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The doxorubicin-streptozotocin combination for the treatment of advanced well-differentiated pancreatic endocrine carcinoma: a judicious option?

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Abstract

Due to their rarity, only few trials have studied the role of the doxorubicin-streptozotocin (DS) combination in advanced well-differentiated pancreatic endocrine carcinomas (AWDPEC). However, the published results are inconsistent. We reviewed all AWDPEC (5-year period, 45 patients) treated in our institution with the DS combination for: objective response rate (ORR), progression-free survival, overall survival (OS) and toxicity. An ORR of 36% (95% Confidence Interval (CI) 22–49) was obtained, with 16 partial responses (PR). The mean duration of PR was of 19.7 months. Two and 3-year OS rates were 50.2 and 24.4%, respectively. Toxicities were mainly digestive (grade $\geqslant 3$ vomiting, 13%) and haematological (grade $\geqslant 3$ neutropenia, 24%). Previous systemic chemotherapy and malignant hepatomegaly were associated with a poorer ORR ($P=0.033$, $P=0.016$) and OS ($P=0.008$, $P=0.045$). Multivariate analysis demonstrated previous chemotherapy as the only independent predictive-factor for survival ($P=0.013$). In conclusion, our data confirm the sensitivity of AWDPEC to the DS combination, with an ORR of 36% and a remarkable median response duration of 19.7 months, and suggests that it could be considered as a valid option in first-line therapy.

Keywords: Neuroendocrine carcinoma; Chemotherapy; Pancreas

1. Introduction

Pancreatic endocrine carcinomas (PECs) are rare malignancies, accounting for less than 2% of all gastrointestinal tract malignant tumours and less than 1% of endocrine tumours [1]. They can be classically divided in 2 groups, based on the potential presence of typical clinical symptoms at disease onset: ''functional'' and ''non-functional'' pancreatic tumours, respectively [2–4]. Approximately half of PECs express at least one active hormone, such as insulin, gastrin, glucagon or somatostatin. These are responsible for intermittent and often typical, but non-specific, symptomatology. Non-functional tumours are usually diagnosed at a later stage, based upon symptoms related to the tumour burden itself [4].

Therapeutic management of PEC represents a challenge for the physician. Treatment choice is dictated by pathological differentiation and the stage at diagnosis, as well as by the presence of hormone-related symptoms. Well-differentiated PEC (WDPEC) are usually slow-growing tumours that sometimes allow for therapeutic abstention. However, they can display accelerated progression, requiring a much more aggressive attitude to treatment. In the case of localised WDPEC, surgery remains the only curative treatment. However,

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in the peculiar situation of multiple gastrinomas as part of the MEN1 syndrome, the debate is still open.

WDPEC are considered relatively chemosensitive neoplasms and in cases of a high tumour burden and/or rapidly progressive metastatic disease, chemotherapy is an appropriate therapeutic option [5–9]. First data concerning chemotherapeutic effectiveness in WDPEC date back to 1968, when Murray-Lyon and colleagues reported a case of insulinoma responding to streptozotocin [9]. Since then, several chemotherapeutic agents, including doxorubicin and dacarbazine (DTIC), have been evaluated as single agent therapy. Both demonstrated interesting effects in advanced WDPEC (AWDPEC), with 20–30% response rates, and a tolerable toxicity profile [6,8]. Later, Moertel and colleagues demonstrated, in a prospective randomised trial comparing doxorubicin-streptozotocin (DS), streptozotocin/5-fluorouracil and chlortozotocin, an objective response rate (ORR) of 69% with a median survival of 26.5 months in the DS arm, results that were significantly superior to those of the other 2 regimens. This association became thereafter a standard therapy for progressive AWDPEC. However, a recent study failed to confirm the outstanding anti-tumour activity of the DS combination [10]. Such discrepant results prompted us to review our institution experience of DS in AWDPEC treatment, with three main aims: (1) ORR, (2) toxicity, (3) prognostic parameters of objective response and survival.

2. Patients and methods

2.1. Patients

All patients included in our study had been followed in our institution from January 1995 to December 1999. Presence of histologically-confirmed measurable, but unresectable, AWDPEC was necessary for patient inclusion. Pathological diagnoses were all reviewed by a single pathologist and thereafter classified according to the updated World Health Organisation (WHO 2000) classification. Performance status (PS), as well as haematological and non-haematological (cardiac, renal, hepatic, digestive and neurological) toxicities were reviewed for all patients and graded numerically according to the WHO scale. Both functional and non-functional tumours were included in the study. Biological evaluation included dosage of: neuron-specific enolase (NSE), calcitonin, glycoprotein α-subunit, 5-hydroxyindolacetic acid (5-HIAA), in addition to gastrin and pancreatic peptides [11]. After 1996, chromogranin A replaced NSE measurement. Morphological investigations included, for each patient: abdominal computerised tomography scanner (CT-scan) and somatostatin receptor scintigraphy. Cardiac ultrasonography was also performed to detect potential doxorubicin-induced cardiotoxicity.

2.2. Treatment

Patients were treated with combination of doxorubicin (intravenous (i.v.) injection of 50 mg/m^2/day, on days 1 and 22 of each six-week treatment-cycle) and streptozotocin i.v. injection of 500 mg/m^2/day for 5 consecutive days, every six weeks). Any grade 3 or 4 side-effects resulted in a 25% dose reduction for subsequent cycles. Treatment was stopped in cases of disease progression or life-threatening toxicity.

2.3. Response and survival evaluation

All patients were monitored every other month by radiological investigations, including CT-scan, ultrasonography and/or magnetic resonance imaging (MRI).

Objective response was evaluated through the measurement of one or more target lesions: primary tumour (if $\geqslant$30 mm), metastatic disease and/or lymph node involvement (if $\geqslant$20 mm). Patients were considered as achieving a partial response (PR) when a tumour mass regressed in such a way that the product of its largest perpendicular dimensions was reduced by 50%, while a minor response (MR) was defined as a reduction of 25% to 49%. Progressive disease (PD) was defined as an increase of $\geqslant$25% of these measurements, and stable disease (SD) as the lesions between PD and MR. Biochemical response was defined as a relevant marker level reduction of $\geqslant$50%. Time to progression was calculated from the first DS administration to disease progression. Survival was calculated from the first DS administration.

2.4. Statistical analysis

Predictive factors of response were ascertained by the chi-square test. The Kaplan–Meier method was used to analyse overall survival (OS), and time to disease progression. Prognostic factors for a longer survival were determined through univariate analysis with the log rank test. Variables tested consisted of: age, gender, performance status, primary tumour resection, presence of malignant hepatomegaly previous chemotherapy and/or chemoembolisation. Multivariate analysis was performed according to the Cox model using the BMDP software and the 2L program. Statistical significance was defined as $P < 0.05$.

3. Results

Between January 1995 and December 1999, 45 consecutive patients suffering from unresectable AWDPEC

were evaluated: 27 men (60%) and 18 women (40%) with a median age of 54 years (ranging from 22 to 75 years). Patient characteristics are summarised in Table 1. Most patients had a PS $\leqslant$ 1.

Forty-two out of 45 patients (93%) had metastatic disease when chemotherapy was started, including 87% with liver metastases, responsible for radiological malignant hepatomegaly in 56% of them. Eleven patients had received previous chemotherapy, including 5-fluorouracil plus cisplatin (CDDP) or 5-fluorouracil plus streptozotocin. Six patients received more than one regimen prior to the DS administration. Chemoembolisation using doxorubicin had been previously performed in 4 patients. Sixteen patients (36%) had previously undergone pancreatic surgery. Twenty patients had documentation of tumour-related hormone production. Among them, 10 were classified as having a functional tumour (including 3 insulinomas, and 2 gastrinomas).

Table 1
Patient characteristics

	N (%)
Total number of patients	45
Gender male/female	27/18
Median age (years)	54
WHO performance status	
0	34 (75)
1	7 (16)
2	3 (7)
3	1 (2)
Metastatic sites	
Liver	39 (87)
Lymph nodes	18 (40)
Peritoneum	3 (7)
Others	12 (27)
Previous treatment	
Curative/palliative surgery	6 (13)/10 (22)
Radiotherapy	4 (9)
Chemotherapy	11 (24)
Chemoembolisation	4 (9)
Somatostatin analogues	11 (24)
Functional tumour	20 (44)
Insulinoma	3 (7)
Gastrinoma	2 (4)
Glucagonoma	1 (2)
Vipoma	2 (4)
Others	12 (27)
Non-functional tumour	25 (56)
Symptoms	
Abdominal pain	17 (38)
Anorexia	3 (7)
Vomiting	2 (4)
Weight loss $>10\%$	6 (13)
Abdominal mass	7 (16)
Malignant hepatomegaly	25 (56)
Peritoneal carcinomatosis	4 (9)
Others	19 (42)

WHO, World Health Organisation.

3.1. Treatment

Twenty-seven (60%) patients received $\geqslant$5 DS courses, with 17 patients (38%) receiving 6 courses. The median cycle number was 4 (range 2–7), and the mean cycle number $\pm$ the standard error of the mean (SEM) was 4.2 ± 1.7.

3.2. Toxicity

In our series, the DS treatment was globally well-tolerated (Table 2). None of the patients developed severe chronic renal insufficiency. Grade 3–4 neutropenia and thrombocytopenia occurred in 11 (24%) and 8 (18%) patients, respectively, with 3 patients requiring hospitalisation for neutropenic fever. Three out of 45 patients (7%) developed grade 1–2 cardiac toxicity, leading to doxorubicin discontinuation in 2 of them (after 6 and 7 chemotherapeutic courses, respectively). Other side-effects, including vomiting and diarrhoea, were mild and easily controlled with supportive care. No treatment-related death was reported.

3.3. Response to therapy

Based upon radiological monitoring, and according to WHO criteria, 16 of our patients (36%) achieved a PR (95% Confidence Interval (CI) 22 to 49%), corresponding to our overall response rate (ORR), whereas 7 (16%) patients achieved MR and 4 (9%) SD. Eighteen patients (40%) experienced progression. Among the responding patients, 14 (88%) received the

Table 2
Toxic side-effects of doxorubicin-streptozotocin treatment per patient

	WHO Grade *N* (%)				
	0	1	2	3	4
Digestive toxicity					
Vomiting	29 (64)	7 (16)	3 (7)	5 (11)	1 (2)
Diarrhoea	39 (87)	2 (4)	2 (4)	2 (4)	0
Stomatitis	40 (89)	2 (4)	3 (7)	0	0
Nephrotoxicity	39 (87)	2 (4)	4 (9)	0	0
Cardiotoxicity	42 (93)	1(2)	2 (4)	0	0
Neurotoxicity	45 (100)	0	0	0	0
Haematological toxicity					
Leucopenia	31 (69)	2 (4)	2 (4)	3 (7)	7 (16)
Neuropenia	30 (67)	2 (4)	2 (4)	4 (9)	7 (16)
Thrombocytopenia	35 (78)	0	2 (4)	4 (9)	4 (9)

WHO, World Health Organisation.

DS combination as first-line therapy. Interestingly, 6/16 patients with PR were reconsidered for resection of metastatic sites. Curative resection of the lesions was obtained in 4 of these 6 patients. Two of them are free of disease 3 and 7 years, respectively after the beginning of DS administration.

Complete follow-up was achieved for all patients. Two- and 3-year overall survival rates were 50.2 and 24.4%, respectively (median survival was 24 months). Median progression-free survival was 16 months. Mean duration of objective response (OR) was 19.7 months, with 5 particularly long responses (24, 26, 27, 38+ and 84+ months). Mean durations of MR and SD were 16.1 and 18.3 months, respectively. A biological response was also observed in 9/10 (90%) patients suffering from functional tumours.

Univariate analysis demonstrated that previous systemic chemotherapy and the presence of malignant hepatomegaly were significantly associated with worse outcomes in terms of OR and survival (Table 3). Indeed, patients treated with DS as a first-line therapy experienced a median survival of 22.4 months compared with 5.5 months for patients previously treated with chemotherapy ($P=0.008$). Chemoembolisation prior to treatment also worsened the OS prognosis ($P=0.006$). In a multivariate analysis using the Cox model, previous systemic chemotherapy was identified as the only independent significant prognostic factor of a shorter survival time ($P=0.013$).

4. Discussion

WDPEC are rare tumours usually considered by most authors to be rather chemosensitive, especially to streptozotocin-based regimens [5,7,12]. Moertel and colleagues obtained, in the only AWDPEC prospective randomised trial published to date, a remarkable ORR of 69% with median survival of 26 months in 36 patients treated with the AS combination [7]. However, in light of the WHO criteria, this ORR is now considered to be an overestimation. Indeed, clinical regression of malignant hepatomegaly, as well as tumour marker decrease, was then regarded as treatment response.

Based exclusively on WHO radiological response criteria, our study confirms WDPEC sensitivity to DS combination, with a significant ORR of 36%. A median survival of 24 months, and a quite remarkable mean response duration of 19.7 months were also noted. Due to a divergence in the evaluation criteria our results cannot be compared directly with those obtained by the Eastern Cooperative Oncology Group (ECOG) [7]. However, the size of our AWDPEC series, which is the largest published to date, allows for the accurate evaluation of ORR, progression-free and OS. We can also, using the same response criteria and study design, reasonably compare our results with the surprisingly modest ORR (6%) obtained by Cheng and colleagues in a recent retrospective analysis of 16 AWDPEC patients treated with the same DS combination regimen [10].

To our knowledge, no data concerning previous administration of chemotherapy as a response and survival prognostic factor in AWDPEC have been published. Sequence of the chemotherapy regimen administration appears nonetheless to play a certain role in AWDPEC management. Indeed, we demonstrated that previous systemic chemotherapy jeopardised the response to DS combination, as well as survival. This finding could, in part, be explained by the previous administration of 5-FU/streptozotocin given to some of the patients. Our results suggest that, since the DS combination appears to be the most effective

Table 3
Significant prognostic factors of response to therapy and overall survival in univariate analysis

	Response to therapy			Overall survival		
	N	Objective response%	*P* value	*N*	Deaths%	*P* value
Prior systemic chemotherapy						
Yes	11	18	0.0033	13	85	0.008
No	34	41		32	53	
Malignant hepatomegaly						
Yes	25	24	0.016	25	76	0.045
No	20	50		20	45	
Prior chemoembolisation						
Yes	4	0	NS	4	100	0.005
No	41	39		41	56	
Previous primary tumour resection						
Yes	16	31	NS	16	75	NS
No	29	38		29	55	

N, number of patients; NS, non-significant.

treatment in AWDPEC (at last in our hands), this regimen should therefore ideally be administered as first-line chemotherapy in patients with rapidly progressive disease.

Previous doxorubicin chemoembolisation was also associated with a poor survival. Although statistically significant, this association might be biased by the fact that this option is usually performed in patients with substantial non-resectable and, in particular, advanced liver involvement. This assumption could also, in part, account for the fact that radiologically-confirmed hepatomegaly, secondary to major liver metastatic involvement, was also significantly associated with a short survival and poor tumour response to the DS combination. Altogether, our results suggest that maintenance of DS administration should be reconsidered in the presence of a delayed response and of any poor survival and/or response prognostic factor, and especially in cases who have received previous systemic chemotherapy.

Resection of liver metastatic disease has gained acceptance as a potential curative option and, in patients with colorectal cancer, as one of the best approaches to improve survival [13,14]. Since neuroendocrine carcinomas are often slow-growing tumours responsible for debilitating symptoms related to tumour burden and/or hormone production, aggressive resections of advanced diseases have been encouraged by some authors [15–20]. Lo and colleagues studied 64 hepatic resections for advanced PEC, and found a 5-year-survival rate of 49% and a disease-free survival at 3 years of 53% for patients who had undergone a curative resection [20]. Carty and colleagues reported even better results with a 5-year survival rate after complete resection of 79% [18]. However, since most patients suffering from metastatic WDPEC are diagnosed with major malignant and non-resectable liver enlargement, WDPEC are rarely considered for curative surgery. In selected individuals, liver transplantation should then be considered, based upon age, PS, symptoms, tumour growth rate and extension of the disease to other organs [21].

Interestingly, in our series, 6/17 responding patients became candidates for resection, after significant tumour shrinkage was observed following DS administration. Curative resection was achieved in 4 cases, whereas palliative surgery was performed in 2 patients. As for metastatic CRC [22,23], one should keep in mind, for advanced WDPEC, the potential role of DS combination administered in a "neoadjuvant setting".

The role of primary tumour resection remains controversial [24–30]. Two recent studies showed a better 5-year survival for patients with primary PEC resections ($P < 0.001$ in both studies) [29,30]. Madeira and colleagues showed a significantly better 5-year overall survival rate when the tumour was <3 cm (86% versus 42%, $P = 0.0011$) [30]. Our study did not demonstrate any survival advantage for patients previously resected for their primary tumour. However, all of them were already suffering from metastatic liver disease at the time of resection, creating a bias in the survival evaluation.

The DS combination therapy was associated with tolerable adverse events, with grade 3–4 toxicities limited to gastrointestinal and/or haematological side-effects. Nausea and vomiting were also less common in our study than in the study of Moertel and colleagues, likely thanks to better prevention and management with new anti-emetic drugs. Although observed in 24% of the patients, grade 3–4 neutropenia was quite well tolerated, with only 3 patients requiring hospitalisation for febrile neutropenia. The occurrence of nephrotoxicity was particularly low in our series, as well as cardiac toxicity, which is commonly observed following the use of anthracycline regimens. To prevent cumulative toxicity, treatment was interrupted in the 2 patients experiencing grade 2 cardiotoxicity. No death-related toxicity was observed in our series.

Tumour growth control was achieved in 60% of our population, with a remarkable mean response duration (PR and MR of 19.7 and 16.1 months, respectively and stabilisation of 18.3 months).

In conclusion, our data confirm that the doxorubicin-streptozotocin combination is an efficient option for advanced well-differentiated pancreatic endocrine carcinomas, particularly when administered to chemo-naïve patients. It is a well-tolerated regimen that can lead to resection of metastatic liver disease and subsequent survival improvement.

However, new drugs for the treatment of this disease need to be tested, particularly anti-angiogenic agents.

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