A PHASE I TRIAL OF HIGH DOSE TAMOXIFEN (TAM) AND WEEKLY DDP IN THE TREATMENT OF METASTATIC MELANOMA.
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We have previously demonstrated that TAM is synergistic with DDP in clinical trials in patients with metastatic melanoma. In the laboratory we have demonstrated that this synergy is dependent upon TAM, which is not the result of a TAM effect on any of the known mechanisms of DDP resistance. In the laboratory TAM will make sensitive cells more sensitive, DDP resistant cells sensitive and will interfere with the ability of the tumor cells to develop resistance to DDP. In order to improve upon the complete response rate of this regimen we initiated a phase I trial evaluating the objective response rate in patients treated with increasing doses of TAM in combination with a weekly dose of DDP (50mg/m²). Patients were treated weekly for 3 weeks, given a 2 week rest, then treated weekly X 3 again. Response evaluation occurred at 4 and 9 weeks after the start of therapy. The starting dose of TAM was 160 mg/day and has been increased to a current dose of 320 mg/day. No responses were observed in patients treated at TAM doses less than 240 mg. In 7 patients treated above this dose there has been 1 CR, 2 PRs, 1 progressive disease and 2 too early to determine. Toxicity has been primarily hematologic in nature at the higher doses. There have been no episodes of thrombosis to date. Correlative laboratory studies of DDP and TAM pharmacokinetics as well as serial evaluations of the effect of TAM/DDP on the expression of GADD 153 and p53 are in progress. Supported by NIH grant CA 52151.

PREDICTORS OF LONG-TERM SURVIVAL IN STAGE IV MELANOMA.
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Retrospective review of the records of 59 pts who presented with or developed as first site of recurrence nodal or intranodal metastases. 20 had achieved a CR (10 to chemotherapy and 2 to immunotherapy). Thus, the LTS were more likely to have undergone a complete resection of their metastases than the controls (56% vs. 14%; p=0.019). And, the LTS were also more likely to have achieved a CR or PR with initial chemotherapy or immunotherapy (40% vs. 5%; p=0.001). ([Supported by grant CA-09207-18].

ROLE OF CT SCAN'S IN THE STAGING OF MELANOMA PATIENTS WITH LOCAL/REGIONAL DISEASE. A.C. Buzaid, L. Tinoco, M. Ross, S. Legros, R. S. Benjamin. The University of Texas M. D. Anderson Cancer Center, Houston, TX 77030.

Introduction: We have previously shown that CT scans of the brain, chest, abdomen and pelvis have a low yield in detecting occult metastases (mets) in patients (pts) with primary melanoma (J Clin Oncol 11:638, 1993). Objectives: To study the value of CT scans in the staging of melanoma pts. Methods: Retrospective review of the records of 99 pts who presented with or developed as first site of recurrence nodal or intranodal metastases. Results: Of the 99 pts 36% had achieved a PR (10 to chemotherapy and 2 to immunotherapy). When the scan identified either regional or distant disease which was not appreciated on physical examination: false positive (FP), when the scan revealed a radiologic abnormality which was not chage for at least 6 months or was proven to be histologically benign; false negative (FN), when a pt had symptoms suspicious for mets and was subsequently found to have mets, but all imaging studies were nondiagnostic; true negative (TN), when all imaging studies were negative for mets in a asymptomatic pt. Results: TP - 11 pts, FP - 21 pts, FN - 1 pt, and TN - 66 pts. Of the 11 pts with TP findings, only 2 were symptomatic. Lung mets were identified in 5 but in only 2 the chest CT identified disease which was not visible on chest-x-ray (CXR). CT of the abdomen or pelvis revealed mets in 5 pts. CT of the pelvis, however, was normal in all 32 pts with recurrent disease above the waist line. CT or MRI of the brain showed no evidence of brain mets in any patient, although it showed asymptomatic skull mets in 1. The most common CT finding were hypodense lesions and noncalcified lung nodules. Conclusion: 1) TP are observed in about 10% of the pts. Because FP are more common than TP findings, histologic diagnosis of recurrence is advisable; 2) CT or MRI of the brain are not necessary in asymptomatic pts; 3) chest CT adds very little to a CXR and is not routinely indicated. In light of the cost-conscious environment of the current health-care system, our results are of practical importance.

COMBINATION CHEMOTHERAPY TOGETHER WITH INTERFERON-ALPHA (IFN) IN METASTATIC MELANOMA (MM). A MULTICENTER PHASE II STUDY.

Chemoimmunotherapy with dacarbazine (DTIC), vincristine (VCR), bleomycin (BLM), ifosfamide (IFNa) and 5-fluorouracil (5FU) have shown a promising response rate of 62% in 45 patients (pts) with initial stage IV MM. We started a multicenter phase II study in order to confirm these results. Treatments consisted of DTIC 200 mg/m² d1, VCR 1 mg/m² d1-4, BLM (5 mg d2), IFNa 50uni. subcut. d1, 300 uni. subcut. d4, and 300 uni. subcut. d11. All pts were entered every 2 months for response, and weekly for toxicity. Currently 23 pts are entered and 18 are evaluable. One pt died on day 5 of treatment of unknown cause and is not included in the response evaluation. Five pts are too early. Pts characteristics are male/female 11/7, median age 57 yrs (33-74), median PS 0 (0-2). Sites of metastases were skin 11, lymph nodes 10, lung 9, liver 9, bone 2, brain 4, other 7 pts. Median number of metastatic sites was 4 (1-9). Prior treatment: surgery for metastases 8, radiotherapy 5, chemotherapy 3, immunotherapy 3 pts. Pts received a median of 4 (1-6) cycles. Seven pts achieved a CR (RR 41%, 95%Cl 18-67%), all systemically no pretreated, 3 pts SD and 7 pts PD. Two PR occurred in pts with previously irradiated brain metastases. Progression with brain metastases occurred in 5 of 6 pts without initial brain metastases. In 4 pts with PD after 2-4 cycles who chemotherapy was continued but IFNa was interrupted every 2 wks for 2 weeks, no response was seen, which is in contrast to previous observations. Median duration of response and survival are in excess of 5 months. Toxicity grade 1/11 (WHO) consisted of fatigue 7 pts, nausea/vomiting 5, leukocytopenia 4, flu-like symptoms 2, nausea/vomiting 1, pulmonary fibrosis 1, neurotoxicity 2, and death. 1 dose were reduced in 8 pts. We conclude that this regimen is active in pts with metastatic melanoma with high-volume disease. In pts in whom chemotherapy or immunotherapy is recommended. Toxicity may be substantial, but this schedule is feasible in an outpatient setting. Accrual will continue, and updated results will be presented.