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Treatment upon Metastatic Pancreatic Nets: Does Chemotherapy Still Play a Role in the Area of Targeting Treatment?

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Metastatic pancreatic NETs comprise a heterogeneous group of malignant tumors with various hormone production and clinical presentation. For decades patients with metastatic pNETs and functional tumors (hormone related symptoms) have been treated with somatostatin analog plus cytotoxic treatment mainly streptozotocin plus 5-fluorocil or doxorubicin [1]. The most malignant tumors, so called G3 tumors, have been treated with cisplatinum plus etoposide [2]. During the last year, two so called targeted agents have been registered for treatment of pancreatic NETs. It is the first time since early 1980s when streptozotocin was approved by FDA for treatment of pancreatic NETs that we have two new agents registered for treatment. Both sunitinib and everolimus have provided significant antitumor responses in randomized phase III trials with prolongation of PFS (Progression-free survival) of 4-6 months. No overall survival benefit has so far been demonstrated mainly because of crossover design in both trials. The cost for treatment with these two agents is significant and therefore it is time to compare these two therapies with traditional cytotoxic treatment.

Results from a phase III placebo controlled trial support the efficacy of sunitinib a multi tyrosine kinase inhibitor that target PDGF, RVGF, CKIT, RET and FLT-3 in progressive pancreatic NETs. Sunitinib was first studied in a phase II study in 107 patients including 66 patients with pancreatic NETs. The objective response rate was 16.7% in pancreatic NET and stable disease was seen in 68%. The placebo controlled phase III study of sunitinib, 37.5 mg/day in patients with progressive well-differentiated pancreatic NET (G1, G2) recruited 171 out of 340 planned patients. The primary end-point of the study, PFS, was superior in the sunitinib arm with 11.1 months compared to 5.5 months in the placebo arm. The objective remission rate was less than 10%. Adverse events were rarely grade 3/4 included hypertension, neutropenia and hand/foot syndrome [3]. Sunitinib (Sutent®) has recently been approved by the FDA and EMA for treatment of advanced and progressive well-differentiated pancreatic NETs. The use everolimus in pancreatic NETs is supported by a large phase II trial with 160 patients and a placebo controlled phase III trial with 410 patients. One subgroup of the patients received prior octreotide and continued the treatment while starting everolimus. A high rate of disease stabilization after prior tumor progression was accompanied by favourable PFS, 9.7 and 16.7 months with or without concomitant octreotide, respectively. In the placebo control trial a prolongation of PFS of 6.4 months was reached with everolimus compared to placebo (11.0 vs. 4.6 months) [4]. There was a consistent benefit among subgroups, including age, gender, region of origin, tumor grade WHO-performance status and prior use of either long-acting somatostatin analog or chemotherapy. The rate of tumor remission was however low, 5%. The most frequent grade 3-4 side effects were stomatitis, anemia, hypoglycaemia and some patients also developed pneumonitis. FDA and EMA have approved everolimus (Afinitor®) for treatment of progressive neuroendocrine tumors of pancreatic origin in patients with unresectable, locally advanced or metastatic disease. Chemotherapy is recommended in pancreatic NETs (G2, NEC, G3). So far results with systemic chemotherapy is poor in patients with well-differentiated metastatic midgut NETs (G1 tumors). Systemic cytotoxic treatment is indicated in patients with in-operable progressive pancreatic NETs using combinations of streptozotocin and 5FU or doxorubicin with objective response rate in the order of 35% to 40% [5]. There is a long standing experience with streptozotocin based chemotherapy since the 1980s. From a single retrospective trial (30 patients) temozolomide based chemotherapy is promising in pancreatic NETs combined with capecitabine. Even the high partial remission rate of 70% reported for this drug combination as first line chemotherapy together with a favour median PFS of 18 months further investigation of this chemotherapy in prospective comparative trials is warranted [6]. Efficacies reported by other trials high grade pancreatic NETs, NEC, G3 have demonstrated sensitivity to the combination of cisplatinum plus etoposide but also to a combination of capecitabine, bevacizumab plus temozolomide [7]. Encouraging results has also been reported for 5FU, capecitabine in combination with oxaliplatin or irinotecan [8]. Furthermore, Peptide Receptor Radiotherapy (PRRT) is available in Europe for patients with metastatic pancreatic NETs with objective response rates in the range of 35% to 40% [9].

In the light of above referenced results it is not quite clear how the treatment algorithm for metastatic pancreatic NETs should be constructed. In Europe chemotherapy is still first-line option (streptozotocin plus 5FU/doxorubicin) based on well-known effects well tolerated, low cost and possibility to use for long-term management of the disease some patients have been treated up to 9 years continuously with this combination. However, since sunitinib and everolimus have been registered for treatment of metastatic well-differentiated pancreatic NETs more colleagues have started to use these drugs. No comparative trial between these two drugs and chemo has so far been provided and this is warranted. The so called targeted agents are significantly more expensive and the long-term side effects are not well eluted. PRRT is still not available world-wide and can be accepted as second or third line treatment in patients not any longer responding to chemo or targeted agents. The answer to the question posed in the introduction will be: Yes, there is still a role for chemotherapy until comparative studies show a benefit of targeted agents.

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