the terminology and diagnostic criteria proposed by the WHO world national multidisciplinary panel of experts from one of the 2% of all lung malignancies [5]. The existing evidence on is a welcome guidance for these rare tumours (1 to pulmonary neuroendocrine (NE) tumours in this edition of effort.

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references

Pulmonary carcinoid: a rare thoracic malignancy, a high need for better defined systemic therapy
The latest ESMO clinical practice guideline on neuroendocrine bronchial tumours goes back to 2012 [1]. To complement its existing guidelines, ESMO organises consensus conferences to focus on specific issues in each type of tumour. A group of experts address selected clinically relevant questions for which the existing evidence—as used in standard guidelines—is limited or less clear. For lung cancer, the 2nd ESMO Consensus Conference on Lung Cancer was held on 11–12 May 2013 in Lugano [2–4]. Pulmonary carcinoids (PCs) were not part of that effort.

Therefore, the comprehensive consensus report of the European Neuroendocrine Tumour Society (ENETS) on pulmonary neuroendocrine (NE) tumours in this edition of Annals of Oncology is a welcome guidance for these rare tumours (1 to 2% of all lung malignancies) [5]. The existing evidence on optimal treatment of PCs is indeed limited, with no large randomised, controlled trials (RCTs) specifically dedicated to the medical therapy of PCs.

This consensus also has great significance because an international multidisciplinary panel of experts from one of the world’s leading Neuroendocrine Societies (ENETS) has endorsed the terminology and diagnostic criteria proposed by the WHO Classification since 1999 [6], in 2004, and now in the recent 2015 WHO Classification. Because a completely different classification system is utilised by pathologists and clinicians for NE tumours in other sites such as the pancreas and gastrointestinal tract, it is frequently proposed that the thoracic physicians also adopt the same system. However, in the thorax, small-cell carcinoma (SCLC) is the dominant NE tumour and the terminology and criteria for distinguishing SCLC from typical and atypical carcinoid (AC) as well as large-cell neuroendocrine carcinoma (LCNEC) are well established. The PCs are distinguished from the far more aggressive LCNEC and SCLC by means of mitotic cell count and presence of necrosis and lack of combinations with other carcinoma types such as adenocarcinoma and squamous cell carcinoma. PCs are often referred to as ‘low-grade’ tumours, but they comprise two quite different entities. Typical carcinoid (TC) is indeed often localised. After complete resection, 5- and 10-year survival rates are as high as 90% [7]. AC, however, is ‘intermediate grade’ and more prone to locoregional lymph node and distant spread, and may have a 5-year survival rate of only 44% [8], an outcome actually quite close to the one of resected non-small-cell lung cancer.

The staging classification of PCs is settled since they were taken along in the last tumour node metastasis (TNM) staging revision in 2007 [9]. Less clear is the optimal preoperative staging algorithm. A CT scan of chest and upper abdomen is standard. The role of fluoro-deoxy-glucose positron emission
tomography (FDG–PET) scan, or more specific somatostatin receptor (SSTR) directed radionuclide imaging such as octreotide single-photon emission computed tomography or the more sensitive gallium-68 DOTATOC/DOTATATE PET scan [10], is far less defined. In the well-differentiated TC, FDG–PET may be false-negative [11], and SSTR directed imaging will be more rewarding. In the less differentiated AC, SSTR directed imaging may become less reliable, as the expression of SSTRs may be lower, while FDG–PET on the other hand may perform better. A true algorithm on which patient needs which test is at present not available, but one could argue that patients with TC do not need all these extra tests, given their excellent prognosis after resection, while those with AC deserve more in-depth assessment.

As for therapy, the role of surgery as initial therapy in patients without extra-thoracic spread is well established. Anatomical resection and systematic lymph node sampling/dissection is recommended. Surgery and other ablative techniques may also be of value in case of limited metastatic disease. The role of adjuvant therapy remains unknown. Many questions, however, remain in place regarding systemic therapeutic approaches in patients with more advanced disease.

Somatostatin analogues (SSAs) are the standard treatment of symptom control in PCs with a carcinoid syndrome [12]. Their role as anti-tumour agent, for PCs in particular, is less clear. The randomised PROMID study compared octreotide LAR 30 mg i.m. every month to placebo [13]. Only 85 of the planned 162 patients could be enrolled over 8 years. The median time-to-progression was significantly different, 14.3 months in the octreotide LAR group and 6 months in the placebo group. Similar data were reported recently with lanreotide aqueous-gel formulation in the CLARINET study [14]. The 2-year progression-free rate was 65.1% for the lanreotide group and 33.0% in the placebo group. Overall survival and quality of life were not significantly different.

However, both of these trials did not include patients with PC. The first [13] was conducted in well-differentiated metastatic midgut NE tumours, while the latter [14] was in pancreatic, midgut and hindgut NE tumours. PCs are considered to be related entities as they also have a NE morphology, and as they are—based on their common embryonic origin—part of the ‘foregut’ tumours, including the upper intestinal, lower respiratory and hepato-biliary-pancreatic tract.

In reality, there are important differences between PCs and digestive NE tumours. First, the clinical differences already mentioned by the authors, e.g. in diversity of hormone-related symptoms, number of patients with distant metastases at diagnosis, prevalence of bone, cutaneous and brain metastases. Secondly, the pathological classification remains quite different. Digestive NE tumours are separated according to their degree of differentiation, with the Ki-67 immunohistochemistry mandatory to grade the tumour according to the WHO classification. This is why the CLARINET study listed the inclusion criterion of NE tumours of grade 1 or 2 (i.e. with a proliferation Ki-67 antigen index <10%). In contrast, as mentioned above, PCs are classified in the group of NE thoracic neoplasms according to the mitosis count and presence of necrosis, with the Ki67 only a possible marker to distinguish the high-grade LCNEC/SCLC from PC in small biopsy samples. In the lack of good evidence, this consensus document argues to consider SSAs as first-line systemic anti-proliferative treatment in advanced unresectable PC as well, provided that a SSTR directed radionuclide imaging is positive.

This a reasonable approach, taking into account that the data on other systemic options for PCs, such as chemotherapy, are of very low grades of evidence. Most cytotoxic agents (such as fluorouracil, temozolomide, dacarbazine, streptozotocin) have limited efficacy and quite some toxicity. Moreover, here as well, the majority of the patients in these studies had digestive NE tumours, and the number of patients with PC is often below 10. For AC, a platinum–etoposide regimen can be advocated in analogy with SCLC.

Looking at the recruitment difficulties in e.g. the PROMID study, it will be challenging to get specific PC data. In the NE studies, the number of PCs is in general low, as only about one quarter of NE tumours are from the respiratory tract. Moreover, solid information for systemic therapy is most needed for ACs, and the actual number of ACs in these studies is even lower, given the ratio of about 10:1 for TC:AC in the group of PCs.

As PCs are on average tumours with a low mitotic count, our best bet for progress may lie in better understanding of the biology of these tumours, hopefully leading to targeted drugs that—even in the absence of response—may lead to durable disease stabilisation and better outcome. In that respect, there is still a long way to go, with—as the authors’ state—no role at present for any molecular testing in clinical practice. In clinical trials, the best data at present are for mammalian-target-of-rapamycin (mTOR) or angiogenesis inhibiting strategies.

The role in tumour cell growth of the phosphatidylinositol 3-kinase (PI3K)–Akt–mTOR pathway has been described in PCs [15]. In sequencing studies (be it in pancreatic NE tumours, but forget just as PCs) it was documented that 14% of these tumours have mutations in genes involved in the mTOR pathway [16]. The mTOR inhibitor everolimus was studied in a RCT comparing octreotide LAR plus everolimus 10 mg per day with octreotide LAR plus placebo in 429 patients with low- or intermediate grade NE tumours and carcinoid syndrome, 44 of which were PCs. There was a 5-month difference in median progression-free survival (16.4 versus 11.3 months) [17]. Based on these and other data, everolimus is registered by EMA for unresectable or metastatic, well- or moderately differentiated NE tumours of pancreatic origin, not in patients with PCs. Further preclinical work has recently shown that double blockade of the PI3K–Akt–mTOR and KRAS pathways may be more effective [18]. Ongoing studies, such as LUNAR (comparison of everolimus versus the SSA pasireotide versus both combined) and RADIANT4 (comparison of everolimus versus placebo in non-functional NE tumours) will further define the role of everolimus in NE tumours and PCs in particular.

Finally, PCs are highly vascular tumours. Therefore, anti-angiogenic drugs deserve further exploration as well. Up till now, data are limited to small phase II studies with agents such as sunitinib, sorafenib, bevacizumab or pazopanib, where promising disease control rates were reported, including a few in PCs.

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references


Proven efficacy, equitable access, and adjusted pricing of anti-cancer therapies: no ‘sweetheart’ solution

As medical oncologists, we are often asked whether all cancer patients will be treated by some sort of targeted therapy in the next 10 years. Despite three decades of extraordinary progress in cancer research—translating basic molecular mechanisms to clinical care—too many patients across the globe, including developed regions, will not benefit from these developments. That is the current reality. Our efforts, based on promising weaponry against cancer, must be nourished and nurtured as a community to ensure that we continue to expand our efforts and our successes for an increasing number of patients.

As a single entity, cancer is the biggest cause of mortality worldwide with an estimated incidence of 14.1 million people and 8.2 million cancer deaths in 2012. Given the dire projections—cancer cases are forecast to rise by 75% totalling ~25 million over the next 20 years [1]—we must act now to reach a consensus among our medical colleagues, funding agencies, legislative bodies, patient groups, and other key stakeholders, or we cannot hope to sustain the progress we have made thus far against this looming challenge.

The European Society for Medical Oncology’s Magnitude of Clinical Benefit Scale (ESMO-MCBS) is undeniably an important and much needed tool to assess the clinical benefit for cancer medicines aimed at providing decision makers with expanded information on the efficacy and value of oncology treatments [2]. Aligned with ESMO’s committed efforts to shape oncopolicy towards facilitating equal access to optimal, affordable care to patients throughout Europe, this latest initiative represents a first step in addressing issues surrounding prioritization of such efforts relying on the expected magnitude of benefit of our treatment options. By adopting a rational, consistent approach to gauging the scale of clinical cancer benefit of new anti-cancer medicines, the ESMO-MCBS promises a transparent and more reliable assessment of just what can be expected from these novel treatments. The clinical studies that will clearly benefit from positive endorsement will be those cancer medicines graded as proven as opposed to promising; those that bring substantial improvements to duration of survival and/or quality of life of our patients [3]. This will not only benefit the credibility of drugs or treatment interventions with the highest scores (which, will be highlighted in the ESMO guidelines in the hope that they will be rapidly implemented by health authorities across Europe) but also, help us to better manage the hype and inflated expectations that are by-products of clinical findings being wrongly (or prematurely) positioned...