Take home messages

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Systemic Therapeutic Options for Carcinoid
Marianne Pavel, Mark Kidd, and Irvin Modlin
Semin Oncol. 2013; 40: 84-99
Circa 481 pazienti in 15 studi
1972-2009
**Promid and Clarinet**

**Promid**

- Octreotide LAR 30 mg, IM, every 28 days
- Placebo, IM, every 28 days
- Randomization 1:1
- Continuation of treatment if no progression
- Primary end point: time to tumour progression

- Treatment was continued until CT or MRI documented tumor progression
- Follow-up until death
- CT and/or MRI was evaluated by a blinded central reader


**Clarinet**

- Lanreotide autogel 120 mg, SC, every 28 days
- Placebo, SC, every 28 weeks
- Randomization 1:1
- 1st End point: PFS within 96 weeks
- End point primario: Time to disease progression or death

- Treatment continued until tumor progression or death
- Estimated study completion June 2013

Neuroendocrine gastro-entero-pancreatic tumors: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up

K. Öberg¹, U. Knigge², D. Kweekkeboom³ & A. Perren⁴ on behalf of the ESMO Guidelines Working Group

Table 10. Summary of recommendations

- The diagnosis of NET should be confirmed by histopathology (CgA, synaptophysin Ki-67).
- The current classification and staging systems should be applied in the clinic.
- Somatostatin receptor imaging besides standard imaging (CT and MRI) is part of standard of care.
- Resection of locoregional disease in patients with small intestinal NET (carcinoids) is recommended.
- **Somatostatin analog therapy is first-line therapy in all functional NET and small intestinal NET G1/G2.**
- Everolimus and sunitinib are registered for pancreatic NETs based on two phase III randomized trials.
- Temozolomide alone or in combination with capecitabine is promising for treatment of pancreatic NETs.
NCCN Guidelines Version 2.2013
Carcinoid Tumors

MANAGEMENT OF LOCOREGIONAL UNRESECTABLE DISEASE AND/OR DISTANT METASTASES

If complete resection possible → Resect primary + metastases

Locoregional unresectable disease and/or distant metastases
- Imaging:
  - Multiphasic CT or MRI
  - Consider octreoscan
- Consider 5-HIAA
- Consider chromogranin A (category 3)

Asymptomatic, low tumor burden
- Observe with markers and scans every 3-12 mo or Octreotide®

Locally symptomatic from primary tumor
- Consider resection of primary tumor

Clinically significant tumor burden
- Octreotide®
- Octreotide®
- Echocardiogram

Carcinoid syndrome

Octreotide, if not already receiving and
Consider hepatic regional therapy (arterial embolization, chemoembolization, radioembolization [category 2B]) or
Consider cytoreductive surgery/ablative therapy (category 2B)
- Consider everolimus (10 mg/d) (category 3)
- Consider cytotoxic chemotherapy (category 3), if no other options feasible

See Surgical Principles for Management of Neuroendocrine Tumors (NE-C).

For symptom control, octreotide 150-250 mcg SC TID or octreotide LAR 20-30 mg IM every 4 weeks. Dose and frequency may be further increased for symptom control as needed. Therapeutic levels of octreotide would not be expected to be reached for 10-14 d after LAR injection. Short-acting octreotide can be added to octreotide LAR for rapid relief of symptoms or for breakthrough symptoms.

Lanreotide is approved for symptom control in Europe. Lanreotide has a similar mechanism of action as octreotide and may be preferable in patients who have difficulty tolerating an IM versus SC injection.

Resection of a small asymptomatic (relatively stable) primary in the presence of unresectable metastatic disease is not indicated.

For tumor control, the PROMID study (J Clin Oncol 2009;27:4656-4663) used octreotide LAR 30 mg IM every 4 weeks.

If signs and symptoms of heart disease or planning major surgery.

Includes ablative techniques such as radiofrequency, microwave, and cryotherapy. There are no randomized clinical trials and prospective data for these interventions are limited. However, data on the use of these interventions are emerging.

Only if near complete resection can be achieved.

Anticancer agents such as capecitabine, dacarbazine, 5-FU, interferon, oxaliplatin, and temozolomide can be used in patients with progressive metastases for whom there are no other treatment options. See Discussion for details.

Note: All recommendations are category 2A unless otherwise indicated.

Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
Objective:
• Determine effect of pasireotide LAR (PAS) vs octreotide LAR (OCT) on symptoms in NET

Methods:
• PAS (60 mg) or OCT (40 mg) q28d; stratified by main baseline symptoms (diarrhea/flushing)
• Objectives: primary, symptom response (SR) at 6 mo; secondary, tumor response (TR) & safety; exploratory PFS analysis

Results:
• N=110; PAS=53 & OCT=57 pts at interim analysis suggesting futility for SR (study halted)
• At 6 mo, symptom response was similar for PAS & OCT
• Most common G3/4 AEs: hyperglycemia, diarrhea, abd. Pain
• Investigator-assessed median PFS: 11.8 mo (PAS) & 6.8 mo (OCT), HR=0.46; P=0.045
PAS Significantly Prolonged PFS by 5 months

Kaplan-Meier median PFS
PAS: 11.8 months, 95% CI [11.0–not reached]
OCT: 6.8 months, 95% CI [5.6–not reached]
Hazard ratio = 0.46, 95% CI [0.20–0.98]

\[ P = 0.045 \text{ (log-rank test)} \]

Presented during the ASCO Annual Meeting 2013 as a poster discussion on Monday, June 3rd, McCormick Center. Abstract #4031.

Materiale ad esclusivo uso formativo ISF Novartis, non utilizzabile per informazione scientifica presso operatori sanitari.
RADIANT- 4 Study
Advanced (unresectable or metastatic) well differentiated non functioning progressive GI and lung NETs

N = 279

RANDOMIZE

2:1

Everolimus 10 mg/day + best supportive care n = 186

Placebo + best supportive care n = 93

PFS assessment until PD as determined by central radiology review

Cross-over to open-label only after IA and DMC recommendation

- Primary Endpoint: PFS by central radiological assessment, (local supportive)
  - HR target value/ PFS median: 0.59/ 5 to 8.5 months

- Interim analysis at 60% of PFS events

- Stratification by tumor site, WHO and prior SSA

ClinicalTrials.gov identifier: NCT01524783
• Treatment with somatostatin analogs and alpha interferon might be an option for functional tumors with clinical symptoms (III,B) (PR in 5-10%, SD in 30-50%, symptomatic improvement in 40-60%).

• In non-functioning tumors the use of somatostatin analogs is still controversial, but after the PROMID study indicating antitumor efficacy by octreotide LAR in small intestinal NETs it is now widely accepted also for non-functioning tumors of other origins (III,B).
Volendo delineare una ipotetica sequenza terapeutica ideale sceglierei per i pazienti con pNET metastatico non resecabile

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1 = massimo disaccordo; 2 = disaccordo; 3 = accordo; 4 = più che d’accordo; 5 = accordo assoluto
Grazie dell’attenzione