NEN PRECEPTORSHIP
LA PRATICA CLINICA NELLE NEOPLASIE NEUROENDOCRINE
5/6 Aprile 2018 | IEO, Istituto Europeo di Oncologia - Milano
Criteri di scelta della terapia non chirurgica

Carlo Carnaghi

Humanitas Cancer Center
Effect of Tumor Heterogeneity on the Assessment of Ki67 Labeling Index in Well-differentiated Neuroendocrine Tumors Metastatic to the Liver: Implications for Prognostic Stratification

Zhixiai Yang, MD, PhD, Laura H. Tang, MD, PhD, and David S. Klimstra, MD

Abstract: The Ki67 labeling index is integral to clinical management of patients with neuroendocrine tumor (NETs). A grading scheme recently endorsed by the World Health Organization (WHO) for gastroenteropancreatic NETs classifies well-differentiated NETs based on the Ki67 labeling index, which relies on the premise that a lower labeling index is associated with a better prognosis and that well-differentiated NETs should be stratified into grades 1, 2, and 3. Tumor heterogeneity, in contrast, makes the assessment of Ki67 labeling index challenging due to the potential for microscopic foci of high proliferation within a tumor. In our study, the Ki67 labeling index was assessed in 86 well-differentiated NETs, and the Ki67 labeling index was found to be significantly lower in tumors with higher Ki67 labeling index and higher Ki67 labeling index. In particular, the Ki67 labeling index was higher in tumors with lower Ki67 labeling index, and the Ki67 labeling index was lower in tumors with higher Ki67 labeling index. In conclusion, our findings suggest that the Ki67 labeling index may be a useful tool for prognostic stratification of well-differentiated NETs, and that the Ki67 labeling index may be a useful tool for prognosis of well-differentiated NETs.
One Hundred Years After “Carcinoid”: Epidemiology of and Prognostic Factors for Neuroendocrine Tumors in 35,825 Cases in the United States

**NETs survival has improved since the introduction of SSAs**

*The median OS of pts diagnosed with advanced NETs was significantly longer in 1998-2004 compared to 1973-1987 timeframe (SEER database)*

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**Median Survival in Metastatic Midgut NETs**

Yao JC et al. JCO 2008

Erickson B., Presented at ENETS Barcelona 2016
Watch and wait policy in advanced neuroendocrine tumors: What does it mean?

*It has never been specifically investigated…!* How to define morphological (radiological), functional (receptorial? metabolic?) or biochemical progression? With which threshold? Could be detrimental to start therapy only when tumor-related symptoms arise?

Fazio N. World J Clin Oncol 2017

<table>
<thead>
<tr>
<th></th>
<th>W &amp; W</th>
<th>Octreotide and Lanreotide</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cost of administration</td>
<td></td>
<td>The estimated per-cycle were $5241.73 for 30-mg octreotide LAR and $6000 for 120-mg lanreotide</td>
</tr>
<tr>
<td>Risk of delay</td>
<td></td>
<td>Time since diagnosis &lt; 4 vs &gt; 4 months (p 0.08)</td>
</tr>
<tr>
<td>Time of exposure</td>
<td></td>
<td>62 months</td>
</tr>
<tr>
<td>Adverse events</td>
<td></td>
<td>Occurring more often than with placebo, and in &gt;5% of patients.</td>
</tr>
<tr>
<td>Cost per episode</td>
<td></td>
<td>Cholelithiasis $7839.24 Abdominal pain $1997.73</td>
</tr>
</tbody>
</table>

ClinicalTrials.gov

Asymptomatic Small Pancreatic Endocrine Neoplasms (ASPEN)

NCT03084770

G1

Midgut o Pancreas

- Carico Malattia Elevato
- Sintomi
- Possibili complicanze da T
- Sindrome
- Lieve PD

Analogos SST

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PFS

\[
\text{PFS} = \frac{\text{Patients with Progression-free Survival}}{100}\]

- Lanreotide: 120 mg
  - 32 events, 101 patients
  - Median not reached

- Placebo
  - 60 events, 103 patients
  - Median, 18.0 mo (95% CI, 12.1–24.0)

\[P < 0.001\] for the comparison of progression-free survival

\[\text{Hazard ratio for progression or death, 0.47 (95\% CI, 0.30–0.73)}\]

No. at Risk

<table>
<thead>
<tr>
<th></th>
<th>Lanreotide</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>101</td>
<td>103</td>
</tr>
<tr>
<td>1</td>
<td>94</td>
<td>101</td>
</tr>
<tr>
<td>2</td>
<td>84</td>
<td>87</td>
</tr>
<tr>
<td>3</td>
<td>78</td>
<td>76</td>
</tr>
<tr>
<td>4</td>
<td>71</td>
<td>59</td>
</tr>
<tr>
<td>5</td>
<td>61</td>
<td>43</td>
</tr>
<tr>
<td>6</td>
<td>40</td>
<td>26</td>
</tr>
</tbody>
</table>

Caplin ME et al. NEJM 2014

Distant

\[\text{Median survival} \]

- 1973-1987: 18 months
- 1988-2004: 39 months

Yao JC et al. JCO 2008
G2 (SSTRs+) Ki67 <10%

Midgut or Pancreas

Analogo SST

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**Table 3.** Prognostic Factors for Time to Progression or Tumor-Related Death Adjusted for Treatment Based on the Per-Protocol Analysis

<table>
<thead>
<tr>
<th>Factor</th>
<th>Bivariate Analysis</th>
<th>Multivariate Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>P</td>
<td>HR</td>
</tr>
<tr>
<td>Octreotide LAR v placebo*</td>
<td>&lt;.0001</td>
<td>0.27</td>
</tr>
<tr>
<td>Functional active tumor v inactive tumor</td>
<td>.2420</td>
<td>1.38</td>
</tr>
<tr>
<td>Liver involvement &gt; v ≤ 10%</td>
<td>.0009</td>
<td>2.81</td>
</tr>
<tr>
<td>Chromogranin A elevated v not elevated</td>
<td>.3098</td>
<td>1.36</td>
</tr>
<tr>
<td>Karnofsky performance status ≤ v &gt; 80%</td>
<td>.6518</td>
<td>1.21</td>
</tr>
<tr>
<td>Age ≥ v &lt; 63 years</td>
<td>.1709</td>
<td>1.47</td>
</tr>
<tr>
<td>Primary tumor not resected v resected</td>
<td>.1040</td>
<td>1.60</td>
</tr>
<tr>
<td>Time since diagnosis ≥ v &lt; 4.3 months</td>
<td>.0806</td>
<td>0.62</td>
</tr>
</tbody>
</table>

Abbreviation: HR, hazard ratio.

*P value and effect size are only presented for multivariate analysis.

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Caplin ME et al. NEJM 2014

Rinke A, et al. JCO 2009
**G2 Ki67 >10%**

**Midgut**

- Basso carico di malattia
- Assenza sintomi
- No controindicazioni

**Everolimus (Analogo SST)**

**Liver tumour burden**

<table>
<thead>
<tr>
<th>Grade</th>
<th>None</th>
<th>≤10%</th>
<th>&gt;10% to 25%</th>
<th>&gt;25%</th>
<th>Unknown</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1</td>
<td>34 (17%)</td>
<td>119 (58%)</td>
<td>29 (14%)</td>
<td>21 (10%)</td>
<td>2 (1%)</td>
</tr>
<tr>
<td>Grade 2</td>
<td>14 (14%)</td>
<td>61 (63%)</td>
<td>8 (8%)</td>
<td>14 (14%)</td>
<td>0</td>
</tr>
</tbody>
</table>

**Tumour grading**

<table>
<thead>
<tr>
<th>Grade</th>
<th>0-1</th>
<th>2-4</th>
<th>6-9</th>
<th>10-0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1</td>
<td>194</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 2</td>
<td>107</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Kaplan-Meier median progression-free survival
Everolimus 14.0 months (95% CI 11.2-17.7)
Placebo 5.5 months (95% CI 3.7-7.4)
HR 0.39 (95% CI 0.28-0.54)
p<0.0001 by stratified one-sided log-rank test

Table 2  Treatment response by RECIST (n = 18)

<table>
<thead>
<tr>
<th>RECIST responses</th>
<th>No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete response (pathologically proven)</td>
<td>1 (5.5)</td>
</tr>
<tr>
<td>Partial responses</td>
<td>10 (55.5)</td>
</tr>
<tr>
<td>Stable disease</td>
<td>4 (22.2)</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>3 (16.8)</td>
</tr>
</tbody>
</table>

Fine RL. et al  Cancer Chemother Pharmacol. 2013
Diabete
Uso steroidi
Dislipidemia
Patologie respiratorie croniche
Sintomi
Carico di malattia
Interazione farmaci (trova)
Pancreas

Everolimus
Rischio sanguinamento
Sindrome
Interazione farmaci (trova)
Abuso di Pompelmo (;)
Patologie concomitanti
• Ipertensione Arteriosa
• Cardiopatia
• Tireopatia
• Insufficienza renale
• Concomitanti

Sunitinib
Diabete
Uso steroidi
Dislipidemia
Patologie respiratorie croniche
Sintomi
Carico di malattia
Interazione farmaci (trova)

Cap-Tem
Leuco-piastrinopenia
Omozigosi mutazione DPYD
Insufficienza renale
Sindrome

PRRT*
Insufficienza Renale
Leuco-piastrinopenia
Accessibilità geografica
PET gallio negativa/disomogenea

1 2 3 4
No significant influence of creatinine clearance (25-178 mL/min) was detected on oral clearance (CL/F) of everolimus.
G2 Ki67 >10

Pancreas

- Rischio sanguinamento
- Trombosi A-V
- Sindrome arteriosa
- Cardiopatia
- Tireopatia
- Insufficienza renale

SUNITINIB

Alternativa

Most frequent adverse events during sunitinib treatment.

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Overall</th>
<th>Grade 1-2</th>
<th>Grade 3-4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>18 (22.5%)</td>
<td>15 (18.8%)</td>
<td>3 (3.8%)</td>
</tr>
<tr>
<td>Asthenia</td>
<td>18 (22.5%)</td>
<td>12 (15%)</td>
<td>6 (7.5%)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>16 (20%)</td>
<td>16 (20%)</td>
<td>-</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>15 (18.8%)</td>
<td>8 (10%)</td>
<td>7 (8.8%)</td>
</tr>
<tr>
<td>Mucositis</td>
<td>14 (17.5%)</td>
<td>12 (15%)</td>
<td>2 (2.5%)</td>
</tr>
<tr>
<td>Palmar-plantar erythodysesthesia</td>
<td>8 (10%)</td>
<td>7 (8.8%)</td>
<td>1 (1.3%)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>7 (8.8%)</td>
<td>6 (7.5%)</td>
<td>1 (1.3%)</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>5 (6.3%)</td>
<td>5 (6.3%)</td>
<td>-</td>
</tr>
<tr>
<td>Fever</td>
<td>5 (6.3%)</td>
<td>4 (5%)</td>
<td>1 (1.3%)</td>
</tr>
</tbody>
</table>

Sunitinib Drug Interactions

A total of 464 drugs (1783 brand and generic names) are known to interact with sunitinib.

- 60 major drug interactions (160 brand and generic names)
- 398 moderate drug interactions (1587 brand and generic names)
- 6 minor drug interactions (36 brand and generic names)

Raymond E. et al. NEJM 2011

www.drugs.com
Prospective phase II trial, 60 pts with P-NETs were enrolled. mPFS was 21.1 months in FDG PET positive patients and 68.7 months in the FDG PET-negative group (P< 0.0002)

<table>
<thead>
<tr>
<th>PFS</th>
<th>mOS</th>
</tr>
</thead>
<tbody>
<tr>
<td>FDG (positive vs. negative)</td>
<td>5.15 (1.42–18.75)</td>
</tr>
<tr>
<td>HR (95 % CI)</td>
<td>0.013</td>
</tr>
</tbody>
</table>

G2 Ki67 >10

Pancreas

- Insuff. Midollare
- Insufficienza renale
- Sindrome
- Cardiopatia ischemica
- Mutazione DPYD

N

Y

CAP-TEM

Nicola!!!

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**Table 3. Differences in primary tumor site response rates**

<table>
<thead>
<tr>
<th>Response by tumor site</th>
<th>n (%)</th>
<th>PR, n (%)</th>
<th>SD, n (%)</th>
<th>PD, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pancreatic NET</td>
<td>15 (52)</td>
<td>3 (20)</td>
<td>5 (33)</td>
<td>7 (47)</td>
</tr>
<tr>
<td>Nonpancreatic NET</td>
<td>14 (48)</td>
<td>2 (14)</td>
<td>9 (64)</td>
<td>3 (22)</td>
</tr>
<tr>
<td>Overall</td>
<td>29 (100)</td>
<td>5 (17)</td>
<td>14 (48)</td>
<td>10 (34)</td>
</tr>
</tbody>
</table>

Abbreviations: NET, neuroendocrine tumor; PD, progressive disease; PR, partial response; SD, stable disease.

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**Guillermo Crespo et al, Future Oncology 2017**

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**Conventional**

Maximum Tolerated Dose (MTD)

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**Metronomic**

Continuative low dose

Angela Lamarca, Melissa Frizzi, Jorge Barriuso, Mairéad G McNamara, Richard A Hubner, Juan W Valle

Figure 2: Use of morphology (well-differentiated versus poorly differentiated) to guide the choice of chemotherapy regimen for the management of patients diagnosed with EP-G3-NECs.

Figure 3: Patients are assumed to have a Ki67 of ≥20%. In addition, is Ki67 used to guide choice of chemotherapy regimen?
Errore più comune

Non considerare la possibilità di arruolare il paziente in un trial clinico
Grazie!!!