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ORIGINAL ARTICLE

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Extended cycle streptozotocin/5-FU chemotherapy for maintenance therapy in pancreatic neuroendocrine tumors

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Abstract

Purpose The standard of care treatment for patients with advanced pancreatic neuroendocrine tumors (pNET) is a combination of streptozotocin and 5-FU. Although widely used, little is known about the best long-term strategy with these substances.

Methods We here report our experience of 28 patients treated with streptozotocin/5-FU for advanced pNET with special consideration for long-term management using an extended cycle protocol.

Results Standard 6-weekly Moertel protocol resulted in a median progression-free survival of 21 months (range 3–128) and a median overall survival of 69 months (range 3–157+) in the whole cohort. Thirteen of the 28 patients were switched to an extended 3-month cycle protocol for maintenance therapy. Of these 13 patients, 2 achieved complete remission, 1 partial remission, and 8 stable disease as best response while 2 showed progressive disease following switch to the extended protocol, resulting in an additional median progression-free survival of 23 months. Median overall survival after the start of chemotherapy in this patient group was 69 months (21–157+). Patients benefitted from extended periods free of chemotherapy-associated side effects after switching to the extended cycle protocol.

Conclusions Switching to an extended cycle protocol of 3 months for maintenance therapy following initial standard cycles may achieve long-term disease stabilization in selected patients with advanced pNET with good patient acceptance.

Keywords Neuroendocrine tumor · Chemotherapy · Streptozotocin · 5-FU

Introduction

Treatment of patients with neuroendocrine tumors (NET) is difficult due to generally low response rates to classical chemotherapy. One exception is streptozotocin (STZ)-based therapy for pancreatic NET (pNET) [1]. Despite more recently developed targeted therapies (i.e., everolimus and sunitinib) treatment with STZ in combination with 5-fluorouracil (5-FU) or doxorubicin is still the treatment of choice according to current guidelines of the European Neuroendocrine Tumor Society (ENETS) [2]. STZ has been used in the treatment for NET since four decades. The first randomized studies in NET treatment by Moertel et al. established STZ as an effective treatment for pancreatic but not for small bowel NET [1, 3, 4]. Since then, various groups reported divergent results on efficacy and side effects of STZ in retrospective studies [5–7] with remission rates of 28–43% and disease control rates (DCR) of up to 90% in the short term. However, little is known about the long-term management of patients under STZ-based chemotherapy. The NET group from Uppsala, Sweden, has reported some selected patients receiving chemotherapy for more than 60 months [7], but until now, no specific stopping rules have been formulated once tumor stabilization has been achieved. Although therapy is generally well

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tolerated, a continuous 6-week chemotherapy regimen—each cycle with 5 consecutive days of chemotherapy—may impair quality of life in affected patients. Since current guidelines are indistinct on treatment duration, many apply 6 cycles of chemotherapy and re-start treatment if tumor progression occurs.

We here report our experience of 28 patients treated with STZ/5-FU for advanced pNET focusing on treatment duration and disease stabilization. Special attention was paid to a subgroup of 13 patients undergoing long-term treatment with cycle lengths of 3 months for prolonged disease control of pNET.

Patients and methods

We retrospectively collected data of all 32 patients treated with STZ/5-FU for advanced pNET at our institution between 2002 and 2018. Thirty patients received at least 3 cycles of chemotherapy with STZ/5-FU, while 2 patients were excluded from analysis because of discontinuation after the first cycle due to side effects (1 patient) or personal request (1 patient). Chemotherapy was given following the original Moertel protocol for 5 consecutive days every 6 weeks [1]. Supportive therapy consisted of volume expansion by infusion of G5% (500 ml) and NaCl solution (500 ml) and anti-emetic therapy with 8 mg dexamethasone and 3 mg granisetron prior to administration of STZ/5-FU bolus followed by another 500 ml infusion of Ringer's lactate solution. Restaging was performed after 3 cycles by computed tomography (CT) or magnetic resonance imaging (MRI) and every 3 cycles (every 4 months) thereafter. Response assessment was performed according to RECIST 1.1 criteria [8]. In 4 out of 30 patients no continuous radiological documentation was available at our site due to external radiological staging; in 2 of these patients, response assessment was based on conclusive written radiology reports while the remaining two patients without conclusive follow-up reports were excluded from analysis. Patients with stable disease for more than 6 (after 2010) or 12 (before 2010) cycles of chemotherapy were offered an extended cycle protocol with 3 months cycle length for maintenance therapy. These patients were staged every 2 cycles (every 6 months). A flow chart of treatment groups and patient outcome is shown in Fig. 1.

The local ethics committee approved collection and analysis of data (Ärztekammer Hamburg, WF-023/13). Data collection and analysis was performed following the STROBE guidelines for retrospective observational studies [9].

Kaplan–Meier survival curves were employed to evaluate progression-free survival (PFS) and overall survival (OS) using Graphpad Prism5.

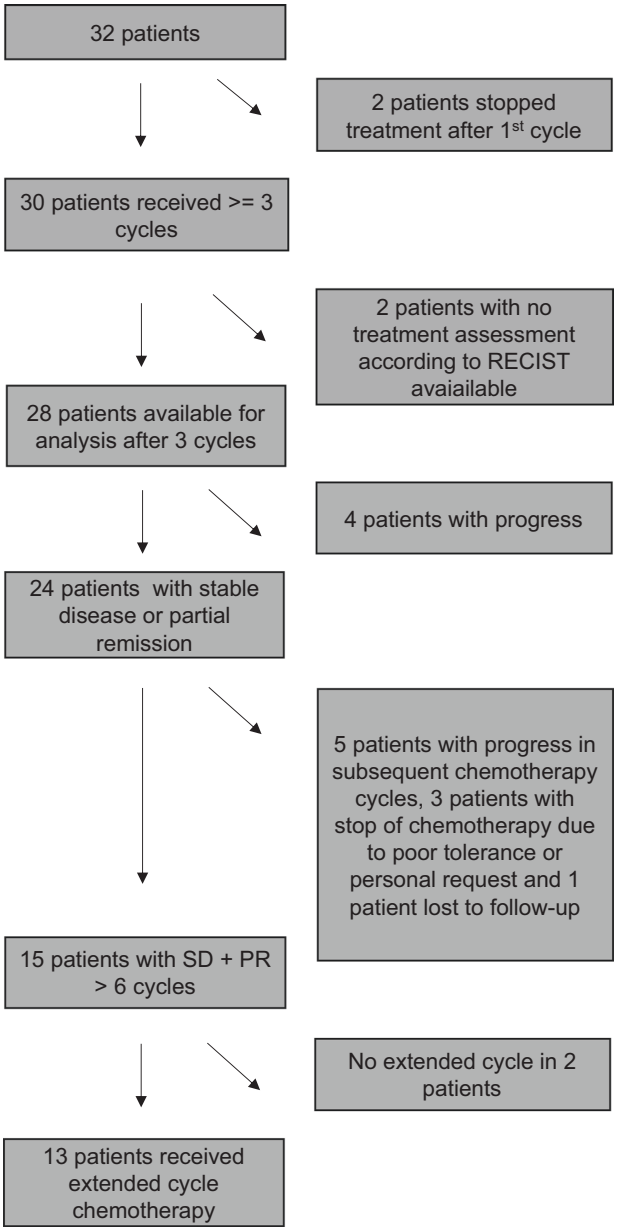

Fig. 1 Patient flow chart. Flow chart showing treatment and outcome of patient groups

Results

Patient characteristics

Demographic characteristics of our patient population are shown in Table 1. Except for two patients, all presented with liver metastasis. 15 patients had additional lymph node metastasis and 3 had bone metastasis. 6 patients received prior somatostatin analogues. Surgical resection of the primary tumors and concurrent liver metastasis prior to the start of chemotherapy was performed in 15 and 7 patients, respectively. Of the 15 patients with surgical resection 4

Table 1 Patient characteristics

Age (median)	63 (28–78)
Sex	16 m, 12 f
Ki67 index (median)*	5% (1–30%)
Tumor grading*	5× G1, 19× G2, 1× G3
SMS scintigraphy pos.	23/28 (82%)
Prior use of somatostatin analogues	6/28 (21%)
Functional NET	5/28 (18%)
MEN-1 associated	1/28 (4%)
Resection of primary tumor	15/28 (54%)
Resection of liver metastases	7/28 (25%)
No prior tumor directed treatment	11/28 (39%)
Synchronous liver metastases	22/28 (79%)
Metachronous liver metastases	4/28 (14%)
Time to development of metachronous metastases	45.5 months

*Available for 25 out of 28 patients

received somatostatin analogues prior to start of chemotherapy, thus 11 patients of the cohort were treatment-naive when chemotherapy was started. Functionally active tumors were present in 5 out of 28 patients; these included 2 gastrinomas, 2 insulinomas, and 1 carcinoid syndrome. The two gastrinoma patients were symptomatically well controlled by PPI treatment. The two insulinoma patients were without clinical hypoglycemia after resection of the primary in one and resection of the primary and debulking of liver metastases in the other. The carcinoid syndrome patient had only minor symptoms, which were unaffected by chemotherapy. One patient had MEN-1 syndrome presenting with metastasized functionally active gastrinoma. Other tumor manifestations in this patient included a prolactinoma (concurrently treated with carbergolin) and a thymus carcinoid, which had been successfully resected two years prior to start of chemotherapy. The diagnosis of a metastasized gastrinoma from the pancreas has been verified by biopsies of the liver lesion and pancreatic primary tumor.

Occurrence of liver metastasis was synchronous in 22/28 and metachronous in 4/28 patients. In the latter, median time from initial resection of the primary to the occurrence of liver metastasis was 45.5 months. Ki-67 staining was available for 25 patients and showed a median index of 5% (range 1–30%). Median follow-up was 40 months (range 6–157 months). Two patients are still on active treatment at the time of manuscript submission. Patients received a median of 9 STZ/5-FU chemotherapy cycles (range 3–36).

Patient outcome

Initial staging after the first 3 cycles of STZ/5-FU showed partial remission (PR) in 7, stable disease (SD) in 17, and progressive disease (PD) in 4 patients. This corresponded to a disease control rate of 86% at this time point. The individual overall best responses in all patients were 2× complete remission (CR), 8× PR, 14× SD, and 4× PD. This corresponds to a response rate (CR + PR) of 36% in the whole cohort. In three patients PR became apparent after more than 6 cycles of chemotherapy following an initial response classified as SD. In the 13 patients without resection of the primary tumor, PR of the latter was observed only in two, while the other 11 patients achieved only SD ($n = 10$) or PD ($n = 1$) as best response of the primary tumor.

Of the 5 patients with functionally active tumors at diagnosis 1 achieved CR (insulinoma), 2 PR (1 insulinoma, 1 gastrinoma), and 2 SD (1 gastrinoma, 1 carcinoid syndrome) as best response under chemotherapy.

Median PFS was 21 months (range 3–128 months). Disease control rates at 1, 2, and 5 years were 64.3%, 39.3%, and 14.3%, respectively. Median OS at manuscript submission was 69 months (range 3+ –157+ , with both of these patients still alive) (Fig. 2). Subgroup analysis revealed a significantly better chemotherapy response in patients with prior resection of the primary tumor (23 vs. 17 months PFS, $p = 0.036$) and a trend towards better response in patients with Ki-67 index ≤ 10% (32 vs. 16 months, $p = 0.070$). There was no significant difference for progression-free survival in patients with age < 65 years vs. > 65 years or positive vs. negative octreoscan, respectively (Fig. 3).

Outcome in patients with extended cycle length

In 13 out of 28 patients, STZ/5-FU cycle length was extended to 3 months when disease control was established for a prolonged period under chemotherapy as assessed by CT or MRI scan. All patients having stable disease or partial remission following at least 6 cycles (time period from 2010 onwards) or 12 cycles (time period before 2010) were offered an extended cycle length of 3 months for maintenance therapy. Alternatively, patients were offered a continuous 6-week cycle protocol or a chemotherapy pause with close follow-up and the option to re-start chemotherapy once progress becomes apparent. 13 out of 15 patients offered these options decided to commence with the 3-month extended cycle protocol and two patients opted for chemotherapy pause. Of these 13 patients, 6 had PR and 7 had SD as best response before they switched to the extended cycle protocol. The median number of cycles before extension was 7 (range 6–27). After extension to 3-month cycles, median PFS was 23 months (range 7–114), corresponding to a median PFS after the initial start of chemotherapy of 44 months (17–128) (Fig. 4). Median OS after the start of chemotherapy in this patient group was

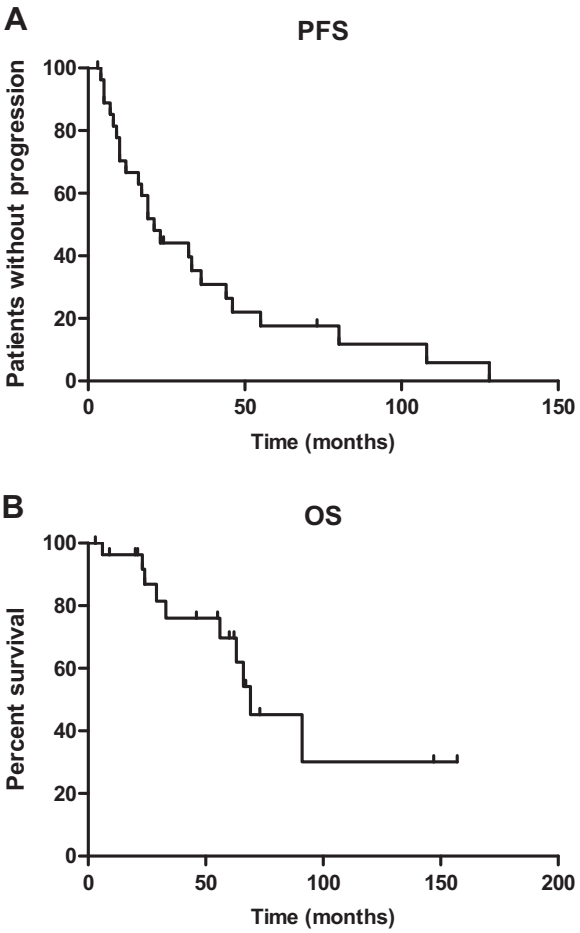

Fig. 2 Overall patient outcome. Kaplan–Meier survival curves for progression-free survival (PFS) (**a**) and overall survival (OS) (**b**) in all patients treated with STZ/5-FU

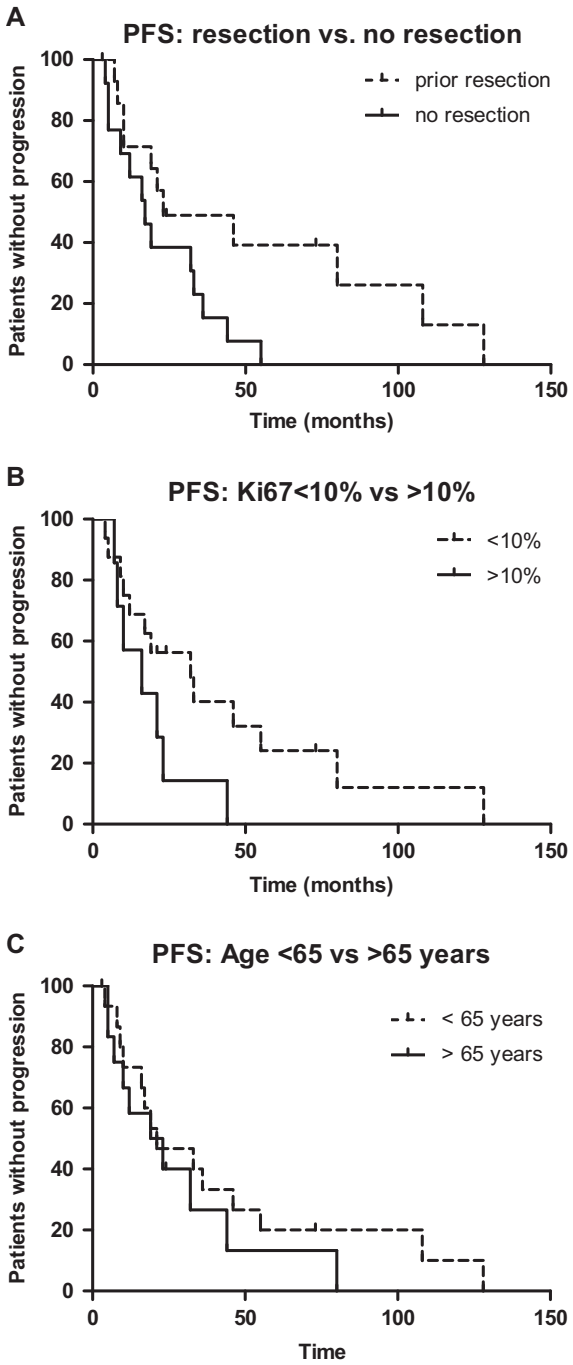

Fig. 3 Subgroup analysis of patient outcome. Kaplan–Meier survival curves for progression-free survival (PFS) depending on resection or no resection of the primary tumor (**a**), low (≤10%) or high (>10%) Ki-67 index (**b**) and age ≤65 years or >65 years (**c**)

69 months (21–157+) with five patients still being alive at the date of manuscript submission. This is in contrast to the median OS of 46 months in the 15 patients who were not switched to the extended cycle protocol. Three of the 5 patients with functionally active tumors (2 insulinoma, 1 gastrinoma) were in the extended cycle group. Of these, 1 insulinoma patient achieved a prolonged CR (46 months), 1 insulinoma patient achieved a prolonged PR (24 months, still ongoing) and the MEN-1 patient with functional active gastrinoma achieved a prolonged SD (44 months).

The best response after start of the extended 3-month cycle length was CR in 2, PR in 1, SD in 8 and PD in 2 out of 13 patients. CR continued for 7 years in one patient (still alive, OS 157+ months after the start of treatment) and for 46 months in another patient (still alive, OS 60+ months after the start of treatment). Of the 9 patients with PR or SD median PFS was 23 months and median OS was 56 months after switching to extended cycle protocol. Prior resection of the primary tumor compared to non-resection (80 vs. 36 months, $p = 0.10$) as well as PR as best response to the 6-week cycle regimen compared to SD (94 vs. 33 months, $p = 0.005$) was associated with longer PFS (Fig. 4). Although quality of life (QoL) was not measured systematically by validated oncologic QoL surveys, patients reported improved subjective well-being after switching to

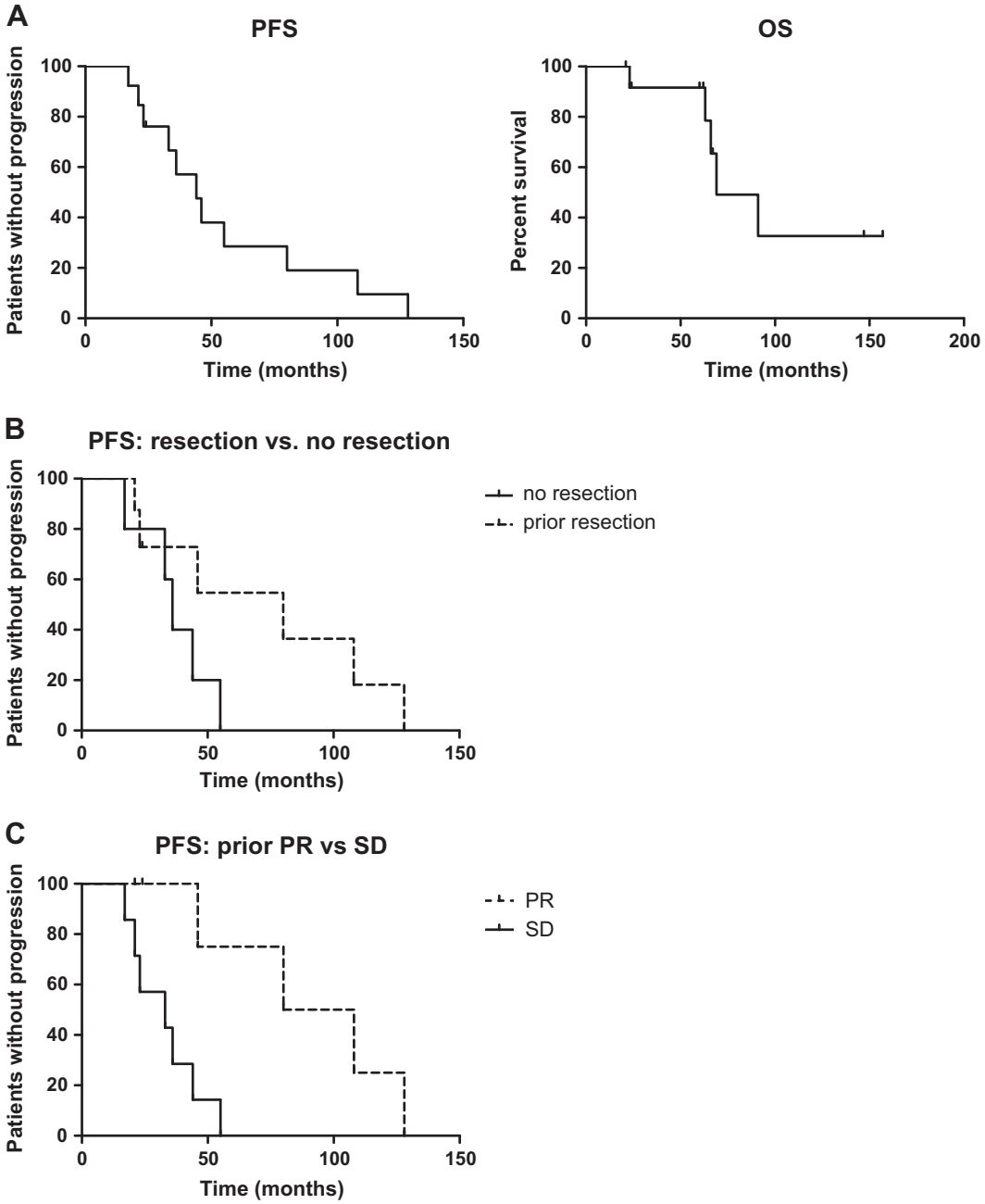

Fig. 4 Patient outcome in the extended cycle cohort. Kaplan–Meier survival curves for PFS and OS in patients treated with extended cycle STZ/5-FU (**a**). Subgroup analysis of patients treated with extended cycle length STZ/5-FU with regard to resection or no resection of the primary tumor (**b**) and partial remission or stable disease as best response towards the initial 6-week cycle protocol (**c**)

the extended cycle protocol. This may have been due to a reduction of hospital days and longer periods without chemotherapy-associated side effects.

Treatment safety

Chemotherapy with STZ/5-FU was well tolerated with no grade 3 or 4 toxicities. The majority of patients reported fatigue, appetite loss, and mild to moderate nausea for a 5–10 day period following chemotherapy. Dose reduction was necessary in 4 patients (2× leukopenia, 2× prolonged fatigue) without loss of efficacy. A mild increase of serum creatinine was observed in 3 out of 28 patients with a median increase of 31% of baseline values. One patient developed overt diabetes mellitus after the first two cycles of treatment, but this was type 2 diabetes with clinical signs of insulin resistance rather than STZ-associated insulin-deprived diabetes.

Discussion

Based on recent placebo-controlled trials for hormonal or targeted therapies in patients with pNET, PFS, and long-term disease control rather than (partial) remission have come into focus as primary treatment goals. Presumably, this is owed to the fact that only few patients achieved minor or even partial remission upon treatment with lanreotid, everolimus or sunitinib [10–12]. In contrast, STZ-based chemotherapy offers a chance for partial or complete remission with comparable toxicity to molecular targeted therapies and is therefore recommended by current ENETS guidelines [13]. However, efficacy data are still sparse and no stop-rules exist. We performed our retrospective analysis since no data exist on what to do once diseased stabilization is achieved after using STZ/5-FU beyond the initial 6-week Moertel protocol.

In our cohort of 28 pNET patients, chemotherapy with STZ/5-FU was well tolerated and resulted in disease stabilization in the majority of patients. We observed a response rate of 36%, which is in line with three other retrospective studies (response rate 28–43%) from Berlin, Marburg and Uppsala [5–7]. We observed a significant increase of PFS in patients with prior resection of the primary tumor and still a trend for prior resection of the primary tumor as a positive predictive factor for PFS in the extended cycle cohort. This positive trend was also present in the subgroup of patients presenting with synchronous metastatic disease. Our observation is in line with results from Marburg and Uppsala NET study groups showing a favorable disease course in pNET patients with resected primary tumor [5, 7]. Other retrospective reports also suggested beneficial effects by resection of the primary tumor even in the presence of unresectable metastatic disease independent of further treatment [14, 15]. Interestingly, in our patients, the primary pancreatic tumor showed only a PR in 2 out of 13 patients under STZ/5-FU treatment but slow continuous progression in the remaining patients. It may be speculated that local factors, i.e., tumor heterogeneity, tumor microenvironment, and others, contribute to the divergent response of the primary tumor and corresponding metastases. Based on the depicted and our own results, we recommended resection of the primary tumor to pNET patients with unresectable liver metastases if organ-preserving pancreatic resection is surgically feasible.

Reliable biomarkers to predict chemotherapy response prior to treatment are still lacking. Although the prognostic roles of Ki-67 labeling index for overall survival in pNET patients is well established, its usefulness as a marker to predict treatment response is still under debate. In line with other reports [16, 17], we observed a trend towards a longer PFS in patients with a low Ki-67 index (<10%), but no difference in remission rates. Our own experience with good response in patients with low Ki-67 index and in functionally active insulinoma patients together with the reported data from Marburg [5] suggest, that a high neuroendocrine differentiation (i.e., functional activity, low Ki-67 index, high SSTR expression) might be linked to a more favorable response to STZ/5-FU. The reason for this observation is unclear, but may be associated with different intracellular mechanisms of chemotherapy metabolism in well-differentiated vs. less differentiated pNET. A current phase III clinical trial (SEQTOR) evaluating STZ/5-FU vs. everolimus treatment in pNET patients will likely illuminate these associations and help to identify biomarkers for future response prediction.

Since it is not known when to stop treatment once tumor stabilization has been achieved our most interesting results concern disease courses of pNET patients after switching to an extended 3-months cycle length for maintenance therapy aiming at long-term tumor control. We are convinced that—although therapy is generally well tolerated—a continuous 6-week chemotherapy regimen impairs quality of life in the long-term. Indeed our patients switched to the extended cycle protocol reported a better tolerance of chemotherapy compared to prior 6-week cycles and prolonged periods of normal life unaffected by therapy (e.g., no active treatment and free of chemotherapy side effects for more than 10 weeks). As current guidelines are indistinct on treatment duration, various tertiary care centers currently apply 6–9 cycles of STZ/5-FU chemotherapy and re-start treatment if progress occurs, as reported by the NET study groups of Marburg and Berlin. To our knowledge, only the group from Uppsala has reported an extended cycle protocol in some patients in their analysis of 112 pNETs, but they did not depict a detailed subgroup analysis of patient outcome after treatment extension [7]. Our patients were offered either a watch-and-wait strategy after the first 6–12 cycles—including alternative treatment strategies once recurrence would occur—or STZ/5-FU treatment extension, and acceptance of the latter was great (13 out of 15 patients). The extended cycle protocol led to long-term disease stabilization for a median of an additional 21 months after the switch. This is much longer, than the reported benefit from randomized trials for targeted therapies of 11.0 months with everolimus and 11.4 months with sunitinib [10, 11]. However, our good results were achieved in a selected patient group, i.e., with initial tumor response and prior resection of the primary tumor. The next challenge will be early identification of those patients, likely to benefit from the extended cycle protocol. One could consider a prospective clinical trial in the patient group receiving STZ/5-FU with one arm receiving treatment extension and another arm with treatment stop and re-start once progression occurs. In addition, the extended cycle protocol was well tolerated since no patient had to stop treatment because of adverse effects. This

may impose an advantage over targeted therapy where dropout rates under real-life conditions were as high as 20% due to side effects of everolimus or sunitinib [18].

Since extended cycle duration (e.g., four treatments per year) can achieve long-term tumor stabilization in selected patients with good patient acceptance, this treatment regime might offer an alternative to molecular targeted therapies in the long-term management of pNET patients including the chance for partial remission.

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Compliance with ethical standards

Conflict of interest J.S. and D.B. received travel assistance, speaker honoraria, and research funding from Novartis and IPSEN. The remaining authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The local ethics committee approved retrospective collection and analysis of patient data without written informed consent from patients (Ärztekammer Hamburg, WF-023/13). A written informed consent of patients was not deemed necessary due to anonymous data analysis performed in accordance with local governmental guidelines. This article does not contain any studies with animals performed by any of the authors.

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