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Research Article

Renal function in patients receiving streptozocin for locally advanced or metastatic digestive neuroendocrine tumours: results of the Streptotox-FFCD0906 study

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RUNNING TITLE: Streptotox study

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Statement of Ethics

Published research must comply with the guidelines for human studies and should include evidence that the research was conducted ethically in accordance with the World Medical Association Declaration of Helsinki. In the manuscript, authors should state that subjects (or their parents or guardians) have given their written informed consent and that the study protocol was approved by the institute's committee on human research.

Declaration of interests

☐ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☒The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

C/**A** (Consulting/advisory relationship), **RF** (Research Funding), **E**(Employment), **ET** (Expert Testimony), **H** (Honoraria), **OI** (Ownership Interests), **IP** (Intellectual Property Rights/inventor/patent holder), **SAB** (Scientific Advisory Board), **Other**

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Abstract

Introduction. Streptozocin can impair renal function. The purpose of this study was to evaluate the evolution of renal function in patients receiving this anti-mitotic for the treatment of locally advanced/metastatic digestive well differentiated neuroendocrine tumours. **Methods.** A prospective and a retrospective cohort of patients with normal

baseline renal function were analysed. The primary endpoint was the incidence of a decrease in the estimated glomerular filtration rate ≥ 25% during treatment. Secondary endpoints were the evaluation of glomerular filtration rate changes, the impact of combined nephrotoxic treatments, other toxicities, compliance, and the objective response rate. **Results.** After screening 142 patients, 27 were included in the prospective and 84 in the retrospective cohort. A decrease in estimated glomerular filtration rate ≥ 25% was observed in 32 patients (30%): respectively four (15.4%) and 28 patients (34.1%) among respectively 26 and 82 patients with numerous measures ($P = 0.0097$). Altogether, 39 patients (35%) experienced grade 1-2 renal toxicity, while no grade 3-4 occurred in the prospective and 1 occurred in the retrospective cohort. Renal toxicity was more frequent in the retrospective cohort with a less careful follow up. As best responses, objective response was achieved in 27% of patients with pancreatic primary tumours, disease control in 78.9% of patients with pancreatic primary tumours, in 87% of those with small bowel tumours and in 72.7% of patients with other primary locations. **Conclusions.** Strongly recommended for pancreatic NET, streptozocin is associated with frequent mild renal toxicity but low occurrence of renal impairment in patients with baseline normal renal function and under adequate hydration.

Keywords: digestive neuroendocrine tumours, renal function, streptozocin

Abreviations:

NETs: neuroendocrine tumours; pNETs: duodeno-pancreatic neuroendocrine tumours; STZ: streptozocin or streptozotocin; eGFR: estimated glomerular filtration rate; PC: prospective cohort; RC: retrospective cohort; MDRD: Modification of Diet in Renal Disease; OR: objective response; sbNETs: small bowel NETs.

Introduction

Digestive neuroendocrine tumours (NETs) account for less than 1.5% of digestive tumours in most Western countries [1]. However, in recent decades, there has been a trend towards an increasing incidence of digestive NETs [2]. Survival rates depend mainly on tumour differentiation, most NETs being well-differentiated. For metastatic disease, 5-year survival rates are around 50% for well-differentiated NETs [1]. The treatment of well-differentiated digestive NETs depends on the stage of the disease, differentiation, spread and site.

Systemic chemotherapy is recommended by ENETS [3] for the unresectable, well-differentiated duodeno-pancreatic NETs (pNETs) if progressive, G2, symptomatic or bulky and in G3 neuroendocrine neoplasms. Chemotherapy may be considered in NET of other sites (stomach, colon or rectum) under certain conditions (G2 tumor, rapidly progressive disease and/or after failure of other therapies, or if SSTR imaging is negative). In the French guidelines [4], the indications moreover include the presence of bone metastases and a positive FDG-TEP. Systemic chemotherapy is not mentioned among the treatments of the well-differentiated small bowel NETs (sbNETs) in the North American guidelines [5]. It is not recommended by ENETS [3] in nonpancreatic NET unless G2 NET (Ki-67 >15%), tumors displaying aggressive biological behavior (RECIST progression in 3–6 months) or in those which are SSTR negative. Systemic chemotherapy can be used in well-differentiated metastatic sbNETs after somatostatin analogs, hepatic embolization, radionuclide and targeted therapies, in case of contra-indication or failure of these treatments, as an option in the French guidelines [4].

During the study, the first cytotoxic used was streptozocin or streptozotocin (STZ), approved by FDA in 1982 and French health authorities in 1985. It was used in intra-arterial procedure during the chemo-embolization or in a systemic administration,

commonly with doxorubicin [6,7], or 5FU [9]. The authorization was renewed by EMA in 2018 for the systemic treatment of adult patients with inoperable, advanced or metastatic, progressive and/or symptomatic, well-differentiated, G1 or G2 neuroendocrine tumours of pancreatic origin, in combination with 5-Fluorouracil but not doxorubicin despite of the great advantage with this anthracycline in terms of overall survival [6]. It was justified by the cumulative toxicity of doxorubicine, that leaded Moertel to recommend a limited number of cycles before a therapeutic break [7]. Alternative chemotherapies have not an EMA/FDA approval in the absence of prospective randomized studies: temozolomide alone [9,10] or associated with capecitabine [11], dacarbazine alone [12,13] or with 5FU [14], oxaliplatin with gemcitabine [15], 5FU [16] or capecitabine [17], irinotecan with 5FU [18].

Renal toxicity was reported in clinical studies in the seventies. Some renal dysfunction was described in a very large range: 28 to 100 % of patients [19,20,21,22] receiving STZ. Animal models and clinical reports suggest initial proximal tubule and dose-dependent cumulative renal toxicity [22]. Glycosuria, hypophosphatemia, tubular acidosis and low molecular-weight tubular proteinuria, biological markers of proximal tubular toxicity, generally occur first, before the decline in renal function. The treatment rarely leads to anuria. Serum creatinine, estimated glomerular filtration rate (eGFR), plasma electrolytes, proteinuria and glycosuria have to be measured before, during, and after treatment with STZ, to avoid more severe kidney injury. Mild to moderate proteinuria is one of the first signs of renal dysfunction, and when it occurs, dose reduction is recommended. Treatment must be interrupted in cases of increased proteinuria and severe renal dysfunction.

The purpose of the Streptotox-FFCD0906 study was to evaluate more accurately, prospectively and retrospectively, the evolution of renal function in patients receiving STZ for a well-differentiated digestive NET.

Materials and Methods

Patient population

Patients with histologically proven, locally advanced or metastatic, digestive NET, receiving or having previously received STZ were eligible. The other inclusion criteria were: patients aged at least 18 years, eGFR > 60 ml/min at the start of STZ treatment, and 24-hour proteinuria < 500 mg before treatment.

Patients of the prospective cohort (PC) were verbally informed and provided written informed consent. Patients of the retrospective cohort (RC) were given the information sheet. The study was conducted in accordance with the Declaration of Helsinki and was declared to the appropriate French authorities responsible for supervising computerized individual data files and ensuring the respect of ethical requirements.

Study design

This was a French, observational only, multicentre study involving two cohorts: a PC, which included *de novo* STZ-treated patients followed for 12 months, and a RC, which was based on data collected during and 3 months after treatment in patients treated with parenteral STZ and saw in consultation during the inclusion period. In the PC, the biological assessment before and after each cycle included creatinemia, glomerular filtration rate, calculated with the Modification of Diet in Renal Disease (MDRD) formula [23], blood nitrogen, serum electrolytes, including calcium and phosphorus, 24-hour proteinuria, glycosuria, microalbuminuria and beta-2 microalbuminuria. The analyses were done in each centre. If biological abnormalities occurred, a dose decrease or treatment interruption was recommended and adapted by the investigators to each patient, according to the protocol used in the center.

For budget reasons, it was not possible to perform a continuous monitoring during the inclusion phase of the study.

The primary endpoint of this study was the proportion of patients who experienced a decrease in the eGFR (MDRD formula) of at least 25% during STZ treatment compared with the baseline value: the lowest value during treatment included the value at the last cycle and the value after the end of treatment. The 25% threshold was chosen as clinically relevant in clinical nephrology and often chosen as end-point in trial assessing degradation of renal failure.

The secondary endpoints were eGFR changes during the treatment, the impact of combined nephrotoxic treatments, other toxicities, compliance, and objective response (OR) rates. Four subgroups of patients were defined according to renal function changes (eGFR decrease ≥ 25%, eGFR decrease between 15 and 25%, change in eGFR < 15%, and eGFR increase > 15%). These thresholds were chosen as clinically relevant. The renal function outcome was also studied according to the six-group KDIGO classification, which includes eGFR [24]. Combined nephrotoxic treatments were recorded. Additionally, predictive biological parameters of renal dysfunction were assessed.

In the PC, the response rate was assessed by the investigators and reviewed during the local multidisciplinary staff meetings using the RECIST criteria. In the RC, it was assessed from clinical records.

Patients were recruited over 24 months from December 2010 to July 2012. For each cohort, the study was conducted according to routine practices in terms of treatment and follow-up.

Statistical analysis

Given the paucity of data regarding the primary objective and in light of routine observed data, the proportion of patients presenting a decrease in eGFR ≥ 25%

following STZ treatment was estimated at 10%. An overall sample of 140 patients with locally advanced/metastatic digestive NETs was required for a two-sided alpha risk 5%. Hypotheses was for the 2 cohorts to achieve a global sample size of 140 patients. The scheduled distribution of patients was 30 patients in the prospective cohort and 110 patients in the retrospective cohort for feasibility reasons in this relatively rare pathology.

Data were described using means, medians and ranges or counts and percentages as appropriate. The two cohorts were compared using the Student test or Wilcoxon test for quantitative variables and Chi^2 or the Fischer Exact test for qualitative variables. For each variable, the number of missing data was mentioned, and these data were excluded from the analysis without replacement procedures.

Results

Patients' characteristics

110 patients were included in the RC between 24/10/10 and 29/02/2012 and 30 patients were included in the PC between 16/12/2010 and 04/07/2012.

In the PC, of the 31 patients screened, three were excluded for exclusive intra-arterial treatment, and one patient was excluded from the analysis because of baseline proteinuria exceeding the cut-off defined by inclusion criteria (Figure 1). The main characteristics of patients and tumours are summarized in Table 1. The median time from diagnosis to STZ treatment was 5 months (range: 1 to 128 months). All patients presented a well-differentiated NET. Relevant comorbidities were diabetes in five patients (18.5%), and high blood pressure in six patients (22.2%). Before the start of STZ, seven patients (27%) had received a previous treatment consisting of chemotherapy (n = 3), and/or somatostatin analogue (n = 4), and/or

chemoembolization (n = 1), and/or surgery (n = 1), and/or radiofrequency ablation (n = 1). STZ was the non-surgical first-line treatment in 15/22 pNETs and in 5/5 small bowel NETs (sbNETs).

In the RC, of the 110 patients screened, 10 were excluded for exclusive intra-arterial treatment, 14 did not have a well differentiated tumour and two patients were subsequently excluded from the analysis because of missing baseline eGFR values (Figure 1). The 84 remaining patients presented a well-differentiated NET. Relevant comorbidities were diabetes in 16 patients (19%), and high blood pressure in 13 patients (15.5%). Before the start of treatment, 31 patients (37%) had received a previous treatment consisting of chemotherapy (n = 7), and/or somatostatin analogue (n = 18), and/or interferon (n = 2), and/or chemoembolization (n = 9), and/or surgery (n = 3), and/or radiotherapy (n = 1). STZ was the non-surgical first-line treatment in 38/54 pNETs, in 6/18 sbNETs and in 6/12 other tumours.

The proportion of pancreatic tumours (Table 1) tended to be higher in the PC than in the RC (81.5% *vs*. 64.3%, p = 0.09).

The duration of follow up was on an average 6.42 months (standard deviation = 2.92) in the PC and 7.42 months (standard deviation = 4.47) in the RC.

Streptozocin treatment

Among the 27 patients of the PC, the intravenous treatment was polychemotherapy consisting of a combination of STZ with doxorubicin, fluorouracil, or epirubicin (Table 2). The dose of STZ was reduced in only one patient because of severe myelemia leading to treatment interruption after the second cycle.

In the RC, one patient first received five cycles of intravenous STZ and then two cycles of intra-arterial STZ. The characteristics of the intravenous STZ treatment are described in Table 2. All patients received polychemotherapy and all 16 dose reductions were due to toxicity. For three of the 44 patients who received doxorubicin

as the combined chemotherapy, this agent was changed to fluorouracil for the last cycles. Two patients concurrently received a somatostatin analogue, and seven concurrently received bevacizumab and fluorouracil.

Of note, a higher proportion of patients in the RC than in the PC received fluorouracil (38% *vs.* 25.9%) whereas more patients in the PC received doxorubicin ($p = 0.014$). Overall, the cumulative doses given were similar in both cohorts ($p = 0.27$), with more cycle delay in the PC and more dose reductions in the RC.

Some patients (half in the PC, one third in the RC) with stable disease or a response to treatment were allowed a therapeutic break or underwent a surgical procedure. The main reasons for treatment interruption in both cohorts are presented in Table 2 (response, stability or therapeutic break in 40%). No treatment was stopped for a grade 3-4 renal toxicity. When the treatment was stopped for toxicity, a renal grade 1-2 toxicity was described in 77% of the 22 patients versus in 19/89 (21%) patients with a treatment's interruption for another reasons. In the patients with a stop of treatment because of toxicities, 76 % had received up to 3 cycles; the number of cycles in this group was a median 3, on average 3.37, versus respectively 4 and 4.44 in case of interruption for another causes ($p=0.64$). The median number of received cycles was 5 (range 2-17) when the treatment was stopped for pause and 3 (range 1-8) when it was stopped for progression. The treatment was stopped for toxicities after one cycle only in 5 patients: one with a grade 1 only renal toxicity, two with grade 2 renal toxicity associated with other toxicities particularly digestive, one with grade 3 hypokalemia and grade 3 hepatic toxicity, and one (in the RC) for other ungraded toxicity.

Efficacy

Disease control was observed in 79% of 71 patients with pNETs, 87% of 23 patients with sbNETs and 73% of the 11 patients with another primary tumour site

(Supplemental table 1). Six patients were surgically treated after response or stability on chemotherapy: 2 in the PC and 4 in the RC.

Renal function

For the 108 patients of the two cohorts, a decrease in the eGFR ≥ 25% occurred in 32 patients (30%).

For 26 patients of the PC with eGFR values available at baseline and during treatment, a decrease in the eGFR ≥ 25% occurred in four patients (15.4%) (Figure 2 and Table 3). In contrast, the eGFR improved in 19.2% of patients. According to the KDIGO classification, 20% of patients developed mild renal impairment, no patient severe worsening (grade 3b-5) of renal function (Supplemental Table 2). The evolution of the main biological parameters between the first and the last cycle is presented in Supplemental Table 3, which shows that no major biological changes occurred during the treatment.

For 82 patients of the RC with eGFR values available at baseline and during treatment, a decrease in eGFR ≥ 25% occurred in 28 patients (34.1%) while eGFR improved in 2.4% (Figure 2 and Table 3). Changes from baseline to the lowest eGFR during and at the end of treatment were greater in the RC than in the PC ($p = 0.0041$ and $p = 0.06$, respectively). According to the KDIGO classification, 20 patients (23.8%) with normal renal function at baseline experienced at least one episode of significant renal impairment (stage 3a = 19, stage 4 = 1) (Supplemental Table 2).

Figure 3 shows changes in plasma creatinine during and after the treatment in each cohort.

Data about concomitant treatments was available for 82 patients of the two cohorts. These treatments were anti-hypertensive agents (N=16), NSAID (N=4), glycopeptides (N=1), but no aminoglycosides. The iodine injection during the TDM staging was considered as a nephrotoxic associated treatment by the investigator in

5 patients but not kept in the analysis: the TDM with injection is required for each staging in patients with a good renal function and so the iodine injection was under-reported by the large majority of investigators. Of the 20 patients who received a least one concomitant nephrotoxic treatment, 5 (25%) developed renal impairment, whereas of the 91 patients without concomitant nephrotoxic treatment, 37.4% presented renal toxicity (p=0.29). After addition to the list of nephrotoxic treatments of bevacizumab's concomitant administration (7 patients) and previous administration of large iodine doses used in chemo-embolizations (10 patients), renal impairment was observed in 37% patients with nephrotoxic associated or previous treatments, and 34.5% patients without these treatments.

The univariate analysis of the renal impairment showed no statistically significant risk factor with the items, sex, age, primitive tumor location, presence of metastases, diabetes, arterial hypertension, concomitant nephrotoxic treatment, number of cycles and STZ dose. The renal impairment, in these two different univariate analysis was identified with eGFR ≥ 25%, then with the CTC-NBI classification (all grade of renal toxicity).

Although the early diagnosis of tubular impairment was planned for all patients in both the PC and RC study, data as follows were recorded for only 110 patients: proteinuria in 38 patients, glucosuria (no cases), microalbuminuria (eight), beta-2 microalbuminuria (two), kaliemia (73), natremia (12), chloremia (11), calcemia (six), phosphoremia (five). Given the high number of these missing data, the results are not provided.

According to the NCI-CTC classification, grade 1-2 renal toxicity (serum creatinine level or eGFR) was observed in less than 35% of patients in each cohort. No grade 3-4 renal toxicity occurred in the PC versus one in the RC (Table 4).

Safety

Sixty percent of patients in each cohort presented at least one episode of toxicity during the treatment (Table 4). Grade 3-4 CTC-NCI toxicity occurred in four patients (14.8%) and 13 patients (15.5%) in the PC and RC, respectively. Overall, the main toxicities were digestive (nausea-vomiting), renal and haematological. No deaths due to toxicity were reported. The interruption of treatment was decided because of toxicity (mostly low grade), as described above, in about 20% patients.

Discussion

To our knowledge, this is the first study to explore streptozocin-related renal toxicity with a fixed dose and using the rigour of a PC combined with a retrospective analysis of routine practice. Treatment regimens were 500 mg/m² from day 1 to day 5 every 6 weeks always combined with another cytotoxic agent, for a median duration of 3 to 4 cycles. Even though the sample sizes and the populations of the two cohorts were different, the trends in terms of toxicity and efficacy were similar. This study showed that in routine practice, STZ led to mild renal toxicity.

The limits of this study were the sample size of the PC, the monitoring of the study in the PC and the absence, especially in the RC, of biological results, such as proteinuria, glucosuria, microalbuminuria, beta-2 microalbuminuria, serum electrolytes, that could alert the medical team to the presence of possible renal toxicity. It would probably have been useful to measure these blood and urinary parameters before each cycle of STZ. In fact, in our series, proteinuria was routinely tested with a urinary dipstick but if the result was negative, it was not reported in the medical record.

Furthermore, the risk of renal dysfunction on a long time was not evaluated in our study because of the short follow up after the end of the treatment.

Renal toxicity, including nitrosourea, is a well-known side-effect of STZ [19]. In the light of the results of old studies, renal tubular damage was considered a major

limiting toxicity. Pharmacological studies of the urinary excretion of STZ have shown that a significant proportion of the N-nitroso group of each total dose is found intact in the urine. A high concentration of this pharmacologically active compound, which is able to spontaneously release an active methyl group under physiological conditions, may be responsible for the observed renal tubular toxicity [19,20]. Therefore, it is now clearly recommended that active urine output be maintained during and following treatment to ensure dilution of the drug to the lowest possible concentration while it passes through the renal tubules. However, the incidence of renal toxicity during treatment with STZ is heterogeneous and depends on the chemotherapy schedule and the population treated. One old study, involving 106 patients (with very heterogeneous doses and a wide range of malignancies), reported proteinuria in 28%, a decrease in creatinine clearance in 27% and an increase in BUN and/or serum creatinine in 7% [21]. A systematic review of chemotherapy in NETS showed that severe renal toxicity ranges from 0 to 25% in randomized trials, without a clear definition of toxicities [22]. In three large monocentric retrospective studies, the rate of NCI-CTC grade 3-4 renal toxicities did not exceed 5% [23,24,25], as in our series. Our study, with a defined dose of STZ and used in NETs only, showed that up to 35% of patients developed a grade 1-2 renal toxicity, with only 1% of grade 3-4 toxicities. Overall changes in the KDIGO class, using eGFR according to MDRD formula [17], did not exceed stage 3a in the PC. Changes were greater in the RC. We observed a decrease in eGFR ≥ 25% in 15.4% of patients of the PC and in 34.1% of patients of the RC. Nonetheless, changes remained moderate with no final renal failure. The different results between the two cohorts could be explained by differences in the recruitment of patients: the rigour of a prospective trial, which included selected patients who benefited from better follow-up compared with routine practice in the RC, which probably better reflects ‘real life’ care. In the prospective

285 setting, with closer follow-up of renal function, eGFR improved in 19.2% of the
286 patients. These differences indicate that renal function should be carefully monitored
287 and patients better hydrated during administration of the drug. Hydration before and
288 after each STZ administration, as is the case for cisplatin, is now recommended.

289 The other toxicities of STZ have been described previously and are manageable
290 even though there is great variability between studies, regimen and patients for each
291 side effect [19,21,26]. In all these series, the doses of STZ were often higher than
292 500 mg/m^2 for 5 days every 6 weeks. Nonetheless, data provided by the literature are
293 consistent with those described in our study, showing mainly digestive and
294 haematological adverse events. Nausea and vomiting are now well controlled with
295 anti-5HT3 and corticosteroid treatments. Of note, no deaths due to toxicity were
296 reported in our whole population.

297 The good safety profile was confirmed by treatment compliance. The main
298 reasons for treatment interruption were similar in the two groups and due to toxicity in
299 20% of cases. Some investigators used the stop of treatment (even in the event of
300 grade 1-2 renal toxicity) instead of dose reductions, probably because the dose
301 adaptations are not well standardised. It could partially contribute to the low level of
302 heavy renal impairment in our study. Treatment interruptions because of disease
303 progression were frequent in the RC (41.7%), whereas treatment interruptions for an
304 objective response and stabilization, as proposed by Moertel *et al*. in 1992 [5],
305 seemed more frequent in the PC.

306 In terms of efficacy, the objective response for pNETs was about 27%, which
307 corresponds to the most recent data in the literature with the streptozocin-doxorubicin
308 combination (ranging from 6 to 39%) [22,27,28]. In our study, disease control was
309 mainly observed in patients with pNETs and sbNETs. For sbNETs, the ORR was low
310 (5.5%) and disease control high (100%), but primary tumours in the small bowel are

311 usually less aggressive, and the use of cytotoxics as the first line of treatment is not
312 currently recommended by European or French guidelines [8,16]. Despite these
313 guidelines, 11 patients in our cohorts were treated with STZ in the first line. The
314 tumours were probably considered highly progressive by the investigators.

315 Furthermore, targeted therapies, including single agents, have been evaluated
316 in this setting and showed that sunitinib and everolimus could be useful, with
317 response rates of 9.3% and 5%, respectively [6,7]. In addition, these therapies
318 significantly improved survival parameters compared with placebo. Given the
319 potential renal toxicity of STZ, the first-line use of targeted therapies could be
320 envisaged for patients with primary pNETs, even though our study showed that the
321 risk of renal complications was moderate when treatment with STZ was delivered
322 carefully. A prospective trial is in progress to confirm this finding [31]: the European
323 SEQTOR trial, which is investigating the combination of streptozocin-fluorouracil
324 followed by everolimus in comparison with the inverse sequence, could help
325 practitioners choose the best strategy for pNETs. The PRODIGE 40 - BETTER 2 is
326 comparing the combination 5FU-streptozocin versus telozolimide-capecitabine,
327 associated or not with the anti-angiogenic, bevacizumab, for the treatment of pNETS.
328 Today, first-line cytotoxics, such as STZ, are not recommended for sbNETS. In these
329 patients, who are likely to receive several subsequent treatments for their metastatic
330 disease, it could be of interest to start with a loco-regional hepatic approach
331 (embolization or chemo-embolization), radionuclide therapy or targeted therapies in
332 order to reduce cytotoxic adverse effects.

333 In conclusion, STZ is an active antimitotic chemotherapy drug that has a place
334 among the treatments for advanced/metastatic well-differentiated pNETs. Our results
335 highlight that renal toxicity seems to be moderate with a positive benefit/risk ratio in
336 favour of STZ for patients with adequate renal function before the start of treatment.

Its renal toxicity could limit its use in frail patients. The early detection of tubular toxicity could be obtained by following serum electrolytes, glycosuria, microalbuminuria and beta-2 microalbuminuria more closely. Adequate hydration must be provided before and after each dose of STZ and should be recommended more strongly in the guidelines.

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TABLE 1 Patients' and tumour characteristics in the prospective and retrospective cohorts

Characteristic	Prospective cohort	Retrospective cohort	*P*
Number of patients	27	84	
Sex, n (%)			0.286
Male	14 (51.9)	54 (64.3)	
Female	13 (48.1)	30 (35.7)	
Age, years			0.08
Mean (± standard deviation)	61.48 (± 13.25)	55.63 (± 12.01)	
Median (range)	65 (32-81)	54.5 (28-81)	
Tumour site, n (%)			0.0897
Pancreas	22 (81.5)	54 (64.3)	
Small bowel	5 (18.5)	18 (21.4)	
Other*	0	12 (14.3)	
Metastases, n (%)	23 (85.2)	78 (92.9)	0.22
Baseline eGFR, ml/min/1.73m²			0.77
Mean (± standard deviation)	91.84 (± 24.3)	93.82 (± 25.57)	
Median (range)	84 (60-161.5)	89.65 (47.7-195.5)	
Baseline serum creatinine, µmol/L			
Mean (± standard deviation)	74.96 (± 18.76)	77.17 (± 17.67)	
Median (range)	73 (48-107)	75 (41-137)	

*Colon or rectum 4, stomach 1, gastrinoma 1, metastatic liver without chest abnormality 5, hepatic and pulmonary metastases without visible primary location 1.

TABLE 2 Description of streptozocin-based chemotherapy in prospective and retrospective cohorts

Treatment characteristics	**Prospective cohort**	**Retrospective cohort**	***P***
Number of patients with data	27	78	
Regimen, n (%)			
500 mg/m² d1-d5, q6w	27 (100)	78 (100)	
Combined chemotherapy, n (%)			*0.014
Doxorubicin	18 (66.7)	41 (48.8)	
5 fluorouracil (5-FU)	7 (25.9)	32 (38)	
Epirubicin	2 (7.4)	1 (1.2)	
Doxorubicin then 5-FU	-	3 (3.6)	
5FU + bevacizumab		7 (8.3)	
Number of cycles: median (range)	3 (1-12)	4 (1-17)	0.09
Cycle delay †: n (%)	7 (28) ‡	13 (16.7) ‡	*0.03
Dose reduction: n (%)	1 (3.7) ‡	16 (20.5) ‡	0.05
Cumulative dose: g/m²			0.266
Median (range)	7.5 (1.5-15)	8,25(1.5-25.62)	
Main reasons for treatment interruption **n (%)**			
Number of patients	27	84	
Patients with toxicity	6 (22.2)	16 (19.0)	
Disease progression	7 (25.9)	35 (41.7)	
Therapeutic Break	12 (44.4)	28 (33.3)	
Patient's decision	1 (3.3)	1 (1.2)	
Other	1 (3.7) ¶	4 (4.8)	

† More than 50 days between two consecutive cycles.

‡ Number of cycle delay and dose reduction were calculated for the 25 patients having received at least two cycles in the prospective cohort and for the 78 without missing data in the retrospective cohort.

* Difference between cohorts statistically significant.

¶ Other reasons for treatment interruption in prospective cohort: investigator's decision (n = 1).

¤ Other reasons for treatment interruption in retrospective cohort: cholangitis (n = 1), streptozocin out of stock (n = 1), investigator's decision (n = 2).

TABLE 3 Changes in renal function during treatment

Parameters	Prospective cohort	Retrospective cohort	*P*
Change† from baseline to eGFR at last cycle, n (%)			**0.0041
Number of patients	23	68	
Deterioration (eGFR decrease ≥ 15 %)	**5 (21.7)**	**25 (36.8)**	
Stability	9 (39.1)	37 (54.4)	
Improvement (eGFR increase > 15 %)	9 (39.1)	6 (8.8)	
Change† from baseline to post-treatment eGFR at first follow-up, n (%)			0.06
Number of patients	18	55	
Deterioration (eGFR decrease ≥ 15 %)	**4 (22.2)**	**26 (47.3)**	
Stability	9 (50.0)	24 (43.6)	
Improvement (eGFR increase > 15 %)	5 (27.8)	5 (9.1)	

† Changes were calculated if both baseline and target values were measured.

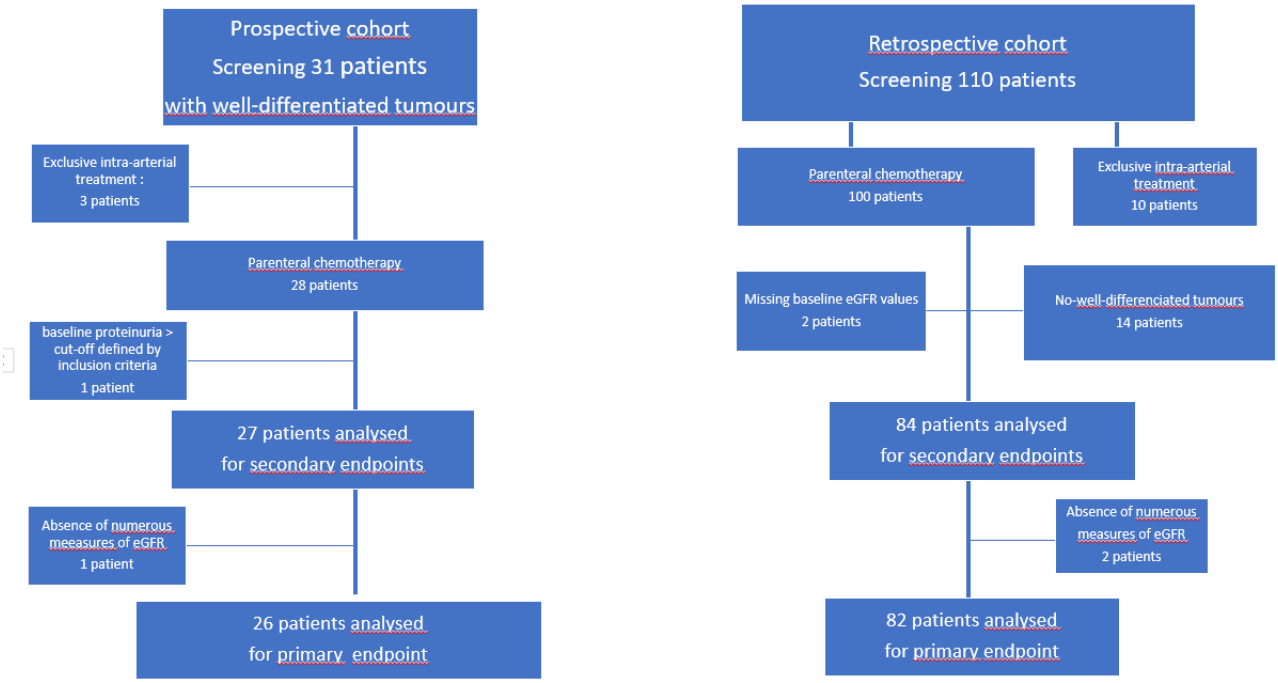
** Difference between cohorts statistically significant.

TABLE 4 CTC-NCI toxicities occurring during treatment, per patient

	Prospective cohort (n = 27)		Retrospective cohort (n = 84)	
Toxicity, n (%)	**All grade**	**Grade 3-4**	**All grade**	**Grade 3-4**
All toxicities	16 (59.3)	4 (14.8)	51 (60.7)	13 (15.5)
Digestive	10 (37)	2 (7.4)	35 (41.7)	3 (3.6)
Renal	9 (33.3)	-	30 (35.7)	1 (1.2)*
Haematological/infection	3 (11.1)	1 (3.7)	20 (23.8)	7 (8.3)
Asthenia	2 (7.4)	-	11 (13.1)	-
Liver	1 (3.7)	1 (3.7)	12 (14.3)	2 (2.4)
Anorexia	-	-	1 (1.2)	-
Alopecia	-	-	5 (6.0)	-
Fever	1 (3.7)	-	2 (2.4)	-
Headache	-	-	2 (2.4)	-
Other	3 (11.1)	2 (7.4)	13 (15.5)	2 (2.4)

*After 3 cycles. No concomitant nephrotoxic treatment. Patient with complete response.

Figure 1. Flow chart



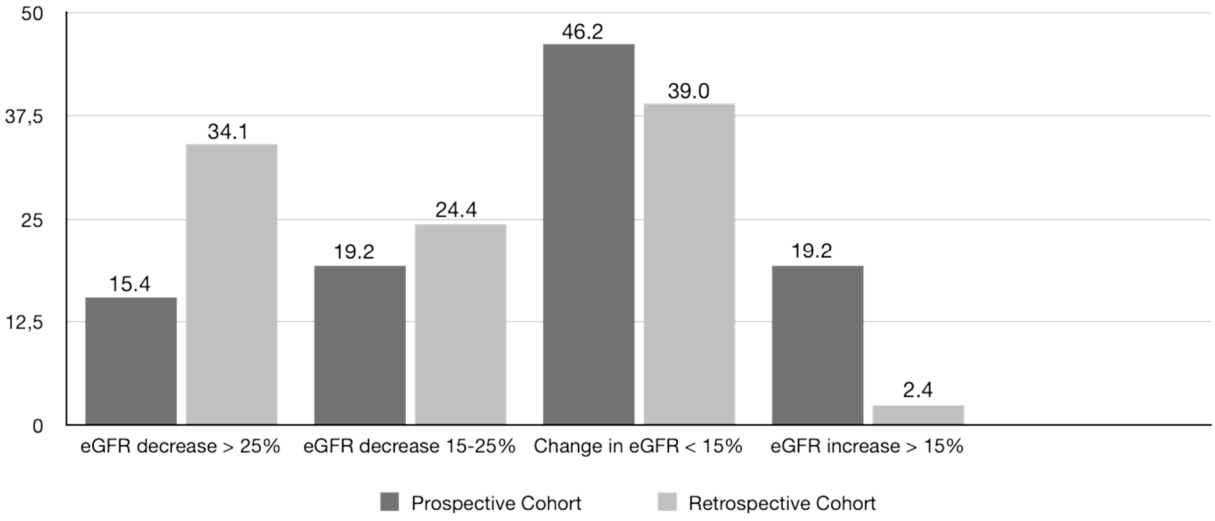


Figure 2. Percentage of patients with eGFR (MDRD) modification in the prospective (N = 26 patients) and retrospective cohort (N = 82 patients) during the treatment or after the last cycle. P-value for comparison of the 2 cohorts: 0.005

Figure. 3. Plasma creatinine during and after the treatment cycles.

