%)	53/341 (15,5%)	83/347 (23,9%)
3y-OS	89%	79%
5y-OS	81%	72%
HR (95%CI)	0,59 (0,42-0,84)	
Log-rank	p < 0,003	

Perspectives