26 P

MONITORING OF NEUROTOXICITY OF TAXANES

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Because the clinical use of taxanes might be limited by neurotoxicity, we have determined both clinical and electrophysiological neurological functions in 14 patients treated with paclitaxel/cisplatin (cumulative paclitaxel doses 175-1225 mg/m², cumulative cisplatin doses 100-700 mg/m²) and in 6 patients treated with docetaxel (cumulative doses 100-400 mg/m²). Among the paclitaxel/cisplatin group, 12 patients developed sensory symptoms. Additional weakness was seen in 8 patients but motor nerve conduction studies of the peroneal nerve revealed impaired function in 13 patients. Three courses of docetaxel resulted in sensory neuropathy and a decrease in orthodromic sensory conduction velocity of the lateral plantar nerve in 3 patients. Docetaxel did not result in clinical motor neuropathy or altered motor nerve conduction of the peroneal nerve. In both groups, severity of clinical and electrophysiological neurotoxicity progrediently increased with cumulative drug doses. In conclusion, patients treated with paclitaxel/cisplatin developed sensory and motor neuropathy, whereas patients treated with docetaxel only developed sensory neuropathy. Careful neurological and electrophysiological monitoring might allow to detect early symptoms of neurotoxicity and thus to avoid severe neurotoxicity.

27 P

SECOND LINE CHEMOTHERAPY WITH MODULATION OF DRUG RESISTANCE IN PATIENTS WITH ADVANCED SOFT TISSUE SARCOMA

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Metastatic soft tissue sarcoma constitutes a major therapeutic problem potentiated by the development of drug resistance. The present pilot study was therefore undertaken in order to study the possibility of modulation of drug resistance by tamoxifen in patients with metastatic soft tissue sarcoma after the administration of combined cytostatic therapy consisting of ifosphamide (1.5 g/m²), adriblastin (50 mg/m²) and DTIC (200/m²), all on days 1-4; (IFADIC).
12 patients with soft tissue sarcoma who experienced progression under or following treatment with IFADIC underwent second-line chemotherapy with Epirubicine 60mg/m² (days 1 and 22), CCNU 80mg/m² (day 1) (ECC) and high-dose Tamoxifen (480mg/day, day -1 to +1) in an endeavour to modulate drug resistance. Under this very well tolerated, low toxic regimen, 1 patient with lung metastases experienced complete remission (duration: 5 months +) and 1 patient partial remission (duration: 6 months). 1 final patient experienced stable disease for 12 months thus resulting in an overall response rate of 3 out of 12 patients. We conclude that this low-toxicity regimen might be effective in heavily pretreated patients with soft tissue sarcoma thus making the use of high-dose tamoxifen a possible canditate for modulation of drug resistance in metastatic soft tissue sarcoma.

28 O

BATIMASTAT POTENTIATES CISPLATIN ACTIVITY ON HUMAN OVARIAN CARCINOMA XENOGRAFTS

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Batimastat (BB94) is a synthetic metalloproteinase inhibitor with antimetastatic and antiangiogenic activity. We investigated the antineoplastic activity of BB94 in combination with cisplatin (DDP) against human ovarian carcinoma (HOC22) xenografts transplanted ip in nude mice. BB94 (60 mg/kg ip) was given alone, concurrently with or after DDP treatment (4 mg/kg iv) for two weeks. Treatment with BB94 alone on early stage HOC22 increased the survival time of the mice (ILS=56%), but was not active on late stage tumor. BB94 given concurrently with DDP cured all the mice with early stage HOC22 and increased the survival time of the mice with late stage tumors (ILS=48%). BB94 given after DDP significantly increased the survival of mice (ILS=162%). Response was assessed by cytohistological analysis and serum CA125. These data show that BB94 is active against human ovarian carcinoma xenografts after initial or concomitant tumor reduction with DDP and provide the rationale for its use with or after reductive chemotherapy.

29 P

Gemcitabine: an active well tolerated drug for advanced non small cell lung cancer (NSCLC). F. de Braud, E. Munzone, F. Nole', T. De Pas and M. S. Aapro, European Institute of Oncology, Milan, Italy.

Gemcitabine is a new antimetabolite that has shown activity in a wide range of solid tumours. Until 1994 to January 1996, 16 patients (pts) (M/F= 10/3 median age 57, range 41-73) with advanced NSCLC received Gemcitabine as single agent in an out-patient setting at the Medical Oncology Division of the European Institute of Oncology. Performance status was 0-1 in 15 of them and 2 in one case. Nine were chemonaive, and 7 were previously treated with cisplatin based chemotherapy (3 refractory and 4 responsive and relapsed). The planned schedule was to administer Gemcitabine as 30 minutes infusion on day 1, 8 and 15 q 4 weeks (one cycle) at the starting dose of 1250 mg/sqm in 10 pts, 1000 in 5 and 800 in 1. Overall 159 administrations (for a total of 61 cycles) were given. The worst reported toxicity was: Grade 3 hematological in 11 administrations (4 pts), grade 2 fever in 13 (4 pts), grade 2 nausea or vomiting in 2 (2 pts). The dose has been reduced by 25% in 4 administrations (3 pts). Among the 13 pts with measurable disease there were 3 partial responses, 7 stable diseases (SD) and 3 progressive diseases (PD). We confirm that Gemcitabine is an active and well tolerated new drug for NSCLC. Further studies in combination with other agents are warranted.

30 P

OUR EXPERIENCES WITH IFOSFAMIDE

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Ifosfamide was developed in the laboratoris of ASTA Pharma AG and intoduced in Germany as early as 1977; however its clinical use was restricted by its dose - limiting urotoxicity. Since the introduction of mesna in 1982 the urotoxicity of ifosfamide can now be controlled, higher ifosfamid doses can be administered. Ifosfamide, like cyclophosphamide, belongs to the group of oxazaphosphorines. Regarding the profile of action of both compunds, there are important differences in: chemical structure, pharmacodynamics, metabolism, pharmacokinetics, pharmacotherapeutic characteristics and detoxification. The authors presented their experiences with Ifosfamide, which were used in combined chemotherapy. They analysed response rate and toxicity of chemotherapy in 128 patients with lymphoma malignum, testicular cancer, lung cancer and soft tissue sarcoma. Response assesment was made according to recent WHO principles. All evaluated patients received at least 2 courses of chemotherapy.

31 P

IMMUNOLYMPHOSCINTIGRAPHY AND SENTINEL NODE BIOPSY IN MELANOMA.

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Sentinel node biopsy (s.n.b.) is now a well accepted way of managing patients presenting with high risk primary melanoma. The surgical technique has two major problems: I) the sentinel node (s.n.) in a lymph node station is not always close to the skin incision, necessitating a larger operative field. II) the lymphatic drainage can sometimes skip the first nodal station and, as a result, the s.n. will be located in different lymph node regions. Percutaneous lymphoscintigraphy using ^{99m}Tc labeled colloid has been shown to resolve both these problems but can not help to define the presence of microscopic metastases. We have now investigated eight patients following a protocol designed to detect preoperatively microscopic metastases in regional nodes. Six patients were clinical stage I and, except the initial two patients of the series, all received both s.n.b. and percutaneous lymphoscintigraphy, while two patients were stage II and received percutaneous lymphoscintigraphy only as positive controls. The percutaneous lymphoscintigraphy technique we developed differs from the standard technique as used an anti-melanoma labelled monoclonal antibody (185 ^{99m}Tc F(ab')$_2$ MoAbs 255.28S, Sorin Biomedica) instead of a non specific radiotracer like colloid. An equal amount of radiotracer was also injected in the contralateral side as a control. Dynamic images were acquired for the first 5 minutes after injection, followed by static views at 10, 15, 30 minutes and 1, 3, 24 hours post injection. In all six patients studied with percutaneous lymphoscintigraphy the s.n. was easily visualized at least 15 minutes after injection of the radiotracer. In four cases no stained lymphatic vessels and nodes were found during s.n.b.; of these, three received percutaneous lymphoscintigraphy and two presented microscopic metastases on the nodes biopsied following the findings of percutaneous lymphoscintigraphy only. To date, one false negative s.n. has been recorded: this was the first patient of the series, who developed clinically evident nodal metastases 9 months after the s.n.b.. This is one of the two patients who did not receive preoperative percutaneous lymphoscintigraphy. Finally, the differences found with percutaneous immuno-lymphoscintigraphy did not show a specific result linked to the presence of F(ab')$_2$ in radiotracer uptake between both sides on each patient, whether the patients were stage I or stage II. There were no complications following percutaneous lymphoscintigraphy. This pilot study demonstrates that percutaneous lymphoscintigraphy is a safe and effective method of detecting the s.n..