Introduction

- Gastroenteropancreatic neuroendocrine tumors (GEP-NETs) are a genetically diverse group of malignant solid tumors that arise in the neuroendocrine cells throughout the body.
- Although GEP-NETs have historically been referred to as ‘carcinoid’ tumors (reviewing current knowledge, GEP-NETs have the potential to become malignant and metastatic).
- Like other malignant solid tumors, survival time in patients with GEP-NETS is associated with tumor differentiation and metastatic spread.
- A medical therapy with an antiproliferative effect and an established well-accepted safety profile would be a valuable management option compared with other more invasive/aggressive treatments for patients with metastatic GEP-NETs.

This poster reviews the antiproliferative effect of octreotide sc and LAR from early uncontrolled studies to the definitive results of the PROMID trial with octreotide LAR 30 mg. Potential future medical therapies and ongoing studies are also listed.

Epidemiology of GEP-NETs

- In the US, there has been a significant increase in the incidence of GEP-NETs from 1973–2004.
- 14% of patients with GEP-NETs have regional or distant metastasis at diagnosis.
- Patients with poorly-differentiated tumors and distant metastasis have a worse prognosis than patients with well-differentiated, differentiated histology and localized/regional disease, respectively.

Rationale for an antiproliferative effect of octreotide sc and LAR

The biological basis for the antiserotonin and antiproliferative effect of octreotide LAR

- Octreotide LAR is a somatostatin analog with high affinity binding to sst1, sst2 and sst5, somatostatin receptor subtypes which are expressed in the majority of GEP-NETs (Table 1).
- Octreotide LAR has antiangiogenic and direct antitumor effects through multiple receptor-mediated signal transduction pathways. Indirect antitumor effects are mediated via inhibition of angiogenesis, suppression of growth factors and growth-promoting hormone synthesis/secretion or immunosuppressive effects.

Octreotide LAR demonstrates a significant antiproliferative effect

- Phase III trials of octreotide LAR in patients with advanced, metastatic GEP-NETs with or without carcinoid syndrome showed a significant improvement in overall survival.

Table 1. Somatostatin receptor subtypes, sst

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<thead>
<tr>
<th>sst subtype</th>
<th>Receptor expression</th>
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<tbody>
<tr>
<td>sst1</td>
<td>Glial cells, tumors</td>
</tr>
<tr>
<td>sst2</td>
<td>Adipose tissue, tumors</td>
</tr>
<tr>
<td>sst3</td>
<td>Pancreas, tumors</td>
</tr>
<tr>
<td>sst4</td>
<td>Liver, tumors</td>
</tr>
<tr>
<td>sst5</td>
<td>Pancreas, tumors</td>
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Figure 1. Annual incidence of NETs in the US between 1973 and 2004.

Figure 2. Median survival time increased significantly in patients with GEP-NETs and distal metastases diagnosed 1984–2004 compared with those diagnosed 1973–1983, coinciding with the introduction of octreotide LAR (Figure 3).

Figure 3. Median survival time increased significantly in patients with GEP-NETs and distal metastases diagnosed 1984–2004 compared with those diagnosed 1973–1983, coinciding with the introduction of octreotide LAR (Figure 3).

Figure 4. Octreotide LAR 30 mg significantly increases TTP in patients with well-differentiated, metastatic, midgut NETs, regardless of functional status.

Figure 5. PROMID subgroup analysis of TTP in patients treated with octreotide LAR 30 mg or placebo (Figure 5).

Figure 6. Scatter plot analysis of TTP in patients treated with octreotide LAR 30 mg or placebo (Figure 5).

Impact of the PROMID trial on clinical practice

- The findings of the PROMID trial will likely lead to the increased use of octreotide LAR to include both functioning and nonfunctioning NETs.
- The US National Comprehensive Cancer Network (NCCN) has recently updated treatment guidelines for foregut, midgut and hindgut NETs, expanding the use of octreotide LAR.
- Octreotide LAR is now a treatment option for asymptomatic, nonfunctioning and nonresectable metastatic tumors of the midgut (Figure 4).

Potential future medical therapies for patients with GEP-NETs

- Phase II trials of pasireotide LAR in combination with octreotide LAR in patients with metastatic midgut NETs (Figure 5), an inhibitor of mTOR (a central effector of net growth, metabolism, and endocrine axis), are ongoing in patients with gastrointestinal (GI) and pancreatic NETs (Table 3). A potential synergistic effect may be seen when these two agents are administered in combination.

Conclusions

- The incidence of GEP-NETs is rising. Most patients present with metastatic GEP-NETs and are unable to achieve cure after surgery.
- The PROMID trial confirmed the antiproliferative benefit of octreotide LAR 30 mg in treatment-naive patients with well-differentiated, metastatic midgut NETs, regardless of tumor functional status.
- Patients with functioning or nonfunctioning metastatic NETs of the midgut should now be considered for treatment with octreotide LAR 30 mg.
- Octreotide LAR 30 mg in treatment-naive patients with midgut NETs has shown promising results; data in mid and long term proves to be a treatment option for patients with severe metastatic disease.
- Evaluation of patients in treatment with octreotide LAR is ongoing.

References