Melanomas

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THE CLINICAL SIGNIFICANCE OF ONCOGENE EXPRESSION IN MALIGNANT MELANOMA.

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Malignant melanoma continues to pose a therapeutic and epidemiological challenge. However, the answers to outstanding questions will only be found with greater understanding of tumour biology. Considerable interest centres on the molecular genetics of cancer and, in particular, the behaviour of oncogenes. Using flow cytometry, we have studied expression of the protein products of two oncogenes, p53 and c-myc, in human melanoma. In addition, the proliferation kinetics of these tumours have been measured using bromodeoxyuridine with an *in vivo* technique. These parameters have been related to the clinico-pathological features of each tumour. We have investigated both fresh and fixed material (ethanol and paraffin-embedded) in both a prospective and retrospective study. To date, our results show both oncogenes to be frequently over-expressed in melanoma; p53 was expressed in 77% of primary lesions and 83% of metastases, while c-myc was found in 67% of primary tumours and 88% of secondaries. The level of expression of c-myc was associated with tumour proliferation and outcome. No such relationship was evident with p53. Consideration of these markers may lead to improved tumour characterisation and an objective platform upon which to design future therapy.

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EFFECT OF CALCIUM-CHANNEL BLOCKERS AND PROTEIN KINASE C INHIBITORS ON MELANOMA CELL GROWTH AND DIRECTIONAL MIGRATION IN VITRO.

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In malignant melanoma active movement of cancer cells is considered to be essential for tissue invasion. Various mechanisms, such as the Ca^{2+}-calmodulin-protein kinase C (PKC) cascade are considered to play a role in tumor cell functions.
In this study the antimigratory effect of drugs interfering with steps of this pathway was investigated using the assay of directional migration combined with computer assisted image analysis. Besides this, the effect on melanoma cell proliferation was assesed.
Untreated K1735-M2 melanoma cells showed a migration rate of 377+-22µm/day. The calcium channel blockers verapamil and devapamil showed a slight reduction of motility (10 µmol verapamil: 382+-31µm/day; 10 µM devapamil: 383+-27µm/day); growth rates were not impaired. 2µM of the PKC-inhibitor dequalinium considerably decreased the migration rates (154+-7µm/day); other PKC-inhibitors, as tamoxifen and H-7, showed a clear dose dependent effect on melanoma cell directional migration, whereas growth rates were not affected dose-dependently.
Conclusions derived from this study are: 1. One critical target of the Calcium-calmodulin-PKC pathway in K1735-M2 melanoma cells might be the inhibition of proteinkinase C by different compounds. 2. Inhibition of melanoma cell directional migration is not consequently combined with inhibition of growth. 3. The assay of directional migration combined with computer assisted image analysis may be used for the screening of potential antiinvasive drugs.

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FREQUENCY OF HLA CLASS I ANTIGENS IN ISRAELI-JEWISH PATIENTS WITH ADVANCED MELANOMA

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The association between malignant melanoma and the expression of HLA class I antigens was studied in a group of 43 melanoma pts in comparison to 110 normal controls in the Israeli-Jewish population. The study group consisted of 25 pts with metastatic disease, 13 pts with stage II (involved lymph nodes) and 5 high-risk pts with advanced primary tumor. The expression of HLA-A and B locus antigens' in melanoma pts differed from that observed in the normal population. The frequency of HLA - A 24 (A9) was significantly ($p < 0.05$) higher in melanoma pts (37.2% in melanoma as compared to 16.6% in the normal population). HLA-B38 was also higher in melanoma pts (32.5% vs 20.6%), while HLA- B35 was lower in melanoma than in controls (20.9% vs 33.2%). A positive correlation was found between advanced (metastatic) disease and the expression of A 24 antigen : the frequency of metastatic disease was 93% (13/14) amongst those expressing A 24 antigen as compared to 58% (25/43) of total pts studied. This finding suggests that HLA class I antigens in general and A24 in particular may play a role in the biologic behavior of malignant melanoma.

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CUTANEOUS MELANOMA IS LESS FRIGHTENING IF TREATED IN OUTPATIENT REGIME.

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Since it has been established that for all melanomas, irrespective of thickness, survival is independent of width of resection margins, the Division of Diagnostic Oncology and Outpatient Surgery, Istituto Nazionale Tumori, Milan, initiated a new cutaneous melanoma (CM) management protocol, beginning in 1988. Two hundred and ninety CM patients, 120 (41%) males and 170 females (59%) have undergone excision with local anaesthesia as outpatients. Patients in whom the clinical diagnosis was not certain CM (125 cases), the initial excision (1-2 mm from margins) was for biopsy only and a subsequent wider excision was performed. This second "radical" resection was also performed in outpatient regime, 10-15 days after the initial surgery, if the thickness of the CM lesion was < 2 mm (85 cases), if greater patients were admitted and resection with 2-3 cm margins was performed (40 cases). When the resection was with 1 cm margins (clinical melanoma) and the histological evaluation revealed a lesion thickness of ≤ 2 mm (165 cases) this treatment was considered definitive. One hundred and sixty-five patients (56.8%) had a CM of thickness ≤ 0.76 mm, 76 (26.2%) had CM > 0.76 ≤ 2 mm and 49 (17%) had CM > 2 mm. Follow up was 24 months (mean), disease recurrence in 3 patients was apparently unrelated to the type of excision performed on the primary tumor. Outpatient surgery seems the best way to manage a workload characterized by the need to examine growing numbers of pigmented skin lesions, and at the same time permits diagnosis of a large number of thin, and therefore curable melanomas even when in situ (18.2%). Day Hospital surgery is appreciated by the patients, it reduces the psychological stress associated with admission and is much less costly than hospitalization.

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INTERLEUKIN2-ALPHA-INTERFERON COMBINED WITH CIS-PLATYL THERAPY IN METASTATIC MALIGNANT MELANOMA (MMM) PATIENTS : RESULTS OF TWO CONSECUTIVE TRIALS. D.Khayat*, E Antoine*, O Rixe*, JM Tourani*, E Vuillemin*, Ch Borel*, A Benhammouda*, L Thill+, C.Franks #, G Auclerc*, M Weil*, Cl Soubrane* et P Banzet° (*) Medical Oncology Dept, Salpetriere Hospital Paris, France, (°) Medical Oncology Dept., Laennec Hospital Paris, (+) Roche France Laboratory, Neuilly sur Seine, (#) Eurocetus BV, Amsterdam, The Netherlands,(°) Surgery Dept, St Louis Hospital, Paris,
Since February 91, 61 eligible patients (pts) with progressive MMM were entered into two consecutive chemoimmunotherapeutic trials. From 02/91 to 04/92, 39 evaluable pts have been treated with two monthly induction cycles of: cisplatyl (CDDP) 100mg/m² on day 1, rIL2 18 MUI/m²/d by 24 hours intraveinous infusion on day 3-6 and 17-21, and simultaneous subcutaneous INF 9MUI three times weekly. In order to try to increase the response rate (RR) Tamoxifen (TAM) was added to the same dose and schedule regimen of CDDP-IL2-IFN and was given from day -4 to day +5 at each CDDP administration. Since 04/92, 22 pts were included and 4 patients are too early to be evaluated.

	without TAM (n=39)	with TAM (n=18)
ECOG PS	0 (0-2)	0 (0-2)
Prior treatment with chemotherapy	33 (85 %)	20 (91 %)
Follow-up (week)	42 (16-95)	22 (8-36)
Toxicity (gr. III-IV):n (%)		
anemia	15 (38)	10 (55)
neutropenia	14 (35)	8 (45)
thrombopenia	10 (26)	8 (45)
renal toxicity	2 (5)	4 (17)
hypotension	17 (43)	11(61)
Response rate		
OR	21 (54 %)(95% CI:38-70)	9 (50 %) (95 % CI : 26-76)
CR	5 (13 %)	2(11 %)
Resp. duration (months)		
CR	3, 3, 16+, 17+, 20+	1,3+, 2
PR	5 (2.5-16+)	2+, 2+, 3+, 4.5,4.5+, 6+, 9+
Med. survival (months)	10.5 (2-21.5)	not reached

Response rates were similar in the two studies with responses obtained both on visceral {(TAM+:7/18 (39%); TAM-:11/18 (41%)}or non visceral metastatic sites {(TAM+:16/22 (7 %); TAM-:11/18 (52%)}. We confirm here on 57 evaluable pts the high activity of CDDP-IL2-INF combination (RR ≥50%) suggesting a potential synergism between CDDP and IL2-INF, and the ability of this type of combination to induce responses in heavily chemotherapy-pretreated patients. Although these regimens could be given safely (no life-threatening toxicity), TAM increased significantly the haemotological toxicity without enhancing neither the response rate nor complete response rate. However, in no case, an ICU supportive care was required. A large European multicenter randomized study is planned, comparing IL2-CDDP-IFN to CDDP-INF to assess definitively the value of IL2 in chemo-combinations for MMM pts.

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PHASE-II-STUDY OF FOTEMUSTINE, CISPLATIN AND HIGH-DOSE TAMOXIFEN IN METASTATIC MALIGNANT MELANOMA.

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Del Prete (1984) and McClay (1992) reported high response rates (51%) in malignant melanoma patients receiving the combination BCNU, DTIC, C and T. In this study Fotemustine (F) 100 mg/m²), a novel nitrosourea, was given 4 h. before cisplatin (C) (100 mg/m²) with 22 hours of hydration every 4 weeks. From the 2nd cycle on T (160mg) was given daily for 7 days before each cycle. A pharmacokinetic study of F was also performed. Response evaluation was performed after 2 cycles. Of the 38 pts included 3 had prior chemotherapy, and 7 local radiotherapy. No anti-coagulant prophylaxis was given. 2 pts are not eligible due to transplanted melanoma, 1 refused therapy after 1 cycle, 1 progressed whithin 2 weeks and 6 are too early for evaluation. Of the 29 evaluable pts there was 1 CR, 8 PR, 9 stable disease and 11 with progression. Toxicity (WHO): nausea and vomiting grade 1-2 was seen in 19 pts and grade 3 in 4 pts. Renal toxicity was seen in 12 pts (10 with grade 1-2; 2 with grade 3). Thrombocytopenia was seen in 17 patients (8 with grade 1-2; 5 with grade 3; 4 with grade 4. Ototoxicity grade 1-2 in 7 pts. Lecopenia grade 1-2 in 15 pts and grade 3-4 in 4 pts. 3 patients experienced DVT. The pharmacokinetic data did not reveal any significant differences between responders and nonresponders before and after introduction of T. Conclusion: The drug combination has good antitumor activity in malignant melanoma, but is less active than the recent published combinations with tamoxifen. Thrombo-embolic events are rare when tamoxifen is administered over a short period of time.