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FOTEMUSTINE, DACARBAZINE (DTIC) AND INTERFERON α-2A (IFN) TREATMENT OF METASTATIC MELANOMA. PRELIMINARY DATA

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Purpose: This phase II study was undertaken to define the toxicity and therapeutical activity of a Fotemustine-DTIC-IFN combination in patients (pts) with metastatic melanoma.

Methods: Treatment consisted of Fotemustine 100 mg/m^2 i.v. d 1, DTIC 250 mg/m^2 d 2–5 every 3 weeks. IFN 3 MUI was administered i.m. 3 times a week throughout the chemotherapy administration.

Results: At the time of this analysis (08-03-1995) 35 pts (20 M, 15 F; age range 24–75 years; 26 chemotherapy-naive; 26 with visceral or SNC involvement) have been treated for a total of 125 courses. Twenty-six pts are presently evaluable for response (3 non-eligible for major protocol violation, and 6 too early). One CR and 5 PR have been observed for a 23% ORR [95% C.I.:9–44]. The patient with CR had skin, lymph nodal and renal involvement at beginning of the treatment.

Toxicity: 32 pts are evaluable for toxicity for a total of 122 courses. The treatment has been generally well tolerated. Toxic deaths have not been registered. Leucopenia and thrombocytopenia of grade 3–4 have been observed in only 2.5% and 6.5% of the total delivered courses respectively. Grade 3 anemia occurred in one patient. IFN-related fever occurred in 11.5% of the courses and was always mild.

Conclusions: Fotemustine-DTIC-IFN combination seems a well tolerated and quite effective treatment for patients with metastatic melanoma. Since we chose a 35% ORR as target activity level, and considered 20% ORR as the lowest level of interest, at least 7 responses in 31 evaluable pts are required in the first-stage of the trial to continue the accrual to a total of 53 pts.

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DACARBAZINE-VINDESINE VS DACARBAZINE-VINDESINE-CISPLATINUM IN DISSEMINATED MELANOMA—A RANDOMIZED PHASE III TRIAL

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In a phase III study of disseminated malignant melanoma performed in Sweden and Norway, 326 patients were randomized to receive treatment with the combination Dacarbazine (DTIC) and Vindesine (VDS) with or without addition of Cisplatin (CDDP). The study was designed to reveal a clinically significant survival difference when the three drugs were combined. DTIC was given i.v. at a dose of 250 mg/sqm days 1 to 5 every four weeks and VDS was given i.v at a dose of 3.0 mg/sqm day 1 weekly. CDDP was given i.v. at a dose of 100 mg/sqm day 1 every 4 weeks. There was no statistical significant difference regarding total survival between the treatment arms ($P = 0.22$). What was clearly demonstrated was an increased toxicity in the treatment arm containing CDDP. Two hundred and sixteen patients were evaluable for response in compliance with the WHO criteria. With the DTIC-VDS regimen 9.9% patients obtained a complete remission and 10.8% patients a partial remission with an overall response rate of 20.7%. With the triple regimen DTIC-VDS-CDDP 16.2% patients obtained a complete remission and 15.2% patients a partial remission with an overall response of 31.4%. The difference in objective response rates observed between the treatment arms is not statistically significant ($P = 0.1011$). In conclusion this study did not show any significant increases in median survival time or objective response rate. The study has demonstrated a clinically significant increase in toxicity and we suggest that this triple regimen does not merit further use in patients with disseminated malignant melanoma, which earlier phase II studies have indicated.

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ISOLATED LIMB PERFUSION FOR STAGE IIIA-IIIAB MELANOMA: TNF + L-PAM AND L-PAM + HYPERTHERMIA

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The aim of this report is to compare two different approaches using ILP. Two series of patients with stage IIIA or IIIAB melanoma were treated by ILP at the National Cancer Institute, Milan. Forty-four patients (group 1) received α-tumor necrosis factor (α-TNF; 1–4 mg) plus melphalan (50–100 mg) and mild hyperthermia (39°C), while 133 patients (group 2) were treated using melphalan (50–100 mg) and hyperthermia (40.5°–41°). No significant differences were obtained in terms of both overall response rate (complete plus partial responses) in the two series of patients (70.4% in group 1; 87.2% in group 2) and relapse rate (34.1% in group 1; 44.4% in group 2). A significant difference in the appearance of new relapses was observed (6 months for group 1; 13 months for group 2). After a median follow-up of 11 months in group 1, 52.3% of patients have no evidence of disease, and 31.8% are alive with disease. In group 2 after a mean follow-up of 43 months, 30% of patients have no evidence of disease, and 8.3% are alive with disease. In conclusion, our experience did not confirm the impressive results demonstrated by other authors using α-TNF by ILP.

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THE EUROPEAN EXPERIENCE IN TNFα ISOLATED LIMB PERFUSIONS FOR NONRESECTABLE EXTREMITY SOFT TISSUE SARCOMAS: 85% RESPONSE RATE; 87% LIMB SALVAGE

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Goal: Achieve limb salvage in patients with irresectable soft tissue sarcoma (STS) of an extremity by ILP with TNFα ± IFN-gamma and Melphalan.

Material and Methods: 120 patients (pts) with nonresectable STS of the extremities were treated without IFN (65) or with 0.2 mg IFN (55) s.c. on the 2 days prior to a 90 minutes ILP with 0.2 mg IFN, 4 mg TNF (leg) or 3 mg TNF (arm), and 10 mg/L (leg)—13 mg/L (arm) limb volume of Melphalan at 39–40 °C. In 20% of the patients there were multiple sarcomas in the extremities. Residual tumors were resected (after 2–6 months) after maximal shrinkage (often 90%–100% necrotic). TNFα/IFN Boehringer Ingelheim GmbH.

Results: In 55 patients treated with TNF + IFN + Melphalan: 20 CR (36.4%), 29 PR (52.7%), 6 SD (11%); in 65 patients treated with TNF + Melphalan: 20 CR (30.8%), 33 PR (50.8%), 12 NC (18.4%). Median follow up of first 55 pts 18 + months (9 + −40 + months). Most tumors became resectable 2–3 months after ILP. Limb salvage rate was 49/55 (87.3%) and 56/65 (86%). Toxicity was moderate (grade I–II) and transient grade III liver toxicity. There were no toxic deaths.

Conclusion: Isolated limb perfusion with TNFα, ± IFN-gamma and Melphalan is safe and very effective against locally advanced extremity soft tissue sarcomas.

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DERMATOFIBROSARCOMA PROTUBERANS: CONTROL BY RADIATION

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Dermatofibrosarcoma protuberans is an exceptionally low grade malignant fibroblastic neoplasm of the dermis. Metastasis are almost unknown following successful treatment of the primary lesion. Histopathologically, DFSP closely resembles benign fibrous histiocytoma. These lesions locally infiltrate and exhibit a high local regrowth rate following conservative surgery. We have employed radiation in the management of 16 patients for their DFSP alone or in combination with surgery. No patient has been lost to follow-up with the most recent examination at 2 to 10 years post treatment. The tumors were primary (11) and recurrent (5). Local control has been achieved in 14 of the 16; 9 of 11 primary and 5 of 5 recurrent DFSP. Treatment has been radiation and