Folketinget
Folketingspartiernes sundhedsordførere
Christiansborg
1240 København K

16. januar 2006
Kaa/af

Vedlagte til Deres orientering.

Med venlig hilsen

Kristian Aabo
overlæge, dr.med.
medicinsk onkologisk afsnit
Viborg Sygehus

Formand for Kræftens Bekæmpelse
Anne Thomassen
Kræftens Bekæmpelse
Strandboulevarden 49
2100 København Ø

Viborg d. 16. januar 2006.

Kære Anne Thomassen.

Det var med interesse og forbavselse, at jeg d. 4. januar 2006 så TV-2 Nyhederne offentliggøre resultaterne af det af Kræftens Bekæmpelse sponsorerede fase 2 forsøg på Herlev Sygehus med hepatisk arterial infusion af cytostatika (HAI) til højt selekterede patienter med levermetastaser fra kolorektalcancer. Et beskedent materiale nuvel.

Det er glædeligt, at så mange patienter kan reddes med denne behandling. Vi må så håbe, at resultaterne holder.

Desværre har fase 2 resultater ofte ikke kunnet eftervises i randomiserede forsøg. Således har randomiserede undersøgelser indtil nu ikke kunnet vise en overlevelsesgevinst til fordel for HAI sammenlignet med konventionel systemisk intravenøs kemoterapi til denne patientgruppe på trods af, at HAI har været anvendt i 45 år (se venligst vedlagte publikationer). Konklusionen i disse arbejder er, at HAI, som iøvrigt ikke er uden komplikationer, ikke kan anbefales som rutinebehandling på nuværende tidspunkt - iøvrigt den samme konklusion, som vi kom til i en artikel i Ugeskrift for Læger (publiceret 22.3.2004) omhandlende patienter behandlet i Hammelburg, Tyskland.

Jeg forstår, at netop Hammelburgbehandlingerne var årsagen til, at Kræftens Bekæmpelse ønskede en dansk undersøgelse af regional kemoterapi for levermetastaser fra kolorektalcancer. I forbindelse med publiceringen af vores artikel i Ugeskrift for Læger, blev denne offentlig kaldt noget makværk af direktøren for Kræftens Bekæmpelse, Arne Rolighed. Dette gav efterdønninger i det onkologiske etablissement. Dette har han nu gentaget i Ekstrabladet d. 5.1.

Jeg skal derfor her udtrykke min misfornøjelse med Arne Roligheds opførsel på TV-2 Nyhederne d. 4.1., hvor han med slet skjult skadefryd, idet han fremviste forsiden af vores artikel, hoverende opfordrede til, at denne nye, fantastiske behandling, som nogle danske kræftspecialister ikke har kunnet anbefale, snarest på baggrund af de allerede opnåede resultater indføres i hele landet, hvorfor politikerene må til lommerne.

Inden HAI ukritisk indføres som standardbehandling i Danmark bør der nødvendigvis udføres randomiserede forsøg, som sammenligner denne behandling med konventionel systemisk behandling. Den ultimative effektparameter er ikke responsrate, men overlevelse. Kun en forbedring af overlevelsen for disse patienter kan retfærdiggøre en generel indførelse af behandlingen. Jeg må derfor fastholde, at regional kemoterapi for levermetastaser fortsat er eksperimentel, og at enkelte patientforløb ikke kan retfærdiggøre Arne Roligheds offentlige

miskreditering af visse kritiske danske kræftspecialister. Udtalelserne er med til at skabe utryg hed hos kræftpatienterne og endnu engang sætte systemet i selvsving. Mange af undertegnedes patienter ønsker nu "Herlevs mirakelbehandling". Arne Rolighed har således endnu engang skabt uro omkring kræftbehandlingen i Danmark til skade for patienterne og for Kræftens Bekæmpelses troværdighed.

Med venlig hilsen

Kristian Aabo
overlæge, dr.med.
medicinsk onkologisk afsnit
Viborg Sygehus.

Kopi til:
Direktør Arne Rolighed, Kræftens Bekæmpelse
Formand for Dansk Selskab for Klinisk Onkologi, ledende overlæge Niels Holm, OUH
Kræftstyregruppen, Sundhedsstyrelsen
Overlæge Benny Vittrup, onkologisk afdeling, Herlev Sygehus
Indenrigs- og sundhedsminister Lars Løkke Rasmussen
Folketingspartiernes sundhedsordførere
Formanden for Amtsrådsforeningens sundhedsudvalg, amtsborgmester Bent Hansen
Redaktionen TV-2 Nyhederne

Intra-arterial Floxuridine vs Systemic Fluorouracil for Hepatic Metastases From Colorectal Cancer

A Randomized Trial

J. Kirk Martin, Jr, MD; Michael J. O'Connell, MD; Harry S. Wieand, PhD; Robert J. Fitzgibbons, Jr, MD; James A. Mailliard, MD; Joseph Rubin, MD; David M. Nagorney, MD; Loren K. Tschetter, MD; James E. Krook, MD

• **Seventy-four patients with liver metastasis from proved colorectal primary adenocarcinoma were entered into a prospective, randomized clinical trial to evaluate treatment with intra-arterial floxuridine compared with standard outpatient therapy with fluorouracil delivered by intravenous bolus injection. Eligible patients were randomized to hepatic arterial chemotherapy with an implanted infusion pump or systemic chemotherapy. No crossover between treatment arms was permitted, and patients were followed up to progression and death. Objective tumor response was observed in 48% of patients receiving intra-arterial floxuridine and in 21% of patients receiving intravenous fluorouracil. Time to hepatic progression was significantly longer in the group given intra-arterial therapy: 15.7 vs 6.0 months. However, time to overall progression (6.0 vs 5.0 months) and survival (12.6 vs 10.5 months) were not statistically different. Based on these data, we cannot recommend treatment with intra-arterial floxuridine as given in this study for metastatic colorectal cancer to the liver.**

(*Arch Surg.* 1990;125:1022-1027)

The liver represents the most common site for visceral metastases from colorectal carcinoma, and in only about 5% of patients with colorectal liver metastases are the lesions surgically resectable for cure.[1-3] For unresectable lesions, standard intravenous fluorouracil produces a 15% to 20% response rate.

In 1982, Ensminger and associates[4] at the University of Michigan, Ann Arbor, reported an 83% response rate of hepatic metastases to the ongoing intra-arterial infusion of floxuridine by implanted pump. Investigators around the country were immediately interested in confirming this observation. While the data represented the results of an uncontrolled trial, others documented similar response rates in phase II studies.[5-7]

Our trial was stimulated by the data of Ensminger et al. The intent was to duplicate the method used, including the same drug and intra-arterial dose, and compare it in a prospective, randomized fashion with simple intravenous bolus fluorouracil. Since survival was the end point for both arms, we chose not to permit any crossover between treatment arms at the time of failure. By so doing, we hoped to preclude the difficulties inherent in two other phase III trials.[8-10] Neither of these could definitively address the impact of therapy with intra-arterial floxuridine on survival since patients in whom intravenous floxuridine treatment failed were allowed to cross over to intra-arterial therapy at the time of tumor progression.

SUBJECTS AND METHODS

Between November 1982 and October 1987, 74 patients with liver metastases from known colorectal primary adenocarcinomas were entered into a prospective, randomized clinical trial to evaluate treatment with intra-arterial floxuridine compared with standard outpatient therapy with fluorouracil given by intravenous bolus injection. Eligibility criteria included biopsy-proved unresectable liver metastases of colorectal origin and no evidence of extrahepatic metastases. All patients were ambulatory and all had measurable metastases and/or symptoms attributable to the metastases. Patients with small, asymptomatic liver metastases were not included in this study. Furthermore, patients with jaundice, underlying nonmalignant liver disease, ascites, prior chemotherapy, leukopenia, or thrombocytopenia were excluded. Eligible patients underwent evaluation, which included review of outside pathologic slides, routine clinical examination, chest roentgenography, and computed tomographic scanning of the abdomen. If no evidence of disease outside the liver was noted, patients were eligible for randomization.

Patients were then stratified according to performance status (as formulated by the Eastern Cooperative Oncology Group [ECOG],

Accepted for publication April 20, 1990.

From the Department of Surgery (Drs Martin and Nagorney), Division of Medical Oncology (Drs O'Connell and Rubin), and the Cancer Center Statistics Unit (Dr Wieand), Mayo Clinic, Rochester, Minn, and the Duluth (Minn) Clinic Community Clinic Oncology Program (Dr Krook); Creighton University, Omaha, Neb (Drs Fitzgibbons and Mailliard); and Sioux Community Cancer Consortium Community Clinic Oncology Program, Sioux Falls, SD (Dr Tschetter).

Read before the 97th Annual Meeting of the Western Surgical Association, St Louis, Mo, November 15, 1989.

Reprint requests to Department of Surgery, Mayo Clinic Jacksonville, 4500 San Pablo Rd, Jacksonville, FL 32224 (Dr Martin).

Randomized, Multicenter Trial of Fluorouracil Plus Leucovorin Administered Either Via Hepatic Arterial or Intravenous Infusion Versus Fluorodeoxyuridine Administered Via Hepatic Arterial Infusion in Patients With Nonresectable Liver Metastases From Colorectal Carcinoma

By Matthias Lorenz and Hans-Helge Müller for the German Cooperative Group on Liver Metastases

Purpose: **To assess the efficacy and tolerability of three treatments for patients with documented adenocarcinoma of the colon and/or rectum who have undergone complete resection of primary tumor and have nonresectable liver metastases that do not exceed 75% of the liver volume.**

Patients and Methods: **A total of 168 patients at 25 treatment centers were enrolled onto this prospective, multicenter, randomized study. The three treatment arms were as follows: (1) fluorouracil (5-FU)/leucovorin (LV) administered via hepatic arterial infusion (HAI), (2) 5-FU/LV administered via intravenous (IV) infusion, and (3) fluorodeoxyuridine (FUDR) administered via HAI.**

Results: **Median times to disease progression for the three treatment arms were as follows: 9.2 months for patients treated with HAI 5-FU/LV, 6.6 months for IV 5-FU/LV, and 5.9 months for HAI FUDR. Median survival times for patients treated with HAI 5-FU/LV, IV 5-FU/LV, and HAI FUDR were 18.7 months, 17.6 months, and 12.7 months, respectively. There was a nearly two-fold increase in time to progression in addition to a survival benefit among patients with an intrahepatic tumor burden of less than 25% who were treated with HAI 5-FU/LV. The most common adverse events were stomatitis, nausea and vomiting, skin irritation, diarrhea, and elevated serum levels of liver enzymes. Some patients exhibited severe reactions, including biliary sclerosis and chemical hepatitis.**

Conclusion: **Although the use of HAI 5-FU/LV as a means of treating liver metastases after resection of colorectal carcinoma warrants further investigation, it cannot be recommended as a routine therapeutic measure at this time.**

J Clin Oncol 18:243-254. © 2000 by American Society of Clinical Oncology.

COLORECTAL CANCER is one of the most common malignancies of both men and women in Europe and North America.[1,2] In Germany, approximately 40,000 to 47,000 cases are diagnosed each year.[3] As many as 50% of patients with colorectal carcinoma present with synchronous or will develop metachronous liver metastases.[4-6] In approximately one half of these patients, metastatic disease is confined to the liver[7,8]; however, curative resection of liver metastases is possible in less than 25%.[8,9] In patients with colorectal carcinoma and nonresectable isolated liver metastases, hepatic tumor burden, performance status, and site of the primary tumor are regarded as important prognostic factors.[10-13]

Because of the dual blood supply to the liver and the fact that liver metastases larger than 0.5 cm derive most of their blood supply from the hepatic artery, hepatic arterial infusion (HAI) of cytotoxic agents has been used since 1959 in an effort to maximize local concentration and improve response.[14,15] The fluorouracil (5-FU) analog fluorodeoxyuridine (FUDR) is used for the intrahepatic treatment of liver metastases because of its favorable pharmacokinetic properties, nearly complete intrahepatic removal, and minimal systemic toxicity.[16,17] An implanted FUDR infusion pump has facilitated treatment on an outpatient basis and has resulted in improved quality of life.[18]

The response rates with HAI FUDR in patients with metastatic colorectal carcinoma vary from 30% to 88% in phase II trials.[19-23] These encouraging results led to the investigation of HAI FUDR (0.2 to 0.3 mg/m^2/d for 2 weeks every 4 weeks) in randomized trials.[24-30] In five of these seven trials, HAI FUDR was compared with FUDR administered systemically for 14 days every 28 days and 5-FU

From the Department of General and Vascular Surgery, Johann Wolfgang Goethe-Universität, Frankfurt am Main, and Institute for Medical Biometry and Epidemiology, Philipps-Universität, Marburg, Germany.

Submitted December 28, 1998; accepted August 17, 1999.

Sponsored by the Donors Association for the Promotion of Sciences and Humanity in Germany (Essen) and supported by the German Cancer Society (Frankfurt am Main), B. Braun-Dexon GmbH (Spangenberg), and Wyeth-Lederle (Münster, Germany).

Address reprint requests to Prof Dr Matthias Lorenz, Department of General and Vascular Surgery, Johann Wolfgang Goethe-University, Theodor-Stern-Kai 7, 60590 Frankfurt am Main, Germany; email m.lorenz@em.uni-frankfurt.de.

0732-183X/00/1802-243

Intrahepatic arterial versus intravenous fluorouracil and folinic acid for colorectal cancer liver metastases: a multicentre randomised trial

David J Kerr, Colin S McArdle, Jonathan Ledermann, Irving Taylor, David J Sherlock, Peter M Schlag, John Buckels, David Mayer, Dionne Cain, Richard J Stephens, on behalf of the MRC and EORTC colorectal cancer study groups

Summary

Background The liver is the most frequent site for metastases of colorectal cancer, which is the second largest contributor to cancer deaths in Europe. We did a randomised trial to compare an intrahepatic arterial (IHA) fluorouracil and folinic acid regimen with the standard intravenous de Gramont fluorouracil and folinic acid regimen for patients with adenocarcinoma of the colon or rectum, with metastases confined to the liver.

Methods We randomly allocated 290 patients from 16 centres to receive either intravenous chemotherapy (folinic acid 200 mg/m², fluorouracil bolus 400 mg² and 22-h infusion 600 mg/m², day 1 and 2, repeated every 14 days), or IHA chemotherapy designed to be equitoxic (folinic acid 200 mg/m², fluorouracil 400 mg/m² over 15 mins and 22-h infusion 1600 mg/m², day 1 and 2, repeated every 14 days). The primary endpoint was overall survival, and analysis was by intention to treat.

Findings 50 (37%) patients allocated to IHA did not start their treatment, and another 39 (29%) had to stop before receiving six cycles of treatment because of catheter failure. The IHA group received a median of two cycles (0–6), compared with 8·5 (6–12) for the intravenous group. 45 (51%) IHA patients who did not start or did not receive six cycles switched to intravenous treatment. In both groups, grade 3 or 4 toxicity was uncommon. Median overall survival was 14·7 months for the IHA group and 14·8 months for the intravenous group (hazard ratio 1·04 [95% CI 0·80–1·33], log-rank test p=0·79). Similarly, there was no significant difference in progression-free survival.

Interpretation Our results showed no evidence of an advantage in progression-free survival or overall survival for the IHA group; thus continued use of this regimen cannot be recommended outside of a clinical trial.

Lancet 2003; **361:** 368–73. Published online Jan 21, 2003
http://image.thelancet.com/extras/02art3088web.pdf
See Commentary page 358

Department of Clinical Pharmacology, University of Oxford, Radcliffe Infirmary, Oxford OX2 6HE, UK (Prof D J Kerr FRCP); **Department of Surgery, Glasgow Royal Infirmary, Glasgow, UK** (Prof C S McArdle FRCS); **Department of Surgery and Oncology, University College London, London, UK** (J Ledermann FRCP, Prof I Taylor FRCS); **North Manchester General Hospital, Manchester, UK** (D J Sherlock FRCS); **Department of Surgery, Robert Roessle Klinik, Humboldt University, Berlin, Germany** (P M Schlag MD); **Liver Unit, University Hospital Trust Birmingham, Birmingham, UK** (J Buckels FRCS, D Mayer FRCS); **Cancer Division, Medical Research Council Clinical Trials Unit, London** (D Cain MSc, R J Stephens)

Correspondence to: Prof David J Kerr
(e-mail: david.kerr@clinical-pharmacology.oxford.ac.uk)

Introduction

Colorectal cancer is the second largest contributor to cancer deaths in Europe, with around 150 000 new cases per year. Although surgery of curative intent is undertaken in 60–75% of patients, 50% will relapse with local recurrence, peritoneal carcinomatosis, or distant metastases. The liver is the most common site of metastasis; about 80% of patients who die have hepatic disease, and up to 20% of patients presenting at first relapse have disease macroscopically confined to the liver.[1]

For patients with advanced disease, there is no doubt that systemic chemotherapy with fluorouracil is still the therapeutic mainstay some 40 years after it was introduced. This drug has greater survival and quality-of-life benefits than the best supportive care.[2] At the time this trial was designed—ie, before the emergence of new drugs such as irinotecan and oxaliplatin—the treatment approach was to provide an optimum dose, schedule, and mode of delivery, of fluorouracil and folinic acid.[3,4] Intrahepatic arterial (IHA) chemotherapy relies on the premise that cytotoxic drugs have steep dose-response curves, and that fluorouracil undergoes arterial extraction at first pass, thus generating high drug concentrations in the liver (an 80–100-fold advantage compared with intravenous administration). The liver has a dual blood supply, and metastatic nodules more than 1 cm in diameter are vascularised via the hepatic artery. Therefore, there is a compelling pharmacological rationale for IHA chemotherapy for hepatic metastases.[5–9]

Before we started this trial, seven randomised trials comparing IHA with intravenous infusion of fluoropyrimidines (fluorouracil or floxuridine) or best supportive care had been published.[10–16] However, several features of these trials have made interpretation difficult: most trials allowed crossover from intravenous adminstration to IHA; the trials tended to be underpowered; in two trials, the comparator group was best supportive care or ad hoc chemotherapy; and the drugs, doses, and schedules used often differed substantially between IHA and intravenous groups. Floxuridine is not licensed for use in the UK and the implantable pumps required for its delivery were prohibitively expensive; therefore, a fluorouracil-based schedule was developed.

One of the most widely used European intravenous regimens, the de Gramont regimen,[4] combines fluorouracil and folinic acid, administered for 48 h every 2 weeks. This regimen has served as the standard group in consecutive trials done by the Medical Research Council's (MRC) colorectal cancer group. An IHA regimen was tested in a phase 1 clinical and pharmacokinetic study, with the same agents and schedule as the de Gramont regimen, adjusted to induce the same level of toxicity and steady-state venous fluorouracil concentrations as that in the intravenous regimen.[17] 43 patients who had not had previous chemotherapy participated in the trial. Objective responses were seen at each dose level, and there was an overall