Does chemotherapy given directly to the liver improve survival in patients with hepatic metastasis?

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A study using hepatic arterial infusion to deliver treatment to colorectal cancer patients with liver metastases is unlikely to lead to wholesale changes in clinical practice, but may spur new studies into the role of local delivery of triple combination chemotherapy in these patients.

A randomised study of intravenous chemotherapy with 5-fluorouracil and leucovorin (folinic acid [FA]) versus prolonged hepatic arterial infusion (HAI) of fluorodeoxyuridine in patients with unresectable hepatic metastases from colorectal cancer (see opposite) has shown significantly improved overall survival, response rates and time to hepatic progression for fluorodeoxyuridine HAI, although time to extrahepatic progression was significantly shorter. Are these data sufficiently compelling for us to consider fluorodeoxyuridine HAI a new standard therapy for chemotherapy-naive patients with hepatic metastases?

The pharmacokinetic principles underpinning fluorodeoxyuridine HAI and 5-fluorouracil are compelling, as first-pass arterial extraction following HAI delivers a large fraction (60–80% of the delivered dose) of the cytotoxic agent directly to the liver. Given the steep dose-response curves and narrow therapeutic windows associated with these agents, significantly enhanced cytotoxic drug delivery results in higher intratumoural drug concentrations and higher consequent tumour-cell kill.

There are a few interpretative problems with the current study: the trial is rather small, especially for the marker component of the study; it is not a true comparison of the contribution of hepatic arterial delivery of chemotherapy, because the cytotoxic agents and the schedules for the two arms of the study are different; and it is possible that a degree of patient selection operated across the trial, as implied by the surprisingly long median duration of survival for patients receiving bolus 5-fluorouracil/FA.

Other well-designed trials comparing HAI and intravenous chemotherapy in this setting have not shown survival benefits for regional drug delivery.

The largest such study[1] randomised patients to identical 5-fluorouracil/FA regimens administered via the hepatic artery or intravenously. The use of ports rather than pumps in this study may have contributed to a higher technical failure rate in the HAI arm and therefore to the null effect.

It could be argued that HAI is technically cumbersome and expensive, requires a laparotomy, and has been bypassed by innovations in the management of hepatic metastatic colorectal cancer such as intravenous combination chemotherapy with irinotecan and oxaliplatin, the anti-angiogenic agent bevacizumab[2] and the anti-EGFR antibody cetuximab. Review of sequential clinical trial data from patients with advanced colorectal

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cancer suggests that median survival has risen over the past two decades from around 6 months to 24 months with modern systemic chemotherapy.[3]

On balance, however, the results of Kemeny et al. seem a timely reminder that we should adapt HAI to embrace advances in systemic chemotherapy.

Ongoing trials are exploring HAI of oxaliplatin[4] in combination with regional or systemic infusional 5-fluorouracil and bevacizumab or cetuximab.

Given the differential extrahepatic progression rate seen in the current study, a number of these studies are likely to unite regional and systemic treatment, but it could well be possible to administer drugs that are not limited by hepatobiliary toxicity via the hepatic artery in order to saturate the liver, and allow 'spillover' to generate equivalent venous concentrations, toxicity and pharmacokinetic properties to conventional intravenous schedules.

It is extremely unlikely that HAI fluorodeoxyuridine will be adopted wholesale as a novel frontline therapy for hepatic metastatic colorectal cancer, but this paper will serve as an important spur for the relevant phase II triple combination studies to be initiated using HAI chemotherapy.

Details of the references cited in this article can be accessed at www.cancerworld.org/cancerworld

Synopsis

N Kemeny, D Niedzwiecki, DR Hollis, et al. (2006) **Hepatic arterial infusion versus systemic therapy for hepatic metastases from colorectal cancer: a randomized trial of efficacy, quality of life, and molecular markers (CALGB 9481).** *J Clin Oncol 24:1395–1403*

Background. Metastasis to the liver occurs in approximately 60% of patients with metastatic colorectal cancer, and most patients with these liver tumours eventually die of their disease. Whereas the blood supply for normal liver parenchyma is via the portal vein, hepatic metastases receive most of their blood supply from the hepatic artery, so interest has been focused on the use of hepatic arterial infusion (HAI) for administering chemotherapy.

Objective. To assess whether HAI extends survival and improves tumour response and quality of life in patients with colorectal cancer that has spread to the liver.

Design and intervention. In this cooperative group trial, between 15 January 1996 and 29 December 2000, nine sites randomly assigned patients to receive either HAI with fluorodeoxyuridine, leucovorin (folinic acid [FA]) and dexamethasone or systemic chemotherapy with intravenous infusion of fluorouracil and FA. Resection of the primary tumour had been performed 3–4 weeks previously. No crossover between the study arms was permitted. All patients had histologically confirmed colorectal carcinoma with unresectable liver metastases over less than 70% of the liver parenchyma, and no extrahepatic disease on radiology. Patients with a previous or concurrent malignancy or impaired haematological or renal function were excluded.

Outcome measures. The primary endpoint was overall survival; toxicity, tumour response and quality of life were also evaluated.

Results. Patients receiving HAI (n=68) lived longer than those receiving systemic chemotherapy (n=67), with a median overall survival of 24.4 versus 20 months (P=0.0034). In comparison with the systemic chemotherapy group, patients receiving HAI had superior response rates (47% vs 24%; P=0.012) and longer time to disease progression in the liver (9.8 months vs 7.3 months; P=0.034), but shorter time to extrahepatic progression (7.7 vs 14.8 months; P=0.029). Diarrhoea, neutropaenia, and stomatitis were more frequent in the systemic chemotherapy group than the HAI group. Bilirubin elevation occurred in 18.6% of patients receiving HAI, but this was temporary in most cases. Improved physical functioning was observed in the HAI group at the three-month and six-month quality-of-life follow-up evaluations. For both methods of treatment, women fared better than men. Median survival was 29.4 and 22 months, respectively, for women and men in the HAI group, and 20.1 and 18.3 months, respectively, for women and men receiving systemic therapy (interaction P=0.016). A greater proportion of men than women receiving HAI had biliary toxicity (37% and 15% respectively; P=0.05).

Conclusions. HAI provides superior survival and better physical functioning than systemic therapy with the same agents for patients with metastasis of colorectal cancer to the liver.

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