memo (2012) Vol. 5: 63–65
DOI 10.1007/s12254-012-0339-y
Printed in Austria

memo
magazine of european medical oncology

Pancreatic neuroendocrine tumours – new therapeutic concepts

M. Troch, B. Kiesewetter, Markus Raderer

Division of Oncology and cancer research, Department of Internal Medicine I, Medical University of Vienna, Vienna, Austria

Received 6 November 2011; accepted 23 February 2012

Neuroendocrine tumours (NETs) are rare tumours with their clinical behaviour depending on the location of the primary and grade of differentiation. Recently, a number of randomised studies have been published focussing on pancreatic NETs which have demonstrated the efficacy of new therapeutic approaches including thyrosin-kinase inhibition and targetting the mTOR pathway. The objective of this review is to briefly sum up systemic treatment options in well differentiated pancreatic neuroendocrine tumours which are currently available.

Keywords: Pancreatic neuroendocrine tumours, systemic treatment.

Introduction

Pancreatic neuroendocrine tumours are rare, accounting for about 1–2% of all pancreatic neoplasms, with an apparently increasing prevalence and incidence over the last three decades [1]. In 2010, the WHO has established a new staging and grading system for neuroendocrine tumours originating at gastroenteropancreatic sites. Neuroendocrine tumours are currently divided into well differentiated neuroendodrine tumours, grade 1 or 2 [G1, G2] and poorly differentiated carcinomas, grade 3 [G3] characterised by a completely different clinical behaviour [2].

Neuroendocrine tumours (NETs) are graded with respect to the microscopical appearance and the proliferation index, using mitoses per high powerfield and/or the Ki 67 staining index. [3] Neuroendocrine tumours show a heterogenous clinical course depending on the location of the primary tumour (pancreas versus gastrointestinal tract NET) and histological grading with different response patterns to various treatment strategies. Due to the rarity and heterogeneity of pancreatic NETs only a limited number of prospective, randomised trials are available, which nevertheless have led to advances in understanding and management in recent months. In this article, we will briefly summarise recommended treatment options for well differentiated neuroendocrine tumours (G1 and G2) of the pancreas.

Up to 60% of pancreatic NETs present at an advanced stage with a median survival of 23 months for metastatic disease as opposed to patients with localised disease who show a median overall survival of 124 months [4]. This is most probably due to the possibility of radical surgery, which is the only potentially curative treatment option. In patients with hepatic metastases, the role of resection of the pancreatic primary is controversely discussed in the literature. While retrospective data have suggested a marginal benefit, this has not yet been substantiated by prospective controlled trials and the trend might have been due to a selection bias [5].

Systemic treatment in advanced stage pancreatic neuroendocrine tumours

Somatostatin analogues

Somatostatin analogues (SST-A) have clearly demonstrated their impressive potential to control symptoms caused by ectopic peptide/hormone secretion (sometimes termed “carcinoid syndrome”), i.e. flush and/or diarrhoea. Pancreatic NETs are non-functioning in the majority of patients, with a negative impact for non-functioning tumours in terms of overall survival having been reported in the literature [6], probably reflecting more intensive work-up and thus potential earlier detection in patients with peptide/hormone-induced symptoms.

While their use in an attempt to control symptoms is clearly established, there are currently no data to suggest an antiproliferative effect of SST-A in pancreatic NETs, either alone or in combination with Interferon-alpha. Currently, a large randomised study (CLARINET) including 200 patients is being performed to compare the use of the SST-A lanreotide versus placebo in non-functioning NETs including those of pancreatic origin [7].

Chemotherapeutic agents and new drugs

As opposed to intestinal NETs, pancreatic NETs have been shown to be susceptible to systemic treatment (including chemotherapy and targeted agents) to a certain extent.

Correspondence: Markus Raderer, MD, Division of Oncology and cancer research, Department of Internal Medicine I, Medical University of Vienna, Währinger Gürtel 18-20, 1090 Vienna, Austria.
E-mail: markus.raderer@meduniwien.ac.at

Recently, two drugs have been approved for treatment of this rare malignancy as a result of phase III studies.

Historically, the islet-cell toxin streptozotocin has been used in the treatment of pancreatic NETs, and good activity with objective response rates up to 69% for the combination of streptozotocin 500 mg/m² i.v. day 1–5 and doxorubicin 50 mg/m² i.v. day 1 has been reported [8]. While older trials have used either radiological criteria or a decrease in tumour markers for defining response to therapy, more recent studies have assessed this combination relying on objective definitions of response by applying RECIST criteria. Side effects of streptozotocin-based chemotherapy were predictable and well manageable with respective supportive therapy including hydration and antiemetics, and consisted mostly of mucositis, diarrhoea neutropenia and fatigue in up to 19% of patients. In a cohort of 84 patients treated with streptozotocin, doxorubicin and fluorouracil outside of a clinical trial, a progression free survival (PFS) of 18 months was achieved and the overall median survival was 37 months [9], which compares favourably to time to progression seen in trials of targeted therapies.

Promising results were published with the combination of two oral chemotherapeutic agents (which are both not yet registered in this indication), i.e. capecitabine 750 mg/m² twice daily, day 1–14 plus temozolomide 200 mg/m² once daily, day 10–14. In this retrospective analysis, 30 patients were included and a high objective response rate (assessed in a blinded way according to RECIST criteria by a radiologist and a medical oncologist) of 70% (partial response) with a median PFS of 18 months was documented. Toxicities were moderate and only 12% grade 3 and 4 toxicities were observed. Although the authors have cautioned that this is a retrospective analysis, these data appear nevertheless promising and deserve further study [10].

Another systemic treatment option which has become available quite recently is the multikinase-inhibitor sunitinib. Based on the results of a phase III study comparing sunitinib at a dose of 37.5 mg daily versus placebo, sunitinib has been approved for treatment of pancreatic NETs. The study was terminated early after including 171 patients, 86 of whom received sunitinib and 85 placebo. As opposed to previous studies in NETs (which are sometimes prone to spontaneous stabilisation even in the absence of treatment), radiologically verified demonstration of progressive disease within 12 months before study entry was required. As expected, the objective response rate was relatively low at 9.3% (*vs.* 0% in the placebo arm), but the principal endpoint progression free survival (PFS) was statistically significant with 11.4 months in the sunitinib arm versus 5.5 months in the placebo group. Side effects were not only and predominately diarrhoea in the treatment arm, but also vomiting, nausea, asthenia fatigue, neutropenia, stomatitis and dysgeusia were reported. Interestingly, fatigue, vomiting and asthenia were also commonly seen in the placebo group [11]. For an overview of the medication discussed in literature see Table 1.

The largest randomised trial in pancreatic NETs to date has compared the m-TOR inhibitor everolimus versus placebo in 410 patients with documented disease progression within the last 12 months. In total, 207 patients received everolimus at a dose of 10 mg daily and 203 were given placebo, and additional therapy with octreotide for symptom control was allowed. The PFS was again statistically significant at 11.0 *vs.* 4.6 months, which appears comparable to the data obtained with the use of sunitinib. At time of analysis, there have not been enough events to assess the median overall survival, and the potential cross-over after progression makes it virtually impossible to assess OS (as was also the case in the trial with sunitinib). Moderate drug related side effects including stomatitis, rash, diarrhoea, fatigue and infection were commonly observed in the treatment group. Grade III and IV toxicities were more frequent in the treatment group than in the placebo-arm (Anemia 6% *vs.* 0%, Hyperglycemia 5% *vs.* 2%), but were manageable in these patients. As with sunitinib, however, the rate of objective responses was low (5% versus 2% in the placebo arm, again underscoring the potential for spontaneous growth arrest in these tumours). Therefore, relevant tumour shrinkages are not to be expected, and both agents do not appear suitable for potential neo-adjuvant approaches. In addition, the approval for both sunitnib and everolimus strictly requires documented progression before administration of the drugs [12].

Everolimus has also been shown to be feasible and active after cytotoxic therapy. Recent data, however, have suggested that the effect of everolimus might be augmented by concomitant administration of SST-A. A non-randomised evaluation has included 160 patients who were treated with everolimus 10 mg daily. Patients who had been on octreotide for at least 3 months before study entry received the combination of both everolimus and octreotide. The response rate was 9.6% *vs.* 4.4% and the PFS was 9.7 months *vs.* 16.7 months.

Tab. 1: Current systemic treatment option for pancreatic NETs

Reference	Treatment	No of patients	Response rate	Median OS	Median PFS
Moertel et al. 1992	Streptozotocin + doxorubicin/ Streptozotocin + fluorouracil	105	69%* 45%*	2.2 years 1.4 years	20 months/ 6.9 months
Kouvaraki et al. 2004	Streptozotocin + doxorubicin + fluorouracil	84	39 %	37 months	18 months
Strosberg et al. 2011	Capecitabine/temozolomide	30	70%	–	18 months
Raymond et al. 2011	Sunitinib/placebo	171	9.3%/0%	–	11.4 months/5.5 months
Yao et al (Radiant 3) 2011	Everolimus/placebo	410	5%/2%	–	11.0 months/4.6 months
Yao et al. 2010	Everolimus/ + octreotide	160	9.6%/4.4%	24.9 months/–	9.7 months/16.7 months

*response not according to RECIST criteria.

Side effects were moderate including stomatitis, diarrhea, rash, fatigue, nausea and asthenia. These data suggest that the combination of everolimus and SST-A might be beneficial; however, this was a stratified patient cohort and not a randomised trial [13].

Conclusion

Pancreatic neuroendocrine tumours are often diagnosed at an advanced stage, but as localised surgery is the only curative treatment option so far, radical surgery should be performed whenever possible. However, it should again be emphasised that surgical resection should be performed in high volume centers with large experience in managing such patients in order to minimise perioperative complications. Resection of the primary in the presence of metastatic disease is not universally recommended (as opposed to intestinal NETs) and should be considered on an individual basis [3].

Despite increasing data from prospective randomised trials in advanced pancreatic NETs no clear treatment algorithm to favour one treatment option over the other is established which is reflected in the American and European NET-guidelines. [14, 15]. The use of SST-A in patients with symptoms is clearly recommended, however, in asymptomatic patients no benefit could be demonstrated so far. Although there is some evidence that everolimus is effective after treatment failure of streptozotocin based treatment regimens, application of streptozotocin-based regimens as first line therapy depends on the experience of the respective center with this drug.

There is common consensus that neoadjuvant or adjuvant strategies cannot be recommended in daily clinical practice, as the induction of an objective tumour response is exceedingly rare using novel agents and has not been clearly studied in this setting with conventional streptozotocin-based therapies. The recently published data with capecitabine and temozolomide require further verification in a prospective study.

It needs to be strongly emphasised that therapy is only recommended after documented progression in otherwise asymptomatic patients, because pancreatic NETs might show spontaneous stable disease for a prolonged period of time even without any treatment and due to the potential side effects of various treatment strategies.

In summary, new systemic treatment approaches have become approved in the last year, but it should be mentioned that the choice of therapy should be based on individual features (i.e. expected side effects and comorbidities).

Conflict of interest

The authors declare that there is no conflict of interest.

References

[1] Modlin IM, Oberg K, Chung DC, et al. A Gastroenteropancreatic neuroendocrine tumours. Lancet Oncol, 9(1): 61–72, 2008.

[2] Klöppel G, Rindi G, Anlauf M, Perren A, Komminoth P. Site-specific biology and pathology of gastroenteropancreatic neuroendocrine tumors. Virchows Arch, 451(Suppl. 1): S9–27, 2007. Epub 2007 Aug 8.

[3] Rindi G, Arnold R, Bosman FT, et al. Nomenclature and classification of neuroendocrine neoplasms of the digestive system. In: WHO Classification of Tumours of the Digestive System, 4th ed, Bosman TF, Carneiro F, Hruban RH, Theise ND. (Eds), International Agency for Research on cancer (IARC), Lyon 2010. p.13.

[4] Yao JC, Hassan M, Phan A, et al. One hundred years after 'carcinoid': epidemiology of and prognostic factors for neuroendocrine tumors in 35,825 cases in the United States. J Clin Oncol, 26: 3063–72, 2008.

[5] Capurso G, Bettini R, Rinzivillo M, Boninsegna L, Delle Fave G, Falconi MRole of resection of the primary pancreatic neuroendocrine tumour only in patients with unresectable metastatic liver disease: a systematic review. Neuroendocrinology, 93(4): 223–9, 2011.

[6] Thompson GB, Van Heerden JA, Grant CS, et al. Islet cell carcinomas of the pancreas: a twenty-year experience. Surgery, 104: 1011–7, 1988.

[7] Study of Lanreotide Autogel in Non-functioning Entero-pancreatic Endocrine Tumours (CLARINET), clinicalTrials.gov Identifier: NCT00353496.

[8] Moertel CG, Lefkopoulo M, Lipsitz S, et al. Streptozocin-doxorubicin, streptozocin-fluorouracil or chlorozotocin in the treatment of advanced islet- cell carcinoma. N Engl J Med, 326: 519–23, 1992.

[9] Kouvaraki MA, Ajani JA, Hoff P, et al. Fluorouracil, doxorubicin, and streptozocin in the treatment of patients with locally advanced and metastatic pancreatic endocrine carcinomas. J Clin Oncol, 22: 4762–71, 2004.

[10] Strosberg JR, Fine RL, Choi J, Nasir A, Coppola D, Chen DT, Helm J, Kvols L. First-line chemotherapy with capecitabine and temozolomide in patients with metastatic pancreatic endocrine carcinomas. Cancer, 117(2): 268–75, 2011. doi: 10.1002/cncr.25425.

[11] Raymond E, Dahan L, Raoul JL, et al. Sunitinib malate for the treatment of pancreatic neuroendocrine tumors. N Engl J Med, 364(6): 501–13, 2011.

[12] Yao JC, Shah MH, Ito T, et al. RAD001 in Advanced Neuroendocrine Tumors, Third Trial (RADIANT-3) Study Group. Everolimus for advanced pancreatic neuroendocrine tumors. N Engl J Med, 364(6): 514–23, 2011.

[13] Yao JC, Lombard-Bohas C, Baudin E, et al. Daily oral everolimus activity in patients with metastatic pancreatic neuroendocrine tumors after failure of cytotoxic chemotherapy: a phase II trial. J Clin Oncol, 28(1): 69–76, 2010.

[14] Kulke MH, Anthony LB, Bushnell DL, et al. North American Neuroendocrine Tumor Society (NANETS) NANETS treatment guidelines: well-differentiated neuroendocrine tumors of the stomach and pancreas. Pancreas, 39(6): 735–52, 2010.

[15] Falconi M, Bartsch DK, Eriksson B, et al. O'Toole D ENETS Consensus Guidelines for the Management of Patients with Digestive Neuroendocrine Neoplasms of the Digestive System. Well-Differentiated Pancreatic Non-Functioning Tumors Neuroendocrinology, 2011.

