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TAXOTERE IN ADVANCED MALIGNANT MELANOMA: A FASE-II TRIAL OF THE EORTC EARLY CLINICAL TRIALS GROUP.

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Taxotere (T) is synthesized from needles of the European yew, Taxus Baccata and inhibits mitosis by stabilizing microtubuli. In B16 malignant melanoma T has more than twofold activity compared to that of Taxol and it has antitumor activity in pleotropic drug resistant cell lines. T was administered, 100 mg/sqm i.v. over 1 hour, without prophylactic steroids, antihistaminics or antiemetics, every 3 weeks. None of the patients had received previous chemotherapy. Response evaluation was performed after two cycles. Of the 38 patients entering the study 35 have been evaluated: 5 had PR, additional 2 had PR needing confirmation after 4 weeks, 8 NC, 13 progressive disease and 7 were not evaluable. The main toxicity was neutropenia CTC grade >2 in 73/118 cycles (CTC grade 3 in 36/118;CTC grade 4 in 37/118). Fatigue/malaise CTC grade 1 and 2 was found in 45/118 (CTC grade 3 in 3/118). Nausea and vomiting CTC grade 1 and 2 was seen in 34/118 and skin toxicity grade 1 and in 28/118 cycles. Hypersensitivity reactions were seen in 20/118 (CTC grade 1 and 2 in 18/118; CTC grade 4 in 1/118). Dose reduction was necessary in 12/118. Alopecia was seen in 28/37 patients. Conclusion: neutropenia is the major T toxcicity, without premedication hypersensitivity reactions may occasionally be serious. Taxotere has some antitumor activity in malignant melanoma.

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IN VIVO KINETIC STUDY AND BIODISTRIBUTION OF Tc-99m-F(ab')2 OF ANTIMELANOMA ANTIBODY.

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Modern imaging techniques can provide possibility for detailed whole body distribution of the tracers. The aim of this study was to evaluate the in vivo kinetics of Tc-99m-F(ab')2 of the 225.28S against HMW-MAA, after s.c. or i.v.inj. Study subjects were 10 patients with a histologically confirmed diagnosis of melanoma (UICC Stage I-IV). A whole body and SPECT gamma diagnostic system Philips was used for the scintigraphic recordings. Specific regions of interest(ROIs) for the heart, liver, spleen and tumor lessions were selected on the recorded images and the relative radioactivity concentrations for each ROI were determined. Blood was drawn just before and at 2, 5, 30, 60, 90 min. and 4, 6, 24h p.inj. and was used to follow up the blood clearance of Tc-99m-F(ab')2. It was observed a lower percentage of positive scans of metastases in liver, lung, spleen and skin because of the poor tumor to background ratio. According to our observations, the s.c. route of injection is preferred over the i.v. one, with the obvious advantage of reducing the vascular background and non-specific accumulation.

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LYMPHOKINE-ACTIVATED KILLER (LAK) CELLS ACTIVITY, PHENOTYPIC MARKERS AND MITOGEN RESPONSES OF PERIPHERAL BLOOD MONONUCLEAR CELLS (PBMC) ISOLATED FROM MELANOMA PATIENTS UNDERGOING COMBINED IMMUNOTHERAPY AND CHEMOTHERAPY. Eisenthal A, Skornick Y, Ron I, Sakuth V and Chaitchik S. Sourasky Medical Center, Tel-Aviv, Israel.

We have analyzed different immunological parameters of PBMC isolated from melanoma patients, who underwent chemotherapy of DTIC and Carboplatin followed by immunotherapy of low doses IL-2 and IFN-alpha, administered subcutaneously. PBMC from fourteen patients were isolated before chemotherapy, before immunotherapy and post immunotherapy. After chemotherapy, a decrease in CD16+ cells and an increase in CD4+ cells correlated with a substantial decrease in the generation of LAK activity. After immunotherapy, an increase in CD16+ cells correlated with an increase in the induction of LAK activity. A comparative analysis between responding (5/14 patients) and non-responding patients (9/14), revealed statistically significant differences in the generation of LAK activity and response to ConA, following chemotherapy and in the percentage of CD16+ cells, after immunotherapy. Based on our findings, we propose to extent such a study to a larger cancer population for revealing a possible correlation between selected immunological parameters and clinical responsiveness.

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ORAL TROPISETRON (TRO) IN THE PROPHYLAXIS OF DACARBAZINE (DTIC) INDUCED NAUSEA AND EMESIS

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With conventional antiemetic prophylaxis, patients under DTIC chemotherapy often suffer from severe nausea and vomiting. We performed a double-blind, randomised, multicenter trial in order to compare the prophylactic effect of two different dosages of tropisetron in DTIC-treated patients with melanoma. Before start of their first DTIC-course, patients were randomised to receive 5 or 10 mg tropisetron orally once daily on each chemotherapy day.

90 patients in 5 dermatological centers entered the study, 45 patients were randomised to each group. All patients received DTIC ≥ 150 mg/m²/d for 1 - 10 days. TRO was very effective in prevention of DTIC-induced emesis: On day 1, only 3 patients in the 5 mg group and 1 patient in the 10 mg group vomited 1 - 2 times and 7 patients under 5 mg and 5 patients under 10 mg felt nauseous. Efficacy was maintained throughout the cycle. Patients judged efficacy and tolerability as "very good" or "good" in 76 % and 77 %, respectively. Side effects (headache, constipation) were mild and well tolerated.

Conclusion: 1) TRO is highly efficacious and well tolerated in prevention of DTIC-induced nausea and emesis. 2) No difference in efficacy could be stated between 5 and 10 mg TRO once daily p.o.

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PREOPERATIVE CRYODESTRUCTION (PC) OF SKIN MELANOMA (SM): PHASE I STUDIES

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5 pts with clinical stage I malignant melanoma and 12 pts with clin. stage II have been undergone a treatment according to the scheme: 1) PC and local radiation therapy 20 - 30 Gy (2-3 days before the operation), 2) operation - extensive excision of the tumour with regional lymphadenectomy, 3) chemotherapy.

- Cryodestruction has been done on 8 pts 1 - 5 days before the operation (Group 1). SM of the 9 pts has been frozen immediately before the excision (Group 2).

In the process of treatment natural killers and tumour markers (Ferritin, CEA, AFP) have been determinated in blood.

In some cases postoperative histological studies (in Group 1) showed complete change in morphological character of SM. This kind of cryoradiative pathomorphism of the tumour testifies to expedience of the PC of SM.

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REPEATED TUMOR INFILTRATING LYMPHOCYTES (TIL) INFUSION IN METASTATIC MALIGNANT MELANOMA (MMM). Ravaud A, Coulon V, Legrand E, Delaunay M, Bussières E, Bui NB, Gualde N. Fondation Bergonié, 33076 Bordeaux (France).

Patients (pts) with MMM, with accessible(s) site(s) for which expanded TIL could allow to 10^{10} or more for a first infusion, were included in this trial. They received TIL every 21 days for 2 pts, every 15 days for 3 pts and every 8 days for 4 pts. If progressive disease was notified during TIL therapy, IL-2 (Proleukin) at $18x10^6$ UI/m² was given, following TIL infusion for 3 to 5 days, by a constant infusion. Study is on going, 8 pts have been treated. The average number of TIL infused was $1.4x10^{11}$ (range 0.75-2.35). Predominant TIL phenotype was CD8+/CD4- in 4 pts, CD4+/CD8- in 3 pts and CD56+ in 1 pt. TIL phenotype varied along the times of culture and infusion. IL-2 was given to 3 pts. Toxicity (WHO grading) with TIL alone was : hypotension grade 3 : 1 pt ; vomiting grade 3 : 1 pt ; severe coagulopathy : 1 pt ; fever grade 2 : 5 pts ; fatigue grade 2 : 2 pts ; headache : 2 pts, pericarditis effusion grade 1 : 2 pts. No objective response was seen, but 2 pts presented a transitory minor response (25 %< ≤ 50 %) on a liver and a subcutaneous lesion, with TIL alone.

We concluded that repeated TIL infusions in MMM are feasible, with possible grade 3 toxicity and minor evaluable objective response.