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Advances in small bowel neuroendocrine neoplasia Banck and Small intestine

Michaela S. Banck and **Andreas S. Beutler**

Department of Medical Oncology, Mayo Clinic, Rochester, Minnesota, USA

Abstract

Purpose of review this review aims at summarizing progress in clinical trials and basic science redefining the diagnosis and treatment of well differentiated small intestine neuroendocrine tumors (SI-NET).

Recent findings—Two clinical trials demonstrated antitumor activity of the long-acting somatostatin analogues octreotide LAR and lanreotide for advanced SI-NET. The mTOR inhibitor everolimus is another treatment option for patients with SI-NET, but awaits definitive proof of benefit in the ongoing RADIANT-4 study. Two whole exome/genome-sequencing studies reported in the past year provided the first genome-wide analysis of large sets of SI-NET at nucleotide resolution. Candidate therapeutically relevant alterations were found to affect SRC, SMAD genes, AURKA, EGFR, HSP90, and PDGFR as well as mutually exclusive amplification of AKT1 or AKT2 and other alterations of PI3K/Akt/mTOR signaling genes. The gene CDKN1B is inactivated by small insertions/deletions in 8% of patients with SI-NET suggesting cell cycle inhibitors as new candidate drugs for SI-NET. Circulating tumor cells and tumor-derived RNA in the blood are promising clinical tests for SI-NET.

Summary—Clinical and genomic research may merge in the near future to re-shape clinical trials and to define the ‘personalized’ treatment options for patients with SI-NET.

Keywords

genome sequencing; small bowel carcinoid; small intestine neuroendocrine tumor; somatostatin analogue

INTRODUCTION

Well differentiated small intestine neuroendocrine tumors (SI-NET) are the most common malignancies of the small bowel (0.86 new cases each year per 100 000 persons in the United States). SI-NET are indolent tumors (survival measured in years), yet resistant to cytotoxic chemotherapy [1,2] and, if advanced (surgically unresectable), usually fatal.

Correspondence to Andreas S. Beutler, MD, Department of Medical Oncology, Mayo Clinic, Rochester, Minnesota 55905, USA. Tel: +1 507 284 1843; beutler.andreas@mayo.edu.

Conflicts of interest

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The authors have declared, that no conflict of interest exists.

Recent clinical trials – reviewed below – tested ‘targeted’ antineoplastic drugs redefining the standard of care for patients with advanced SI-NET. Trials performed to date did not select patients on the basis of molecular tumor characteristics or genome analysis. Although other areas of oncology saw the introduction of exome/genome-wide tumor DNA-sequencing since 2008, SI-NET remained the terra incognita of tumor genetics until recently. Two studies published in the past year provided a ‘catch up’ for the SI-NET field reporting the first genome-wide analyses of genetic alterations at nucleotide resolution in this tumor type. Furthermore, new options for detecting tumor-derived RNA or tumor-cells in the blood of SI-NET patients were published. The current review juxtaposes the recent progress in these – at present still separated – areas of research to outline how basic, translational and clinical research directions may merge in the near future to re-shape clinical trials, and thereby define better ‘personalized’ treatment options for patients with SI-NET.

CLINICAL TRIALS

Well differentiated neuroendocrine tumors (NET) can arise from neuroendocrine cells of many organs. First described collectively as ‘carcinoids’ 100 years ago [3], it is now known that clinical behavior and prognosis of NET differ depending on the organ of origin, tumor grade (G1–G2), and proliferative behavior (Ki-67-index; number of mitoses per are) as reflected in the most recent WHO classification [4,5]. Nevertheless, NET continue to be viewed as one entity and are often pooled as one group even in modern clinical trials. It remains unknown, however, whether treatment results should be generalized across all NET and whether histological types defined by grade predict treatment responses. As discussed below, clinical and genomic data suggest to consider pulmonary NET, pancreatic NET (PNET), and SI-NET separately and to extrapolate results from one tumor subtype to the other only with caution.

Walter and Kryzynasowska [6¥] provided an informative analysis of all phase II/III clinical trials studying systemic treatment in NET published between 2004 and 2012. The authors identified seven phase III and 39 phase II NET-trials conducted between 2000 and 2011. The result of their analysis highlights many of the problems inherent in NET clinical research: most of the studies were single arm trials (36 of 46). Only 16 of the 46 studies were prospectively registered in ‘clinicaltrials.gov’; a clearly defined primary endpoint (PEP) was described in 33 of the 46 trials. Only eight trials included more than 100 patients; 35 studies enrolled heterogeneous study populations including patients with two or more different NET types. Five trials enrolled a homogenous population of patients with only carcinoids.

Rinke *et al.* [7¥¥] were the first to test the antitumor effects of the somatostatin analog (SSA) octreotide with the PROMID study, a randomized, placebo-controlled double blind phase III trial in a relatively homogenous population of patients with unresectable well differentiated (G1; Ki67 < 2%) SI-NET. SSAs were initially designed in the 1980s to palliate carcinoid syndrome [8,9]. Somatostatin binds to somatostatin receptors (sst_1-sst_5) and inhibits the release of neuroendocrine hormones (the cause of the sometimes fatal carcinoid syndrome). Soon, however, SSAs were noted to have a cytostatic effect in preclinical models of SI-NET [10] and in small, nonrandomized clinical trials. In the PROMID study, 85 SI-NET patients

with or without carcinoid syndrome were randomized to octreotide LAR or placebo. PFS in the octreotide LAR group was 14.3 versus 6 months in the placebo group. The authors concluded that that the octreotide LAR has antitumor effects in SI-NET, which should become the first choice of treatment in this setting. Critics noted that the study was terminated early after a planned interim analysis and that the number of individual patients was small with only 43 patients randomized to the octreotide LAR arm. However, based on the large effect size and marked level of statistical significance (HR = 0.34, $P = 0.000072$) octreotide LAR became standard of care for patients with unresectable SI-NET and 'clinically significant tumor burden' as reflected in the guidelines of the National Comprehensive Cancer Network listing octreotide LAR as the only systemic treatment recommendation for SI-NET presently [11].

Two additional studies suggesting antitumor activity of SSA in SI-NET have recently been presented at international meetings (available in abstract for only). In the CLARINET study [12¥¥], 204 patients with nonfunctioning well or moderately differentiated GEP-NET (G1 and G2) were randomized to lanreotide autogel 120 mg or placebo. Patients were enrolled over a period of 5 years (2006–2011). The PEP was PFS in the overall study population consisting of PNET (45%); duodenal NET (7%); unknown primary NET (13%); and SI-NET (36%≈ 73 of 204 patients). After 24 months of treatment, 62% of patients in the treatment group had not progressed, whereas only 22% of patients in the control arm had not progressed. The PEP, median PFS, could, therefore, not yet be determined in the treatment arm; median PFS in the control arm was 18 months.

Wolin *et al.* [13¥] studied pasireotide LAR in 110 patients with GEP-NET (including 84 patients with SI-NET) and compared disease-related symptoms including diarrhea and flushing to octreotide LAR. Here, the PEP was not PFS but better symptom response with pasireotide at 6 months. PFS was a secondary endpoint. Although the study was terminated early for failure to reach the PEP, there was a statistically significant difference in PFS, 11.8 months in the pasireotide group versus 6.8 months in the octreotide group. As the study was not designed to detect a difference in survival including PFS only as an exploratory endpoint, this result was considered hypothesis generating. The authors concluded that further phase III studies are warranted to investigate the antiproliferative effects of pasireotide LAR.

Pavel *et al.* [14¥¥] reported the largest clinical trial in the NET field, the RADIANT-2 study. RADIANT-2 was a randomized, double-blind, placebo controlled phase III study of the mTOR inhibitor everolimus (10 mg daily) versus placebo, both in conjunction with octreotide LAR (30 mg intramuscular every 28 days). The study group consisted of 429 patients with NET of different organ sites including 224 SI-NET. Median PFS in the treatment group was longer than in the control group, but the result failed to reach the predefined threshold for study-wide significance. The 'sister-study' RADIANT-3, a double-blind phase III study of the same drug combination in 410 patients with PNET had shown an increase in median PFS from 4.6 months in the control arm to 11.0 months in the everolimus arm, which was statistically significant [15]. This result from the PNET population together with the notion that the RADIANT-2 was 'hindered by discordance between central and local review resulting in informative censoring' [16] has prompted re-testing of everolimus

for NET in the RADIANT-4 trial, which is currently enrolling patients (clinicaltrials.gov: NCT01524783).

SI-NETs are highly vascular tumors [17]. Chan *et al.* [18¥] conducted a prospective phase II study using the anti-VEGF monoclonal antibody bevacizumab (5 mg/m^2/day on days 1 and 15) together with temozolomide (150 mg/m^2 p.o. daily on days 1–7 and days 15–21 of a 28-day cycle). The PEP was response rate by RECIST criteria. No responses were seen among the seven SI-NET patients enrolled, whereas five responses were observed among 29 NET of other origin.

Fine *et al.* [19¥] reported a retrospective single-institution study of capecitabine (600 mg/m^2 p.o. twice daily on days 1–14) and temozolomide (150–200 mg/m^2 p.o. daily on days 10–14 of a 28-day cycle) in 18 patients with GEP-NET including 14 PNET. Ten of the 14 PNET and one patient with a 'duodenal carcinoid' had a response. Strosberg *et al.* [20] reported a response rate of 70% with the same drug combination in a retrospective review of 30 patients with PNET. These results, while highly encouraging, await testing in prospective studies that are currently in preparation. Furthermore, similar results as in PNET have not been reported for SI-NET. Therefore, capecitabine and temozolomide is not supported by the current literature for use in patients with SI-NET.

GENOMICS OF SMALL INTESTINE NEUROENDOCRINE TUMOR

Banck *et al.* [21¥¥] reported whole exome sequencing (WES) of tumors and matched germline DNA of 48 patients with SI-NET representing a cohort with typical characteristics and long available clinical follow-up. Tumor samples were histopathologically homogeneous consisting of primary tumors that were well differentiated. WES consists of short-read, massively parallel ('nextgen') sequencing of more than 20 000 human genes and bioinformatic comparison of data from the tumor and the normal tissue to identify 'somatic' genetic alterations that is mutations found only in the malignant tissue. In SI-NET, the study found point mutations termed single nucleotide variants (SNV) at an average rate of 0.1 SNV per 10^6 nucleotides (range 0–0.59) placing SI-NET among genomically stable cancers characterized by a low mutation rate such as rhabdoid tumors or myeloid leukemia [22]. Somatic SNV were found in 197 genes with a preponderance of cancer genes that included FGFR2, MEN1, HOOK3, EZH2, MLF1, CARD11, VHL, NONO, FANCD2, and BRAF. The study technology also allowed for analysis of somatic copy number alterations (SCNA) that is large amplifications and deletions that can be responsible for the inactivation of tumor suppressors or the overexpression of growth-promoting genes. SCNA analysis found the recurrent loss of chromosomes 11 and 18 and gains of chromosomes 4, 5, 19, and 20 reported previously by array comparative genomic hybridization [23,24] and further added higher-resolution, patient-level data. The results of all genetic alterations determined by WES were then integrated across the entire dataset to identify the mechanisms recurrently genetically altered in SI-NET. Candidate therapeutically relevant alterations were found in 35 patients, including SRC, SMAD family genes, AURKA, EGFR, HSP90, and PDGFR. Mutually exclusive amplification of AKT1 or AKT2 was the most common event in the 16 patients with alterations of PI3K/Akt/mTOR signaling.

Francis *et al.* [25¥¥] reported a multi-institution study of WES of 29 primary SI-NET and whole genome sequencing (WGS) of 15 primary SI-NET. The study emphasized an analysis of small insertions and deletions (indels) finding recurrent, heterozygous inactivating indels in the cell cycle inhibitor gene CDKN1B ($p27^{kip1}$) in 8% of SI-NET. The report provided CDKN1B indel analysis in the WES and WGS-sequencing cohorts as well as additional validation through targeted CDKN1B resequencing of archival SI-NET and additional analysis of the SI-NET tumor cohort by Banck *et al.* [21], thereby representing a total of n=140 SI-NET tumors in the report [25]. Interestingly, as Francis *et al.* [25] [26] point out, germline mutations of CDKN1B are known to cause MEN-4, a rare autosomal dominant cancer syndrome in humans with a phenotype resembling that of MEN-1 including parathyroid and pituitary adenomas and tumors of endocrine glands including PNET [27]. Most importantly, the inactivation of CDKN1B discovered by Francis *et al.* suggests that cell cycle inhibitory drugs may be of interest for at least a subset of patients with SI-NET. Other results reported by Francis *et al.* corroborated findings by Banck *et al.* on mutational characteristics of SI-NET providing additional data on somatic alterations to the census of genetic abnormalities in SI-NET.

NOVEL DIAGNOSTIC TOOLS

A blood test for tumor-derived RNA was reported by Modlin *et al.* [28¥]. The test uses reverse transcriptase polymerase chain reaction (RT-PCR) to quantify 51 NET marker-transcripts and control transcripts in patient whole blood. The sensitivity and specificity of the test to determine whether a patient has a NET was 79–88% and 94%, respectively, suggesting that it is superior to measuring chromogranin A (specificity 85%; sensitivity of 68%) [29]. How the test score is computed from the 51 transcripts appears not to be fully documented in the report. Furthermore, while blood samples from various clinical centers were employed in the test development, additional studies such as prospective measurements in clinical trials of NET treatment will be required to determine the utility of the test for making clinical decisions.

Circulating tumor cells (CTCs) are under investigation for prognostication and prediction of therapeutic efficacy in multiple malignancies. Khan *et al.* [30¥] recruited 175 patients with metastatic G1 and G2 SI-NET and used the ‘cell search’ system employing the epithelial cell surface marker EPCAM-7, to isolate CTC from whole blood. Fifty-one % of SI-NET patients had no CTC, 49% had at least 1 per 7.5 ml blood. The presence of at least one CTC correlated with worse PFS and OS (hazard ratios of 6.6 and 8.0, respectively; $P < 0.001$). The authors propose to add the presence of at least 1 CTC/7.5 ml blood to the list of poor prognostic features in metastatic NET.

CONCLUSION

Long-acting SSAs slow progression of SI-NET asis indicated by two recent randomized controlled trials. While Although everolimus might be a rational treatment option, definitive proof of efficacy is still lacking, and the drug should be offered through enrollment into the RADIANT-4 trial, if possible. Whole exome/genome sequencing of SI-NET provide nucleotide-resolution maps of mutated cancer genes and candidate therapeutically actionable

alterations including, as a new candidate approach, cell cycle inhibitors in the 8% of SI-NET patients with an inactivating indel mutation in the cell cycle regulator gene CDKN1B. Clinical and genomic research may merge in the near future to re-shape clinical trials and to define the 'personalized' treatment options for patients with SI-NET.

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KEY POINTS

- The standard of care for SI-NET consisting of treatment by noncytotoxic, ‘targeted’ drugs has been updated by two recent clinical trials confirming antitumor activity of long-acting SSA.
- The mTOR inhibitor everolimus is a rational treatment option for patients with SI-NET, but lacks definitive proof of benefit and, if possible, should be offered through the ongoing RADIANT-4 clinical trial.
- While Although SI-NETs have been the terra incognita of tumor genetics until recently, two studies have been reported in the past year providing the first genome-wide analysis at nucleotide resolution of large sets of SI-NET.
- Blood CTC and tumor-derived RNA are under investigation as clinical tests for SI-NET.
- Clinical and genomic research may merge in the near future to re-shape clinical trials and to define the ‘personalized’ treatment options for patients with SI-NET