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Original Research

Streptozocin/5-fluorouracil chemotherapy is associated with durable response in patients with advanced pancreatic neuroendocrine tumours

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Abstract ***Background:*** The role of systemic chemotherapy for pancreatic neuroendocrine tumours (pNET) is controversially discussed. Objective response rates (RR) reported for streptozocin (STZ)-based chemotherapy are variable and novel targeted drugs have recently been approved. However, the sequence of treatment remains unclear. We aimed to evaluate the efficacy of STZ plus 5-fluorouracil (STZ/5-FU) in a large pNET cohort.
Methods: Data from 96 pNET patients treated with STZ/5-FU were analysed retrospectively. Endpoints of the study were RR, time to tumour progression (TTP) and overall survival (OS).
Results: Mean age of patients at the start of chemotherapy was 57.6 years (range, 32.1–80.4). STZ/5-FU was the 1st line treatment in 56.3%. 11.5% had G1, 79.2% G2 and 6.3% G3 neoplasms. Baseline progression was evident in 74%. Objective response rate was 42.7%. 40.6% of patients showed stable disease as best response while 16.7% showed progressive disease. Treatment was discontinued due to toxicity in 16 patients. Median TTP and OS were 19.4 (95% confidence interval (CI), 13.6–25.2) and 54.8 months (95% CI, 34.7–74.9), respectively.

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In Cox regression analysis, Ki67 > 15% was the only negative prognostic factor for TTP (hazard ratio (HR), 3.3; $P < 0.001$), confirmed by multivariate analysis (HR, 6.7; $P = 0.001$).
Conclusions: STZ/5-FU was associated with considerable RR. Treatment was associated with durable TTP especially in patients with Ki67-index of ⩽15%. These findings along with good tolerability strengthen the value of this two-drug chemotherapy for the management of unresectable pNET.

1. Introduction

Pancreatic neuroendocrine tumours (pNET) are rare neoplasms originating from neuroendocrine cells and constitute less than 3% of all pancreatic malignancies [1]. Recent reports estimate an annual incidence from 0.32 to 0.43 per 100,000, increasing since the 1970s [2,3]. There is a high heterogeneity including functionality, tumour growth and histological features of pNET, which represents a therapeutic challenge [4,5]. Due to the indolent clinical course, the majority of patients with pNET are diagnosed at an advanced stage with distant metastases, ranging from 60% to 86% at initial diagnosis [3,6–8]. Therefore, curative surgical resection as mainstay can only be achieved in a few cases, and palliative medical treatments are required. Based on two large placebo-controlled phase-III-studies, the new molecular targeted drugs everolimus (mTOR inhibitor) and sunitinib (multiple tyrosine kinase inhibitor) have recently been approved for the therapy of pNET [9,10]. In contrast, there is long standing experience with the use of streptozocin (STZ)-based chemotherapy in pNET since the 1980s, and STZ-based regimens are considered a standard therapy in advanced pNET according to European guidelines [11,12]. Initial studies with prospective design by Moertel et al. reported objective response rates (RR) ranging from 45% to 69% for STZ-based chemotherapy in pNET [13–15]. These results have been criticised as overly optimistic due to reliance on in part non-radiographic criteria and following studies investigating STZ-based chemotherapy reported RR varying between 6% and 53% [7,13,16–21]. Further, it remains unclear if a three-drug regimen is superior to a two-drug regimen in pNET. In the absence of any comparative trial of targeted drugs versus systemic chemotherapy, there is no clear recommendation for therapy sequencing in pNET. Systemic chemotherapy still seems an attractive approach for potential high RR.

Our aim was to assess the efficacy of the two-drug-regimen with STZ/5-FU administered according to the standard protocol used in the largest pNET-study-cohort reported up to date [15].

2. Patients and methods

2.1. Patients

Approval for data collection and analysis was obtained upon admission to our institution. Ninety-six consecutively treated patients (58 male, 38 female) with locally advanced or metastatic pNET who received chemotherapy with STZ/5-FU between August 1998 and January 2014 were included in the study. Patients who had received prior treatments were also included. 30 patients received prior somatostatin analogue therapy mainly for functionality ($n = 13$) or because of low liver tumour burden <10% ($n = 10$) and/or low grade tumour ($n = 9$ with Ki67-index <5%). To be eligible, patients had to have histopathologically verified pNET including positive immunohistochemistry for chromogranin A (CgA) and/or synaptophysin. Information on grading as measured by Ki67 staining was available in 93 patients [22]. Demographic and clinical data were retrieved from medical records including radiological and pathological reports. In 93 patients, original imaging was available. In general, circulating CgA levels were measured at the beginning of STZ/5-FU chemotherapy and every 3 months while chemotherapy was ongoing and were available in a subset of 67 patients (Table 1). CgA measurement was performed using a radioimmunoassay (RIA) (CisBio, France) with values in the normal range from 19 to 150 μg/L. In three patients, CgA was measured at an external laboratory. Biochemical response was defined as >30% decrease of baseline CgA levels and indicated as best response (lowest CgA level) achieved during chemotherapy.

2.2. Chemotherapy

The median time from diagnosis to onset of chemotherapy was 11.3 months (range, 0.3–212.6). The standard regimen consisted of STZ (500 mg/m^2), in combination with 5-FU (400 mg/m^2) and was administered intravenously once daily on days 1–5. Most patients received chemotherapy cycles every 6 weeks ($n = 87$). Five patients received cycles every 5 weeks.

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