Basic research supported developments of chemotherapy in nonresectable isolated colorectal liver metastases to a protocol of hepatic artery infusion using mitoxantrone, 5-FU + folinic acid and mitomycin C.

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OBJECTIVE: Since the developments in systemic chemotherapy of metastasized colorectal cancer have not resulted in substantial gains in survival times, we wished to improve the course of isolated nonresectable colorectal liver metastases (CRLM) by hepatic arterial infusion treatment. BACKGROUND: Patients (pts) with CRLM have a worse fate than those pts whose liver metastases could be resected. Systemic (i.v.) chemotherapy for CRLM colorectal metastases does not improve survival to a relevant level (median survival time (med. surv.) after 5-Fluorouracil + Folinic Acid (5-FU + FA) i.v.: 6.4-14.3 months (m)). Hepatic artery infusion (HAI) with 5-Fluorode-oxyuridine (5-FUDR) has been demonstrated in a metaanalysis of randomized trials to be superior to i.v. treatment/palliative care (med. surv.: 15 vs. 10 m). The benefit of HAI with 5-FUDR, although recommended as treatment for CRLM, is severely compromised by the 5-FUDR induced hepatotoxicity, leading eventually to sclerosing cholangitis (SC)/liver scirrhosis. We have stepwise developed a protocol for HAI of CRLM, which is superior to HAI with 5-FUDR, and, most evidently, to systemic chemotherapy.

PATIENTS/METHODS: Between 1982-1997, 222 CR (L) M patients were treated within subsequent protocols (Table). In protocol A, 68 CRLM pts received HAI with 5-FUDR (A1: nonrandomized pts; A2: randomized pts). In protocol B (randomized pts.), 46 pts received 5-FUDR i.a. (via HAI) + i.v. In protocol C, systemic chemotherapy with 5-FU + FA was conducted in 34 pts with metastasized colorectal cancers, including CRLM. In protocol D 5-FU + FA was delivered via HAI in 25 pts with CRLM. In protocol E, based on in vitro phase II studies and the results of protocol D, Mitoxantrone and Mitomycin C were added to 5-FU + FA (MFFM). Fifty (50) CRLM pts received HAI with MFFM. RESULTS: The response rates, med. surv. times, systemic toxicity and SC rates are shown in the table. HAI with MFFM produced objective responses in 66%, the med. surv. was 27.4 m, and no SC occurred. The ports surgically placed for HAI, e.g., in protocols D and E, functioned in 90%, 82%, and 76% 6, 9, and 11 m after start of the HAI. Quality of life in protocol E was high. Nine pts from protocols D + E with either partial (PR, 7 pts) or complete (CR, 2 pts) remissions received a secondary liver resection without hospital mortality, and 7/9 pts are living 2-58 m after liver resection, 2/9 pts died 11 and 22 m after resection. [table: see text] SUMMARY/CONCLUSIONS: Our learning curve to achieve optimal treatment of CRLM resulted in a protocol using HAI with MFFM. The results of this protocol (E) including the high remission rate, long median survival time, good port function, high quality of life, and, most interestingly, the possibility to downstage and resect primarily nonresectable metastases, seem to be superior to HAI with 5-FUDR of 5-FU + FA and to systemic chemotherapy with 5-FU + FA. This hypothesis is currently examined in a phase III study (HAI with MFFM vs. 5-FU + FA i.v.).

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