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POSTER

Clinical presentation, pathological features and natural course of metastatic uveal melanoma (MUM) as an orphan and commonly fatal disease

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Background: Uveal melanoma (UM) is a rare disease characterized by an unpredictable course and variable outcome ranging from cure by local treatment to the occurrence of untreatable metastasis. The current project is focused on the characteristics of the metastatic phenotype of the disease. **Methods:** We performed data collection in 76 patients with metastatic uveal melanoma (MUM) treated in Leuven between 1957–2008. Statistical analysis involved nonparametric tests, Kaplan Meier and log rank test.

Results: The median age at diagnosis was 58 years (range 30–94). Common initial treatments were surgery (71%), brachytherapy (20%) and external beam radiotherapy (7%). 73% of primary tumor arose in choroid and 27% in ciliary body; 51% had large size, 28% medium and for 21% we have missing data. Only 19% of pts had pure spindle cell type, 49% had mixed, 15% pure epithelioid, 15% spindle with epithelioid component. Extrascleral and venous invasion were found respectively in 24% and 16% of cases. MUM was more common in women (f:m ratio 48:28). Synchronous metastases were found in only 9% of cases, all others had metachronous disease after a median interval of 40 months (range, 7–420). Statistical analysis failed to identify predisposing factors for MUM with the exception of a significant negative correlation between age at diagnosis of UM and time until metastatic disease (Spearman $p = -0.4$, $p < 0.001$). Metastasis in more than 1 organ, usually liver plus another site, was seen in 47% of cases. The most frequent metastatic site was the liver (96%), followed by lung (24%), subcutaneous (16%), bone (11%) and brain (3%) lesions. The median OS from diagnosis of UM was 47 months (range, 2–236), and only 5 months in patients with MUM (range, 1–128). 65% of MUM patients qualified for further treatment, including systemic therapy (60%), radiotherapy (7%) and surgery (7%). Systemic therapy (45 pts) included mainly chemotherapy (50%), chemotherapy plus hormones (12%), immunotherapy (3%) or hormonal therapy alone (3%). The most common drugs given were DTIC (43%), cisplatin (27%), tamoxifen (10%) or phase I agents (8%). Patient benefit (PR+SD) was seen in 16/45 patients (36%), including 2 PR.

Conclusions: In this orphan disease with female predominance metastases occur late, is mainly found but not confined to the liver, and is associated with high morbidity, as >1/3 of pts do not qualify for further therapy. Advances in MUM can only be achieved by networking of sites interested in this tumor type with systematic collection of data and tissue to improve our understanding of the molecular biology of the disease.

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Ipilimumab in the common daily practice: feasibility, safety, efficacy and long-term follow-up in heavily pretreated metastatic melanoma patients

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Background: Effective anti-tumor responses are being observed in metastatic melanoma (MM) patients (pts) treated with the anti-CTLA-4 antibody Ipilimumab in clinical trials; however, no data support the feasibility and clinical effectiveness of Ipi use in the daily practice of MM. We report on a single Institution experience utilizing Ipilimumab within a compassionate program for MM pts.

Methods: 27 stage III (2) or IV (25) pts (14 males, 13 females), median age 55 (23–77) years, ECOG performance status 0–1, with MM (23 cutaneous, 3 uveal, 1 mucosal) progressing to 3 median (1–5) systemic therapies for metastatic disease received Ipilimumab. Eight pts had evidence (6) or history (2) of brain metastases and 11 elevated (>1× upper limit of normal [ULN]) LDH values. In the induction phase (IF) pts received Ipilimumab (10 mg/kg i.v.) q3 weeks (wks) for 4 cycles; following a 12 wks rest treatment was repeated q12 wks in the maintenance phase (MF). Tumor assessment

(TA) per modified World Health Organization Criteria was performed at baseline, week (wk) 12 (±2) and wk 24, then every 12 wks. Adverse Events (AE) and immune related AE (irAE) were collected according to Common Terminology Criteria for Adverse Events version 3.0.

Results: All pts received at least one Ipilimumab dose, and 21/27 completed the IF; the remaining 6 pts, were withdrawn for disease progression (3 pts), or AE severity (3 pts) while in PD, SD and PR. Eleven pts entered the MF. TA at wk 12 showed partial response (PR) in 1/21 or stable disease (SD) in 5/21 pts. TA at wk 24 showed PR and SD in 3/11 and 5/11 pts, respectively, with an ongoing clinical benefit (SD + PR + CR) of 30% (8/27 pts); these pts are still on treatment. Long-term follow-up of pts reaching wk 48 showed PR in 2/6 and SD 4/6 pts. The median overall survival is 29 wks (2–55). Slow, steady declines in tumor volume and appearance of new lesions with subsequent shrinking of total tumor burden has been observed. One patient experienced Grade 3 AE (myocardial infarction considered unrelated to treatment), 1 patient Grade 4 irAE (pancytopenia) and 2 pts had Grade 3 irAE (diarrhea).

Conclusions: Ipilimumab treatment is feasible, safe and clinically effective also in the common daily practice and in heavily pretreated, progressing, MM pts. A sizeable proportion of these pts experiences durable clinical benefit and long-term survival.

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POSTER

The Italian experience on the feasibility and safety of ipilimumab therapy in pretreated metastatic melanoma patients

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Background: Clinical trials and single institution experiences have shown effective anti-tumor responses in pre-treated metastatic melanoma (MM) patients (pts) receiving the anti-CTLA-4 monoclonal antibody ipilimumab. We report the Italian (7 Institutions) experience on feasibility and safety of ipilimumab treatment of MM patients within a compassionate use program.

Materials and Methods: Seventy-two pts (43 males, 29 females), median age 57 (23–80) years, ECOG performance status 0–2, with MM (51 cutaneous, 12 uveal, 2 mucosal, 7 unknown primary), progressing to 3 median (1–5) systemic therapies for metastatic disease initiated ipilimumab treatment between February and September 2008. In the induction phase (IF) pts received ipilimumab (10 mg/Kg i.v.) q3 weeks (wks) × 4 cycles; after a 12 wks rest, upon physician judgement, pts received maintenance dosing q12 wks. First tumor assessment (TA) per modified World Health Organization criteria was performed at the end of the IF. Adverse Events (AE) were collected according to Common Terminology Criteria for Adverse events version 3.0.

Results: All pts received at least one ipilimumab dose, 43/72 completed the IF; the remaining 29 pts were withdrawn for early disease progression. Twenty out of 43 pts entered the MF. TA performed at the end of the IF showed partial response (PR) in 4 or stable disease in 12 pts, with a clinical benefit of 22%. Grade 3 AE were reported in 8% (6/72) pts (2 diarrhea, 1 epigastric pain, 1 myocardial infarction, 1 tumor pain, 1 neurological event).

Conclusions: Ipilimumab treatment in heavily pretreated MM pts is feasible and safe, and results in early clinical benefit in a sizeable proportion of patients.

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POSTER

eNOS plays a critical role in the tumor initiation and progression in chronically stressed mice

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Background: Recent studies show that the stress has an influence on immunological, neurochemical and endocrinological functions. In addition

it has been demonstrated that the stress can influence the development and the growth of some tumors, although it's in the microenvironment its not yet understood. So we decided to study the role of stress in the tumor initiation and the progression in an orthotopic model of melanoma murine cell line not hormone-dependent B16.

Materials and Methods: Thirty eight-week-old male C57BL/6 and ten eNOS^{-/-} mice were injected subcutaneously (s.c.) with the suspension of B16F1 5.10⁵/mouse in the hind right footpad. One week before the tumor injections, we placed the animals in a conic tube (Falcon) two hours daily for a total of 21. A group of animals not stressed in which we injected B16F1, was used as positive control. S-propranolol hydrochloride, a non-selective β -adrenoreceptor, (Sigma; 2 mg/kg/d) was given form 7 days before initiation of restraint stress. The tumor growth and progression was monitored by caliper measurement and subjected to Magnetic Resonance Imaging (MRI) with a 1.5 Tesla system (Magnetom Symphony, Syngo MR 2002B, Siemens, Erlangen, Germany) and a phased array coil.

Results: Our data show that chronic stress induce thymic atrophy, infact the weight of thymus in stressed animals was significantly lower than what was observed in control animals ($P = 0.04$ data not shown), and increased tumor burden (443%) respect to control group and 224% respect to group treated with propranolol, and angiogenesis by upregulation of VEGF and eNos levels in stressed mice.

Conclusion: Our work shows that inhibition of eNOS pathways has a crucial role in both tumorigenesis and tumor growth stress related in melanoma murine cell line not hormone-dependent and improve the prognosis of cancer of patients stressed.

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POSTER

Electrochemotherapy with intravenous bleomycin in the treatment of cutaneous and subcutaneous metastases: results of a prospective single centre trial

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Background: Electrochemotherapy (ECT) is an emerging treatment modality for cutaneous and subcutaneous metastases from different tumour types; it combines electroporation with injection of a chemotherapeutic agent, resulting in an enhanced drug uptake by tumour cells.

The aim of the study was to evaluate clinical activity and tolerability of ECT with i.v. bleomycin and to prospectively analyse the response increase associated to repeated sessions, in a large series of cutaneous metastases treated at a single institution ($n = 936$).

Patients and Methods: According to the ESOPE (European Standard Operating Procedures of Electrochemotherapy) guidelines, a total of 36 patients with cutaneous/subcutaneous metastases were enrolled: 27 suffered from melanoma, 6 from Kaposi's sarcoma, 1 patient respectively from squamous cell carcinoma, breast cancer and angiosarcoma. All patients were treated under general sedation with i.v. bleomycin using CliniporatorTM.

Results: Overall, a response was obtained in 32/36 patients (88%). Among melanoma patients, a response was obtained in 24/27 (88%) after the 1st ECT, with a complete regression (CR) in 11 (40%). Two patients obtained a CR after the 2nd ECT course, while 10 underwent 3 to 5 treatments to achieve local tumour control. A response was obtained in 93% metastases, with lower response rates in $>1 \text{ cm}^2$ lesions. After a median follow-up of 24 months, none of the CR nodules relapsed. The repeated ECT sessions determined a new response in 29/42 (69%) re-treated lesions, with responses obtained also in $>1 \text{ cm}^2$ lesions. The local tumour control rate was 68% at 2 years. A response was achieved in all patients with Kaposi's sarcoma, with response duration ranging between 9 to 26 months. A good clinical response was also obtained in patients with metastatic squamous cell carcinoma and breast cancer. Treatment was well tolerated and no systemic side effects were recorded.

Conclusions: ECT represents a new therapeutic tool in treatment of cutaneous/subcutaneous metastases, thanks to its impressive clinical activity and good tolerability, coupled with an adequate cost/effectiveness ratio. Its clinical activity indicates a specific role in the treatment strategies of relapsed/refractory cutaneous melanoma patients, who show a low response rate to standard chemotherapy. Repeated ECT sessions are associated with a response increase in re-treated lesions which could allow to overcome the reduced activity in $>1 \text{ cm}^2$ sized metastases.

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POSTER

Primary mucosal melanomas: a difficult diagnosis and a bad prognosis

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Background: Primary mucosal melanomas are rare, biologically aggressive neoplasms. The authors evaluated primary mucosal melanomas diagnoses between January 2000 and December 2006.

Material and Methods: Retrospective study based on clinical data, collected from 33 patients' records, including demographics, histology, stage, treatment and survival. Data were analyzed using SPSS software (version 16.0; SPSS, Inc., Chicago, IL). Survival analyses were calculated using the Kaplan Meier method and compared using the log-rank test. Overall survival (OS) was defined as the interval between diagnosis and last follow-up visit or death from any cause. Progression free survival (PFS) was defined as the interval between surgery or the last adjuvant treatment and date of relapse or death from any cause.

Results: Median age was 71 years (34–89), 42% had their diagnosis made in the seventh decade. Women were more affected than men (1.5:1). The more frequent presenting symptoms were haemorrhage and nodule. The distribution of head and neck, female genital tract, anal/rectal and oesophagus was 36.4%, 36.4%, 24.2%, and 3.0%, respectively. Fifteen cases (45%) were diagnosed with locoregional advanced clinical stage and 6 (18%) with distant dissemination. Surgery was performed in 75% pts, radiotherapy 30.3%, chemotherapy 15.2% and IFN-gamma 4%; Six patients had the best supportive care. Local control was achieved in 55%, but the rates of locoregional and distant recurrences were 33% and 58% respectively. The more frequent metastatic sites were lymph nodes, lungs and brain. Median OS was 20 months (95% CI 4.2–35.7) and PFS 24 months (95% CI 3.5–44.5), with median follow-up 25 months. A statistical significant difference in median OS was identified according to age ($p < 0.001$); OS in the younger group (<50 years) was higher. Lymph node metastasis and primary site didn't affect survival. The 5-year OS was 28%.

Conclusions: The aggressiveness of this entity and the difficulty in its management make the prognosis dismal. Clinical trials should be encouraged.

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POSTER

Non-cutaneous melanomas: not so rare entity – our experience at a centre in India

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Background: Non cutaneous melanoma (NCM) has been described as a rare disease in the literature with its incidence upto eight percent of all malignant melanomas (MMs). There is an acute paucity of data regarding this entity in the literature. The aim of this study was to assess the incidence, treatment characteristics, and overall outcome of NCMs in patients attending a tertiary cancer care centre in India.

Materials and Methods: It was a retrospective analysis done in the patients who were treated at radiotherapy department, All India Institute of Medical Sciences, New Delhi, between 1995 and 2005. The patient's details were retrieved from their individual departmental record.

Results: Out of the total 69 patients of MM, 42 (60%) cases of NCMs were found. There were 22 (52%) mucosal lesions and 20 (48%) ocular lesions. The median age of patients was 48 years with equal incidence in both sexes. Maximum cases of mucosal lesions were from head and neck region (50%) followed by gastrointestinal (36%) and genito-urinary (9%) tract. Overall, 93% of the cases presented as single lesion with majority in the advanced stage (III or IV) at presentation. In one-fourth of cases, the malignant lesion was preceded by a long standing pre-malignant lesion. Regional lymphadenopathy and distant metastases were seen in 12% and 26% cases respectively. There was a significantly less incidence of lymphadenopathy in NCMs in comparison with its cutaneous counterpart. Of all the treated patients, 45% achieved complete response, 19% partial response, and others had either stable or progressive disease. The median duration of follow up (DOFU) was 9.7 months in NCMs Vs 19.3 months in cutaneous melanomas. Likewise, median recurrence free survival was 10.7 months in NCMs Vs 24.4 months in cutaneous melanomas. Operability at presentation was the only factor that influenced DOFU.

Conclusion: Although sample error may be contributory to some extent due to the present study being retrospective in nature and a peculiar referral