average 3% annually over a 25-year period in Sweden in contrast to cutaneous melanoma (CMM) which increased 5–6% annually during the same time period. We now characterize the MMV in terms of clinical and histopathological features and compare the results both with CMM and within the hairy and glabrous skin compartments of the vulva.

Methods: 219 consecutive cases from the Swedish Cancer Registry were investigated. All clinical records, pathology reports and histological slides were reviewed by us. Uni-and multivariate analyses were also carried out.

Results: Clinical amelanosis was common. The density of melanoma in vulvar glabrous, but not hairy, skin was about 2.5 times more common than in the body skin, on average. Histogenetic types dominated by the mucosal lentiginous melanoma, reversed the order of incidence in CMM, but were similar to those of palms and soles. Pre-existing nevi were found exclusively in the hairy vulvar skin, significantly related to superficial spreading melanoma, but rare in the vulva. Inborn biological aggressiveness in MMV was indicated by thick tumors and ulceration – independent predictors of tumor specific survival.

Conclusion: MMV not exposed to UV light and in several important respects different from CMM should constitute a convenient model for studying pathogenic mechanisms of MM other than UV light exposure.

1508 POSTER

Ectopic expression of allbb3 integrin in human melanoma modulate organ metastasis

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Purpose: Literature data indicated that rodent tumors can express thrombocyte integrin allbb3 ectopically. Therefore we have postulated that human melanoma may also express this ectopic thrombocyte integrin.

Methods: Expression of the allb chain in human melanoma cell lines (7) was studied at genetic as well as protein level using RT-PCR, Western blotting and immunocytochemistry. By stable transfection, high and low allb-expressing melanoma clones were isolated. In human melanoma samples (30) allb and av expressions were studied using double label immunohistochemistry and confocal microscopy.

Results: All the human melanoma cell lines studied, expressed allbb3 to various extent both at genetic as well as protein level. High av expressing clones colonized the lung and liver, while high-allb expressors colonized the brain and bone in SCID mice. On the contrary to the constitutive homogenous expression of the av chain in fresh human melanoma samples, the expression of the allb chain was gradually increased with the Breslow stages.

Conclusion: Our experimental and pathology data indicate that the megakaryocytic cell line-specific allbb3 integrin is expressed ectopically in human melanoma cell lines and skin primary melanomas. Experimental data indicate that av and allbb3 integrins may control the organ-preference of the metastatic process.

1509 POSTER

Phase II trial of 4-hourly temozolomide (TMZ) in advanced malignant melanoma (MM)

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TMZ is a methylating imidazotetrazine that has shown promising activity against MM. Its activity depends on the transfer of a methyl group to guanine in DNA at the O^6 position. The protein O^6-methylguanine-DNA methyltransferase (MGMT) repairs this lesion in a stoichiometric, auto-inactivating reaction, and is a major determinant of cell resistance to TMZ treatment. MGMT levels are depleted after TMZ dosing, but recover by 24 hours – the time of subsequent dosing. Optimizing the schedule of TMZ so that subsequent doses are given at the MGMT nadir (4 hours after the last dose) might enhance the effectiveness of TMZ against MM.

Material and Methods: Patients (pts) with advanced MM were treated with TMZ 1000 mg/m^2 (or 750 mg/m^2 if they had received prior chemotherapy), equally split into 5 doses over a 16-hour period, repeated every 28 days, for up to 6 courses.

Patients: 30 pts were entered into the study (14 M/16 F); median age was 57 yrs (29–83) and median WHO PS 1.20 pts had visceral metastases and 4 pts had received prior treatment.

Results: 28 pts were evaluable for toxicity and 25 for response. Eighty-three courses of TMZ were administered (median 2). Dose reductions were required in 45.7% of cycles and treatment was delayed on 9 occasions. The main toxicities observed were grade 4 thrombocytopenia in 12 pts (42.8%) and grade 4 neutropenia in 11 pts (39.2%), associated with infection in 8 cases. There were no treatment-related deaths. There were 7 responses (1 CR), for an ORR of 24%, with 5 SD (17%) and 13 PD (45%). Median overall survival was 6.1 months and median time to progression 1.8 months.

Conclusion: The 4-hourly schedule of TMZ is likely to enhance methylation in tumour and normal tissue, compared with the standard 5-day regimen. The compressed schedule has activity against MM, but the observed myelosupression, although readily managed, precludes its wider application.

1510 POSTER

Proteolytic enzymes prevent B16 melanoma metastasizing in C57B16 mice

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Purpose: Aim of the study was to examine antimetastatic effect of proteolytic enzyme (trypsin, chymotrypsin, papain) mixture on syngenic B16 melanoma in C57B15 mice. We intended to confirm our previous positive pilot results (Wald et al, Life Sci 1998)

Methods: 140 mice were included into experiment:

Control group 1 (C1) – rectal administration of saline from the day of melanoma B16 cell transplantation (20 animals)

Control group 2 (C2) – rectal administration of saline from the day of primary B16 melanoma extirpation (20 animals)

Enzyme group 1 (E1) – rectal administration of enzyme mixture from the day of B 16 melanoma cell transplantation (50 animals)

Enzyme group 2 (E2) – rectal administration of enzyme mixture from the day of primary B16 melanoma extirpation (50 animals)

Survival of mice and B16 melanoma generalization were observed for 100 days. All animals were dissected and organs were histologically examined.

Results:

(1) primary tumor size was significantly smaller in E1 group than in the groups E2, C1, and C2 (73.8 mm^3 in comparison to 302.4 mm^3, 298.9 mm^3 and 293.8 mm^3, respectively). In 36% of the group E1 animals, primary tumor did not grow at all.

(2) average survival of mice dependent on the B16 melanoma generalization was 27.25 and 28.65 days, respectively, in control groups (C1 and C2), while in the enzyme groups (E1 and E2) it was 72.06 and 53.5 days, respectively

Conclusions: Mixture of proteolytic enzymes (trypsin, chymotrypsin, papain) showed antimetastatic and antiproliferative effect on B16 melanoma in C57Bl6 mice.

1511 POSTER

C-myc expression as a new prognostic factor in melanoma

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Purpose: C-myc gene lies on the long arm of chromosome 8q (24) and encodes a nuclear phosphoprotein of 62 kDa that is known to play a key role in the control of proliferation. Our study was aimed to examine how expression of c-myc oncoprotein influences the average period of patient survival in melanoma, and to check any relationship between c-myc expression and a lesion thickness.

Methods: 49 patients treated in the years of 1990–92, aged 19–82 (average age 57), with different locations of melanoma were taken into the study. C-myc oncogene expression was examined by 'In Situ' hybridisation method.

Results: Patients' ages, lesion localisation, and histopathological parameters were analysed. It was found that there is a correlation between high c-myc expression and a short patient's survival and a short disease-free interval. The study also confirmed the correlation between melanoma lesions > 3 mm thick (Clark IV–V) and high expression of c-myc oncoproteins. Low c-myc expression was related to favourable prognosis for the patients.

Conclusion: The examination of the expression of c-myc oncoprotein is a very good prognostic marker in cutaneous melanoma, especially in thick lesions.