

SUMMARY OF SPEAKERS' PRESENTATIONS

Treatment of Pancreatic Neuroendocrine Tumors

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Pancreatic neuroendocrine tumors (pNETs) are rare neoplasms that arise in the endocrine tissues of the pancreas. They are low to intermediate grade neoplasms and have a more indolent course compared to more frequently seen pancreatic adenocarcinoma. These tumors can secrete a variety of peptide hormones resulting in different clinical syndromes. However, between 50 to 75 percent of pNETs are nonfunctioning.

Surgery is currently the only treatment modality that may achieve cure. Patients with advanced, unresectable pNETs, cure is generally not possible. The goals of oncologic treatment include palliation or prevention of symptoms and cytoreduction of bulky tumors to improve survival. For patients with potentially resectable liver-isolated metastatic pNETs, surgical resection of the hepatic metastases along with the primary tumor is recommended. Although the majority of cases will not be cured by surgery, given the slow growing nature of the tumor, extended survival is sometimes possible. Other treatment options for patients with unresectable hepatic predominant symptomatic metastatic disease include embolization, chemoembolization, radiofrequency ablation (RFA), and cryoablation. Occasionally, systemic therapy may also convert cases wherein surgery may render the patients disease free.

Poorly differentiated neuroendocrine carcinomas have a bad prognosis. They are generally treated with platinum based chemotherapy. Patients having low to intermediate grade tumors with symptoms of hormone hypersecretion from a pNET should be managed with somatostatin analogs and other agents as appropriate to the specific syndrome. In general, initial therapy for insulinomas consists of carbohydrates and *diazoxide*, which directly inhibits the release of insulin from insulinoma cells. *Everolimus* can also be highly effective in improving glycemic control in patients with insulinoma. For patients with gastrinoma, high doses of oral proton pump inhibitors are the treatment of choice. For asymptomatic patients with low volume disease, observation

alone rather than early administration of a somatostatin analog is suggested. For patients who are felt to require therapy because of progressive disease or symptoms related to hormone production, initiation of therapy with a somatostatin analog, *everolimus*, or *sunitinib* is suggested that have all been shown to improve progression free survival (PFS) compared to best supportive care alone, although none of these agents have been compared directly to each other. In the absence of comparative trials, the choice of initial agent may be influenced by the expected toxicity profile. Given a favorable toxicity profile, a somatostatin analog is an appropriate first choice for many patients with use of a targeted agent if there is subsequent disease progression. Everolimus may be of particular value in patients with functioning insulinomas and refractory hypoglycemia. For patients who are symptomatic from tumor bulk, initiation of a somatostatin analog with either a targeted agent or chemotherapy is offered. For patients who are highly symptomatic or who have rapidly enlarging metastases, chemotherapy can be used as an initial treatment because of the higher objective response rate compared to other approaches. There are two acceptable options for therapy, a *streptozocin* based combination or a *temozolomide* containing regimen. In the absence of comparative trials, the choice of regimen should be individualized, considering the convenience of oral rather than intravenous treatment, performance status, and the anticipated side effect profile of both combinations. The role of peptide receptor radioligand therapy (PRRT) in patients with progressive advanced pancreatic NETs is unclear. Targeted radiotherapy using radiolabeled somatostatin analogs could be considered for patients with disease that is otherwise refractory to medical therapy.

In conclusion; pNETs are rare; consequently, randomized trial data to form a robust evidence are limited. Treatment should aim to cure the patient but is often palliative because most patients have evidence of metastasis at presentation. In patients with incurable disease, treatment should aim to maintain a good quality of life as long as possible, recognising that this can be achieved for a number of years in many NETs, even in the presence of metastatic disease. As a result, management of patients with pNETs requires an understanding of the disease process and the importance of a multimodality approach.