Clinics in Oncology

Review Article
Published: 17 Feb, 2017

Hepatic Artery Infusion for Recurrent or Chemo Resistant Hepatic Malignancy

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Abstract

Background: Previously treated Hepatic Colorectal Metastases (CRC) and advanced Hepato Cellular Cancer (HCC) are tumor challenges frequently unresponsive to systemic Chemo Therapy (CT). We reviewed survival outcome in chemo resistant/high risk patients following Hepatic Artery Infusion (HAI) in 21 CRC pts, 10 HCC pts, and 6 miscellaneous metastatic cancers.

Methods: Patient groups: 21 CRC pts, (16M, 5F), mean age 63, 16 had metachronous (DFI-17 mos), and 5 Synchronous CA; liver extent: 76% multiple (>5) mets or extensive bilateral, CEA (ng/m), >100, 8 pts >50 (3pts) and, NA - 7 pts. Previous CT: FU/LV (11 pts), Oxaliplatin (OX) or Irinotecan (IR) 10 pts. Liver surgery: Partial Resection/RFA - 9 pts. HCC 9 pts, cholangio CA 1 pt, M/F 5/5, average age 63. Previous RX Hepatic lobectomy + HAI were done in metastatic lung (1), Breast (1), advanced gallbladder (GBCA) (T3-4) (2 pts); HAI alone was done in Br CA (1) carcinoid (1).

Treatment Protocols: CRC Protocol: HAI-FUDR 12-15mg/kg/d, dexamethasone 2mg/kg/d, Leukovorin 20mg/m^2/d (14 d) plus bolus infusion (d1), Oxaliplatin (OX) 130mg/m^2 (or Cisplatin (CIS) 100mg m^2 d1); Systemic RX: d20-30. OX I>V. 130mg/m^2, capecitabine 750-1000mg/m^2/d x 10 days (also used in Miscel.Grp.). HCC Protocol: HAI-14 d as in CRC Protocol. Bolus infusion d1-doxorubicin 75mg/m^2 or OX or CIS as in CRC schema.

Results: CRC: OS-CRC post start HAI was 17 mos, (2yr/5yr = 27%/6%). HCC OS was 7 mos. Median (3-12 mos in 9 evaluable pts; 1 HCC pt, with recurrence 2 yr. post hepatectomy was treated over 3.5 yrs. with HAI + RFA/TACE - (OS- 67mos). Miscellaneous group included lung (11 mos), Br CA (23, 9 mo) adv. carcinoid (3 mos), GBCA -2 pts >60 mos). Complications included infected pocket (2 pts) and duodenal fistula (1 pt).

Conclusion: Hepatic artery infusion alternating with systemic chemotherapy has apparent survival benefit in selected patients with persistent or progressive chemo resistant cancer from metastatic CRC, HCC or selected cancers (breast, lung, liver, gallbladder cancer) and warrants further study.

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Received Date: *22 Dec 2016*
Accepted Date: *15 Feb 2017*
Published Date: *17 Feb 2017*

Citation:
Wanebo HJ, Sanikommu SR, Taneja C, Begossi G, Belliveau J, Rathore R. Hepatic Artery Infusion for Recurrent or Chemo Resistant Hepatic Malignancy. Clin Oncol. 2017; 2: 1208.

Introduction

Colorectal hepatic metastases occurs as synchronous (20-25%) or metachronous lesions (60%) within 3 years following primary resection of colorectal cancer with most (75%) being unresectable [1-3]. Curative hepatic resection is possible in 15-25% of patients with survival ranging from 30-40% or higher in selected series from specialized centers. Modern Chemotherapy (CT) with 5FU, LV + Oxaliplatin (FOLFOX) OR 5FU, Irinotecan (FOLFIRI) has increased Overall Survival (OS) from the historic 6 months to 21 months in non-resectable patients [4-10]. Recent studies combining biologics with multi drug therapy has recorded responses up to 60% with Overall Survival of 25 months as in Crystal Study: utilizing Cetuximab and FOLFIRI in patients with KRAS Wildtype metastatic CRC Van Cutsem et al. [11]. Unfortunately, 30-35% of CRC pts have KRAS mutated cancers not responsive to biologics and have a recurrence rate of 36-40% [11-16]. Hepatic Artery Infusion (HAI) has provided an alternative to systemic CT failures as well as demonstrating significant survival advantage following hepatic resection and may be a useful adjunct in high risk patients or in good performance patients progressing with multi-drug therapy [17-33].

An earlier experience with hepatic infusion therapy in patients with advanced but not previously treated metastatic colorectal cancer has provided base line information for the current study. HAI-FUDR has a steep dose response curve resulting in a high first pass extraction previously ratio (100-400), fold concentration in the liver (with 15x increase in the tumor compared to <10 fold increase in liver after systemic therapy with 5FU, MMC(3) or Oxaliplatin. HAI has a half life of 15-19 hours. HAI/Irinotecan has an infusion advantage limited to 5 days [21,22, 24,30,32].

Methods

Patients with advanced hepatic malignancy unresponsive to systemic therapy were restaged by clinical and lab exam (LFT, Tumor markers), CT, MRI (conventional and with angiography) or CT angiography. In most cases an operative HAI catheter with infusion pump was placed or occasionally attached to a porta cath via percutaneous placed catheter. Selected resections were done if considered reasonable to augment oncologic outcome for patients with poorly responding lesions after multi drug therapy.

Preoperative imaging included CT scan, (Hepatic focus +/- contrast MRI +/- Angiogram (or CT angiogram), liver function tests including CEA levels, and ICG clearance studies were done in selected patients and were reassessed with CT scans and CEA levels after 2 treatment cycles. Patients were generally re-explored with planned resection if considered resectable or had resections of high risk lesions if easily and safely resected to reduce tumor burden.

Treatment Protocols are listed in Table 3. Colorectal cancer therapy included baseline continuous infusion of FUDR dexamethasone with systemic leukovorin (14 days) and bolus infusion of Oxaliplatin given on day 1 of HAI therapy. Systemic therapy was given after 5-6 day rest period on days 20-30 with bolus infusion of Oxaliplatin/Irinotecan and daily Capecitabine.

Initial Study: Pilot Study

The initial protocol utilized baseline data from earlier studies by Kemeny et al. [17,20,27-29]. Chemo therapy Regimen: (Table 1A) HAI.

A pilot study was carried out in 36 patients with untreated metastatic colorectal cancer, of whom 13 (36%) generated a measurable radiologic response in liver as demonstrated by pre therapy and post therapy volumetric measurements at 2 and 4 months (Table 2). Cross sectional measurements with volume calculation provided data on target lesions before treatment and at designated time points during and after treatment (2 and 4 months minimum). Greater than 50% volumetric regression occurred in 7 of 13 patients (54%) with <50% regression in 6 patients (46%). Progression of liver disease occurred in 7/36 (20%) and stable disease was measured in 16 (44%) of patients (Table 1B). The survival outcome in the 36 patients is shown in Figure 1.

Follow-up study

Patient groups under study include colorectal cancer 21 pts, primary liver cancer 10 pts (9 HCC, 1 cholangio CA), and miscellaneous group (6 pts). (Table 2,3) The colorectal cancer group (Table 2) consisted of 21 pts, 5 with synchronous cancer and 16 with metachronous lesions. Patients were considered failures of previous therapy, or had progressed after previous therapy with 5FU/LV or combination therapy with 5FU and Oxaliplatin or Irinotecan. Ten pts had progressed following previous resections or RFA (9 pts). Primary liver cancer included 10 pts (HCC) in 9 and intrahepatic cholangio CA in 1 (Table 3). A third group consisted of 6 pts having resection of miscellaneous cancers originating in lung (1), breast (2), gallbladder (2) or carcinoid (1) (Table 2).

Hepatic treatment for HCC mimicked the CRC protocol with bolus therapy of Doxorubicin being given on day 1 of the 14 day infusion with FUDR, Leukovorin/ Dexamethasone. Systemic therapy was given as in the CRC protocol with Oxaliplatin/Irinotecan on day 20 and daily Capecitabine on days 20-30. **Major complications** of HAI: Pump malfunction (4 pts required pump replacement), misperfusion 2 pts (required radiologic intervention to occlude gastroduodenal artery flow to duodenum), infected pocket 2 pts, duodenal fistula 1 pt from embedded catheter in duodenal wall.

Current study outcome: (Summarized in Table 4)

Colorectal Cancer Group: Of 21 previously treated pts subjected to HAI post liver recurrence (16 metachronous, 5 synchronous), the median survival was 18 months with 1 pt surviving over 60 month (6%). Among the 10 HCC pts (1 cholangio carcinoma), the median survival was 9 mos with 1 surviving 41 months. The single long term survivor had developed recurrence of HCC following a central hepatic resection at 26 months. Patient received HAI and selective RFA/TACE and survived 3.5 years post recurrence of the HCC (total survival was 67 months).

Discussion

Hepatic arterial chemo infusion was utilized to treat patients having failed or progressed on standardized therapy for hepatic metastases of colorectal cancer (21 pts), hepatocellular carcinoma (9 pts), and 6 miscellaneous hepatic metastases. The focus of this study was on overall survival rather than response rate in the liver which was considered too variable for precise measurements of target lesions in view of the patterns of recurrence in the liver and variability (regression of selected lesions with simultaneous progression of adjacent lesions). An initial study of HAI alone with FUDR, LV in patients with primary CRC recurrence of CRC in liver utilizing volumetric measurements demonstrated objective regression in 13 of 36 pts (36%) with calculated volumetric regression showing >50% volumetric regression in 7 pts (54%) and <50% in 6 pts (46%). Of the remaining 44%, 16 pts had stable disease and 20% (7 pts) showed progression. The median OS was 17 mos and 3 yr survival was 18%. The current treatment group pts included 21 patients with colorectal hepatic metastases CRC, of whom one half had progressed on FOLFOX/FOLFIRI and one half had progressed after resection +/- RFA. The median survival in the group was 17 months. Of the remaining 10 pts with primary liver cancer, there were 9 HCC (1 cholangio carcinoma). Recurrence or progression of disease occurred as failure of resection (4 pts) TACE/RFA (3 pts) and the group had median survival post HAI of 9 months. One patient had developed hepatic recurrence 24 mos after central hepatic resection for HCC and survived 3.5 yrs after initiation of HAI with supplemental RFA/TACE with an overall survival over 5.5 years. The remaining 6 pts represented various problems including advanced/recurrent malignancy (lung 1 pt, Br CA 2 pts, gallbladder CA 2 pts) and advanced hepatic carcinoid 1 pt. Overall survival in the miscellaneous group included 4 mos and 11 mos in the advanced carcinoid pt and lung cancer pt, 10 and 24 mos in 2 Br CA pts (post recurrence), and >60 mos in the 2 gallbladder patients post resection. Treatment was well tolerated

although there were technical problems with pump malfunctions (4 pts), misperfusion (2 pts), duodenal fistula and infected pocket (2 pts in the group of pump treated pts). Major drug toxicity was averted by close hematologic and liver function monitoring and dose reduction as needed. Any suggestion of intolerance to Oxaliplatin in previously exposed pts prompted switching to Cisplatin as the bolus therapy prior to HAI and as part of systemic therapy. Although selected pts showed significant objective responses in the liver, there was marked variability of responses within the same liver segments.

Of interest was a miscellaneous group of previously treated pts including 2 with advanced gallbladder cancer, both of whom survived >60 months after regional resection for Stage III gallbladder cancer, and subsequent HAI. Other patients had more variable outcome (metatastic Br CA pts had OS 23 & 9 mos), lung CA (11 mos), and 1 advanced carcinoid pt (4 mos). These patients represented a highly selected group with good PS and liver only disease.

The largest series of Regional Therapy for metastatic CRC is reported by Dr. Kemeny and colleagues at MSKCC [17,20,23,25,27]. She has also demonstrated significant improved DFS with adjuvant HAI in treated pts *vs.* systemic therapy [23,25,27]. The data is supported by previous reports by Kemeny [17,20] and also confirmed by Lygidakis, [34,35] but not by Lorenz where FU intra hepatic 5FU was used instead of 5FUDR [26].

A CALGB study reported by Kemeny utilized HAI/FUDR/Dex *vs.* Systemic FU/L in a multi center trial and recorded a response rate of 47% in HAI pts *vs.* 24% in systemic therapy pts with 2 yr estimated survival of 51% HAI *vs.* 35% with systemic therapy. The update of overall progression free survival was 31 mos with HAI [23,27].

Kemeny et al. [20] have also explored HAI with FUDR/Dex *vs.* Systemic Irinotecan/Oxaliplatin in 49 pts with non-resectable and previously treated CRC Hepatic Mets (86% had 6) or more segments involved and achieved resectability of 31% (-OS is pending) [25,28,29]. They also used HAI plus FUDR/Dex and systemic Irinotecan in another group of 39 previously treated CRC pts resulting in 18% resection/ablation rate [28,29].

A randomized study by Fiorentini reported on chemonaive pts with unresectable liver mets who were randomized to HAI FUDR +/- Systemic FU/LV [18]. Med survival was 20 months with combined therapy (HAI & Systemic 5 FU/LV) *vs.* 14 mos with HAI alone. HAI with systemic therapy was utilized as second line. In a Phase 2 study by Ducreux (36 pts), 89% had first line therapy, with HAI-FUDR/DEX and systemic Ox/IR *vs.* 15 pts treated with FUDR/DEX+Ox+FU [21]. The med survival was 36 mos in the Ox/IR gp, the RR was 90%, with the median survival of 22 mos in pts receiving Ox/FU. In follow-up study, the median OS was 41 mos in the chemo therapeutic treated group *vs.* 50.8 mos in the patients receiving HAI plus Systemic IR as second line therapy.

Gallagher reported on 39 pts previously treated with Oxaliplatin using HAI FUDR + Systemic Irinotecan therapy which resulted in partial response of PR of 44% and median survival of 20 mos [19].

Boige reported 44 pts with unresectable metastatic CRC of whom 95% had prior Oxaliplatin or Irinotecan or both [24] Therapy included 9 cycles HAI Ox + Systemic FU and leukovorin in 7 pts (10%) who went on to have an RO resection [24]. Ducreux utilized HAI- Ox + systemic FU + LV in 26 pts of whom 5 (19%) had surgical resection [21]. Phase I/II studies by Fiorentini evaluated HAI with

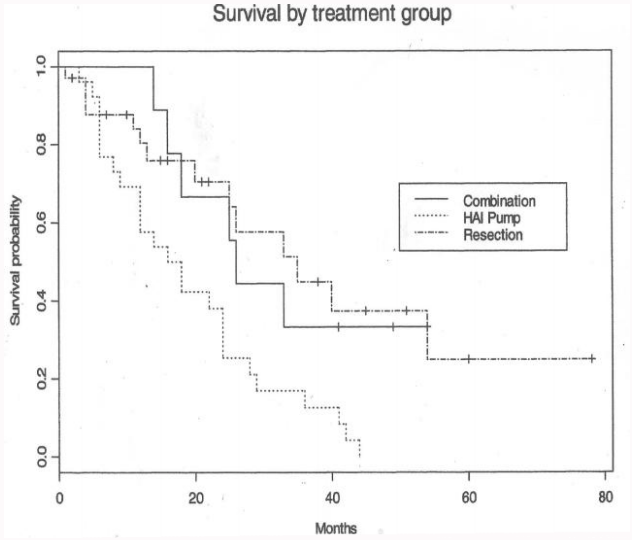

Figure 1: Hepatic Artery Infusion Metastatic Colorectal Cancer.
HAI Pump=36 pts - Initial study of Hepatic Metastasis group treated by HAI (36 pts), Hepatic resection (72 pts) +/- chemotherapy - Total Group.
Hepatic Artery Infusion in Metastatic Colorectal Cancer
HAI Pump 36 pts (combination HAI and Systemic therapy 9 patients), resection in 86 patients. Median OS=17 mos (HAI pump), 26 mos combination HAI and systemic CT and 34 mos with resection.

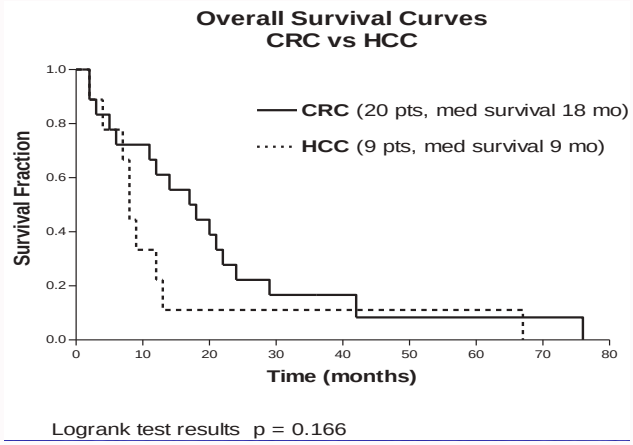

Figure 2: Overall Survival Curves – in 20 colorectal cancer (CRC) *vs.* 9 Primary Liver Cancer pts (9 with HCC).

Irinotecan given at 20mg/m^2/d x 5 days as continuous infusion or as a 200mg/m^2 (30 minutes) infusion in 100cc saline q 3 wks in a Phase II therapy study of 12 pts (6 post FOLFOX progression) [30]. This resulted in 4 PR and 6 progressions. Toxicity included diarrhea and myelosuppression in 6 pts (50%). They considered the 200mg dose to be well tolerated.

Advanced HCC is a greater challenge and is poorly responsive to systemic CT but frequently treatable with TACE/RFA. The BCLC (Barcelona Clinic Liver Ca Group) has utilized TACE based therapy for Stage B (Child B) good PS or (Child A) based on 7 randomized trials and demonstrated median OS ranging from 11-20 mos and RR 27% [33]. For more advanced stage C (portal invasion, N1, M1, PS 1-2), Sorafenib or clinical trial equivalent was recommended [34-36].

In our current study, HAI was examined in a selected group of HCC pts to explore regional CT; in this setting, TACE may provide added benefit and merits study.

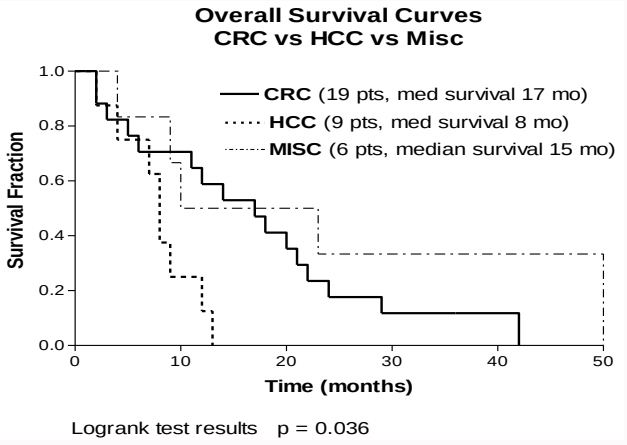

Figure 3: Overall Survival – Colorectal Cancer (CRC) *vs.* Primary Liver Cancer HCC 9, Cholangio CA 1 *vs.* Miscellaneous Hepatic Metastases (6 pts: Br CA (2 pts), Lung CA (1 pt), Carcinoid (1 pt), Gallbladder CA (2 pts).

Conclusion

Hepatic artery infusion alternating with systemic chemo therapy has apparent survival benefit in selected patients with persistent or progressive chemo resistant malignancy from metastatic CRC, HCC, or selected miscellaneous cancers (breast, lung, carcinoid, and gallbladder cancer) and warrants further study.

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