Abstract. Background/Aim: The liver is the most frequent site of metastasis of pancreatic neuroendocrine tumors (PNETs). Moreover, hepatic metastasis is a strong prognostic factor for patients with advanced PNETs and is often difficult to treat and cure. Patients and Methods: We employed our recently developed new transcatheter arterial chemoembolization technique using a fine-powder formulation of cisplatin mixed with degradable starch microspheres (DSM) for the treatment of unresectable hepatic metastases from PNET in five consecutive patients. Results: A total of 24 sessions of TACE was performed. The responses were complete response in one, partial response in three, and stable disease in one patient. All patients were alive at the time of analysis with a median survival of 36 (3-70) months after the initial treatment of TACE. There were no severe toxicities or adverse effects. Conclusion: This new treatment induced a significant effect on hepatic metastases of PNET. The response rate was very high, which has not been achieved even by recent new agents. Our findings may warrant further prospective studies of this therapy.

The liver is the predominant metastatic site of metastasis of pancreatic neuroendocrine tumors (PNETs) (1, 2). Hepatic metastasis usually impairs both daily life and prognosis of patients with PNET. Surgery is the mainstay of treatment for resectable PNET, including distant metastatic sites. However, metastasis often spreads widely in the liver and accompanies extrhepatic metastatic sites which cannot be completely resected. Recent guidelines for the treatment of unresectable PNETs indicate that liver-directed therapy, including transcatheter arterial chemoembolization (TACE), is a potential therapeutic option (3, 4). TACE is a widely accepted treatment for both primary and metastatic liver tumors. Several improvements, including interventional radiological techniques and embolic materials, have been achieved. We have recently developed a new TACE technique using a fine-powder formulation of cisplatin mixed with degradable starch microspheres (DSM), and recently reported its feasibility and efficacy for colorectal liver metastases (5). We have applied this technique to unresectable hepatic metastases from PNET and observed a significant clinical effect. Here, we present five consecutive cases treated with this new therapeutic approach.

Patients and Methods

Between November 2007 and February 2013, five patients with multiple unresectable liver metastases of PNET underwent TACE using cisplatin powder mixed with DSM at Nara Medical University Hospital. A fine-powder formation of cisplatin (100 mg, IA-Call; Nippon Kayaku, Tokyo, Japan) was dissolved in iohexol (300 mg I/ml; Omnipaque; Daiichi-Sankyo, Tokyo, Japan), which produced a high-concentration solution of cisplatin (6.7 mg/ml). DSM (300 mg; mean diameter of 40±5 μm, half-life of 15-30 min at 37°C) were mixed with the total administration dose of cisplatin solution for each patient, which was set at 65 mg/m² as previously described (5). Patients provided written informed consent before treatment according to the rules and regulations of our institution. Responses were evaluated by the Response Evaluation Criteria in Solid Tumors (RECIST) (6).

Results

A total of 24 sessions of TACE were performed (Table I). Four out of five patients had undergone pancreatectomy for the removal of the primary lesion prior to treatments: two underwent pancreatoduodenectomy and two distal pancreatectomy. The hepatic metastases were synchronous in two patients and metachronous in two. One patient was diagnosed as having unresectable PNET histologically-
proven by endoscopic ultrasound-guided fine-needle aspiration. One patient had a history of previous hepatic resection for metastatic PNET. The number of sessions ranged from one to ten for each patient. Only one patient developed liver abscess during the treatment period; he required drainage and fully recovered soon after. There were no other severe toxicities or adverse effects related to TACE in any of the 24 sessions. The best response was complete response in one, partial response in three, and stable disease in one (Figure 1). Thus, the overall response rate was 4/5.

Figure 1. Abdominal computed tomography scan showing long-lasting effect of transcatheter arterial chemoembolization (TACE) on liver metastases of pancreatic neuroendocrine tumor. A, B: Multiple lesions in both lobes of the liver before treatment (arrows). C, D: Shrunken lesions after three sessions of TACE. E, F: Small low-density lesions at 42 months after the last tenth TACE session.
(80%) and the disease control rate was 100%. In patients with partial response, some hepatic metastases completely disappeared and others were reduced in size. All patients survived until the time of analysis and the median survival time was 36 (3-70) months after the initial TACE treatment.

Discussion

Recent clinical trials have shown that the new agents targeting mammalian target of rapamycin and vascular endothelial growth factor pathways have a significant impact on unresectable metastatic PNET (1, 2). However, the response rate to such molecular-targeting agents is considerably low, below 10%. These trials have also shown that the most frequent site of metastasis is the liver (1, 2). Therefore, liver-directed therapy including TACE may have some therapeutic potential in the treatment of metastatic PNET. TACE for the liver is less invasive and may be used when surgical resection is not feasible. It is effective in the control of symptoms and tumor growth. Previous studies have shown that 50-100% of patients had a symptomatic response and 25-86% had an objective tumor response (7-9). The mean survival time has been reported to be 24-32 months (10). Although some cytotoxic agents, such as doxorubicin, in mixtures with lipiodol for conventional TACE have been used, the most suitable chemotherapeutic agent and the embolic material for the liver metastasis of PNET remain to be investigated.

In this study, we have shown that our recently developed technique of TACE had a significant therapeutic effect on multiple liver metastatic PNET tumors. The overall response rate was 4/5 (80%) and the disease control rate was 100%. Importantly, there were no severe adverse events relating to this treatment, except for the development of liver abscess in one patient, who was successfully treated. This new technique may include several potential advantages for the treatment of liver metastatic tumors of PNET. Firstly, a very high dose of cisplatin can be delivered directly to hepatic tumors through the hepatic artery (11, 12), which is impossible by systemic administration because of toxicity. Furthermore, since PNETs are generally hypervascular, the arterial infusion of chemotherapy may be theoretically ideal. Secondly, the mixture of DSM as an embolic material may further enhance the efficacy of cisplatin given by arterial infusion. This can be made possible by using a fine-powder formulation of cisplatin, which is easily soluble even in a small amount of DSM. Since conventional cisplatin formulations require a great amount of water, they cannot usually be used for arterial infusion. In general, TACE is contraindicated for patients with a history of pancreatectoduodenectomy, since it has a high risk for inducing cholangitis and hepatic abscess because of bilioenteric anastomosis (13). In comparison with conventional lipiodol TACE using gelfoam particles, embolization by DSM is transient and can be repeatedly used, with relatively low biliary damage (11). In fact, we were able to treat two patients after pancreatectoduodenectomy with multiple sessions of DSM-TACE, observing complete response in one patient and partial response in the other. This may be a significant advantage of this technique, since metastatic PNETs often require repeated treatments. Thirdly, there were almost no severe general toxicities in this treatment. Therefore, the combination therapy of TACE with other therapeutic options, including recent molecular-targeted therapies, can be considered (1, 2). This may be feasible because the adverse events of each treatment may not overlap. Such multimodal treatment is critically important for unresectable advanced PNET.

In conclusion, our initial experience of our new TACE technique for hepatic metastasis of PNET has shown significant clinical efficacy. The response rate was very high, which has not been achieved even by recent new agents. These promising results may warrant further prospective studies for the treatment of unresectable hepatic metastasis of PNETs.

References


