

Annual Report – Caring for Carcinoid Foundation

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Introduction

Carcinoid cancer research and the application of carcinoid biology to clinical practice is a major focus of our research program. With support from Caring for Carcinoid Foundation, we have initiated a multi-faceted approach to aid in our understanding and treatment of neuroendocrine tumors. Translational research and clinical trial components work in tandem; our approach is designed to facilitate the flow of results and information from one experimental track to another in real time. Our research progress is detailed below.

Clinical Trials of Novel Agents in Patients with Neuroendocrine Tumors.

Standard cytotoxic therapy offers limited benefit to patients with metastatic neuroendocrine tumors. We are interested in developing novel therapeutic approaches for patients with advanced neuroendocrine tumors. In 2006 we reported the results of four studies of investigational agents, and we continue to investigate more potential treatment options for neuroendocrine tumors.

The combination of irinotecan and cisplatin is active against small cell lung cancer and in upper gastrointestinal malignancies, but had never been evaluated in patients with metastatic neuroendocrine tumors. We evaluated this combination in a clinical study, published in *Digestive Diseases and Sciences* in June of 2006.¹ Unfortunately the efficacy of this regimen was similar to other traditional chemotherapies. Out of 18 patients there was only one radiologic response in a patient with poorly differentiated neuroendocrine tumors- and no radiologic responses in the patients with well-differentiated tumors. We concluded that, while there may be some activity associated with this regimen in aggressive tumor subtypes it appears to be inactive against well-differentiated neuroendocrine tumors.

Darcarbazine (DTIC) is an older, intravenous chemotherapy and has shown activity in carcinoid and pancreatic neuroendocrine tumors in early studies, but is rarely used due to its potential side effects. Temozolomide was specifically developed as an oral and less toxic alternative to DTIC. Thalidomide is postulated to have antiangiogenic qualities through its ability to interfere with the VEGF and basic fibroblast growth factor (bFGF) pathways. We evaluated a combination of temozolomide and thalidomide in a clinical trial, with promising results, published in January of 2006 in the *Journal of Clinical Oncology*. Out of 29 evaluable patients with metastatic neuroendocrine tumors 25% experienced radiologic responses. When evaluated according to tumor subtypes, we found that this regimen appeared more active in pancreatic neuroendocrine tumors than in carcinoid tumors. We conclude that this combined treatment is an active oral regimen for the treatment of metastatic neuroendocrine tumors particularly pancreatic neuroendocrine tumors.²

The temozolomide/thalidomide trial does not answer the specific question as to the efficacy of pure antiangiogenic therapy in patients with neuroendocrine tumors. Both carcinoid tumors and pancreatic endocrine tumors express high levels of vascular endothelial growth factor (VEGF) and its receptor (VEGFR), two molecules critical in angiogenesis. We therefore hypothesized that antiangiogenic agents should be effective against neuroendocrine tumors, and that a treatments that targeted these pathways should inhibit the tumor's ability to grow. Based on evidence that recombinant human Endostatin (rhEndostatin) had been shown to have antiangiogenic and antitumor activity in preclinical studies, we first evaluated this agent in patients with neuroendocrine tumors. Our multi-center, phase II study of rhEndostatin was published in the *Journal of Clinical Oncology* in August of 2006. Unfortunately, out of 40 patients who had completed at least one round of therapy there were no partial or complete responses

and biochemical responses were recorded in only 6% of the study population. The majority of patients (80%) reported stable disease as their best response to therapy. Treatment with specific VEGF pathway inhibitors have shown more promising results in neuroendocrine tumors.³

Sutent is a novel, oral agent with antiangiogenic and antitumor activity that specifically inhibits the VEGF receptor (VEGFR). We led a multicenter study of this agent that enrolled 106 patients with advanced, unresectable neuroendocrine tumors. We demonstrated that this treatment was well tolerated; moreover, we observed modest radiologic response rates and a high rates stable disease. Out of 52 islet cell patients, seven had partial responses and 40 had stable disease and out of 39 carcinoid patients, 2 had partial responses and 36 had stable disease. These results were reported at the 2005 annual meeting of the American Society of Clinical Oncology.⁴ We are developing additional trials to use Sutent in combination with other agents to further enhance its activity in neuroendocrine tumors.

In our most recent study, we launched a two-sided attack, combining the oral chemotherapy temozolomide with the VEGF inhibitor bevacizumab, a monoclonal antibody targeting VEGF. Our results were reported at the 2006 meeting of the American Society of Clinical Oncology. We found promising results, with a high level of activity observed in patients with pancreatic neuroendocrine tumors.⁵

Our current efforts are focused on identifying additional novel agents with activity in neuroendocrine tumors, and on exploring novel combinations of VEGF inhibitors in this disease. A number of these efforts will include a newly formed neuroendocrine tumor consortium of institutions dedicated to neuroendocrine tumor research.

Translational Research in Carcinoid Tumors

As part of our research program, we have also established a database of clinical information and biospecimens from patients with neuroendocrine tumors, to serve as a foundation for translational research studies. Since its inception in 2003, over 400 patients with neuroendocrine tumors have enrolled in this prospective clinical and biospecimen database. The scale and range of this information is an invaluable and unique resource in the quest to find a cure for neuroendocrine cancer.

In an initial study utilizing this database, we evaluated clinical prognostic factors in patients with advanced neuroendocrine tumors. In this study, published in May of 2006 in *Digestive Diseases and Sciences*, we found that alkaline phosphatase levels were an independent and accurate prognostic factor for survival. Based on these results, we believe that measuring alkaline phosphatase is a useful clinical tool in making treatment decisions for patients with advanced neuroendocrine tumors.⁶

We have further utilized the resources in the database to identify potential regions of chromosomal loss or gain in carcinoid tumors. In collaboration with Ramesh Shivdasani, MD, PhD, at Dana-Farber Cancer Institute we are currently performing a high-resolution single nucleotide polymorphism array analysis on primary and metastatic small bowel carcinoid tumor specimens. This work should provide further insights into the genetic alterations involved in carcinoid tumorigenesis, ultimately leading to improved treatments for patients with this disease.

Through the use of this database, we also aim to identify genetic factors that contribute to neuroendocrine tumor risk and outcomes, which may in turn reveal information about pathways

that control neuroendocrine tumor growth. Our initial studies in this vein have focused on polymorphisms in genes involved in the p53 tumor suppressor pathway, and genes involved in DNA repair pathways. Genotyping has been completed for several of these polymorphisms, and we have undertaken a preliminary evaluation of potential associations between specific polymorphisms and neuroendocrine tumor risk. Our preliminary analyses suggest that this approach is feasible; as our database continues to grow we will re-evaluate these associations with greater statistical confidence. We anticipate evaluating candidate polymorphisms in additional pathways implicated in cancer development, to assess which biological pathways are important in carcinoid tumorigenesis, thereby discovering how best to target novel therapies for patients with carcinoid tumors.

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References

1. Kulke MH, Wu B, Ryan DP, et al: A phase II trial of irinotecan and cisplatin in patients with metastatic neuroendocrine tumors. *Dig Dis Sci* 51:1033-8, 2006
2. Kulke MH, Stuart K, Enzinger PC, et al: Phase II study of temozolomide and thalidomide in patients with metastatic neuroendocrine tumors. *J Clin Oncol* 24:401-6, 2006
3. Kulke MH, Bergsland EK, Ryan DP, et al: Phase II study of recombinant human endostatin in patients with advanced neuroendocrine tumors. *J Clin Oncol* 24:3555-61, 2006
4. Kulke M, Lenz H, Meropol N, et al: A phase 2 study to evaluate the efficacy and safety of SU11248 in patients with unresectable neuroendocrine tumors. *Proc ASCO:A4008*, 2005
5. Kulke M, Stuart K, Earle C, et al: A phase II study of temozolomide and bevacizumab in patients with advanced neuroendocrine tumors. *Proc ASCO 2006:A4044*, 2006
6. Clancy TE, Sengupta TP, Paulus J, et al: Alkaline phosphatase predicts survival in patients with metastatic neuroendocrine tumors. *Dig Dis Sci* 51:877-84, 2006