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HIGHLIGHT ARTICLE

Prognostic and Predictive Biomarkers in Gastroenteropancreatic Neuroendocrine Tumors

Highlights from the "2013 ASCO Gastrointestinal Cancers Symposium". San Francisco, CA, USA. January 24-26, 2013

Ryan Stevenson[1], Steven K Libutti[2], Muhammad Wasif Saif[1]

[1]Tufts University School of Medicine. Boston, MA, USA. [2]Albert Einstein College of Medicine. Bronx, NY, USA

Summary

Neuroendocrine tumors (NET) are a diverse group of tumors that derive from epithelial cells with neuroendocrine differentiation. Gastroenteropancreatic NETs are a subset of NET that arise from the gastrointestinal tract. The natural history and prognosis varies widely between different gastroenteropancreatic NETs, highlighting the importance of identifying accurate prognostic and predictive biomarkers. At the 2013 ASCO Gastrointestinal Cancers Symposium, De Braud *et al*. (Abstract #186) and Bellister *et al*. (Abstract #163) present data on two new possible biomarkers.

What We Knew Prior to the 2013 ASCO Gastrointestinal Cancers Symposium

Tumors arising in the gastrointestinal tract with cells of neuroendocrine origin are termed gastroenteropancreatic neuroendocrine tumors (NETs). These are uncommon tumors of the gastrointestinal tract, but the incidence and prevalence have increased over the past 40 years [1]. NETs can result in a wide array of symptoms based upon the various molecules secreted by the tumor. Survival is often better when compared to other gastrointestinal malignancies, but prognosis varies widely and depends upon multiple factors including location, tumor grade, sex, and age [1, 2]. Biomarkers, such as chromogranin A have also shown to have prognostic value, although levels can vary due to other unrelated conditions [3, 4].

Along with prognostic markers, predictive markers are becoming increasingly important in gastroenteropancreatic NETs as new therapies have been recently approved. The RAD001 in Advanced Neuroendocrine Tumors (RADIANT)-3 trial showed that everolimus, an mTOR inhibitor, improved progression free survival in pancreatic neuroendocrine tumors compared to placebo and led to the approval of everolimus for the treatment of pancreatic NETs [5]. Similarly, sunitinib, a multi-tyrosine kinase inhibitor, was approved for the treatment of pancreatic NETs basing on improved survival [6]. Benefit has also been seen with carcinoid tumors and markers such as normal chromogranin A levels, performance status, and liver or bony involvement have been predictive of a better response [7, 8].

Key words Biological Markers; Gastro-enteropancreatic Neuroendocrine tumors; PHLPP2 protein, human; Succinate Dehydrogenase

Abbreviations PH: pleckstrin homology; PHLPP2: pleckstrin homology domain leucine-rich repeat protein phosphatase 2; SH: succinate dehydrogenase; SDHB: succinate dehydrogenase subunit B; TCA: tricarboxylic acid

Correspondence Ryan Stevenson
Tufts Medical Center; 800 Washington Street; 02111 Boston, MA; USA
Phone: +1-671.636.2523; Fax: +1-617.636.8538
E-mail: rstevenson@tuftsmedicalcenter.org

What We Learned at the 2013 ASCO Gastrointestinal Cancers Symposium

Loss of Succinate Dehydrogenase (SDHB) in Midgut Carcinoids as a Prognostic Factor: A New Marker of Personalized Cancer Medicine in Neuroendocrine Tumors? (Abstract #186) [9]

Succinate dehydrogenase (SDH) complex is an enzyme complex bound to the mitochondrial membrane and is a key component of the tricarboxylic acid (TCA) cycle (Figure 1). SDH has been shown to be involved in tumor pathogenesis in multiple malignancies including pheochromocytomas, paragangliomas and GIST [10]. SDH gene mutations have been associated with loss of activity of subunit B (SDHB) and increased expression of HIF-1a. De Braud *et al*. evaluated SDHB expression in carcinoid tumors of the midgut for use as a possible prognostic marker. Tumor specimens of 31 advanced midgut carcinoid from "Fondazione IRCCS Istituto Nazionale dei Tumori" were evaluated. All patients had low grade (G1) and metastatic disease (liver). Immunohistochemical staining for SDHB and MIB 1 were performed on primary tumors and liver metastasis and scored based on intensity: 1 (low) or 2 (high).

Twenty primary tumors and 19 metastases were tested with loss of SDHB seen in 70% of primary and 90% of liver metastases. No difference in overall survival was seen. Eleven patients had both primary and liver metastases evaluated and SDHB loss was seen in 82% of metastases compared to 18% of primary tumors. MIB 1 was also increased in metastatic samples *vs.* primary tumors (1.54% *vs.* 0.70%). This study shows a possible correlation between low SDHB expression and more aggressive disease in midgut carcinoid tumors.

Prediction of Prognosis in patients Treated with Everolimus for Extrapancreatic Neuroendocrine Tumors by a Single Nucleotide Polymorphism in PHLPP2. (Abstract #163) [11]

Pleckstrin homology (PH) domain leucine-rich repeat protein phosphatase 2 (PHLPP2) is an inhibitor of mTOR signaling. Bellister *et al*. evaluated a single nucleotide polymorphism in PHLPP2 for its effect on outcomes in patients with extrapancreatic NETs treated with everolimus. Thirty-two patients with NETs were treated with single agent everolimus in this single arm phase II study. Blood samples were taken and RT-PCR was used to detect L1016S SNP in PHLPP2. Progression free survival, overall survival, and response rates were evaluated and a site specific subset analysis was also performed. Overall survival and response rates were not significantly different in wild type *vs*. SNP groups. Progression free survival did not differ significantly between the two groups, but in the subgroup analysis, SNP was predictive of decreased progression free survival in patients with extrapancreatic NETs (16.8 months in wild type *vs.* 7.9 months in SNP; P=0.002).

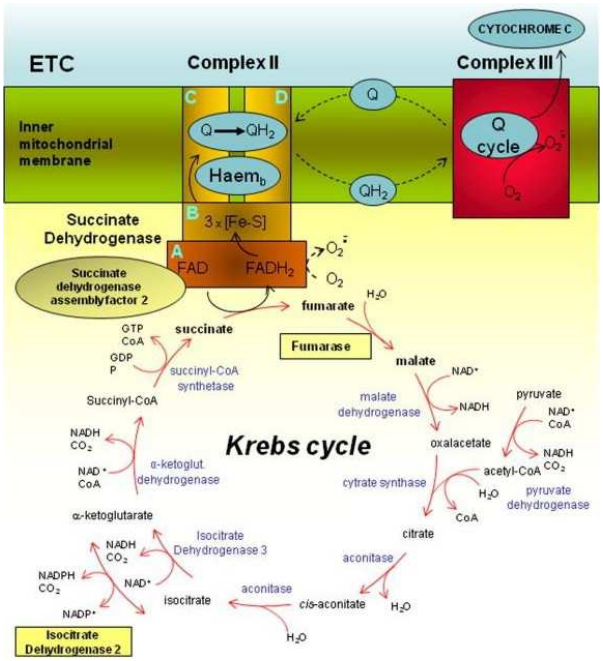

Figure 1. Succinate dehydrogenase (SDH) complex in the tricarboxylic acid (TCA) cycle and electron transport chain. (Published with permission from Barletta *et al.* [12]).

Discussion

The field of gastroenteropancreatic NET has seen an explosion of research interest with the introduction of new targeted therapies in the past few years. Along with finding new therapies, looking for new prognostic/predictive markers to help better stratify risk for aggressive disease and identify patients that will respond to treatment is important. In Abstract #186, De Braud *et al*. showed that loss of SDHB expression was seen more often in metastatic midgut carcinoid tumors and may be prognostic of more aggressive disease [9]. In Abstract #163, Bellister *et al*. evaluated a SNP in PHLPP2 and its effect on prognosis in patients treated with everolimus. The subset of patients with extrapancreatic neuroendocrine tumors showed a significant improvement in progression free survival [11]. Further studies are needed to evaluate these markers and define their clinical significance in monitoring treatment of NETs.

Conflict of interest The authors have no potential conflict of interest

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