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Therapeutic algorithm of pancreatic neuroendocrine neoplasms

Nicola Fazio[1], Lorenzo Antonuzzo[2]

[1] Gastrointestinal and Neuroendocrine Tumors Unit, European Institute of Oncology, Milan, Italy; [2] Oncology Unit, S.C. Oncologia Medica 1, AOU Careggi, Florence, Italy

Introduction

Two third of neuroendocrine neoplasms (NENs) develop from the gastroenteropancreatic (GEP) tract (1). Pancreatic (p)NENs represent 1% of all digestive NENs and <3% of all pancreatic cancers (2). Most pNENs are *non-functioning*, sporadic and advanced at diagnosis (3,4). According to WHO 2010 classification pNENs are classified in three groups (5), on the basis of mitotic index (MI) and/or Ki-67: G1 (Ki67 ≤2% and/or MI <2), G2 (Ki67 3-20 % and/or MI 2-20) and G3 (Ki67 >20% and/or MI >20). G1 and G2 are called pNETs, whereas G3 pNECs.

Bases of treatment

When possible, treatment of patients with pNEN should be established only after the definition of the following three factors:

1) disease characterization
2) clinical assessment of the patient
3) treatment goals

Disease characterization

It includes a right diagnosis, a complete staging and presence of prognostic and/or predictive factors to treatments.

The diagnosis of NEN is essentially based on morphology and immunohistochemical expression of general markers of neuroendocrine differentiation.

A NEN should be "pure", since for "non pure" NEN like "carcinoma with neuroendocrine differentiation" or "mixed exocrine/endocrine carcinoma" staging, prognostic stratification ant treatments are different compared with NEN.

A complete staging work-up of pNETs includes morphological (Computed Tomography, CT-scan, Magnetic Resonance Imaging, MRI, endoscopy, endoscopic ultrasound, EUS) and functional imaging (^{68}Gallium- Positron Emission Tomography, PET-CT-DOTA peptide or Somatostatin Receptor Scintigraphy, SRS). Metabolic evaluation (^{18}Fluorodeoxiglucose, FDG-PET-CT) can be useful in pNECs

Somatostatin receptor (sstr) expression is a positive prognostic factor and predictive of response to Peptide Receptor Radiotherapy (PRRT); ^{18}FDG-PET-CT positivity has been reported to have a negative prognostic value in NETs (6).

Clinical assessment of the patient

Some patient-related factors can influence treatment strategy, including performance status, comorbidities, concomitant medications, and pNEN-related symptoms/syndrome.

Treatment goals

On the basis of the disease characterization and clinical assessment of the patient, a baseline multidisciplinary sharing of early and late treatment goals should be defined.

Late goal of treatment can drive the therapeutic plan of patients. For example, in a totally palliative setting, without the probability of a future radical or high debulking surgery, the therapeutic approach should consider a sequence of therapies for tumor growth control over time; differently in a metastatic setting with some probability of future radical or debulking surgery after cytoreduction the first therapy should be chosen among those with the best probability of objective response.

Treatment options

Somatostatin analogs (SSAs) are indicated in the vast majority of pNEN-related syndromes and in non-functioning progressing pNETs according to experts recommendations and guidelines (7)

However, the only prospective evidence of a role of SSAs in non-functioning pNETs derives from the not yet published CLARINET trial. This is a randomized phase III trial comparing lanreotide autogel 120 mg every four weeks with placebo in patients with advanced enteropancreatic well-differentiated non-functioning NENs, with Ki67 <10% and SRS positive (8). Among 204 randomized patients a 53% reduction of the risk of progression in favor of lanreotide was observed. Forty-two % of patients had a pNET and 84% were untreated.

Chemotherapy has a role in pNECs, with cisplatin/etoposide regimen as a sort of standard of treatment (9). However the high-grade group of NEN is quite heterogeneous. In the recently published NORDIC study , including 305 GEP NECs, (10) patients with Ki-67 <55% were less responsive to platinum-based chemotherapy but survived longer compared with patients with Ki-67 >55%.

In pNETs alkylating-based regimens have been used more frequently.

Temozolomide has been reported to be active in pNENs. Particularly in a retrospective analysis of 30 patients with advanced pNETs Capecitabine/ Temozolamide combination yelded 59% RR and 6% CR (11).

In February 2011 the results of two large randomized phase III trials regarding pNETs were published in the same issue of New England Journal of Medicine. Both trials had a placebo control arm and included advanced radiological progressing pNETs. One studied everolimus 10 mg/day and the other one sunitinib 37.5 mg/day. The former was completed, with 410 enrolled patients and the latter was prematurely stopped due to reached statistical endopoint when 171 patients had been included. (12, 13). On these bases everolimus and sunitinib were approved by FDA and EMA for progressing advanced well/moderatley differentiated pNETs.

Based on evidence it is not clear which is the timing of everolimus and sunitinib related to SSA in pNET patient treatment. In everolimus phase III trial (RADIANT-3 trial) half of patients had received a SSA before everolimus and 40% concurrently. In sunitinib trial 36% had received a SSA before sunitinib and 50% concurrently. No significant difference in PFS benefit were observed related to these subpopulations.

The PRRT has been reported active and potentially effective in pNETs, in particular with ^{177}Lutetium (14, 15).

As for the timing of everolimus related to PRRT Kamp et al. reported an acceptable safety profile of everolimus in 24 patients pre-treated with 177-Lu-Dotatate (16). By contrast Panzuto et al. (ECC-2013 poster) reported a 12-fold higher risk to experience severe toxicity in 169 patients including 85 pNETs) who had received everolimus after PRRT and chemotherapy (17).

An ongoing ENETS trial has been comparing chemotherapy (Streptozotocin + 5-Fluorouracil) followed by everolimus with the inverse sequence in patients with advanced pNETs.

Conclusion

In patients with advanced pNETs SSA, everolimus and sunitinib should be considered based on evidence and regulatory aspects. Also chemotherapy and PRRT can be considered, based on some evidence data, but they should be used within clinical trials.

The main guidelines included these new therapies, but several aspects remain unknown, such as sequence, timing, integration each other.

Patients affected by pNETs should be referred to medical centers with specific experience in the treatment of these rare tumors and with a dedicated multidisciplinary team. The goal of a multidisciplinary team is to decide a "treatment strategy" rather than a sequence of single treatments.

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