

Hepatic arterial infusion in gastric carcinoma liver metastases: a pooled analysis of the literature

Bohuslav Melichar^{1,2}, Karolina Melicharová³

¹ Department of Oncology and Radiotherapy, Charles University Teaching Hospital, Hradec Králové, Czech Republic

² Department of Internal Medicine, Charles University, Faculty of Medicine, Hradec Králové, Czech Republic

³ Department of Gerontology and Metabolic Care, Charles University Teaching Hospital, Hradec Králové, Czech Republic

Melichar B, Melicharová K. Hepatic arterial infusion in gastric carcinoma liver metastases: a pooled analysis of the literature. *Folia Gastroenterol Hepatol* 2004; 2 (4): 156 - 164.

Abstract. Background. Liver-directed therapeutic approaches, e.g. resection or hepatic arterial infusion (HAI), have not been widely used in patients with gastric cancer liver metastases because of frequent presence of extra-hepatic disease, and the published experience is scanty. We performed a pooled analysis of reports of HAI in gastric cancer liver metastases.

Methods. Reports on HAI in gastric cancer liver metastases were identified through searching the MEDLINE database. A total of 47 reports of 192 patients were included in the pooled analysis. The survival was analyzed by the Kaplan-Meier method. Univariate analysis was performed by the log-rank test, and multivariable analysis was performed by the Cox regression method.

Results. Complete response was reported in 19 % and partial response in 45 % of the patients. The median survival of all patients was 14 months. On univariate analysis, survival was significantly longer in patients with objective response, those reported in papers describing 1 or 2 cases, in males, patients with H1 or H2 metastases, and in patients treated by liver resection. On multivariable analysis, objective response, metastasis stage, HAI of anthracyclines and number of patients per report were independent indicators of survival.

Conclusions. HAI may be effective in the rare patient with isolated gastric cancer liver metastases. The prognosis is significantly better in patients who attained an objective response, H1 or H2 metastases, and in patients treated with anthracyclines. Longer survival of patients reported in papers describing 1 or 2 cases is explained by a publication bias that represents the most serious limitation of the present analysis.

Key words: hepatic arterial infusion, gastric carcinoma, liver metastases

Melichar B, Melicharová K. Jaterní arteriální infuze v léčbě jaterních metastáz karcinomu žaludku: souhrnná analýza literatury. *Folia Gastroenterol Hepatol* 2004; 2 (4): 156 - 164.

Souhrn. Východiska. Léčebné postupy zaměřené na játra, např. resekce nebo jaterní arteriální infuze, se u nemocných s jaterními metastázami karcinomu žaludku příliš neuplatňují z důvodů přítomnosti extrahepatického postižení ve většině těchto případů. Publikované zkušenosti na toto téma jsou vzácné. Provedli jsme souhrnnou analýzu publikovaných případů použití jaterní arteriální infuze u nemocných s jaterními metastázami při karcinomu žaludku.

Metodika. Sdělení týkající se jaterní arteriální infuze byly vyhledány pomocí databáze MEDLINE. Celkem 47 sdělení o 192 pacientech bylo zahrnuto v souhrnné analýze. Přežití bylo analyzováno Kaplan-Meierovou metodou. Univariátní analýza byla provedena pomocí log-rank testu, multivariátní analýza byla provedena pomocí Coxovy regrese.

Výsledky. Úplná odpověď byla popsána u 19 % a částečná odpověď u 45 % nemocných. V univariální analýze bylo přežití delší u nemocných s objektivní odpovědí, u nemocných popsaných ve sděleních o 1 či 2 případech, u mužů, u pacientů s H1 nebo H2 metastázami a u nemocných, u kterých byla provedena resekce jater. Objektivní odpověď, stadium metastáz, použití antracyklinů v jaterní arteriální infuzi a počet pacientů popsaných ve sdělení byly nezávislými ukazateli přežití v multivariální analýze.

Závěr. Jaterní arteriální infuze může být účinnou léčbou ve vzácných případech izolovaného metastatického postižení jater při karcinomu žaludku. Prognóza je významně lepší u nemocných, u kterých bylo dosaženo objektivní odpovědi, nemocných s H1 nebo H2 metastázami a nemocných léčených antracykliny. Delší přežití nemocných ve sděleních popisujících 1 nebo 2 případy svědčí pro selektivní publikaci pozitivních výsledků, která je nejzávažnějším omezením provedené analýzy.

Klíčová slova: jaterní arteriální infuze, karcinom žaludku, jaterní metastázy

Introduction

The liver is a common site of metastatic disease in gastric carcinoma, and the prognosis of patients with liver metastases of this tumour is poor. Liver-directed therapeutic approaches have not been widely employed in this setting because of the frequent presence of extrahepatic disease. For example, in one series of patients with synchronous liver metastases and resected primary gastric cancer, liver resection was performed only in 3 out of 29 cases (17). Similarly, among 414 patients treated by liver-directed therapies in another retrospective report, there were only 4 patients with gastric tumours, including patients with gastric sarcomas (65). Several retrospective series have reported the results of liver resection in patients with gastric carcinoma liver metastases (13, 15, 30, 46, 53). Only 10 to 21 patients have been included in each of these reports. Median survival time and 5-year survival rates ranged from 11 to 49 months and 0 to 34 %, respectively. Even less is known about the liver-directed chemotherapy, administered as hepatic arterial infusion (HAI) or chemoembolization in gastric carcinoma metastatic to the liver, the majority of reports being either small studies, case reports, or even pilot studies including patients with different primaries metastatic to the liver. In the largest study of HAI in patients with gastric cancer metastatic to the liver, 20 out of 83 patients were not evaluable, mostly because of early progression (34).

HAI of cytotoxic agents in patients with liver metastases is associated with higher intratumoral drug concentration as well as less systemic toxicity (80). In patients with colorectal cancer liver metastases these theoretical advantages translate into a superior response rate (44) and quality of life (12), but it is not clear whether HAI leads to an improvement in survival. The use of HAI in patients with liver metastases of

other primary tumours is even more disputed. Liver metastases originating from different primary tumours are classified with regard to the use of liver-directed therapies into 3 subgroups: tumours in which the liver-directed therapies are often appropriate (e.g. colorectal carcinoma), occasionally appropriate (e.g. breast carcinoma), or seldom appropriate (e.g. lung carcinoma). Because of the scarcity of the data and mostly poor long-term survival in the largest reported series, regional liver-directed approaches are generally considered to be rarely appropriate in patients with gastric cancer metastatic to the liver (14).

At our centre, only 4 patients with gastric carcinoma liver metastases have been treated using HAI between January 1, 1991 and December 31, 2002 (43). Because of limited experience with HAI in gastric cancer metastatic to the liver in our centre and elsewhere, we performed a pooled analysis of the results from a small series published in English. However, sufficient data on individual patients were available only for a portion of reported cases (25 out of 297 cases; 8 %). Objective response was observed in 12 patients (48 %), and the median survival of all 25 patients was 10 months. On univariate analysis, the survival was significantly shorter in patients who progressed, patients with H3 metastases and in patients not treated by HAI of anthracyclines. Longer survival was observed in patients with complete or partial response. On multivariable analysis, only the absence of complete or partial response and the stage (H1 or H2) of the metastases were independent indicators of survival (43). Reports on HAI published in Japanese and single case reports were not included in this earlier pooled analysis. Because most of the reports about HAI in gastric carcinoma metastatic to the liver were published in Japanese literature and/or as single case report, a more comprehensive analysis inclu-

ding Japanese language reports and reports reporting only one case has been performed, which is presented in this paper.

Methods

Reports on HAI or chemoembolization in gastric carcinoma metastatic to the liver were identified by searching the MEDLINE database and reference lists of publications (Table 1). Only reports with data on individual survival of patients were used for a pooled analysis. A total of 47 papers (listed in Table 2) published between 1984 and 2004 reporting 192 patients were included in the pooled analysis. The median number of cases per report was 2 (range 1 - 20). In the staging system of liver metastases used in most of the reports,

H1 denotes metastases limited to one lobe, H2 denotes few (2 - 3) metastases in both lobes, and H3 denotes massive involvement of both lobes (17,54). Survival was analyzed by the Kaplan-Meier method. Univariate analysis was performed by the log-rank test, and multivariable analysis was performed by Cox regression method using the NCSS 2001 software (Number Cruncher Statistical Systems, Kaysville, Utah, USA). The decision concerning statistical significance was based on $p = 0.05$ significance level.

Results

Unlike in the larger studies, the presence of extrahepatic disease at the diagnosis of liver metastases was stated in only 12 out of 192 patients, and, al-

Table 1

Summary of the reported results of HAI and chemoembolization in patients with gastric carcinoma metastatic to the liver

reference	therapy used	n	CR (%)	PR (%)	median survival (months)
(74)	chemoembolization	12	0 (0)	1 (8)	8
(74)	HAI (5FU+DXR)	12	0 (0)	3 (25)	> 23
(34)	HAI (5FU+MMC+epirubicin)	63	3 (5)	32 (51)	11
(86)	HAI (MMC)	19	5 (26)		3
(86)	HAI (MMC+CDDP)	24	17 (71)		12
(54)	HAI (5FU+MMC+lentinan)	15	ND	ND	4
(54)	resection + HAI (5FU+MMC+lentinan)	9	ND	ND	27
(36)	HAI (5FU+MMC+CDDP+DXR)	21	ND	ND	8
(11)	HAI (5FU+MMC+DXR)	13	ND	ND	12
(37)	HAI (5FU+CDDP)	9	0 (0)	1 (11)	4
(28)	HAI (5FU+MMC)	14	0 (0)	5 (36)	9
(8)	HAI (5FU+CDDP+DXR)	34	4 (12)	18 (53)	15
(35)	HAI + resection	8	ND	ND	12
(31)	HAI + repeated hepatic dearterialization	7	0 (0)	5 (71)	12
(18)	HAI (5FU+CDDP)+ hyperthermia	3	0 (0)	2 (67)	11
(18)	HAI (5FU+CDDP)	10	0 (0)	1 (10)	3
(4)	HAI (5FU+DXR+MMC)	18	1 (6)	8 (44)	6
(79)	HAI (different agents)	16	4 (25)	6 (38)	13
(19)	HAI (5FU+epirubicin+MMC)	7	1 (14)	1 (14)	14
(19)	HAI (different agents)	10	0 (0)	1 (10)	5
(26)	HAI (5FU+MMC+angiotensin II)	6	2 (33)	2 (33)	15
(50)	HAI (5FU+CDDP)	11	1 (9)	5 (45)	11
(71)	HAI (different agents)	11	3 (27)	1 (9)	13
(83)	HAI (5FU+DXR+MMC+ angiotensin II)	15	0 (0)	5 (33)	14
(52)	HAI (5FU+MMC+angiotensin II)	11	3 (27)	3 (27)	12
(67)	HAI (5FU+CDDP)	9	2 (22)	4 (44)	15
(59)	HAI (CDDP + MMC) + oral UFT	20	1 (5)	14 (70)	11
(39)	HAI (different regimens)	7	0 (0)	3 (43)	15
(27)	HAI (different regimens)	6	1 (17)	2 (33)	10
(7)	HAI (MMC + CDDP, 5FU, MTX) + noradrenaline	8	1 (13)	4 (50)	26
(85)	HAI (MMC + CDDP) + oral UFT + hyperthermia	12	1 (8)	8 (67)	7
(73)	HAI (5FU + carboplatin)	13	ND		9

5FU 5-fluorouracil; CDDP cisplatin; DXR doxorubicin; FA folinic acid; MMC mitomycin C; MTX methotrexate; ND not determined; VP16 etoposide

Table 2
Reports with data on single patients used for the pooled analysis

reference	number of patients
(59)	20
(79)	16
(28)	14
(85)	12
(71)	11
(50)	11
(52)	11
(67)	9
(7)	8
(39)	7
(27)	6
(26)	6
(55)	5
(84)	4
(62)	4
(43)	4
(25)	3
(22)	3
(47)	3
(69)	2
(45)	2
(32)	2
(61)	2
(16)	2
(49)	2
(20)	2
(5)	1
(6)	1
(58)	1
(1)	1
(23)	1
(42)	1
(72)	1
(48)	1
(2)	1
(66)	1
(51)	1
(70)	1
(9)	1
(41)	1
(78)	1
(60)	1
(77)	1
(81)	1
(40)	1
(76)	1
(75)	1

Table 3
Results of univariate analysis

variable		survival (months)	p
number of cases per report	< 2 (n = 35)	18	0.001
	> 2 (n = 157)	12	
sex	male (n = 138)	15	0.05
	female (n = 43)	11	
age	< 65 years (n = 89)	13	0.70
	> 65 years (n = 92)	15	
synchronous or metachronous	synchronous (n = 91)	15	0.90
	metachronous (n = 48)	16	
metastasis stage	H1 or H2 (n = 56)	16	0.03
	H3 (n = 71)	11	
HAI fluoropyrimidines	yes (n = 101)	16	0.17
	no (n = 70)	12	
HAI platinum	yes (n = 90)	16	0.54
	no (n = 81)	13	
HAI anthracyclines	yes (n = 40)	18	0.06
	no (n = 131)	14	
HAI MMC	yes (n = 103)	14	0.54
	no (n = 68)	16	
liver resection	yes (n = 13)	29	0.0008
	no (n = 123)	13	
liver-directed procedure other than resection or HAI	yes (n = 24)	14	0.52
	no (n = 112)	15	
objective response	yes (n = 122)	18	0.00001
	no (n = 70)	7	

though sufficient details were missing in some reports, it might be assumed that an overwhelming majority of the patients had no extrahepatic metastases at the time of diagnosis of liver metastases. The median age of patients was 65 years. Among the 192 patients analyzed, complete response was observed in 36 cases (19 %) and partial response in 86 cases (45 %) for an overall response rate of 64 %. Thirty-two patients (17 %) had stable disease, 34 patients (18 %) progressed and 4 patients (2 %) were not evaluable. The median

survival of all patients was 14 months. Proportions of patients surviving at 1, 2 and 3 years were 58 %, 30 % and 18 %, respectively. The median survival times in patients with complete response, partial response, stable disease and progressive disease were 42, 17, 8 and 5 months, respectively. The survival was significantly better in patients who attained complete

Table 4
Results of multivariable analysis

variable	hazard ratio	95 % confidence interval	p
HAI anthracyclines (no vs. yes)	2.34	1.31 - 4.21	0.004
stage of liver metastases (H1 or 2 vs. H3)	0.52	0.33 - 0.81	0.004
number of cases per report (< 2 vs. > 2)	0.37	0.16 - 0.87	0.02
objective response (no vs. yes)	6.12	3.70 - 10.12	0.00001

response compared to patients with partial response ($p = 0.00001$). The survival of patients with partial response was significantly better than in patients with stable disease ($p = 0.004$). The difference in survival between patients with stable disease and progressive disease was not statistically significant ($p = 0.28$). The survival was significantly longer in males, patients with H1 or H2 liver metastases, and in patients treated by liver resection (Table 3). A significant difference was observed based on the number of patients per report. Survival was significantly longer in patients reported in papers describing 1 or 2 cases. No significant differences were observed in survival among patients based on age, synchronous or metachronous metastases, HAI of fluoropyrimidines, platinum compounds or mitomycin C.

The parameters showing significance on univariate analysis with $p < 0.20$ were analyzed by multivariate analysis. Objective response, stage of liver metastases, HAI of anthracyclines and number of patients per report were independent indicators of survival (Table 4).

Discussion

Despite the high frequency of hepatic metastases in metastatic gastric carcinoma, isolated liver involvement in this tumour is rare. Consequently, experience with liver-directed therapies in metastatic gastric cancer is limited. For example, Aoki et al. (4) observed liver metastases (synchronous or metachronous) in 96 out of 1825 patients diagnosed with gastric cancer at a single institution over 10 years. HAI was used only in 18 of these 96 patients. Similarly, Okano et al. (53) reported liver metastases in 90 out of 807 patients (11 %) with gastric cancer treated at a single institution over 13 years. Nineteen of these 90 patients were treated with liver resection. In patients treated by HAI conflicting results have been reported (Table 1). The median survival of patients with gastric cancer liver metastases treated by HAI was reported to range between 3 months and almost 2 years depending on the treatment administered and patient characteristics. Even more striking is the geographical disparity in the use of HAI. Most studies described in Table 1 have been retrospective. The overwhelming majority of these reports come from Japan, but even in Japan, a country with high incidence of gastric cancer, few prospective studies of HAI have been conducted only at the expense of including patients

with extrahepatic disease. In the largest study to date, Kumada et al. (34) enrolled 83 eligible patients. Only 36 out of these 83 patients (43 %) had no extrahepatic disease. Moreover, 20 patients in this study were not evaluable, mostly because of early progression. In other larger cohorts, a significant proportion of the patients had extrahepatic disease. In the report by Arai et al. (8) 15 out of 34 patients (44 %) had extrahepatic disease. In the report by Yonemura et al. (86) 12 out of 43 patients (28 %) treated by HAI had peritoneal dissemination and 9 patients (21 %) had non-resectable primary. In the study by Kumada et al. (34), median survival was 9 and 13 months in patients with or without extrahepatic metastases, respectively. Since it has been demonstrated that the prognosis of patients with extrahepatic disease is significantly worse (34,56), the results of these studies may underestimate the effectiveness of HAI in properly selected patients. The long-term results of liver-directed therapies in hepatic metastases of gastric cancer are therefore generally perceived as disappointing (14). Even among patients treated by liver resection, there have been only few patients surviving 5 or more years (13,15,46,53,56).

The results reported in papers with fewer patients or in single case reports are mostly in stark contrast with the negative experience reported in larger cohorts. Unlike in the relatively large series mentioned above, most of the patients in smaller cohorts or single case reports were more selected and, in most cases, had metastatic disease limited to the liver. The survival of the patients in the pooled analysis presented here is markedly better than the median survival of 5 months reported for gastric cancer patients with liver metastases in general (17,82), and similar to the survival reported for small cohorts of patients with metastatic gastric cancer treated by liver resection. The survival of these patients is also comparable with the survival of patients with colorectal cancer metastatic to the liver reported in randomized clinical trials of HAI (3,10,21,29,57). In some reports on liver-directed therapies in metastatic liver cancers, patients with both colorectal and gastric primary were studied. Among patients treated by liver resection, the survival of patients with gastric carcinoma has been markedly inferior compared to patients with colorectal primary (24,73). On the other hand, the efficacy of HAI has been reported to be more or less comparable in patients with gastric and colorectal carcinoma. In diffe-

rent series of HAI, the survival of patients with liver metastases from gastric carcinoma was comparable (71), slightly better (8,73), or worse (37,68) than the survival of patients with colorectal primary. Unlike in colorectal cancer, only retrospective data supports the efficacy of HAI compared to systemic chemotherapy in gastric carcinoma metastatic to the liver. In the study by Uemura et al. (79), median survival of patients treated by HAI was 13 months while the survival of a matched cohort of patients treated by systemic chemotherapy was significantly shorter (7 months). Aoki et al. (4) reported median survival of 6 months in 18 patients treated by HAI while the median survival in 78 patients treated by systemic chemotherapy was 3 months. One-year survival rates in patients treated by HAI and systemic chemotherapy were 26 % and 12 %, respectively. In the report by Dhar et al. (11) HAI and liver resection were strongest independent predictors of survival in 75 patients with gastric cancer liver metastases. Longer survival in patients treated using HAI was also noted in the retrospective analysis by Yamaguchi et al. (83).

The pooled analysis presented here may be characterized as a "best evidence synthesis" (63) and has obvious limitations. The population analyzed was very heterogeneous. Different combinations and different doses of the cytotoxic agents have been used. HAI was delivered through surgically implanted catheters connected to subcutaneous port systems or reservoirs, or through percutaneously inserted port systems. The publication bias, that may explain better survival of patients in reports of 1 or 2 cases, is quite obvious, and has even been acknowledged in some reports (32,55). It is also evident that better results may be attained by careful selection of the patients (e.g. exclusion of patients with extrahepatic metastases). On the other hand, it would be very difficult to organize a prospective study of sufficient size, as even in large centres it would be possible to accrue only a limited number of patients over a reasonable period of time. Thus, a pooled analysis of data from different institutions may represent the only option to assess the potential efficacy of HAI in gastric cancer metastatic to the liver.

HAI in patients with gastric cancer metastatic to the liver induces an objective response in the majority of patients. Cases of complete response are not exceptional and median survival of patients with complete response is more than 3 years. There seems to exist

a possibility of achieving a cure by combining HAI with liver resection (38). Patients with partial response also had a significantly better survival, and objective response was an independent prognostic indicator in the present pooled analysis. This is in agreement with other reports. Improved survival of responding patients was noted by Sakuma et al. (59). Nagahama et al. (50) reported a significant difference in median survival of 17 months in patients with complete or partial response, and 5 months in non-responding patients. In another study, survival was significantly longer in patients whose tumours were shown to be sensitive *in vitro* to the administered drugs (36).

Although it is evident that the efficacy of HAI (and liver-directed approaches in general) in gastric cancer patients with metastases limited to the liver may be comparable to the efficacy of liver-directed approaches in patients with isolated liver metastases of colorectal cancer, the impact of liver-directed approaches in gastric cancer is more limited because of scarcity of patients with isolated hepatic metastases. HAI of different cytotoxic agents has been used in gastric carcinoma. In most patients, fluoropyrimidines (usually 5-fluorouracil), platinum compounds (usually cisplatin) and mitomycin C were used. In only 23 % of patients anthracyclines (doxorubicin and epirubicin) were administered intraarterially. Other agents used for HAI less frequently included etoposide, methotrexate and alkylating agents as well as biological agents. More recently, paclitaxel (41) and irinotecan (64) were used for HAI in individual patients. In some reports, HAI of cytotoxic agents was combined with angiotensin II (22, 26, 52) or noradrenaline (7). In addition to HAI, many patients were treated by oral fluoropyrimidines. Of the multiple therapeutic agents used, only HAI of anthracyclines was associated with better survival on multivariable analysis. Survival was better in patients who had liver resection in addition to HAI in univariate, but not multivariable analysis. However, the number of patients treated by hepatic resection was very small. HAI was also combined with hyperthermia, chemoembolization, or other liver-directed therapies, but no obvious benefit was evident from these additional procedures. Survival was better in patients with limited liver involvement on both univariate and multivariable analysis. The survival was better in males on univariate analysis, but this was not confirmed by multivariable analysis. There is

anecdotal data suggesting that HAI may be effective specifically in alfa-fetoprotein producing gastric cancer (50,61,64), but other reports did not confirm this observation (33).

In conclusion, the results of the pooled analysis indicate that HAI is effective in those rare patients with isolated liver metastases of gastric cancer. The prognosis is significantly better in patients who attain

ned objective response, have limited metastatic disease and are treated by anthracyclines. The most serious limitation of the present analysis is an apparent publication bias.

Acknowledgement

Supported by a grant from the Ministry of Education of the Czech Republic CEZ-MŠMT 115000021.

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Correspondence to: / adresa pro korespondenci:

Assoc. Prof. Bohuslav Melichar, PhD, Department of Oncology and Radiotherapy, Charles University Teaching Hospital, Sokolská 581, 500 05 Hradec Králové, Czech Republic.
E-mail: melichar@fnhk.cz