Response by Choi criteria to sunitinib plus octreotide LAR in a functional heavily pretreated advanced pancreatic neuroendocrine tumor

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Pancreatic neuroendocrine tumors (PNETs) are rare malignancies that arise from the islets of Langerhans. The role of standard chemotherapy in advanced well-differentiated PNETs remains to be defined. Sunitinib is an oral multitargeted inhibitor with antiangiogenic and antitumor properties that has shown significant improvement in survival in metastatic PNETs, although objective responses by Response Evaluation Criteria in Solid Tumors were only 9%. We herein report on the case of a middle-aged woman with metastatic PNET who was heavily pretreated for her advanced disease with limited success, and who showed clinical, biochemical, and radiological responses by using Choi criteria but not Response Evaluation Criteria in Solid Tumors criteria. To our knowledge, this is the first reported case of treatment with sunitinib in a patient with PNET in response to Choi criteria. *Anti-Cancer Drugs* **22:477–479 © 2011 Wolters Kluwer Health | Lippincott Williams & Wilkins.**

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Introduction

Pancreatic neuroendocrine tumors (PNETs) are rare malignancies that arise from the pancreatic islet cells. After surgery of the primary tumor, there is no clear standard of care, and cytotoxic regimens remain the most frequent approach for the advanced disease [1]. Sunitinib is an oral multitargeted inhibitor of several tyrosine kinase receptors involved in both angiogenesis and tumor proliferation [2]. Recently, sunitinib has been shown to improve both progression-free and overall survival versus placebo in a randomized phase III study conducted in well-differentiated and pretreated PNETs. Despite classical objective response rate by Response Evaluation Criteria in Solid Tumors (RECIST) being low (9.3%; eight of 86 patients), the overall clinical benefit of the patients treated with sunitinib was 72.1% and median progression-free survival was 11.1 months [3].

RECIST criteria remain the standardized method to evaluate tumor response when chemotherapy is used. In this sense, 30% of decrease in the sum of the longest diameter of target lesions is needed to achieve a partial response [4]. In addition, Choi response criteria take into account not only the size but also the density of the target lesions. Accordingly, a response by Choi criteria can be met if there is a 10% decrease in tumor size and a 15% decrease in tumor density on contrast-enhanced computed tomographic (CT) scan [5].

In this study, we report the clinical case of a middle-aged woman with metastatic PNET who was heavily pretreated in subsequent lines for her advanced disease with limited activity, and who responded to treatment with sunitinib and octreotide long-acting release (LAR) clinically, biochemically, and radiologically following the Choi response criteria.

Case report

A 55-year-old woman was admitted to our institution for further investigation of diarrhea (consisting of three to five episodes per day) upper and right abdominal pain, and dizziness in August 2002. No relevant medical history was reported. Laboratory tests showed elevation of liver enzymes with alkaline phosphatase of 319 IU/l (normal range: 40–120 IU/l) with no alteration in tumor markers (α-fetoprotein, carcinoembryonic antigen, and Ca 19-9) or hepatitis serology. Ultrasound and CT scan of the abdomen showed enlargement of the tail of the pancreas and multiple hypervascular liver masses distributed in both lobes, suggesting metastasis. An octreotide scan was taken showing tracer uptake at the same locations that were observed on CT scan earlier. In September 2002, the patient underwent resection of the tail of the pancreas, and biopsy of several hepatic lesions was conducted. The pathology analysis resulted in a positive-to-low proliferative (Ki-67 $< 10\%$) endocrine carcinoma of the pancreatic tail with multiple hepatic metastasis.

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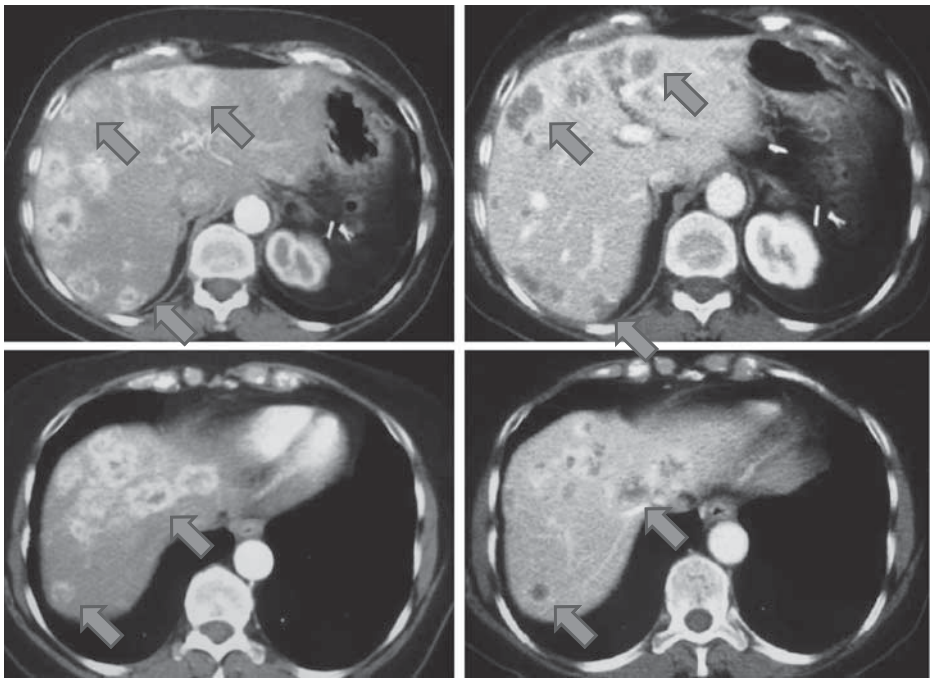
After surgery, the patient's symptoms improved and because of the low proliferation index shown no treatment was provided at this time. In July 2003, the patient again suffered from diarrhea and progression of the hepatic masses was confirmed on CT scan. Treatment with cisplatin (100 mg/m^2 on day 1) and etoposide (100 mg/m^2 on days 1–3) every 21 days was started. After three cycles, the patient experienced grade 3 fatigue and vomiting and radiological progression on CT scan was shown. In September 2003, the patient started a second-line treatment with doxorubicin (60 mg/m^2 on day 1) every 21 days. After six cycles, the patient achieved stable disease as the best response to chemotherapy. The tolerance was acceptable with vomiting and grade 2 asthenia. Symptomatic progression was detected in January 2004 and a new treatment with octreotide (50 μg/day subcutaneously) and interferon-α (5 MU three times/week subcutaneously) was proposed. Treatment had to be stopped due to flu-like syndrome, fatigue, and grade 3 vomiting after just 1 month from the start. The best supportive care to palliate pain and diarrhea was then provided until May 2008 when the patient was enrolled in a clinical trial receiving lanreotide in a long-acting formulation (120 mg intramuscularly/month). Symptomatic response was achieved but no radiologic impact was observed. In December 2008, hepatic progression was detected and the best supportive care was offered. The patient was gradually worsening because of her symptoms until October 2009. The CT scan continued to show progression of the hepatic disease. At this time, a compassionate use of sunitinib (37.5 mg daily) plus octreotide LAR (30 mg intramuscularly per month) was proposed based on recently reported randomized data. The patient accepted and signed the inform consent. After 3 months of treatment, although no response was achieved by the RECIST criteria, there was a clear decrease in the tumor density of the lesions in the CT scan (Fig. 1). Radiological improvement was also accompanied by complete symptomatic response of the diarrhea and asthenia. Moreover, chromogranin A levels decreased from 4.345 ng/ml at the beginning of the treatment with sunitinib to 410 ng/ml (normal chromogranin levels up to 18 ng/ml) after 4 months of treatment. Sunitinib was reasonably well tolerated and only 1 week of rest has been necessary up to now due to grade 2 thrombocytopenia and grade 2 fatigue The patient continued to receive

Fig. 1



Before starting sunitinib After 3 months of sunitinib

Sunitinib and octreotide LAR-induced hypodensity in a 55-year-old woman with metastatic pancreatic neuroendocrine tumors experiencing tumor stabilization according to Response Evaluation Criteria in Solid Tumors criteria. On the left side, the baseline computed tomography scan before starting sunitinib treatment in October 2009 is shown. On the right side, the computed tomography scan after 3 months of sunitinib treatment is shown. Although some of the multiple lesions experienced shrinkage from the initial size, the largest diameters of the main hepatic tumor lesions were similar to that of earlier therapy, yielding tumor stabilization as best response according to Response Evaluation Criteria in Solid Tumors criteria. However, these lesions also show early and important changes in tumor density, suggesting tumor necrosis to be considered as a response by Choi criteria.

treatment with the combination of sunitinib plus octreotide LAR with no dose reduction needed up to September 2010 (11 months after the start).

Conclusion

At present, cytotoxic compounds are preferred as the standard first-line treatment for poorly differentiated or rapidly progressing PNETs. However, the role of standard chemotherapy in advanced well-differentiated PNETs remains to be defined. There is increasing evidence showing that PNETs are more sensitive than carcinoids to standard chemotherapy. Chemotherapy schemes are commonly reserved for those patients with tumor bulk or uncontrolled hormonal production [6].

Treatment with sunitinib has shown a statistical improvement in both progression-free and overall survival in advanced PNETs [3]. Sunitinib has recently been approved by the European Medicines Agency for patients with advanced PNETs. The synergistic effect of the combination of sunitinib and octreotide LAR has not yet been proved prospectively.

It is largely known that multitargeted tyrosine kinases inhibitors such as sunitinib or sorafenib can induce extensive necrosis in metastatic renal cell cancer that correlates with significant clinical benefit although no radiological response by classical RECIST criteria may be found [7–9].

To our knowledge, this is the first reported patient with PNET with clinical, biochemical, and radiological response by Choi criteria to treatment with sunitinib and octreotide LAR in combination.

Radiological responses may be considered to be a suboptimal end point for the evaluation of activity of newly targeted agents in PNETs. Choi response criteria could be helpful to select those patients that may benefit from newly targeted agents, as in the case reported here. We suggest that Choi Response criteria should be evaluated in a prospective way as early predictors of clinical benefit to molecularly driven drugs.

Acknowledgement

The authors declare no relevant conflicts of interest for this manuscript.

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