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Editorial

Neuroendocrine tumors A growing cancer field

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Neuroendocrine tumors (NETs) constitute a diverse group of malignancies which present with a large variety of clinical symptoms. The incidence of 5/100,000 per year and the prevalence of 35/100,000 per year are steadily increasing particularly during the last decades. The reason for this increase is not fully elucidated but greater awareness among physicians, better diagnostic procedures and improved therapy might account for significantly increase in incidence and prevalence over the last years. The diagnosis and clinical management have been significantly improved during the last years thanks to new classification systems (WHO 2000, WHO 2010, ENETS, TNM and grading system) which have clearly improved classification of the various tumors, subdividing into groups with different prognoses. Determination of the proliferation capacity by measurement of Ki-67 (MIB-1) have been of value for subdividing tumors with more benign behaviour from those with more malignant phenotype. Chromogranin A has now been a generally accepted tumor marker both for histopathology and in the circulation and is useful for diagnosis and follow up of treatment of patients. The imaging has been significantly improved during the last years, not only standard irradiation such as CT or MRI, but particularly molecular imaging including somatostatin receptor scintigraphy which nowadays will be replaced by ^{68}Ga -DOTA-Octreotate PET scanning. There are other specific PET tracers for NETs such as fluorodopa and ^{11}C -5HTP. The PET

technique will significantly improve the staging of the disease.

Surgery is still a cornerstone in the management of most patients with NETs, although more than 60% present metastatic disease at diagnosis. However, a more active approach from the surgeons with tumor debulking including resections combined with radiofrequency ablation might facilitate a forthcoming medical treatment. Other means of tumor reduction particularly for liver metastases are embolization/ chemo-embolization and most recently radio-embolization with radioactive ^{90}Y trium micro-beads. Peptide receptor radioactive therapy (PRRT) with ^{177}Lu tetium-DOTA-Octreotate or ^{90}Y trium-DOTA-Octreotate have generated interesting results in patients with metastatic disease and is now being more and more applied with significant antitumor responses in patients with tumors with high expression of somatostatin receptors. The medical treatment consists of biotherapy, chemotherapy and most recently tumor “targeted treatment”. In previous days no randomized trials were available and most medical treatments were based on local experience. Today we have at least four big randomized placebo controlled trials which will have an impact on the future treatment of NET patients. Somatostatin analogs were originally developed for management of clinical symptoms related to NETs but the PROMID-study indicated a clear antitumor effect which have change the guidelines in many countries for management of



NETs. Today it is allowed to use Sandostatin LAR® for treatment of both functioning and so called non-functioning well-differentiated NETs. Two new studies with “targeting agents” have recently been published in patients with pancreatic NETs. One study a randomized control study with sunitinib vs. placebo the other everolimus vs. placebo (RADIANT-3) in pancreatic NETs have demonstrated a significant antitumor effect of both these drugs. Another study with everolimus (RADIANT-2) in well-differentiated small intestinal and lung NETs has also demonstrated a significant antitumor effect and might be a future alternative for treatment of classical midgut carcinoid tumors after progression on somatostatin analog. The sunitinib as well as the everolimus trial in pancreatic NETs will have an impact on the future management of well-

differentiated pancreatic NETs. In previous days these patients were treated with cytotoxic agents such streptozotocin plus 5FU/Doxorubicin or cisplatin plus etoposide for the poorly differentiated tumors. The cytotoxic agent that will compete with the “targeted treatments” will be temozolomide alone or in combination with capecitabine or even bevacizumab, which has demonstrated significant antitumor responses in pancreatic and lung NETs. The precise place of the new “targeted therapies” in the treatment algorithm have to be determined in the future by comparing these drugs with standard cytotoxic treatments or somatostatin analogs including efficacy, side effects and costs. The future treatment will be personalized based on the tumor biology and molecular genetics of the tumor and managed by a multi-disciplinary team.

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Com o apoio dos Laboratórios Pfizer, Lda.



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