

Gastrointestinal Cancers Symposium

General Session V: Cancers of the Pancreas – Multidisciplinary Treatment

Title: Current Approaches to the Management of Neuroendocrine Tumors

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- Dr. Kulke's talk covered the current approaches to the management of gastrointestinal neuroendocrine tumors with a focus on the developments in managing metastatic disease.
- GI neuroendocrine tumors are generally subdivided into two main subtypes: pancreatic neuroendocrine tumors and carcinoid tumors.
 - While there are some differences between these two subtypes, they share a number of clinical features.
 - Tend to be "well-differentiated."
 - Patients often have a fairly indolent clinical course.
 - Grow fairly slowly.
 - With a few exceptions they are often resistant to standard cytotoxic chemotherapy.
 - Ability to secrete neuropeptides resulting in a variety of different hormonal syndromes.
- **Carcinoid Syndrome**
 - The Carcinoid Syndrome is the most common hormonal syndrome. It is generally manifested by diarrhea and episodic flushing (erythema) that starts in the trunk/torso and proceeds up to the face. The flushing can recede as rapidly as it began.
 - Researchers believe carcinoid syndrome is caused by the secretion of serotonin and other neuropeptides into the systemic circulation.
 - Patients with carcinoid syndrome can also develop heart disease, typically affecting the right side of the heart resulting in fibrosis.
- **Treatment for Neuroendocrine Tumors**
 - Treatment with somatostatin analogs, such as octreotide, is well established. Although there isn't a clear answer of how to treat patients who progress on therapy with somatostatin analogs, there are several potential treatment options including: 1) interferon alfa, 2) direct treatment of hepatic metastases, 3) cytotoxic chemotherapy, or 4) targeted therapies.
 - 1) **Interferon Alfa**
 - Mixed results from studies using interferon alfa. Dr. Kulke reviewed the Faiss et al., 2003 publication in the *Journal of Clinical Oncology* where patients were randomized to:
 - Somatostatin alone
 - Interferon alfa alone
 - Treatment with both agents
 - The objective radiologic responses with interferon alfa were relatively low. However, patients all had progressive disease prior to initiating therapy; but on study they experienced a rate of disease stabilization of about 20-30%

suggesting that somatostatin analogue or interferon alfa may have some benefit in stabilizing disease progression.

2) Direct Treatment of Hepatic Metastases

- Liver metastases are a very common site for disease spread in patients with neuroendocrine tumors and are a potentially attractive treatment target.
- For patients with a limited number of hepatic metastases hepatic resection may be a good option. Retrospective data show the 4-year survival rate of those with hepatic resection for neuroendocrine tumors reached closed to 70%. About 90% had an improvement in symptoms.
- However, few patients present with a limited number of liver metastases; most often, patients will have diffuse liver metastases and for these cases hepatic artery embolization is a treatment option for which most data show encouraging success rates.

3) Treatment with Cytotoxic Chemotherapy

- Cytotoxic chemotherapy has shown to improve both response rates and duration of response in patients with neuroendocrine tumors. In general, cytotoxic therapy are less effective in patients with carcinoid tumors than in pancreatic neuroendocrine tumors.
- Studies using streptozotocin in combination with a second chemotherapy agent in neuroendocrine tumors showed the overall response rate was much lower in carcinoid tumors than in pancreatic neuroendocrine tumors.
- Dacarbazine (DTIC) appears to have activity in pancreatic neuroendocrine tumors. Two phase II trials looked at DTIC activity in neuroendocrine tumors; carcinoid tumors had a 16% response rate and pancreatic islet cell tumors had a 33% response rate. Streptozotocin, like DTIC is not commonly used because of toxicity, including high rate of nausea and vomiting.
- More recently temozolomide, an oral analog of DTIC, and less toxic agent has been studied in two small prospective studies which showed higher response rates in pancreatic neuroendocrine tumors than carcinoid tumors. Data suggests temezolomide is a reasonable therapy with less toxicity than streptozotocin or DTIC in patients with pancreatic neuroendocrine tumors.

4) Treatment with Targeted Therapies

- There is extensive interest in using novel therapies targeting the VEGF pathway, for patients with neuroendocrine tumors who may fail on chemotherapy.
- Widely known that neuroendocrine tumors express high levels of both VEGF and its receptor.
 - Carcinoid tumors found to express VEGF 70% of the time.
 - Pancreatic neuroendocrine tumors found to express VEGF 100% of the time (85% express the receptor).
- There are a number of ways to target the VEGF pathway. Bevacizumab targets VEGF itself. A variety of tyrosine kinase inhibitors, including sunitinib and sorafenib, target the VEGF receptor. Used as single agents these therapies seem to show activity in neuroendocrine tumors. The response rates average under 20% and while that doesn't seem very good, Dr. Kulke explains that these agents are not necessarily cytotoxic but rather are cytostatic (prolonging stable disease). He reports that there were very high rates of stable disease reported in a phase II sunitinib trial (93% of carcinoid and 75% of islet cell patients had

- stable disease). He notes that it is difficult to interpret what stable disease means in an indolent tumor.
- One of the most recent developments in neuroendocrine tumors is the study of mTOR inhibitors. At the ASCO 2007 annual meeting, results from a Phase II study at M.D. Anderson of everolimus in 30 carcinoid and 20 pancreatic islet cell cancer patients reported that the carcinoid group had a 13% response rate and the pancreatic islet cell patients had a 20% response rate. This encouraging data led to two randomized studies known as the RADIANT 2 and 3 currently comparing everolimus against placebo in combination with octreotide.
 - Dr. Kulke concluded that there are a lot of options to treat patients with advanced neuroendocrine tumors. Surgery remains the mainstay for patients with localized disease. There are a number of options for metastatic disease starting with chemotherapy particularly for pancreatic neuroendocrine tumors, chemoembolization, interferon alfa, somatostatin analogues, and most recently the use of angiogenesis inhibitors and other novel targeted therapies.