Accomplishments in 2008 in the Management of Gastrointestinal Neuroendocrine Tumors

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I. OVERVIEW OF THE DISEASE PROCESS

I-A. Incidence

The annual incidence of clinically relevant carcinoid tumors has previously been estimated to be 1 to 2 per 100,000 population per year.[1] A recent study, however, suggested that the annual incidence of carcinoid tumors may be higher. In an analysis of the Surveillance, Epidemiology, and End Results (SEER) database, the estimated annual incidence of carcinoid tumors was 5.25 per 100,000 population, and the limited duration prevalence in the United States was estimated to exceed 100,000 individuals.[2] These increases in diagnosed incidence and prevalence are likely attributable, in part, to an increasing awareness of and improved diagnostic strategies for neuroendocrine tumors (NETs).

I-B. Prognostic Factors

Currently, traditional clinicopathologic features remain the primary validated predictors of prognosis in neuroendocrine tumors. The SEER database utilized a general staging system in which patients are divided into "localized," "regional," or "distant" metastatic disease.[3] The World Health Organization has further defined neuroendocrine tumors according to stage, degree of differentiation, tumor site of origin, and proliferative index, as measured by Ki-67 staining.[4] A lack of molecular and genetic prognostic factors has been an impediment to determining the best approach for neuroendocrine tumor patients therapeutically, particularly in light of the promise of novel therapies targeting specific molecular pathways. The identification of molecular and genetic prognostic factors for neuroendocrine tumor patients was noted as a key research priority at a National Cancer Institute summit meeting in September 2007.[5]

Similarly, risk factors for neuroendocrine tumors remain poorly understood. A number of rare inherited syndromes associated with neuroendocrine tumors have been identified, and include multiple endocrine neoplasia type 1 (MEN1), von Hippel–Lindau (VHL), and tuberous sclerosis syndromes.[6] These syndromes, however, account for fewer than 5% of all diagnosed neuroendocrine tumor cases. Risk factors for "sporadic" neuroendocrine tumors are only beginning to be identified. In recent case control studies, diabetes, smoking, and having a first-degree relative with cancer were identified as modest risk factors for neuroendocrine tumors.[7,8]

II. GENERAL THERAPY STANDARDS

The carcinoid syndrome, as well as other hormonal syndromes associated with neuroendocrine tumors, can often be well controlled with somatostatin analogs. The long-acting depot form of the

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Table 1: Ongoing or recently completed randomized trials in neuroendocrine tumors

Sponsor (NCT Trial No.)	Experimental Arm	Control Arm	Tumor Type
SWOG (NCT00569127)	Bevacizumab + octreotide LAR	IFN-α-2b + octreotide LAR	Carcinoid
Novartis (NCT 00412061)	Everolimus+ octreotide LAR	Octreotide LAR	Carcinoid
Novartis (NCT 00690430)	Pasireotide	High-dose octreotide	Refractory carcinoid syndrome
Ipsen (NCT 00353496)	Lanreotide autogel	Placebo	Carcinoid or pancreatic NET
Pfizer (NCT 00428597)	Sunitinib	Placebo	Pancreatic NET*
Novartis (NCT 00510068)	Everolimus	Placebo	Pancreatic NET

* Accrual stopped early for efficacy
Abbreviations: NET = neuroendocrine tumor; SWOG = Southwest Oncology Group

somatostatin analog octreotide is commonly used in the United States and is administered as an intragluteal injection. Lanreotide, another somatostatin analog, appears to be similar to octreotide in its clinical efficacy for carcinoid syndrome, and can be self-administered as a long-acting subcutaneneous injection.[9] Hepatic-directed therapy, including hepatic resection, hepatic arterial embolization, and ablative therapies are commonly used as palliative techniques in patients with hepatic-predominant disease. Although carcinoid and pancreatic neuroendocrine tumors appear histologically similar, there is increasing evidence that pancreatic neuroendocrine tumors are more responsive to chemotherapy than are carcinoid tumors. Streptozocin is an approved treatment for patients with well or moderately differentiated pancreatic neuroendocrine tumors; traditional streptozocin-based regimens used for pancreatic neuroendocrine tumors include streptozocin/5-fluorouracil, streptozocin/doxorubicin, or a three-drug combination of streptozocin/doxorubicin/5-fluorouracil.[10] The widespread use of streptozocin, however, has been limited by concerns regarding its potential for toxicity.

III. ACCOMPLISHMENTS AND LACK OF ACCOMPLISHMENTS DURING THE YEAR

III-A. Somatostatin Analogs

Novel somatostatin analogs that are more broadly targeted and have higher affinities for somatostatin receptors have recently been developed. The potential cytostatic effect of these agents has also been a topic of increasing interest.

- Pasireotide (SOM230) is a multi-ligand somatostatin analog that has exhibited high binding affinity to sst1, sst2, sst3, and sst5.[11] In a phase II trial, 44 patients with metastatic carcinoid tumors whose symptoms of diarrhea and flushing were inadequately controlled by octreotide LAR received pasireotide 300 µg subcutaneously twice per day, escalated to a maximum dose of 1,200 µg twice per day every 3 days until symptom control was achieved. Control of symptoms was achieved in 11 of 44 patients (25%).[12] Pasireotide is currently being compared with high-dose octreotide in patients with carcinoid syndrome refractory to standard-dose octreotide (Table 1).
- In a randomized study, 85 patients with unresectable or metastatic midgut neuroendocrine tumors were randomized to receive treatment with octreotide LAR or placebo. Patients randomized to the octreotide arm had a significantly longer progression-free survival duration (14.3 vs. 6 months; $P = .0037$), which led to early termination of the study.[13] A randomized trial evaluating the effect of lanreotide vs. placebo on progression-free survival is ongoing (Table 1).

III-B. Peptide Receptor–Targeted Therapy

The high rate of somatostatin receptor expression in neuroendocrine tumors provides the rationale for use of radionuclide therapy for patients with inoperable or metastatic disease. The available radiolabeled somatostatin analogs differ from one another in their affinity for the various somatostatin receptor subtypes and in the radionuclides to which they are conjugated. The most frequently used radionuclides for targeted radiotherapy have included indium (^{111}In), yttrium (^{90}Y), and lutecium (^{177}Lu), which differ from one another in terms of emitted particles, particle energy, and tissue penetration.[14]

- [^{177}Lu-DOTA, Tyr^3]octreotate has been used in the treatment of 504 patients with neuroendocrine tumors strongly expressing somatostatin receptors. Efficacy results, reported for 310 of the 504 patients, suggest an overall tumor response rate of up to 30%.[15]

III-C. Selective Internal Radiotherapy (SIRT)

Hepatic arterial embolization is an accepted palliative treatment for patients with advanced neuroendocrine tumors and hepatic-predominant disease. Both bland embolization and chemoembolization have been explored. More recently, radioembolization has also shown promise.

- In a retrospective series of 148 neuroendocrine tumor patients treated with ^{90}Y microspheres, partial or complete responses were observed in 63% of patients, with only mild associated toxicity.[16]
- Partial radiologic responses were observed in 50% of patients in a prospective study, in which 32 patients were treated with ^{90}Y microspheres.[17]

III-D. Cytotoxic Therapies: Temozolomide

Temozolomide is an orally available cytotoxic alkylating agent with a mechanism of action similar to that of streptozocin and dacarbazine. Recent prospective and retrospective studies have suggested that temozolomide-based regimens may be similar in efficacy to streptozocin-based regimens in pancreatic neuroendocrine tumors.[18]

- In the largest of the retrospective series, 18/53 (34%) patients

Table 2: Phase II trials of novel "targeted" agents in neuroendocrine tumors

Agent	Molecular Target(s)	No. Patients	Tumor	Tumor Response Rate (%)	Reference
Imatinib	PDGFR-α, -β; KIT; Bcr-Abl	27	Carcinoid	4	Yao et al, 2007[34]
Bevacizumab + octreotide	VEGF	22	Carcinoid	18	Yao et al, 2008[21]
Sunitinib	VEGFR, PDGFR, C-Kit, RET, FLT3	41	Carcinoid	2	Kulke et al, 2008[23]
		66	Pancreatic endocrine	16	
Sorafenib	VEGFR, B-Raf	50	Carcinoid	7	Hobday et al, 2007[22]
		43	Pancreatic endocrine	11	
Gefitinib	EGFR	40	Carcinoid	3	Hobday et al, 2006[35]
		31	Pancreatic endocrine	6	
Temsirolimus	mTOR	21	Carcinoid	5	Duran et al, 2006[25]
		15	Pancreatic endocrine	7	
Everolimus (RAD001) + octreotide	mTOR	30	Carcinoid	17	Yao et al, 2008[26]
		30	Pancreatic endocrine	27	

Abbreviations: EGFR = epidermal growth factor receptor; mTOR = mammalian target of rapamycin; PDGFR = platelet-derived growth factor receptor; VEGF = vascular endothelial growth factor; VEGFR = vascular endothelial growth factor receptor

with pancreatic neuroendocrine tumors, but only 1/44 (2%) patients with carcinoid tumors ($P < .001$), experienced a partial or complete response to temozolomide-based therapy.[18]

- The cytotoxic effect of temozolomide has been attributed to its ability to induce DNA methylation at the O–6 position of guanine. The sensitivity of tumor cells to alkylating agents, including temozolomide, has been associated with decreased levels of the DNA repair enzyme, O6-methylguanine DNA methyltransferase (MGMT), which, through its ability to restore DNA to its normal form, can prevent chemotherapy-induced cell death.[19] MGMT deficiency appears to be more common in pancreatic neuroendocrine tumors than in carcinoid tumors; potentially explaining the greater sensitivity of pancreatic neuroendocrine tumors to treatment with the alkylating agents streptozocin or temozolomide, and raising the possibility of using MGMT expression as a predictive marker in future studies of these tumors.[18]

III-E. VEGF Pathway Inhibitors

Neuroendocrine tumors are highly vascular, and overexpression of vascular endothelial growth factor (VEGF) has been observed in both midgut carcinoid tumors and in pancreatic endocrine tumors.[20] Therapies targeting VEGF (bevacizumab) and VEGF receptor (sorafenib, sunitinib) have recently been evaluated in the phase II setting in patients with advanced neuroendocrine tumors (Table 2).

- In a phase II trial, 44 patients with advanced or metastatic carcinoid tumors who were receiving a stable dose of octreotide were randomly assigned to treatment with bevacizumab or pegylated inferon-alpha 2b (IFN-α-2b).[21] Four of 22 (18%) bevacizumab-treated patients achieved confirmed radiographic partial responses compared with none of the patients treated with pegylated IFN-α-2b. After 18 weeks, 95% of bevacizumab-treated patients remained progression-free compared with 68% of IFN-α-2b–treated patients. These encouraging results have led to the development of an ongoing study, led by the Southwest Oncology Group, in which patients are randomized to receive either IFN-α-2b or bevacizumab in addition to octreotide, with a primary end point of progression-free survival (Table 1).
- The small-molecule tyrosine kinase inhibitor sorafenib was evaluated in 50 patients with carcinoid and 43 patients with pancreatic neuroendocrine tumors. In a preliminary analysis, responses were observed in 7% of the carcinoid patients and 11% of the pancreatic NET patients.[22]
- In a phase II study, 109 patients with advanced neuroendocrine tumors received repeated 6-week treatment cycles of sunitinib, administered orally at 50 mg once daily for 4 weeks, followed by 2 weeks off treatment.[23] Partial responses were observed in 2% of the carcinoid cohort and 16% of the pancreatic neuroendocrine cohort. An international randomized phase III study to confirm the activity of sunitinib in pancreatic neuroendocrine tumors has recently been stopped early, after preliminary results demonstrated that treatment with sunitinib was associated with a median progression-free survival of 11.1 months, as compared with 5.5 months in the placebo arm.[24] Detailed results of this trial have not yet been published.

III-F. mTOR Inhibitors

The mammalian target of rapamycin (mTOR) is a serine-threonine kinase that participates in the regulation of cell growth, proliferation, and apoptosis through modulation of the cell cycle. mTOR also mediates downstream signaling from a number of pathways, including the VEGF and insulin-like growth factor signaling implicated in neuroendocrine tumor growth. Two rapamycin derivatives have been evaluated recently in neuroendocrine tumors: temsirolimus and everolimus (RAD001) (Table 2).

- In an initial multicenter study, 37 patients with advanced progressive neuroendocrine tumors were treated with weekly intravenous temsirolimus. The intent-to-treat response rate for the cohort was 5.6%. Outcomes were similar between patients with carcinoid and pancreatic neuroendocrine tumors.[25]

- In a second phase II study, 30 patients with carcinoid tumors and 30 with pancreatic neuroendocrine tumors were treated with a combination of the mTOR inhibitor everolimus, 5–10 mg/day, and depot octreotide (30 mg every 4 weeks). The overall tumor response rate in evaluable patients was 17% in carcinoid and 27% in pancreatic neuroendocrine tumor patients.[26] Evaluation of the activity and safety of everolimus in patients with neuroendocrine tumors is ongoing.

III-G. Development of Biomarkers

Recent advances in genomic technology, together with the development of neuroendocrine tumor cell lines, offer the potential for the discovery of novel biomarkers and treatment targets in neuroendocrine tumors. Several studies have demonstrated the feasibility of this approach, although definitive diagnostic and prognostic biomarkers have not yet been identified using these approaches.

- Characteristic allelic imbalances have been observed in both carcinoid and pancreatic neuroendocrine tumors using single nucleotide polymorphism analysis. Of these, loss of chromosome 18 appears to be a characteristic feature of small bowel carcinoid tumors.[27–29]
- Preliminary studies have suggested that gene expression profiling may be a useful tool in differentiating indolent from aggressive neuroendocrine tumors and in identifying novel treatment targets.[30]
- Neuroendocrine tumor cell lines have recently been developed, and, if validated, may further speed the development of novel "targeted" therapies for this disease.[31–33]

IV. WHAT NEEDS TO BE DONE (APPLICATION OF THE ACCOMPLISHMENTS)

Several studies are ongoing to confirm the activity of agents that have demonstrated promising activity in the phase II setting, including phase III randomized trials of bevacizumab, sunitinib, and everolimus. Peptide receptor–targeted radiotherapy has yet to be explored in the randomized setting; however, the approach appears promising and the development of somatostatin analogs with even higher affinity for different somatostatin receptor subtypes has the potential to further enhance therapeutic efficacy. Similarly, the antitumor effects of "cold" somatostatin analogs warrant confirmation in a second phase III randomized trial.

V. CONTROVERSIES AND DISAGREEMENTS

V-A. Histologic Classification and Staging of Neuroendocrine Tumors

Neuroendocrine tumors comprise a wide spectrum of histologies; there is little disagreement that the clinical course of indolent, "well differentiated" neuroendocrine tumors is far different from that of their more aggressive "poorly differentiated" counterparts. There remains widespread disagreement and inconsistency in pathology reporting with regard to use of mitotic index, proliferative index (Ki-67), and other reporting criteria, posing an obstacle to the development of consistent inclusion criteria for clinical trials, as well as interpretation of clinical trial results. Lack of a consistent histologic and classification scheme also poses difficulties in the interpretation of retrospective data in epidemiology studies.

V-B. Clinical Trial Design and End Points

The relatively unique association of neuroendocrine tumors with clinical syndromes related to hormonal secretion has created a need for agents that target hormonal hypersecretion. Somatostatin analogs have had a clear impact in this area; however, there is currently no accepted standard trial design or criterion to rapidly and easily assess efficacy of novel agents in this setting. The indolent nature of many neuroendocrine tumors creates a challenge in assessing the efficacy of novel drugs in the phase II setting, particularly given the apparent cytostatic (rather than cytotoxic) effect of many new agents. Wide variability in the requirement for or interpretation of "progressive disease" prior to study entry makes it difficult to interpret disease stabilization during treatment in single-arm studies.

VI. FUTURE DIRECTIONS

Recent epidemiologic data suggest that neuroendocrine tumors are both more common and more prevalent than initially thought. Despite early concerns regarding the ability to accrue patients and complete large randomized trials, ongoing or recently completed studies of bevacizumab, sunitinib, octreotide, lanreotide, and everolimus have demonstrated the feasibility of rigorously evaluating novel antitumor therapies for this disease. The development of standardized histologic and staging criteria, together with a more standardized approach to evaluating novel agents in early-phase studies, should speed the identification of promising agents worthy of evaluation in the randomized setting. Therapies targeting hormonal symptoms are of equal importance given their potential effects on patient quality of life; well-designed clinical trials and clearly defined efficacy criteria will be critical in accelerating the development of these agents. Finally, rapid progress in technologies for molecular profiling, and early indications of activity associated with "targeted" therapies, offer the very real possibility of identifying new treatment targets and biomarkers predictive of risk, prognosis, and efficacy in gastrointestinal neuroendocrine tumors.

REFERENCES

1. Modlin I, Sandor A: An analysis of 8305 cases of carcinoid tumors. *Cancer* 79:813–829, 1997
2. Yao JC, Hassan M, Phan A, et al: One hundred years after "carcinoid": epidemiology of and prognostic factors for neuroendocrine tumors in 35,825 cases in the United States. *J Clin Oncol* 26:3063–3072, 2008
3. Modlin IM, Lye KD, Kidd M: A 5-decade analysis of 13,715 carcinoid tumors. *Cancer* 97:934–959, 2003
4. Rindi G, D'Adda T, Froio E, et al: Prognostic factors in gastrointestinal endocrine tumors. *Endocr Pathol* 18:145–149, 2007
5. Modlin IM, Moss SF, Chung DC, et al: Priorities for improving the management of gastroenteropancreatic neuroendocrine tumors. *J Natl Cancer Inst* 100:1282–1289, 2008
6. Leotlela PD, Jauch A, Holtgreve-Grez H, et al: Genetics of neuroendocrine and carcinoid tumours. *Endocr Relat Cancer* 10:437–450, 2003
7. Hassan MM, Phan A, Li D, et al: Family history of cancer and associated risk of developing neuroendocrine tumors: a case-control study. *Cancer Epidemiol Biomarkers Prev* 17:959–965, 2008
8. Hassan MM, Phan A, Li D, et al: Risk factors associated with neuroendocrine tumors: A U.S.-based case-control study. *Int J Cancer* 123:867–873, 2008
9. O'Toole D, Ducreux M, Bommelaer G, et al: Treatment of carcinoid syndrome: A prospective crossover evaluation of lanreotide versus octreotide in terms of efficacy, patient acceptability, and tolerance. *Cancer* 88:770–776, 2000
10. Kouvaraki MA, Ajani JA, Hoff P, et al: Fluorouracil, doxorubicin, and strepto-

zocin in the treatment of patients with locally advanced and metastatic pancreatic endocrine carcinomas. *J Clin Oncol* 22:4762–4771, 2004

11. Schmid H, Schoeffer P: Functional activity of the multiligand analog SOM230 at human recombinant somatostatin receptor subtypes supports its usefulness in neuroendocrine tumors. *Neuroendocrinology* 80(suppl 1):47–50, 2004
12. Kvols L, Wiedenmann B, Oberg K, et al: Safety and efficacy of pasireotide (SOM230) in patients with metastatic carcinoid tumors refractory or resistant to octreotide LAR: results of a phase II study. *J Clin Oncol* 24(18S, June 20 suppl), 2006 (abstr 4082)
13. Arnold R, Müller H, Schade-Brittinger C, et al: Placebo-controlled, double blind, prospective, randomized study of the effect of octreotide LAR in the control of tumor growth in patients with metastatic neuroendocrine midgut tumors: a report from the PROMID study group. 2009 Gastrointestinal Cancers Symposium, San Francisco, CA, January 15–17, 2009 (abstr 121)
14. Kwekkeboom D, Bakker W, Kooij P, et al: 177Lu-DOTA,Tyr3 octreotate: comparison with [111In-DTPA] octreotide in patients. *Eur J Nucl Med* 28:1319–1325, 2001
15. Kwekkeboom DJ, de Herder WW, Kam BL, et al: Treatment with the radiolabeled somatostatin analog [177 Lu-DOTA 0,Tyr3] octreotate: toxicity, efficacy, and survival. *J Clin Oncol* 26:2124–2130, 2008
16. Kennedy AS, Dezarn WA, McNeillie P, et al: Radioembolization for unresectable neuroendocrine hepatic metastases using resin 90Y-microspheres: early results in 148 patients. *Am J Clin Oncol* 31:271–279, 2008
17. King J, Quinn R, Glenn DM, et al: Radioembolization with selective internal radiation microspheres for neuroendocrine liver metastases. *Cancer* 113:921–929, 2008
18. Kulke M, Hornick J, Frauenhoffer C, et al: O6-methylguanine DNA methyltransferase deficiency and response to temozolomide-based therapy in patients with neuroendocrine tumors. *Clin Cancer Res* 15:338–345, 2009
19. Gerson SL: Clinical relevance of MGMT in the treatment of cancer. *J Clin Oncol* 20:2388–2399, 2002
20. Terris B, Scoazec J, Rubbia L: Expression of vascular endothelial growth factor in digestive neuroendocrine tumors. *Histopathology* 32:133–138, 1998
21. Yao JC, Phan A, Hoff PM, et al: Targeting vascular endothelial growth factor in advanced carcinoid tumor: a random assignment phase II study of depot octreotide with bevacizumab and pegylated interferon alpha-2b. *J Clin Oncol* 26:1316–1323, 2008
22. Hobday TJ, Rubin J, Holen K, et al: MC044h, a phase II trial of sorafenib in patients (pts) with metastatic neuroendocrine tumors (NET): A Phase II Consortium (P2C) study. *J Clin Oncol* 25(18S, June 20 suppl), 2007 (abstr 4504)
23. Kulke MH, Lenz HJ, Meropol NJ, et al: Activity of sunitinib in patients with advanced neuroendocrine tumors. *J Clin Oncol* 26:3403–3410, 2008
24. Raymond E: Phase III randomised double blind trial of suntinib versus placebo in patients with progressive, well-differentiated pancreatic neuroendocrine tumors. 11th World Congress on Gastrointestinal Cancers, Barcelona, June 24–27, 2009
25. Duran I, Kortmansky J, Singh D, et al: A phase II clinical and pharmacodynamic study of temsirolimus in advanced neuroendocrine carcinomas. *Br J Cancer* 95:1148–1154, 2006
26. Yao JC, Phan AT, Chang DZ, et al: Efficacy of RAD001 (everolimus) and octreotide LAR in advanced low- to intermediate-grade neuroendocrine tumors: results of a phase II study. *J Clin Oncol* 26:4311–4318, 2008 [erratum in *J Clin Oncol* 26(34):5660, 2008]
27. Kulke MH, Freed E, Chiang DY, et al: High-resolution analysis of genetic alterations in small bowel carcinoid tumors reveals areas of recurrent amplification and loss. *Genes Chromosomes Cancer* 47:591–603, 2008
28. Kim do H, Nagano Y, Choi IS, et al: Allelic alterations in well-differentiated neuroendocrine tumors (carcinoid tumors) identified by genome-wide single nucleotide polymorphism analysis and comparison with pancreatic endocrine tumors. *Genes Chromosomes Cancer* 47:84–92, 2008
29. Nagano Y, Kim do H, Zhang L, et al: Allelic alterations in pancreatic endocrine tumors identified by genome-wide single nucleotide polymorphism analysis. *Endocr Relat Cancer* 14:483–492, 2007
30. Duerr EM, Mizukami Y, Ng A, et al: Defining molecular classifications and targets in gastroenteropancreatic neuroendocrine tumors through DNA microarray analysis. *Endocr Relat Cancer* 15:243–256, 2008
31. Van Buren G, 2nd, Rashid A, Yang AD, et al: The development and characterization of a human midgut carcinoid cell line. *Clin Cancer Res* 13:4704–4712, 2007
32. Kidd M, Drozdov I, Joseph R, et al: Differential cytotoxicity of novel somatostatin and dopamine chimeric compounds on bronchopulmonary and small intestinal neuroendocrine tumor cell lines. *Cancer* 113:690–700, 2008
33. Kidd M, Schally AV, Pfragner R, et al: Inhibition of proliferation of small intestinal and bronchopulmonary neuroendocrine cell lines by using peptide analogs targeting receptors. *Cancer* 112:1404–1414, 2008
34. Yao JC, Zhang JX, Rashid A, et al: Clinical and in vitro studies of imatinib in advanced carcinoid tumors. *Clin Cancer Res* 13:234–240, 2007
35. Hobday T, Holen K, Donehower R, et al: A phase II trial of gefitinib in patients with progressive metastatic neuroendocrine tumors: A Phase II Consortium study. *J Clin Oncol* 24(18S, June 20 suppl), 2006 (abstr 4043)

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