Chemotherapy for Metastatic Islet Cell Carcinomas

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Ajani and colleagues (520) performed repetitive hepatic artery embolization with polyvinyl alcohol particles in 22 patients with metastatic pancreatic endocrine tumors and achieved partial remission of measurable hepatic tumor in 12 of 20 evaluable patients. From this experience, the authors suggested this modality for prolonged palliation in selected patients. Marlink and colleagues (521) reported partial responses in all six patients with metastatic islet cell tumors following selective hepatic artery embolization; however, the duration of responses was not reported.

Because of the relative rarity of GEP neoplasms, chemotherapy trials frequently have combined several islet cell tumor subtypes within the same study. The experience from these studies suggests that whereas similar responses may be expected from chemotherapy for several tumor subtypes, there may be differences in the response of others. For example, streptozotocin alone or in combination with 5-fluorouracil is extremely effective against most VIPomas (228) and is moderately effective against gastrinomas and most other islet cell tumors. In contrast, streptozotocin has little activity against glucagonomas, whereas dacarbazine appears to have significant activity (236).

Streptozotocin is a drug that is selectively cytotoxic for pancreatic islet cells. Because of this property, the drug has been used to establish animal models for diabetes and islet cell hypofunction (236). This selective cytotoxicity also provided a rationale for using streptozotocin in neoplastic disorders of pancreatic endocrine cells. In several studies using intravenous and, less commonly, intra-arterial administration, streptozotocin was shown to be active against several pancreatic endocrine cancers, with nearly 40% tumor responses and over 50% hormonal responses reported (254;522-525). More frequent use of this agent is limited by its significant emetogenic and renal toxicities. In the case of symptomatic hepatic metastases from glucagonoma and somatostatinoma, Friesen (526) claims that use of intra-arterial administration of streptozotocin is effective, with reduced incidence of nephrotoxicity, but this has not been confirmed.

Other drugs that have single-agent activity in islet cell carcinoma are chlorozotocin and

doxorubicin. At a dose of 100 to 200 mg/m ^{2} , chlorozotocin resulted in a 53% objective response rate in 13 previously untreated patients (527). In 20 previously treated patients, doxorubicin, 60 mg/m2 every 3 to 4 weeks, resulted in four (20%) objective responses (528).

Several authors have reported that dacarbazine is a highly effective agent for the treatment of pancreatic islet cell tumors, especially glucagon-secreting tumors. Using either 1,250 mg/m ^{2} in divided doses over 5 days or a single dose of 650 mg/m ^{2} , Kessinger and colleagues reported two complete responses and two partial responses of elevated serum glucagon in four patients with glucagonomas (236). Three of four additional patients with malignant islet cell carcinoma associated with glucagonoma syndrome were cited in this report as having responded to dacarbazine alone. In a recently reported prospective study of 48 evaluable patients with advanced islet cell carcinoma, Hahn and colleagues (529) reported 13 patients (27%) with objective responses (including three complete responses) following dacarbazine, 850 mg/m ^{2} given every 4 weeks. The median survival in all patients was 19 months, and the authors concluded that dacarbazine clearly had beneficial activity in patients with advanced islet cell carcinoma.

None of six evaluable patients with islet cell carcinoma responded to etoposide in a phase II study (238). Only 2 of 41 patients with a variety of advanced apudomas responded to carboplatinum (530). No other conventional chemotherapy agents are reported to have activity in this disease.

In a multi-institutional study, streptozotocin combined with 5-fluorouracil was shown to be effective against malignant pancreatic endocrine tumors, with an objective response rate of 63% for a duration of 17.4 months (235;243;523). Furthermore, this combination produced a 37% complete response rate and a more prolonged median survival than streptozotocin alone. However, the combination was also associated with a high prevalence of moderately severe GI, hematopoietic, and renal toxicity (523). A smaller, nonrandomized series of patients receiving the same combination chemotherapy regimen produced similar results, and this study also suggested that the response rate in patients with nonfunctional tumors (50%) may be less than that in those with functional tumors (68%)(243). Although the regimen of streptozotocin and fluorouracil is not considered to be the most active for malignant glucagonoma, responses to the combination have been reported (317).

In a randomized three-arm trial by the Eastern Cooperative Oncology Group, streptozotocin plus 5-fluorouracil was compared to a combination of streptozotocin plus doxorubicin or to chlorozotocin (531). The streptozotocin plus doxorubicin arm was clearly superior to the other two arms with a 69% response rate and a median survival of 24 months. This study, which included 120 patients, has provided an important contribution toward further defining the optimal chemotherapeutic approach for malignant pancreatic endocrine tumors. Several other multicenter chemotherapeutic regimens have now been tried (Table 9), but, in general, their activity is no better than that with single-agent therapy. There has been no prospective investigation of adjuvant chemotherapy in patients with islet cell carcinoma.

Finally, the interferons have been reported to be active in GEP endocrine neoplasms as well. As reviewed by Oberg and colleagues (243), an objective hormonal response of 73% was

observed in patients with malignant pancreatic endocrine tumors treated with human leukocyte interferon, 3 to 6 million units per day subcutaneously. Among their first 22 responders, 6 patients (27%) had a 50% reduction in tumor mass, and 2 patients (9%) had a complete response (532). The median duration of response was 9.5 months. Since 1986, this group has been using recombinant interferon-alpha-2b, 5 million units three times per week subcutaneously or intravenously. An update of their results in 57 patients showed objective responses in 29 patients (51%), with biochemical responses in 27 (47%) and radiologic responses in 7 (12%)(532). The median duration of response was 20 months (range 2–96 months), and response rates were higher in patients with VIPomas (10 of 12 patients) than in those with other tumors. A review of 372 patients treated with interferon from various institutions showed an overall objective response rate of 44% (533). Interferon was well tolerated despite frequent occurrence of a flu-like syndrome, weight loss, and mild myelosuppression.

Suggested Scheme of Management of Neuroendocrine tumors

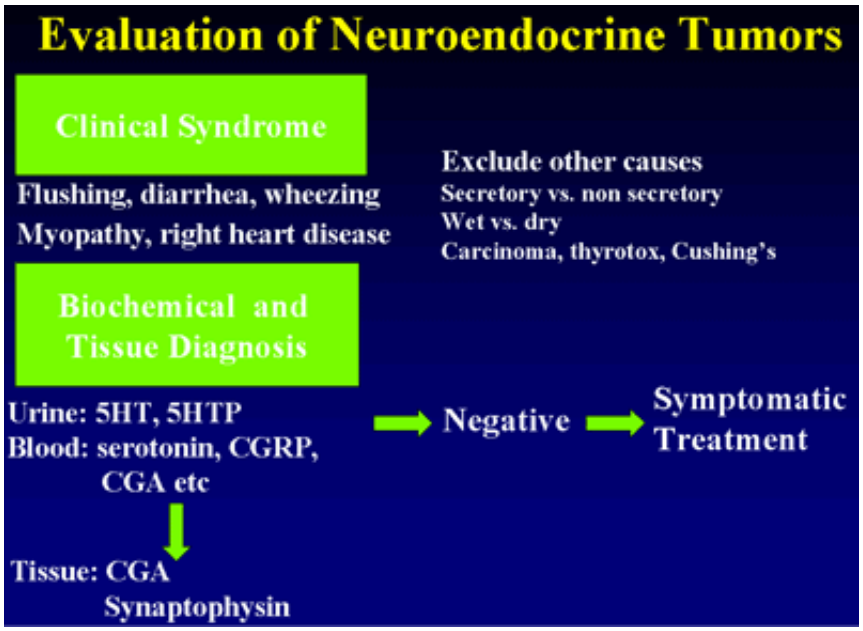

Figure 1

The first objective is to recognize the clinical syndrome that may represent a neuroendocrine tumor base upon the symptoms of flushing, diarrhea etc. Other causes of the symptom complex are excluded and an attempt is made to ascertain the presence of a tumor biochemical and by tissue diagnosis. If all are negative symptomatic therapy is in order. If a tumor is found and is localized without spread it should be removed surgically. In the event that this is not feasible or if there have been metastases, then treatment is to use LAR with Octreotide for escape of symptoms for 3 months. If there is arrest of tumor growth, improvement in the patient's symptoms and reversal of the biochemical abnormalities continue the LAR and reassess at 6 moth intervals. α. In rare instances a liver transplant may be feasible. Whatever the case, these

are slow growing tumors and there is much that can be done to salvage many years of good life.

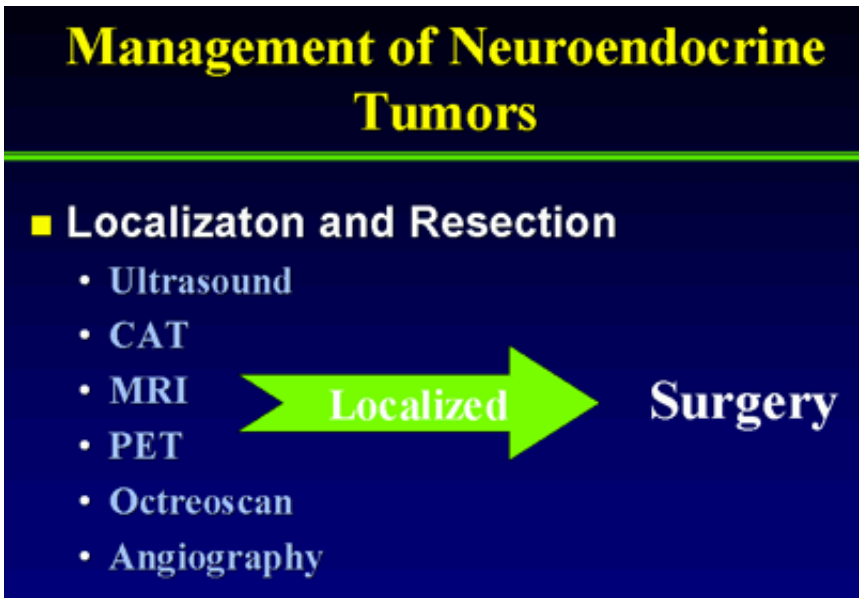

Figure 2

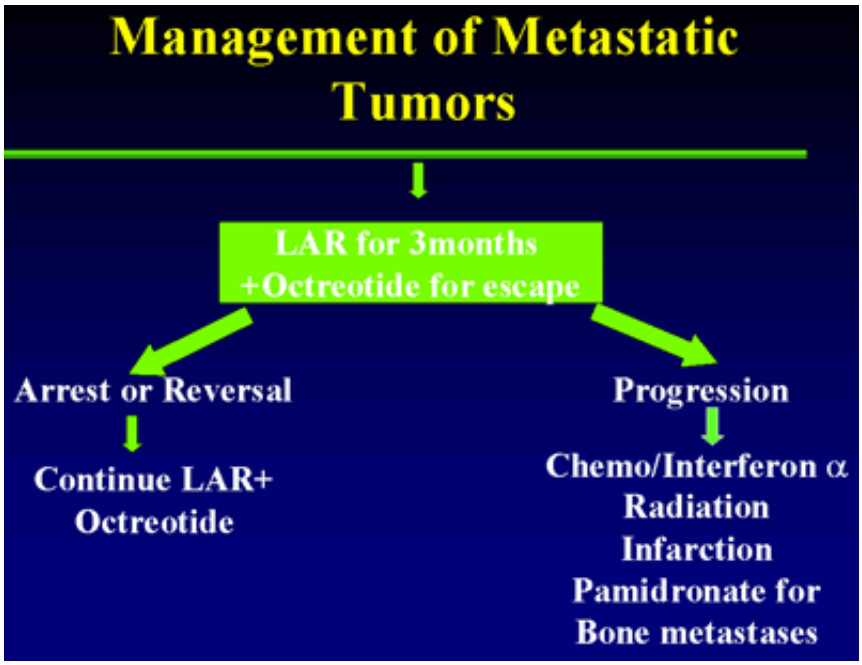

Figure 3

Conclusions

New approaches to the diagnosis and localization of GEP tumors have been stressed, including the importance of circulating hormone levels and sophisticated immunohistochemistry, tracer scanning, and the role of peptide therapy in the management of the symptom complex as well as the tumor. There is, however, much that remains unsolved, requiring diligent research and evaluation if we are ultimately to include neuroendocrine tumors among the curable cancers. An outline of the current approach to management of the patient suspected of harboring a GEP tumor is given in Figure .7.

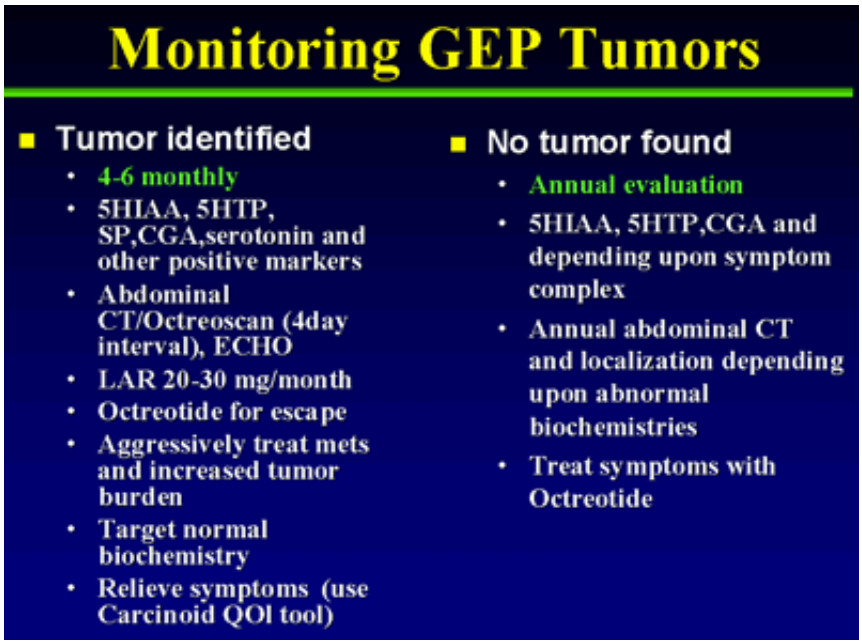

Figure 4

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