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Phase II Trial with Ifosfamide in Pancreatic Cancer

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ADVANCED PANCREATIC cancer is a rapidly fatal disease for which no effective treatment is available and a continuous search for active agents is needed. Some investigators have reported significant activity for ifosfamide, while others have not [1–6]. Therefore, the EORTC Gastrointestinal Tract Group initiated a phase II trial with ifosfamide in patients with advanced adenocarcinoma of the pancreas.

Patients with histologically confirmed pancreatic cancer who were not pretreated and had metastatic disease were accepted for this study. Eligibility included age ≤ 70 years, performance status ≤ 2 and adequate organ functions. Standard WHO response criteria were used. Liver metastases required assessment by computed tomography (CT) scans or ultrasound, while for the primary only CT scans were accepted. Response had to be assessed after every two cycles. Toxicity was graded according to standard WHO criteria.

The treatment schedule consisted of ifosfamide, continuous infusion 1.6 g/m^2 daily for 5 consecutive days (total dose 8 g/m^2), plus mesna uroprotection, 500 mg/m^2 every 8 h, the first dose just before the ifosfamide infusion and the last dose 8 h after termination of ifosfamide. Cycles had to be administered every 4 weeks. Treatment had to be continued until progression or severe toxicity.

A total of 26 patients were entered by 11 institutions from The Netherlands, Belgium and France, of which six entered only 1 patient. 21 patients were fully evaluable. The characteristics of these patients are listed in Table 1. Reasons for non-evaluability were performance status > 2 or insufficient organ status (2 patients), wrong treatment administered (2 patients), wrong histology (1 patient). There were 7 cases with stable disease after two cycles. All other patients progressed after at least one cycle. Cases of early progression and early death for whatever reason (4 cases) were considered failures. The median number of cycles was two, range one to six.

Table 1. Patients' characteristics (evaluable patients)

Patients	21
Male/female	16/5
Age	
Median	52
Range	37–70
Performance status (WHO)	
0	0
1	18
2	3
Site(s) of metastases	
Liver	17
Lung	4
Lymph node only	3
Skin	1

The side-effects were those to be expected and not severe, mostly grades 1–2. There was no grade 4 non-haematological toxicity and no severe myelosuppression. Encephalopathy was not reported. 1 patient experienced a clear partial response, but on review of the pathology was found to have a neuro-endocrine tumour and therefore this case was declared non-evaluable.

In this study no responses were observed in 21 evaluable patients with metastatic pancreatic cancer. Ifosfamide was administered in a fractionated 5-day schedule which is probably optimal for this drug. Because the dose of 8 g/m^2 is quite moderate and higher doses are probably feasible, it cannot be excluded that higher doses would have yielded better results. One good partial response was observed in a patient with a neuro-endocrine pancreatic tumour. In a previous trial of our group, we found insufficient activity of ifosfamide, 5 g/m^2, 24-h infusion, added to epirubicin, 90 mg/m^2, but we thought this might have been due to a suboptimal treatment schedule of ifosfamide [7]. We now confirm the data from the M.D. Anderson Institute [5] and from the Gastrointestinal Tumor Study Group (GITSG) [6], showing that ifosfamide in this dosage has insufficient activity in advanced pancreatic cancer.

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