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INVITED EDITORIAL

Novel therapeutic strategies for neuroendocrine tumours – can eminence replace evidence?

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The treatment of neuroendocrine tumours of the gastroenteropancreatic tract (NET-GEP) is to a large extent accepted to be aiming primarily at lowering symptoms related to the hormonal overproduction these tumours lead to. The introduction of somatostatin analogues (octreotide, lanreotide) several decades ago was indeed a major breakthrough, in that patients could experience symptomatic relief, and that surgery could be performed, from an anaesthesiological point of view, in a more controlled and safe way than before. The surgical procedure in its turn, is most often aimed at removing the primary tumour, and, if technically feasible, debulking metastatic disease. This strategy has been proven to be beneficial in terms of decreasing symptoms and improving quality of life. Still, whether this strategy actually significantly extends patient survival, has not been proven in any traditional randomized clinical trial. Such evidence will of course never be presented: which serious investigator would suggest withholding any patient group a treatment so obviously beneficial for the individual? At the same time, clinicians caring fore NET-GEP patients can bear witness to anecdotal cases who were judged to be beyond cure, but despite this continue to survive year after year with or without symptomatic treatment.

Adjuvant treatment for operated NET-GEP patients with or without demonstrable remaining tumour burden is somewhat more controversial. Should a patient without any clinical sign of disease, radiological or biochemical, be without medication until recurrence is proven? Is the disease-free interval likely to be longer with the post-operative use of somatostatin analogues and/or interferon-α? Even in the case of metastatic or inoperable disease, the superiority of this medical strategy has been very difficult to prove, often due to patient heterogeneity and difficulties to reach sufficient numbers of objects [1,2]. Hence, the strategies vary from centre to centre and may to a large extent be a matter of taste rather than based on convincing results from controlled trials.

With the advent of peptide receptor radionuclide therapy (PRRT) in the 1990s, a completely different therapeutic option could be offered some patients with incurable NET-GEP. In a recent issue of Acta Oncologica, the Erasmus MC group from Rotterdam presented their truly eminent and pioneering experience of this novel strategy [3]. The results presented herein give a broad view of the various options and their possible benefits, and point to other yet unexplored paths of treatment choices for the future. The authors have since several years been presenting their data, not least at conferences on NET-GEP, and their convincing results have led to that several other centres have referred patients to the Rotterdam Clinic, or lately, have adopted this treatment strategy for similar clinical use.

PRRT is today mainly reserved for patients with widespread disease, judged to be progressive, with tumours displaying a comparably low proliferation index. Furthermore, the tumours must show a sufficient somatostatin analogue uptake measured

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by scintigraphy. The role of PRRT in a truly adjuvant setting is yet to be explored. Perhaps this will be the main indication for PRRT in the future?

When can this type of therapy be considered standard treatment, rather than investigational? In this article, it is admitted that it would have been preferable to have randomized trials comparing PRRT to no treatment at all. As chemotherapy is offered NET-GEP patients with preferably poorly differentiated and/or quickly proliferating tumours, controlled trials comparing these treatments will likely not occur. Interestingly, the wish and need for randomized trials is mentioned at another four different places in the article. And indeed, in my own experience, these wishes are repeated several times at each clinical conference on NET-GEP treatment.

It is not hard to explain the lack of level A EBM data for these patient categories. These explanations are true also for many other diagnoses, not least within the field of other endocrine tumours; they are comparably rare, have a relatively indolent clinical course requiring (too) long follow-up, and comprise a considerable heterogeneity. In addition, the treatments are often very expensive, and because of the rarity of the disease, often draw little attention from the industry.

This dilemma becomes even more obvious when we consider other novel therapeutic agents in the pipe-line for NET-GEP patients. These include angiogenesis inhibitors of various types, novel somatostatin analogues (such as pan-receptor agents), the putatively very promising mTOR inhibitors, and also new cytotoxic agents. As several of these drugs are aimed at the same patient groups as is PRRT, the following questions arise: whose responsibility is it to evaluate each one of these treatments? How can we recruit large enough patient series to be able to tell which one of the different therapies significantly improves patient survival and quality of life? In which order should the different treatments be tested? How can possible synergistic effects from combinations of these entirely different strategies be proven? And, last but not least who should pay for these sometimes extremely expensive therapies during their investigational phase? Furthermore can society justify the expenses for them as "standard treatment" without *true* evidence for their beneficial effects?

In my opinion, it is only the rare centres such as that in Rotterdam that have the tools (and the subsequent responsibility) to answer these and similar questions. Their position as leading centre for NET-GEP treatment should be supported by others, for example by efforts to enter patients in trials using detailed protocols aimed at answering clinical questions such as the above-mentioned. This would presumably lead to a significant expansion of the miniscule number of randomized clinical studies in the NET-GEP field. Thus, we are all responsible – if we are serious in our wish for randomized clinical trials, let us start at the next NET-GEP conference by turning our wishes into reality.

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