Neoadjuvant therapy for advanced pancreatic neuroendocrine tumors

Table 1. Grading proposal for foregut neuroendocrine tumors from ENETS

<table>
<thead>
<tr>
<th>Grade</th>
<th>Mitotic count (10 HPF)</th>
<th>Ki-67 index (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>G1</td>
<td>&lt;2</td>
<td>≤2</td>
</tr>
<tr>
<td>G2</td>
<td>2-20</td>
<td>3-20</td>
</tr>
<tr>
<td>G3</td>
<td>&gt;20</td>
<td>&gt;20</td>
</tr>
</tbody>
</table>

*10 HPF: high power field=2 mm², at least 40 fields (at 40× magnification) evaluated in areas of highest mitotic density; *MIB1 antibody; % of 2,000 tumor cells in areas of highest nuclear labeling

In addition, the AJCC has proposed a TNM staging classification significantly different to the ENETS staging system.4 From the surgical point of view, the AJCC staging system incorporates in T4 tumor assessment the importance of anatomical correlation of the tumor with the adjacent vascular structures, which is the cornerstone of resectability in pancreatic neuroendocrine tumors. Of note, the ENETS tumor staging system, which equates tumor infiltration of viscera with major vascular involvement, is not compatible with current clinical practice. It should be stressed that preoperative imaging studies showing possible vascular involvement as well as definite detection of this intraoperatively are usually considered contraindications to surgery.

Aggressive surgery for T4 tumors including superior mesenteric vein reconstruction can be contemplated, but the surgical risk-benefit ratio should be carefully weighed.12,13

**Oncologic perspectives**

Nowadays, the use of neoadjuvant therapy is an established treatment in patients with pancreatic ductal adenocarcinoma (PDAC). PDAC carries the worst prognosis of all malignancies of the alimentary tract. Despite recent advances in imaging studies, only 10 to 20% of patients have resectable disease at the time of presentation. Of the remaining patients, 30 to 40% present with locally advanced tumors. Median survival for these patients is 8-12 months.9

Due to their poor prognosis, such patients are candidates for neoadjuvant therapy with the aim of tumor downsizing (or even disease downstaging) and subsequent resection. Moreover, neoadjuvant therapy is better tolerated by patients and allows for the identification of those patients with rapid disease progression despite therapy who are not expected to benefit from surgery.

Two meta-analyses including series of patients with pancreatic adenocarcinoma have concluded that approximately one third of patients with locally advanced, unresectable or borderline resectable tumors can be resected after neoadjuvant therapy, with survival rates comparable to those of patients with initially resectable tumors.14,15 Therapeutic options include chemotherapy, chemoradiotherapy or a combined approach. Radiotherapy alone has been tried to a lesser extent. However, the optimal regimen in this setting is not to date established.9

**The role of neoadjuvant therapy in the treatment of advanced pNETs**

In regard to neuroendocrine pancreatic tumors, either synchronous or metachronous resection of the primary and metastatic tumors is recommended to be performed whenever possible.12,16,17

Even in the setting of locally advanced tumor and/or metastatic disease, surgery may be the treatment of choice aiming at tumor reduction and palliation of mass effect or hormone-related symptoms.18 Surgical excision should be performed only if more than 90% of the tumor mass can be resected.19 On the other hand, it has been suggested that palliative debulking surgery has no significant effect on survival as compared to palliation without surgery.20

Regarding inoperable pNETs, the current guidelines suggest observation for patients with pNETs G1/G2 who are asymptomatic, with low tumor burden and stable disease. In the case of symptomatic patients with large tumor volume or progressive disease, first-line therapy recommendations include biological agents (sunitinib, everolimus), chemotherapy, arterial embolization, chemoembolization, ablative therapy, cytoreductive surgery, supportive medical care and somatostatin analogs. Patients with inoperable pancreatic NECs should be started on cisplatin- or etoposide-based chemotherapy or offered the chance to participate in clinical trials.18

During the last decade, several institutions have reported response rates of 39% to 71% with nonsurgical treatments in patients with advanced pNETs,21 although the majority of these published studies are