Midgut carcinoids; surgical aspects, biogenic amines and vascular effects

Vries, Harry de

Chapter 7a

FAILURE TO CONFIRM MAJOR OBJECTIVE ANTITUMOR ACTIVITY FOR STREPTOZOCIN AND DOXORUBICIN IN THE TREATMENT OF PATIENTS WITH ADVANCED ISLET CELL CARCINOMA

H. de Vries[1]
N.H. Mulder[2]
E.G.E. de Vries[2]

[1]Department of Surgery, [2] Department of Medical Oncology,
University Medical Centre Groningen, The Netherlands

Cancer 2000;88(9):2194-2195

We read with interest the article by Cheng et al addressing the antitumor effect of streptozocin and doxorubicin in the treatment of patients with advanced islet cell carcinoma.[1] They concluded that they were unable to confirm the findings from the Eastern Cooperative Oncology Group trial published in 1992.[2] In this trial of the 38 patients who received streptozocin and doxorubicin, 36 were evaluable and 69% showed any regression with 14% complete regression. For this study, criteria for response evaluation were a 50% decrease in hormone production; a 30% reduction in hepatomegaly; and measurable tumor reduction, with the product of the perpendicular diameters reduced 50%. Routine use of computed tomography (CT) scan was not indicated. From this study it is in retrospect difficult to calculate how many patients had a response based only on hormone reduction or reduced liver size. Cheng et al. used CT scan, magnetic resonance imaging, or X-rays of bidimensional measurable lesions as the only criteria for response as defined by Miller et al.[3] With the same streptozocin and doxorubicin regimen given to all of their 16 patients with islet cell tumours, Cheng et al. observed 1 objective response, 9 patients with stable disease, and 6 patients with progressive disease. The median overall survival was not yet reached, with 60% alive after follow-up ranging from 10 to 67+ months. We would like to add 6 islet cell tumor patients to this series. From 1995–1999, we treated these patients according to exactly the same chemotherapy scheme. The patients were evaluated as described by Cheng et al.

None of the patients were hormone producers. One patient experienced a partial response, 3 had stable disease, and 2 had progressive disease. Overall survival after initiation of chemotherapy ranged from 4 to 17+ months. Apart from cardiotoxicity, which was most likely due to doxorubicin treatment (with cardiac failure responsive to antidiuretic treatment), no severe toxicity of the regimen was observed. Combining the data from Cheng et al and our results in 2 objective tumor responses out of 22 (9%; 95% confidence interval, 1–29%). Although we find with these criteria a lower response rate than Moertel et al, it is also true that in these two series a good effect on survival cannot be denied. In islet cell tumor studies, to report precisely on the objective regression of tumor size may be of major relevance. If there is a regimen that results in a realistic option to create a reduction in tumor size, this would potentially allow surgical tumor resection and thus increase the potential for curative tumor resection. If the main goal of this regimen is quality of life rather than remission, the objective response rate of only 9% with the

streptozocin/doxorubicin regimen justifies more interest in interferon treatment of patients with islet cell tumours. After an initial study with leukocyte interferon[4], interferon in a doses of 5–6 MU 3–5 times per week resulted in biochemical responses in 50% of the patients and tumor responses in 12%.[5] Surprisingly, this option is not even mentioned in the National Cancer Institute's PDQ information for health care professionals on islet cell carcinoma.[6] Treatment with somatostatin analogs is mentioned in the PDQ, reporting improvement of symptoms but little to no effect on tumor size. Attempts to combine the several options have been initiated. Because of the rarity of the disease, it is difficult to conduct large studies to confirm earlier interesting results or to design studies to improve these results. It will be of major importance to consider future multicenter studies in order to improve the outcomes of patients in this category.

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Chapter 7b

SURGICAL RESECTION OF PRIMARILY IRRESECTABLE CARCINOID LIVER METASTASIS WITH INDUCTION INTERFERON THERAPY WITH A REVIEW OF THE LITERATURE

H. de Vries[1]
I.P. Kema[3]
P.H.B. Willemse[2]
R.C.J. Verschueren[1†]
E.G.E. de Vries[2]

Departments of [1]Surgery, [2]Medical Oncology, [3]Pathology and Laboratory for Clinical Medicine. University Medical center Groningen, The Netherlands

Introduction

Carcinoid tumors are rare. Midgut carcinoids usually grow slowly and are often not detected before the tumor has metastasized to the liver. The carcinoid syndrome will become obvious only in the presence of hepatic metastases or metastatic disease in areas draining directly into the systemic circulation, bypassing the liver. At laparotomy the primary tumor is often smaller than the metastatic lymph nodes and hepatic metastases. The therapy of choice is surgery. The primary goal of surgery is radical resection, even in the presence of liver metastases. When the liver metastases are irresectable, debulking of the primary tumor and metastasis in the mesentery is another option because residual tumor can cause severe complaints such as bowel obstruction and ischemia. Hepatic resection may become easier subsequent to tumor reduction with new drugs. Recombinant Interferon and somatostatin analogs have been used since the late eighties.[1] Interferon has proven to be beneficial in symptom relief, showing in 40-60% of the patients a biochemical response, stabilization of disease in 40-80% and tumor reduction in 10-15% of the patients.[2,3-6] Somatostatin analogs yield little effect on tumor size.[7] Chemotherapy has also only limited antitumor effect.[8-14]
This article reports the effect of interferon alpha on tumor size of an initially irresectable hepatic metastasis. Furthermore the value of serotonin and its metabolites as a marker is discussed.

Case report

In 1986 a 39 years old man suffered from flushes, abundant perspiration and paroxysmal atrial fibrillation. The patient was referred to our hospital suspected of having a paraganglioma. Flushing and a high platelet serotonin (24.6 nmol/10^9 platelets = 4.6 x upper reference level) suggested a carcinoid syndrome. The urine 5-HIAA excretion however, was only marginally elevated. A MIBG scan showed a hot spot in the right lower quadrant of the abdomen and one in the liver, consistent with a neuro-endocrine tumor. The abdominal CT scan showed a large mass in the left hepatic lobe bulging into the right lobe and a 3 cm lesion in the ileal mesentery. In May 1986 a laparotomy was performed. The abdomen was explored via a midline incision. Inspection revealed a solitary hepatic tumor with a 10 cm diameter in segment 4 of the liver bulging over Cantlie's line. The hepatic surgeons considered this metastasis to be unresectable. A tru-cut needle biopsy was performed. A Meckels diverticulum containing the suspected carcinoid was found at 70 cm from the

ileocecal valve. Opposite the diverticulum a metastatic focus with a diameter of 5 cm was found in the ileal mesentery. A 20 cm segment of the ileum was resected with the corresponding wedge of the mesentery. The patient recovered uneventfully and left the hospital one week after surgery.

Histopathological examination revealed a Meckel's diverticulum containing a carcinoid tumor with invasion of the serosal fat. The number of mitotic figures observed, was low. The tumor in the mesentery was a metastasis without residual lymphoid tissue. The hepatic biopsy showed a carcinoid with the same histology. The flushing increased after the operation and interferon alpha medication was initiated in September 1987(2.5 MU subcutaneously once daily). After 3 weeks the frequency and the intensity of the flushes had decreased considerably with a reduction of platelet serotonin and urinary excretion of 5-HIAA (figure 1 panel 1 and 2). In December 1987 because of visual disturbance the dose of interferon alpha was reduced to 50%. In March 1988 the interferon medication was increased to the original dose of 2.5 MU because flushes worsened. Platelet serotonin varied accordingly. Subsequently the frequency of the flushes decreased to the extent that they stayed away for weeks. The CT scan showed a reduction of the hepatic metastasis so it was decided to attempt to resect this metastasis.

The second laparotomy was carried out via a bilateral subcostal incision. A 4 cm metastasis was identified in segment 4 of the liver. Frozen section of the nodes sampled from the celiac trunc and the hepatoduodenal ligament revealed no tumor. Elaborate exploration of the peritoneal cavity yielded no evidence of tumor elsewhere. A left hemi-hepatectomy was tedious because of anomalies of the portal vein. The postoperative course was uneventful. Interferon alpha medication was stopped. The histological aspect of the hepatic metastasis and the initial hepatic biopsy were identical. The resection margin measured 2 mm. Biochemical analysis of the liver metastasis revealed a high quantity of serotonin (36.350 nmol/g wet tissue). The serotonin in platelets and urine normalized(figure1, panel 1). Flushes did not reappear after the resection. In August 1990 the patient resumed work again. MIBG scan, carried out in January 1994, showed no evidence of endocrine carcinoid activity. Fifteen years later in 2004 there is still no sign of clinical or biochemical recurrence.

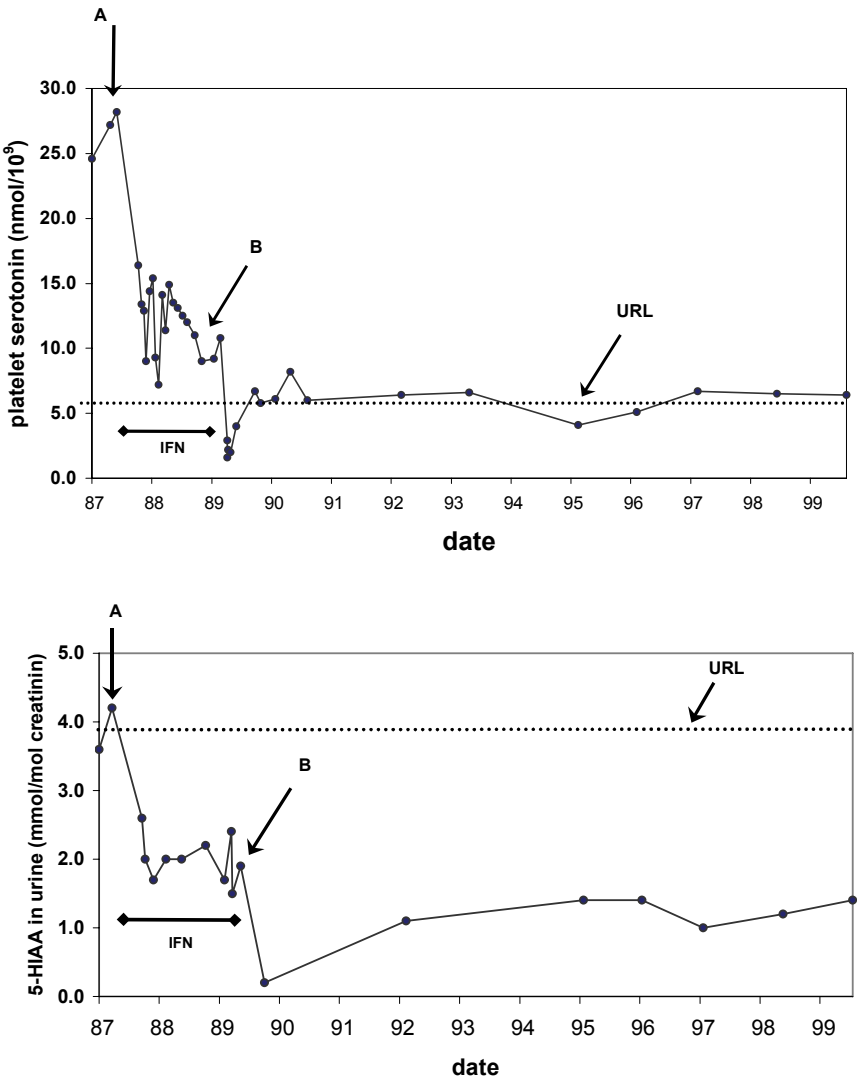

Figure 1:

panel 1: Platelet serotonin content in nmol/10^9 platelets during course of disease
panel 2: 24 hours 5-HIAA excretion mmol/mol creatinine during course of disease
A = resection of primary tumor and mesenteric metastases,
IFN = Interferon,
B = hemi-hepatectomy,
URL = upper reference limit

Discussion

This case shows a long-term remission as result of a response to administration of interferon alpha and subsequent resection of a hepatic metastasis. To our knowledge, this is the first report of the use of interferon alpha aimed to reduce the tumor size prior to resection of a hepatic metastasis. Reduction of the tumor size by interferon alpha[15-18] enabled adequate resection of the hepatic metastasis in our patient. Although the outcome in this patient is not exemplary for the treatment of carcinoids in general, this case supports clinicians favoring aggressive surgical intervention, even in the presence of marginally resectable hepatic metastases.[19,20] When curative resection is impossible, debulking the tumor can still lead to symptom relief and longer survival.[21-23]

Many other treatment modalities have been tried, all aiming at reduction of the tumor load in the liver with subsequent symptom relief, but long-term follow up reports following (neo-adjuvant) treatment of patients with a hepatic metastasis are scarce. Some articles report about dearterialization of the metastases by ligation of hepatic arteries.[24,25] Subsequent publications about chemo-embolization reported a symptom relief in most patients and reduction of biochemical parameters in 60-90% of them. Tumor response varied from stable disease to 80 % reduction with a duration between 12-24 months.[26-30] Some treatments such as radio frequency ablation using a laparoscopically introduced catheter are experimental.[31,32,33] Only a few authors mention good palliative results of (laparoscopic) cryosurgery but no long-term follow up data are available and no cures have been reported.[34-36] Orthotopic liver transplantation has been proposed in patients without extra-hepatic manifestations after initial surgery for the primary tumor.[13,37-39] There is only one report mentioning long-term survival with a 69% five-years survival in 15 metastasized carcinoid patients undergoing liver transplantation. The longest follow-up was 119 months.[13]

In the literature the predominant marker of carcinoid disease is urinary excretion of 5-HIAA. In our patient with a metastasized carcinoid of a Meckel's divertikel, the 5-HIAA excretion was only marginally elevated and therefore of no use. However, platelet serotonin appeared to be an excellent marker reflecting tumor load and treatment response. As mentioned, the tumor of our patient contained a serotonin load of 36.350 nmol/g wet tissue. To put this figure into perspective: as little as 2 g of the tumor contained the equivalent of the normal total body content of serotonin.

Surgery with of without prior systemic medical treatment, is to date the only possibility for cure of a metastatic carcinoid. Diagnosis and treatment of patients with a carcinoid tumor is challenging. As it is a rare disease, it is recommended to treat patients suffering from this disease in a center with an experienced multidisciplinary group. Reducing (hormone producing) tumor tissue must be the primary goal. As long as there is no other curative treatment, surgery remains the cornerstone of cure and locoregional control.

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