Role of somatostatin analogs. Management of carcinoid syndrome: what about the antitumor effect?

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The five year survival rate in small intestinal carcinoid is estimated to reach 60%, even in modern series. As for large intestine colorectal, regional spread and distant metastasis, we have to think in terms of multiple disease because at least 50% of cases present advanced disease, which can be associated with the carcinoid syndrome.

The carcinoid syndrome is found in roughly 25% of the patients with small intestinal carcinoid.

Many secretory products of carcinoids are present, such as peptides and bioactive amines. Several substances may be involved. This means that even in the absence of serotonin, and sometimes histamine as well, other substances like neurokinin may be responsible for the occurrence of carcinoid syndrome. These tumoural products are released into the circulation and subsequently transported to various target organs (Table 1).

Table 1. *Secretory products of Carcinoids.*

Secretory Products of Carcinoids	
	Peptides
	Corticotropin (ACTH)
	Calcitonin
	Pancreatic polypeptide
	Secretin
Bioactive Amines	Cholecystokinin
Serotonin (5-hydroxytryptamine)	Kallikrein
Histamine	Gastrin
Dopamine	Insulin
Norepinephrine, epinephrine	Parathyroid hormone-related protein
	Substance P
	Neurokinin A
	Neuropeptide K
	Encephalins/endorphins
	Neurotensin
	Chromogranin
	ADH (vasopressin)
	Somatostatin
	TRH-like peptide
	Vasoactive intestinal peptide
	Motilin

Regarding symptoms, flushing is present in 1/3 of the patients. When the distance between reports is so huge, flushing is present in the mayority of patients, meaning that data recording was not so accurate. The data are similar for diarrhea and abdominal pain. Bronchoconstriction and pellagra are very rare at presentation.

About 10 to 20% of the patients present plaque-like thickening with endocardium involvement. This is crucial to assess every patient with carcinoid syndrome, because these tumors typically grow due to the presence of peptides in the blood stream, leading in turn to fibrosis, though not only in the heart.

Carcinoid syndrome is an unusual presentation of GI carcinoids. Most primary carcinoids of the GI tract are drained by the portal venous system, and thus most bioamines, such as serotonin and histamine, are cleared by the liver before entry to the systemic circulation. Older patients who use other drugs to control other diseases, such as beta blockers and calcium antagonists, may frequently have flushing. Even patients with GI carcinoid tumors that secrete high levels of these amines may be asymptomatic. For example, if the primary tumor secretes ACTH or other peptide hormones, symptoms due to these products may develop when the tumor is quite small.

Diarrhea is a common symptom of carcinoid syndrome, affecting 38% to 86% of patients at some time in the course of their disease.

Diarrhea most often occurs in conjunction with flushing. It occurs alone in only 10% to 15% of cases. This is important from the clinical point of view because the two symptoms together are seen in 80 to 90% of the cases. Therefore diagnosis can be easily made. Patients complain of several loose stools daily (Table 2).

Table 2. *Frequency of symptoms and mediators.*

Carcinoids		
Symptom	**% Affected**	**Proposed Mediator**
Flushing	**30-94**	Tachykinins*
		Bradykinin
		Norepinephrine
		Histamine
		Serotonin?
Diarrhea	**38-84**	Serotonin
		Prostaglandins
Abdominal pain	**15-72**	Partial obstruction?
		Serotonin?
Bronchoconstriction	**2-19**	Serotonin
		Tachykinins*
		Bradykinin
Pellagra	**2-5**	Excessive tryptophan conversion

The etiology of diarrhea in carcinoid syndrome is unclear. Both mechanical and neurohumoral factors (principally serotonin) have been implicated. Mechanical factors include rapid transit.

Sintomatic medical therapy of diarrea include:

Serotonin antagonists (methysergide, cyproheptadine, ondansetron, ketanserin) are frequently helpful, suggesting a prominent role for serotonin in the pathogenesis of this portion of the carcinoid syndrome. Ondansetron has been particularly effective in treating carcinoid-related diarrhea, apparently through restoration of normal colonic motility.

Somatostatin analogs are helpful due to their direct action, which decreases bioactive amines and peptide hypersecretion. Also, they are able to reabsorb water by a sodium mediated mechanism at the distal ileum.

Racecadotril, a new drug in Italy, is an enkephalinase inhibitor with antisecretory and antidiarrheal actions. It is an effective and safe treatment for acute diarrhea.

Somatostatin Analogues - General considerations

They are the first-line treatment for NETs in receptor positive (> 92 %) . Octreotide (subcutaneous, long acting release LAR) and Lanreotide (subcutaneous, slow release SR, autogel) have similar actions. They present high affinity for sst2, and moderate affinity for sst5. They are safe and well-tolerated drugs. They effectively control tumor-related symptoms (functioning tumors), and decrease tumor markers. However, the control of tumor growth is debatable and may be demostrated. Data on the objective tumor response are difficult to analyze. There are some problems related to treatment with somatostatin analogues, due to the limited number of studies on their antiproliferative effects, and the small number of patients. Moreover, most of the studies, (mainly the older), have used the control of symptoms or the decrease of tumor markers as primary endpoints.

The series of patients have been heterogeneous, and the WHO tumor differentiation (well differenciated endocrine tumors or carcinomas and poorly differenciated endocrine carcinomas) has rarely been observed. Also, TNM grading, (i.e. G1, G2 and G3) is still under analysis.

Disease extension is an important factor for hormone production at the time of inclusion, (2/3 of patients had metastasis and 10 to 15% had distant extrahepatic metastasis. However, this has not been considered).

As for tumor behaviour before treatment, many patients had stable disease for a long time even when untreated. Progression of the tumor was observed before treatment in very few patients. Another problem is the short follow-up and a longer follow-up is mandatory. Few studies now state that somatostatin analogs are able to improve survival.

Somatostatin analogues - Questions

Who is the best candidate for treatment with somatostatin analogs? What is the antiproliferative efficacy of somatostatin analogs in inhibiting tumor growth in progressive disease? Who is the optimal patient for treatment?

As for the patient, survival depends on several prognostic factors. As **for the site** of primary tumor, pancreatic tumors do worse than GI tumors; carcinoids do well. **As for the degree of differentiation**, carcinoids are generally well differentiated. As for presence of metastases: liver metastases are always present (definition of syndrome), and nodal metastasis may or may not be present. Also, **a low proliferative index** and **the weight loss** at the time of diagnosis should be considered.

Aparicio et al, published a fundamental paper in 2001 in the *European Journal of Cancer,* including 35 patients (pancreas 37%, intestine 34%, other 29%), 86% well differentiated whereas only 63% positive for Octreoscan. Patients were divided into two groups: Group 1 (rapid progression) and Group 2 (slow progression). This was the only difference found regarding to response.

This criterium was also used by Bob Jensen at NIH to select patients with very rare aggressive gastrinomas: 53% of responders have very slow progression. This happened in the past, 7 years ago.

Somatostatin analogues respond better in GI disease. Pancreatic site and presence of distant metastasis are independent predictors for non response to treatment. Responders to the analogues have a better survival when compared with non-responders. We can also mention Falcone´s study on well differentiated advanced disease. The predictors were Ki-67 higher than 5%, absence of abdominal pain, weight loss and Cr A over 200.

What about growth control?

If we consider the well designed trials we can see that the maximum number of patients per group ranges between 58 and 51. Complete response is practically absent. Partial response and stabilization are the best results that can be obtained (Table 3).

In the treatment with somatostatin analogues and predictive factors for response, what can we offer to the patient?

As for disease control considering the pooled data, there are more than 400 patients treated with 0% median complete response, 4% median partial response and 47% median stabilization. The duration of response is 12 months (up to 60 months).

As for the symptom control with somatostatin analogues, lanreotide and octreotide allowed thar

Table 3. *Somatostatine Analogues and Growth Control.*

	pts	CR	PR	SD	Analog	Comment
Saltz 1993	34	-	-	50%	OCT sc	
Arnold 1993	21	-	-	36%	OCT sc	*7 non progressive*
Di Bartolomeo 1994	58	-	3%	47%	OCT sc	
Arnold 1996	52	-	-	36.5%	OCT sc	
Faiss 1996	24	4%	4%	46%	LAN sc high doses	
Ricci 2000	15	-	7%	40%	OCT LAR	*11/15 progressive*
Ricci 2000	25	-	8%	40%	LAN SR	*"mostly progressive"*
Aparicio 2001	35	-	3%	57%	OCT sc	
Shojamanesh 2002	15	-	6%	47%	OCT sc	*gastrinomas*
Welin 2004	12	-	-	75%	OCT sc high doses	
Faiss 2004	25	-	4%	28%	LAN sc	
Arnold 2005	51	-	2%	43%	OCT sc	
Butturini 2007	21	-	-	38%	OCT LAR	
Panzuto 2006	31	-	-	45.2%	OCT LAR / LAN SR	
Rodrigues 2008 (abs)	26		11%	64%	OCT LAR/LAN autogel	*progressive?*

flushing disappeard completely in 60-80% of patients, whereas severity was reduced in 50% As for diarrhea, normalization was seen in only 30 %, and stool frequency was reduced in 75%. In conclusion, for a better management of symptoms we must use them with other drugs.

Pasireotide SOM230, a new somatostatin analogue with high binding affinity to four of the five ssreceptors (sst1,2,3,5), may be effective in carcinoid tumors refractory to octreotide. In a phase II, open-label, multicenter trial in metastatic carcinoid tumors whose symptoms were not controlled by octreotide LAR, with symptom control as the primary endpoint, the response was seen in 25% of the patients. Pasireotide safety profile is similar to octreotide LAR. Both diarrhea and flushing could be controlled with pasireotide.

Also analogues have been successfully used together with interferon, as described in many papers by Italian authors. One of these studies showed that response to octreotide or octreotide plus IFN affects survival favorably.

The combined ssanalogue and Interferon therapy leads to 25% tumor stabilization and 7 to10% tumor regression in randomized trial. Interferon is able to reduce the risk of tumor progression in midgut carcinoids.

To conclude, patients who are optimal candidates for treatment should have slowly progressive disease, a WDET, a low Ki67 index (< 5%), absence of distant extra-hepatic metastases, no weight loss, and intestinal carcinoids.