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ORIGINAL ARTICLE

Hepatic arterial infusion in liver tumors of unknown, uncertain or unusual primary: single-center experience

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Summary

Purpose: *The aim of the present study was to analyze a single-center experience with hepatic arterial infusion (HAI) in patients with unknown or uncertain primary or tumors not usually treated with HAI.*

Methods: *A retrospective analysis of 14 patients treated between 1996 and 2003 for liver tumors of unknown, uncertain or unusual primary was performed.*

Results: *All patients were treated with HAI combination regimens based on 5-fluorouracil and folinic acid. The response was not evaluable in most patients, predominantly because of only a single course of therapy could be administered and no cases of partial or complete response were noted. The median survival of all patients was 6.6 months (5-year survival 14%).*

Conclusion: *The present data demonstrate limited efficacy of HAI in patients with liver tumors of unknown, uncertain or unusual primary. HAI should not be offered to these patients.*

Key words: *5-fluorouracil, hepatic arterial infusion, liver tumors, unknown primary*

Introduction

Although, in the Western world primary liver tumors are less common, the liver represents the most common site of metastatic disease. Some aspects of the management of liver tumors are similar irrespective of whether these are primary or secondary (metastatic) liver tumors and also irrespective of the site of the primary. Liver resection is the only therapeutic option offering long-term disease-free status in patients with liver tumors, primary as well as metastatic, but resection is possible only in a minority of patients presenting with a liver neoplasm. Consequently, other liver-directed therapeutic approaches have been explored in patients with tumors not amenable to resection, including radiofrequency ablation or stereotactic radiotherapy. Another liver-directed therapeutic approach that has been investigated in patients with both primary and metastatic liver carcinomas is hepatic arterial infusion (HAI). HAI takes advantage of anatomical targeting of anticancer agents via the hepatic artery with the aim to obtain higher intratumor drug concentration with less systemic toxicity [1]. HAI has been studied in depth in patients with colorectal carcinoma [2-8]. In patients with liver metastases of colorectal carcinoma it could be demonstrated that the postulated theoretical advantage of higher intratumor drug concentrations and lower systemic toxicity

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indeed translates into superior response rate and better quality of life, although it has been more difficult to demonstrate an overall survival benefit. Consequently, the use of HAI in colorectal carcinoma metastatic to the liver was always regarded as controversial [1]. The role of HAI in patients with other primary tumors involving the liver is even less clear and this treatment is regarded by many as experimental. However, promising results were reported in prospective trials or retrospective series that included, among other, primaries patients with liver metastases of uveal melanoma [9], breast carcinoma [10] or biliary tract carcinomas [11-15]. Little is known about the use of HAI in patients with tumors of other primary sites, including tumors of unknown primary site [16,17].

Herein, we present a retrospective analysis of single-center experience with HAI in patients with hepatic metastases of tumors of unknown (or uncertain) primary and tumors in which the indication of HAI was considered uncertain and utilization of this approach is unusual.

Methods

A retrospective analysis was performed of consecutive patients with liver tumors of unknown or uncertain primary treated at the Charles University Medical School and Teaching Hospital in Hradec Kralove, Czech Republic between 1996 and 2003 with at least one course of HAI. Previously we have published results on cohorts of patients treated at this institution with HAI for liver metastases of colorectal carcinoma [18-21], biliary tract carcinomas [11,15], hepatocellular carcinoma [22], melanoma [9,23], breast carcinoma [10], sarcoma [24], gastric carcinoma [25], and renal cell carcinoma [26]. The patients who did not fit into any of the categories described above were also included in the present analysis along with patients with unknown or uncertain primary as the utilization of HAI in patients with these primaries is unusual. The patient charts were searched for relevant information. Survival was evaluated from the implantation of the intraarterial catheter to death (or the patient had to be censored at last follow-up).

HAI was administered through catheters with a subcutaneous port system that were inserted either surgically during an open procedure or percutaneously by an interventional radiologist, or through catheters introduced through the femoral artery by the Seldinger technique as described earlier [18]. HAI regimens used in patients with hepatic metastases of unknown, uncertain or unusual primary were usually based on the administration of 5-fluorouracil and folinic acid with or without cisplatin, or, more rarely, other agents (Table 1). The regimens used have been described earlier [15] and the therapeutic response was evaluated by imaging studies of liver lesions using standard World Health Organization criteria [27].

Statistics

Standard descriptive statistical analyses were used to characterize the present retrospective cohort of patients. Overall survival was evaluated using the Kaplan-Meier method, and the differences between patient subgroups were studied with the log-rank test. The statistical analyses were performed using NCSS software (Number Cruncher Statistical Systems, Kaysville, UT, USA).

Results

Fourteen patients, 7 females and 7 males, aged 54±14 years (range 31-77), with a liver tumor of unknown, uncertain or unusual primary (as defined above) were treated with at least one cycle of HAI (Table 1). At the start of therapy, the primary was considered unknown or uncertain in 7 cases (50%). Among these patients, the diagnosis was subsequently established in two cases (primary liver lymphoma and non-small cell lung cancer in one case each), while in the remaining 5 patients the primary was never determined. Seven patients had primary tumor that was considered an unusual indication for HAI, including two patients with colorectal carcinoid, one patient with pancreatic insulinoma, one patient with anal cancer, one patient with pancreatic carcinoma, one patient with epithelial ovarian carcinoma and one patient with adenoid cystic carcinoma of the submandibular gland. Only one patient (patient 8 with adenoid cystic carcinoma of the submandibular gland) had a surgical procedure that was considered radical (liver resection) at the time of catheter insertion.

Seven patients had HAI administered through catheters implanted either surgically (n=6) or percutaneously by an interventional radiologist (n=1). Seven patients had HAI administered only through single-use catheters inserted using the Seldinger method. Most of the patients treated with single-use catheters had only a single course of HAI, in many cases because extrahepatic spread or other contraindication for the insertion of permanent catheter was found at the surgery for the insertion of the catheter. Nine patients (64%) had tumor limited to the liver while 5 patients (36%) had extrahepatic spread detected around the time of treatment initiation. Six patients had prior systemic therapy. The median time from the diagnosis of the liver tumor to the start of HAI was 86 days (range 5-964).

The objective response was not evaluated in the majority (n=9) of the patients, in most cases because of the insufficient duration of therapy consisting of only one to three courses or because of prior surgical procedure. No complete or partial response was observed in any of the patients. Three

Table 1. Patient characteristics and outcome

Patient no.	*Age (years)*	*Sex*	*Primary considered at the time of therapy*	*Primary determined subsequently*	*Histology*	*Isolated liver involvement (Y/N)*	*Surgical intervention other than catheter insertion*	*Interval from diagnosis of liver metastases to HAI (days)*	*Method of catheter insertion*	*HAI regimen*	*Number of cycles*	*Best response*	*Survival from the start of therapy (months)*
1	59	F	U (history of breast cancer, radiological findings suggestive of cholangiocarcinoma)	U	ND (no biopsy)	Y	none	55	SU	5FU+FA+ CDDP	5	PD	11.1
2	58	F	U	U	basaloid squamous cell carcinoma	Y	none	153	S	5FU+FA+D	5	NE	6.6
3	77	F	U	primary liver lymphoma	lymphoma	Y	none	63	SU	5FU+FA+ CDDP	1	NE	2.2
4	64	M	U	NSCLC	poorly differentiated squamus cell carcinoma	Y	none	5	S	5FU+FA+ CDDP; 5FU + FA + D	8	SD	11.0
5	74	M	U	U	poorly differentiated carcinoma	Y	none	29	SU	5FU+FA+ CDDP	1	NE	2.4
6	31	M	U	U	adenocarcinoma, possibly cholangiocarcinoma	Y	none	29	SU	5FU+FA+ CDDP	1	NE	2.3
7	41	M	pancreas	pancreas	tubular adenocarcinoma	N	none	118	SU	Gem + 5FU + FA	5	SD	5.9
8	50	F	adenoid cystic carcinoma of the submandibular gland	adenoid cytstic carcinoma of the submandibular gland	adenoid cystic carcinoma of the submandibular gland	Y	resection	109	S	5FU+FA	15	NE	70.8
9	54	F	EOC	EOC	serous carcinoma	N	none	185	S	5FU+FA	2	NE	9.5
10	50	M	carcinoid	carcinoid	carcinoid	Y	none	29	S	CPT+5FU + FA (weekly)	35	SD	134.4
11	49	F	Cloacogenic carcinoma	anus		N	none	40	P	5FU+FA+ CDDP + MMC	1	NE	12.3
12	39	F	pancreas (neuroendocrine)	pancreas (neuroendocrine)	insulinoma	N	none	964	SU	5FU+FA+ CDDP	3	NE	5.3
13	73	M	carcinoid	cardinoid	carcinoid	N	none	524	SU	5FU+FA	1	NE	5.9
14	50	M	U	U	Undifferentiated small-cell carcinoma	Y	none	181	S	5FU+FA+ CDDP	5	PD	6.5

5FU: 5-fluorouracil, CDDP: cisplatin, CPT: irinotecan, D: doxorubicin, DOD: died of disease, EOC: epithelial ovarian carcinoma, F: female, FA: folinic acid, M: male, MMC: mitomycin C, N: no, ND: not determined, NE: not evaluable, NSCLC: non-small cell lung cancer, P: percutaneously implanted port system, PD: progressive disease, S: surgically implanted port system, SD: stable disease, SU: single use catheters, U: unknown, Y: yes

patients (21%) had stable disease as the best response, and progressive disease was observed in two patients (14%).

Serious adverse events that required hospitalization were observed in one patient (patient 11) who had extravasation of the cytotoxic drugs that precluded further administration of therapy.

No patients were lost to follow-up. By the time of this analysis all patients have died of disease. The median survival of all patients was 6.6 months (1-year survival 14%). Two patients (14%) survived for more than 5 years, a patient with adenoid cystic carcinoma of the submandibular gland and a patient with colorectal carcinoid. These cases are described in more detail below.

A female patient underwent resection for adenoid cystic carcinoma of the submandibular gland in 1985 (at the age of 39 years). Local recurrence was diagnosed in 1992, but the patient refused treatment at that time. After progression of the tumor that was inoperable the patient underwent radical radiotherapy (total dose 60 Gy) in 1995. A solitary liver metastasis was diagnosed in July 1996. The patient underwent liver resection and simultaneous surgical implantation of the catheter with subcutaneous port system into the hepatic artery in October 1996. The patient was subsequently treated until 1998 with monthly cycles of HAI of 5-fluorouracil and folinic acid for the duration of the patency of the catheter. The patient was subsequently followed. Local recurrence in the submandibular region was diagnosed in April 2001. Palliative chemotherapy with docetaxel was then administered resulting in stable disease. In June 2002 lung metastases were diagnosed. Only symptomatic therapy was possible and the patient died in September 2002, 71 months after the start of HAI. No recurrence of liver metastasis was detected.

A male patient had a tumor of the cecum with multiple synchronous liver metastases diagnosed in December 2002 (at the age of 49). The patient underwent right hemicolectomy and, because the tumor was thought to be colorectal carcinoma, implantation of the catheter with subcutaneous port system for HAI was performed. The histological analysis revealed malignant carcinoid. The patient was treated with HAI with a combination of irinotecan, 5-fluorouracil and folinic acid (35 doses administered in weekly intervals) resulting in stable disease as the best response. The port system was no more patent in November 2003. The patient was subsequently treated in a clinical trial with an experimental agent (patupilone) resulting in stable disease until April 2005. Octreotide was subsequently administered, but progressive disease was evident in January 2006. The patient was then treated with 6 cycles of intravenous combination of doxorubicin and 5-fluorouracil that resulted in stable disease. After progression in September 2008, octreotide in combination with interferon-alpha was administered until June 2011. Monotherapy with octreotide was then continued to control disease symptoms. The metastatic involvement of the liver progressed, and the administration of other anticancer agents was precluded by the manifestation of dilating cardiomyopathy. The patient died of hepatic failure in March 2014, 134 months after the start of HAI.

Discussion

The outcome of patients in the present series of cases that is unique in including patients with liver tumors of primary sites that have been only exceptionally treated with HAI indicates only very limited, if any, efficacy of this therapeutic method in patients with tumors of unknown, uncertain primary or unusual for the treatment with this approach. This contrasts with activity of HAI in some other primary tumors, including colorectal carcinoma, breast carcinoma, uveal melanoma or biliary tract tumors. In fact, the reported data on the efficacy of HAI in patients with liver metastases of unknown primary or primary tumors included in the present cohort are limited [16,17,28]. The data of the present cohort are mature and survival, rather than objective response rate, was the principal parameter of efficacy evaluated. Objective response could not be assessed in most patients in the present cohort, primarily because only a single course of HAI could be administered. In addition, the standards of imaging have changed significantly over the years during which patients in the present series have been treated. Because objective response could not be evaluated in a high proportion of patients, progression-free survival was also not analyzed. On the other hand, objective response and progression-free survival, although frequently used in clinical trials, are only surrogates for survival. The outcome of most of the patients in the present series was poor, with median survival of 6.6 months and only two patients (14%) surviving more than two years. In fact, these two patients were long-term survivors. However, even in these patients the contribution of HAI to the outcome was uncertain as the patient with solitary liver metastasis from adenoid cystic carcinoma of the submandibular gland had also liver resection and long survival of the patient with liver metastases of colorectal carcinoid was due to the indolent behavior of the tumor

and also to multiple subsequent lines of systemic therapy.

Little is known about HAI in patients with tumors of unknown primary site [16,29] despite the fact that metastatic tumor of unknown primary site is a common presentation in medical oncology and the liver is a most frequent site of metastatic disease. Thus, the decision on therapeutic strategy in a patient presenting with liver metastases of unknown primary is a common problem facing the medical oncologist and the multidisciplinary team. The prognosis of these patients is poor, increasing the challenge in this situation. Extrahepatic metastases are present in most patients with liver metastases of unknown primary, and systemic therapy is selected for these patients. In cases of isolated liver involvement, the multidisciplinary team may be tempted to select a liver-directed approach. The data from the present series do not support such strategy. In fact, none of the patient originally considered as having liver metastases of unknown or uncertain primary survived more than a year. The size of the present cohort (or rather series of cases) is obviously limited, reflecting the limited data on this topic published in the literature. HAI should certainly not be recommended in case of isolated liver metastases of unknown primary, and in connection with the general decline of the use of HAI the practice of offering the therapy for patients with unknown or unusual primary has ceased in our center.

HAI has most frequently been used in patients with liver metastases of colorectal carcinoma [30], uveal melanoma [9,31] or biliary tract carcinomas [15]. Metastatic colorectal carcinoma represents by far the most common indication for HAI, but with the introduction of new cytotoxic agents and targeted drugs the use of HAI declined dramatically, and in metastatic colorectal carcinoma the procedure is now rarely used. However, HAI still represents an attractive treatment option for patients with biliary tract carcinomas or liver metastases of uveal melanoma for whom systemic therapy options are still limited. Fraker and Soulen proposed a classification of liver tumors according the appropriateness of liver-directed procedures, including HAI [32]. Primary sites have been represented mostly as anecdotal cases in the present series. In patients with pancreatic adenocarcinoma, no form of liver-directed approach seems to be appropriate, while in patients with epithelial ovarian carcinoma liver resection could be part of surgical debulking in association with systemic chemotherapy, but not HAI. Liver-directed approaches could be of benefit in patients with neuroendocrine tumors, but anecdotal cases from the present series provide no evidence that HAI could modify the course of the disease here. The decision on the therapy has to be individualized in rare presentation like liver metastases of uncommon tumors of the head and neck or anal carcinoma, but liver resection rather than HAI should be the treatment considered here.

Unfortunately, at present there is no data regarding clinical, pathological or laboratory predictive parameters (biomarkers) that could aid in identifying patients with any primary likely to preferentially benefit from HAI. Although biomarkers associated with the properties of tumor cells have been so far in the forefront of research, parameters indicating the host response to tumor cell growth seem to be of equal importance [33]. Future studies should compare the suppression of the immune response by HAI and systemic chemotherapy. Systemic immune activation commonly observed in advanced cancer [34] is associated with decreased immune response [35,36], and effective tumor control could enhance the host immune response against the tumor.

Different cytotoxic agents have been used in HAI. Although, 5-fluoro-2'-deoxyuridine (floxuridine) has been regarded as a standard agent for HAI, a randomized trial in patients with metastatic colorectal carcinoma demonstrated that the activity of 5-fluorouracil is at least comparable to floxuridine [3]. In the present cohort, the HAI regimen included 5-fluorouracil in all patients, and cisplatin was used in combination with 5-fluorouracil in most cases. Both of these drugs have a wide spectrum of activity across a range of primary tumors, but the efficacy of 5-fluorouracil and/or cisplatin in metastatic tumors of unknown primary is limited, and the administration as HAI does not seem to give better results.

Most patients with tumors of unknown, uncertain or unusual primary in the present series received only a single course of HAI. In some of these patients, extrahepatic spread was subsequently detected. With the widespread availability of positron emission tomography/computed tomography (PET/CT), extrahepatic disease may be identified at the start of treatment, leading to better patient selection with potentially better results.

HAI was generally well tolerated in the present retrospective cohort. The toxicities of systemic anticancer treatment, including gastrointestinal side effects induced by cytotoxic drugs [37], or adverse events accompanying the administration of targeted agents [38] may result in a major impact on the patient quality of life. Some side effects are less common with HAI compared to

systemic administration of cytotoxic drugs, and in patients with metastatic colorectal cancer it has been demonstrated that HAI is associated with improved quality of life [8].

In conclusion, the present data indicate no or only very limited efficacy of HAI in patients with hepatic tumors of unknown or uncertain primary, or tumors not commonly treated with HAI. This treatment should not be offered to these patients.

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Conflict of interests

The authors declare no conflict of interests.

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