Case Report

Chemoembolization with Epirubicin in the Treatment of Malignant Insulinoma

Camille Sibertin-Blanc¹, Ecaterina Ileana¹, Laetitia Dahan²*, Guillaume Louis², Muriel Duluc¹, Yves-Patrice Le Treut³, and Jean-François Seitz¹

¹Department of Digestive Oncology, Aix –Marseille University, France
²Department of Radiology, Aix –Marseille University, France
³Department of Digestive Surgery, Aix –Marseille University, France

Abstract

Insulinoma liver metastases are rare because only a minority of insulinomas (10%) is malignant. We report a case of a 54 year-old patient diagnosed with malignant insulinoma with synchronous liver metastases, treated first by systemic chemotherapy by Streptozotocin and 5-Fluorouracil without clinical control of symptoms (hypoglycemia), then by pancreatic resection and seven chemoembolization with Epirubicin of liver metastases. After the first chemoembolization with Epirubicin the patient presented a total control of hypoglycemia and an objective response on liver metastases. Because of difficulties of catheterization of the hepatic artery after seven chemoembolizations, the patient was treated by somatostatin analog, by Sunitinib (in the SUTENT study) for 1 year and then by Everolimus (in the RADIANT-3 study) for 1 year. In front of the progression of liver metastases and recurrence of hypoglycemia, a new chemoembolization with streptozotocin was performed without clinical, biological or radiological response. A second chemoembolization with Epirubicin was performed with a major biological response on tumor markers, reduction of 30% of liver metastases and a total control of symptoms.

INTRODUCTION

Insulinoma is an insulin-secreting, rare neuroendocrine tumor, derived from the beta cells of the pancreas. The incidence in the general population is 4 cases per million a year. Insulinoma is the most common form of pancreatic neuroendocrine tumor accounting for 60% of cases [1] and is most commonly seen between the age of 40 to 60 years, in females. Most of them are adenomas. Malignant insulinoma is a rare disease, representing 10% of these islet cell tumors and the invasion of adjacent organs or the presences of distant metastases are common [1,2]. In the management of metastatic insulinoma, patients with rapidly progressive disease, with local symptoms caused by tumor bulk, or with uncontrolled disease related to hormone secretion require aggressive medical or surgical intervention [3].

Currently, the only curative treatment for malignant insulinoma is complete surgical resection of the tumor and of the metastases. Surgical resection of metastatic disease may offer palliative relief of symptoms related to hormone secretion in carefully selected patients.

Chemotherapy may be used for when ablative techniques have failed or when significant extrahepatic disease is present. Streptozotocin-based combinations remain the first line standard, epirubicin had also shown its efficacy in association with sterptozocin [4]. Theadministration of targeted therapies (sunitinib or everolimus) may also improve progression-free survival, overall survival, and the objective response rate among patients with advanced pancreatic neuroendocrine tumors [5,6]. The somatostatin analogue octreotide may help control hormone secretion.

Hepatic arterial chemoembolization (HACE) is an accepted treatment option of liver metastases of pancreatic neuroendocrine tumor, not amenable to surgical resection or local ablation. Numerous studies have shown that HACE is effective in controlling hormonal symptoms and reducing tumor size in patients with hepatic metastasis from neuroendocrine tumors. It is controversial that chemotherapy in HACE has a major impact on efficacy especially in carcinoid tumors since no chemotherapy had demonstrated its superiority [7-8] and some authors suggested that embolization alone should be sufficient [9].

We report a case of malignant insulinoma with liver metastases illustrating an aggressive multimodal therapy very
good outcome to chemoembolization with Epirubicin, but without response to the chemoembolization with Streptozotocin what substantiates the positive impact of chemotherapy in HACE.

CASE PRESENTATION

A 54-years old man presented several seizures in December 2003 and he was found to be hypoglycemic (grade 2). The patient underwent a formal fast that resulted in hypoglycemia after 24 hours. An abdominal ultrasound discovered several hepatic metastases. A body CT scan found a tumor of the tail of pancreas and liver metastases (Figure 1). A liver biopsy confirmed the neuroendocrine origin of the tumor (well differentiated insulinoma with Ki-67 <5%).

After multidisciplinary team discussion a systemic treatment with Streptozotocin and 5-Fluorouracil was started in mars 2004, but in the absence of control of the symptoms, after one cycle of chemotherapy, a surgical resection was decided. The patient underwent a distal pancreatectomy with splenectomy and cholecystectomy in May 2004.

A first chemoembolization of liver metastases was done in June 2004, with 50mg Epirubicin dissolved in 10 ml of normal saline (0.9%) combined with 10 ml of iodized oil (Lipiodol), which is injected into the branches of the hepatic artery distal to the origin of the gastroduodenal artery. This was followed by embolization with gelatin sponge 2–3 mm particles or microspheres (Spongel) which are placed distally in the distribution of the hepatic artery until a marked decrease in blood flow, is observed. After the first HACE the patient presented a total control of symptoms (no recurrence of hypoglycemia) and a major tumor mass reduction (Figure 2). A new chemoembolization was repeated every 3 - 4 months. From June 2004 to February 2006 the patient underwent 7 chemoembolizations. The HACE was abandoned because the cathatherism of the hepatic artery became very difficult.

In June 2006, the patient presents new episodes of hypoglycemia and a progression of the size of the liver metastases. A treatment by Octreotid30mg LP was administrated every 28 days, with a good symptoms control.

In October 2007, new liver metastases appeared and the patient was included in the SUTENT trial (Sunitinib vs Placebo). The patient presented a good overall response with reduction of 37% the tumor mass after RECIST criteria, until July 2008, when he presented a new progression of the disease.

In September 2008 the patient was included in the RADIANT III trial (RAD001 vs Placebo). In May 2009, the patient was included in the extension phase of the trial, because he was under Placebo. After three months, the patient presented severe hyperglycemia (grade 3) and weight loss. He became diabetic with an HbA1c 8.5% and he required insulin NPH and rapid insulin treatment. Everolimus was reduced to 5 mg daily because a grade II-III stomatitis with influence on the alimentation. The treatment was stopped because of adverse events with grade 3 hypersensitivity pneumonitis and long term unexplained fever, and progression in size and number of the liver metastases.

A new chemoembolization with streptozocin was performed in October 2010 without any efficacy on hypoglycemias (grade 2) or on the Chromogranine A serum levels (4330ng/ml after the HACE vs 4600 ng/ml before – Normal value < 100 ng/ml), or on tumor diameters on CT scan (stable disease in RECIST criteria (+15%)) (Figure 3).

A second chemoembolization with Epirubicin was done in February 2011 with an immediate efficacy on hypoglycemias, a dramatic improvement of Chromogranine A levels (from 4330 to 300 ng/ml) and a major objective response in mRECIST criteria. (reduction of the tumor diameters of 35%) (Figure 4).

DISCUSSION

Malignant or metastatic insulinoma is rare. Patients with malignant insulinoma present with two fundamental challenges...
to the managing clinician. The first is that the tumor is, by definition, metastatic. The second is the unregulated secretion of insulin and proinsulin-related products that leads to severe hypoglycemia.

The main cause of death of patients with malignant insulinoma is liver metastasis that is often present at the time of diagnosis. Some liver metastases are asymptomatic while others produce highly debilitating symptoms due to hormone secretion or pain due to tumor-related hepatomegaly. Liver metastases from functional gastrointestinal endocrine tumors can reduce 5-year survival from 90% to 40% [7]. Complete resection of liver metastases should be considered in all cases. Indeed, after hepatectomy, prolonged survival (41-86% at five years) can be achieved, with low rates of surgery-related mortality (0-6.7%) [10]. Extended liver resection is required in most cases. Since liver metastases are usually multi-focal and diffuse, they are not amenable to partial heptatectomy. Liver transplantation...
has been proposed as a possible treatment for metastatic endocrine tumors. In contrast to nonendocrine tumors, therapy for hepatic metastases from neuroendocrine tumors with liver transplantation is reasonable because the disease may be confined to the liver for extended periods and the growth is slow [11].

Le Treut et al., in a 213 transplantation for liver metastases of endocrine tumors series, which is the largest in the literature, shows that liver transplantation leads to a five years overall survival rate of 52%. Although this rate seems disappointing, it must be recalled that patients indicated for liver transplantation represent a 'worst-case' group because liver transplantation is generally used only after all other alternatives have been exhausted. Five-year survival after diagnosis of metastasis was 69%, i.e. far better than the 20–30% reported in past series of untreated MET [12].

Chemoembolization is a dual therapeutic approach involving concomitant hepatic artery embolization and infusion of a concentrated dose of chemotherapeutic drugs. This combined technique offers several advantages over either individual treatment modality. First, the addition of embolic agents slows efflux of drug from the hepatic circulation, allowing hepatic drug concentrations to reach levels 10- to 25-fold higher than those achieved by simple intra-arterial infusion. The most important factor when considering patients for regional chemoembolization is whether their metastatic disease is confined to the liver. While this is highly desirable, patients with minimal or indolent extrahepatic disease may be candidates if the liver disease is considered the primary source of morbidity [13].

As a result, systemic toxicity is minimized even at high doses. Another advantage is that chemoembolization produces profound tumor ischemia at the time of drug administration. One physiologic consequence of ischemia, tumor hypoxia, is known to potentiate the effect of cytotoxic drugs such as epirubicin by inhibiting intracellular P-glycoprotein pumps and increasing tumor cell uptake of drug. Hypoxia has also been associated with p53 stabilization, which should augment therapeutic efficacy by producing tumor cell apoptosis either directly or in combination with other ischemic stresses such as acidosis and hypoglycemia.

O’Toole and Ruszniewski showed in a metaanalysis that the chemoembolization has proven effective in symptom relief in 63–100% of patients treated. In patients with either progressive or symptomatic endocrine tumours and if metastases are confined to the liver, chemoembolization can be proposed as a first-line treatment [13].

Although several studies have established the beneficial therapeutic effects of chemoembolization for hepatic metastases from neuroendocrine tumors, there is no consensus on the most effective chemotherapeutic agent for use in this procedure. Various chemotherapeutic agents including Doxorubicin, Streptozocin, 5-FU, Cisplatin, Miriplatin (a cisplatin derivative with a high affinity for iodized oil), mitomycin C, Gemcitabine

![Figure 4](image_url)

Figure 4
ChA= chromogranin A, N<98ng/mL; OR: objective response; SD: stable disease; Prog= progression in RECIST criteria; HACE=Hepatic arterial chemoembolization
M= months
and a combination of these agents have been used to perform chemoembolization for hepatic metastases of neuroendocrine tumors [8]. There are several studies that show no difference between the chemotherapeutic drug used for chemoembolisation, and they conclude that the response is due to hepatic arterial embolisation (HAE) with or without chemotherapeutic agent [9]. In a retrospective study at MD Anderson, that included 69 patients with metastatic carcinoid tumors and 54 patients with pancreatic NETs, showed that HAE had higher response rates in patients with carcinoids, whereas HACE seems to be more benefit in patients with pancreatic tumors [14]. A recent French study including 67 patients (24 small bowel and 19 pancreatic) suggests Streptozocine is a positive predictive factor of radiological response in comparison with doxorubicin (HR=21.3 IC 95% 1.48-306,p = 0.025), delaying the time we will face cardiac toxicity [15]. Our patient didn’t respond to a HACE with Streptototoxin, but he had a major clinical (absence of the hypoglycemia), biological (diminution of tumor markers) and tumor mass diminution (with 35% in RECIST) after HACE with Epirubicin. This is not surprising while patient did not present any clinical response to systemic streptozocine initially introduced, its tumour should not be sensitive to this drug. However, this tumour seemed very sensitive to epirubicine which shown its efficacy in metastatic duodenopancreatic neuroendocrine tumour.

Chemotherapy may be used for palliation when ablative techniques have failed or when significant extrahepatic disease is present. Streptozocin-based combinations remain the first line standard, but major objective responses are less common than had been previously thought. The 5-year survival rate in untreated patients is approximately 30% and chemotherapy prolongs life by a mean of 12-24 months [4,16].

Because of the overall modest success of current chemotherapeutic regimens, patients with advanced disease in need of treatment should be encouraged to enroll in clinical trials testing newer antineoplastic agents or newer treatment strategies.

The patient was included in a phase III study that compared the themitargeted tyrosine kinase inhibitor SUNITINIB vs placebo. Our patient was treated 9 months with Sunitinib with the multitargeted tyrosine kinase inhibitor SUNITINIB vs strategies. Trials testing newer antineoplastic agents or newer treatment in need of treatment should be encouraged to enroll in clinical chemotherapeutic regimens, patients with advanced disease prolongs life by a mean of 12-24 months [4,16].

Everolimus (also known as RAD001) is an orally active derivative of rapamycin that inhibits the Ser/Thyrosin kinase, mTOR. Yao et al., showed in a phase III clinical trial that Everolimus, as compared with placebo, significantly prolonged progression-free survival among patients with progressive advanced pancreatic neuroendocrine tumors (the median progression-free survival was 11.0 months with everolimus as compared with 4.6 months with placebo) [6].

In conclusion, this case report we presented a patient with several approved treatments in malignant insulinoma. This patient didn’t respond to traditional chemotherapy, but he had a major response under two targeted therapies (Sunitinib and Everolimus) and he had a total control of symptoms under Somatostatin analogs. He became diabetic under the treatment with Everolimus. The major founding of this case report is that the patient had a significant response the hepatic arterial chemoembolization with epirubicin compared with the hepatic arterial chemoembolization with Streptozotocin, that infirmer the theory that the drug used in chemoembolization is not important and that the response is related with the simply embolization.

REFERENCES


