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Single Agent Paclitaxel in the Treatment of Unresectable and/or Metastatic Pancreatic Adenocarcinoma

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ADVANCED AND/OR metastatic adenocarcinoma of the exocrine pancreas still represents a major challenge for clinical oncologists. Besides the well-recognised difficulties in evaluating the pancreatic area, even with the newer radiological imaging techniques, pancreatic adenocarcinoma is a chemotherapy-resistant malignant neoplasm [1]. 5-Fluorouracil still represents the preferred therapeutic option of many oncologists, although it only induces an objective response in a minority of cases, even if modulated by folinic acid and/or interferons [1]. To date no standard chemotherapeutic treatment exists and a search for new and active therapies for pancreatic adenocarcinoma is thus a major goal for all investigators involved in the fight against cancer [2].

Paclitaxel, a taxane diterpenoid drug recently isolated and extracted from *Taxus Brevifolia*, has been successfully employed in the treatment of several human malignancies, notably metastatic breast and ovarian carcinomas [3]. This drug displays a unique mechanism of biochemical action since *in vitro* paclitaxel is able to bind covalently to the beta subunit of tubulin, stabilising microtubules and eventually blocking depolymerisation [4, 5]. Paclitaxel blocks neoplastic cells in the G2/M phase and it may also act as a radiosensitiser. Recent preclinical studies have shown good antineoplastic activity of paclitaxel against pancreatic cancer heterotransplant [6].

With the aim of testing the clinical activity and the pattern of toxicity of paclitaxel in the treatment of locally advanced, unresectable and/or metastatic pancreatic adenocarcinomas, we carried out a phase II investigation on a series of 14 patients. Prior to the entry into the study, patients had to fulfill the following eligibility criteria: informed consent; histologically proven diagnosis of unresectable and/or metastatic adenocarcinoma of the exocrine pancreas; performance status according to the Karnofsky Index ≥ 60; life-expectancy >2 months; absence of uncontrolled cardiovascular, renal, neurological or infective disease; and geographical accessibility to the centre in order to guarantee follow-up. Patients were staged with physical examination, standard chest X-ray, bone scan, abdominal sonograms and CT scan, EKG, routine chemistry tests, and haematological parameters. Other procedures were employed as needed.

Treatment included single-agent paclitaxel 175 mg/m^2 given in 500 ml of normal saline as a 3 h infusion every 3 weeks. Dexamethasone, 8 mg i.v., plus ranitidine, 50 mg i.v. and diphenhydramine, 50 mg i.v., were given before the paclitaxel infusion. Tropisetron, 5 mg i.v., was employed as antiemetic therapy. After three complete courses of chemotherapy, patients were fully restaged with physical examination, chest X-ray and CT scan of the abdomen. Objective responses were defined according to the standard WHO criteria [7].

14 patients have been treated so far. All patients, but one, had not received surgery or radiotherapy. One patient had had a previous pancreasectomy. No patients had previous chemotherapy. There were 8 males and 6 females with a median age of 62 years (range 44–70) and a median performance status of 80 (range 70–90). Tumour sites included: locoregional neoplasm in 13 patients, liver in 6, extrapancreatic abdominal mass in 1 case, lungs in 1 case, and local recurrency in 1 previously treated with surgery. All enrolled patients were evaluable for both response and toxicity according to WHO criteria [7]. No major objective response was recorded. 5 patients (36%) showed a stabilisation of disease with a median duration of 6 months (range 3.4–8.0 months). The remaining 9 patients progressed. According to Gehan's formula [8], the trial was stopped since no major objective response was seen. Paclitaxel was well-tolerated in most instances. A minor allergic reaction was recorded in one patient (skin rash). Myalgia was reported by 3 patients (21%), alopecia in 8 cases (57%), and grade 3 leucopenia in 4 patients (29%). Neurotoxicity was almost absent. Grade 1–2 constipation occurred in some patients, but it was not possible to determine whether this was due to paclitaxel and/or anti-HT3 anti-emetics. Median survival was 7.2 months (range 3.0–11.0 months).

These data are consistent with those reported by others [9] that failed to observe major objective responses in a series of 20 patients with advanced pancreatic adenocarcinoma. It should be stressed that even if the median survival observed in our study is not outstanding, the impact of paclitaxel on survival cannot be precisely assessed due to the phase II nature of the study and the small size of patients sampled. However, in our opinion, these data do not support the use of paclitaxel in advanced pancreatic adenocarcinoma.

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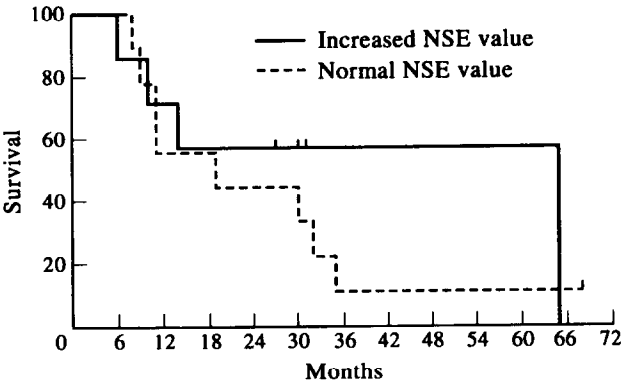

Figure 1. Overall survival according to initial NSE (neuron-specific enolase) value.

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Serum Neuron-specific Enolase (NSE) as a Tumour Marker for the Ewing's Sarcoma Family of Tumours

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EWING'S SARCOMA and peripheral primitive neuroectodermal tumours (PNET) have recently been included in what has been designated the 'Ewing's sarcoma family of tumours' [1], because they share a common molecular pattern. Clinical features have recently been described in adults and they do not seem to differ from those found in children [2]. No serum tumour marker is currently available. These neoplasms commonly express neural differentiation: neuron-specific enolase (NSE) expression, as assessed by immunohistochemical analysis, is found in 15–58% of lesions [3–7]. However, controversial data exist concerning the prognostic value of NSE: Pinto and coworkers [3] reported a better outcome for patients with NSE expression, whereas other authors have not confirmed these results [4–6].

We assessed serum NSE in a series of 21 consecutive adult patients with Ewing's sarcoma or PNET, homogeneously treated in our institution. 13 were male and 8 were female. Ages ranged from 17 to 34 years (median: 21 years). 16 patients had localised disease, whereas 5 had metastases at presentation. 12 patients had Ewing's sarcoma of bone; 1, Ewing's sarcoma of soft tissue; 7, neuroepithelioma and 1, Askin's tumour.

Serum NSE was elevated (> 12.5 ng/ml) prior to therapy in 11 patients (52%), i.e. 7 of 16 patients with localised disease (44%) and 4 of 5 with metastatic disease (80%). Treatment consisted of neoadjuvant chemotherapy combining doxorubicin, ifosfamide, vindesine and cisplatinum, followed by surgery when possible, or radiotherapy. Of 11 patients, 9 with initially elevated NSE (82%) achieved a clinical response to primary chemotherapy. Of these 9, 7 had localised disease. In contrast, only 4 of 10 patients (40%) with initially normal serum NSE responded to therapy ($P < 0.2$).

After primary chemotherapy serum NSE was normal in 17 patients (81%) of whom 14 had localised disease. The remaining 4 patients with elevated serum NSE during the course of chemotherapy had a very poor outcome since all died within the first year of diagnosis. The number of cases with data available on histological response or serum NSE at relapse was insufficient for analysis. Overall survival curves of patients with localised disease according to initial serum NSE were calculated using the Kaplan–Meier method and are presented in Figure 1. Patients with initially raised NSE seemed to fare better long-term. However, statistical significance was not reached ($P = 0.54$), possibly because the number of cases was too small.

In conclusion, serum NSE is elevated prior to therapy in approximately 50% of patients with neoplasms belonging to the Ewing's sarcoma family of tumours. This tumour marker seems to be more frequently elevated in cases of metastatic disease and usually normalises during therapy. Patients with localised disease and elevated serum NSE are likely to achieve a better response to chemotherapy, although statistical significance was not reached in our experience. These findings require further studies for definitive conclusions.

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