9315 POSTER

TSEI – Associated Malignant Melanoma in Mycosis Fungoides

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Introduction: The incidence of MM in the Israeli population according to the Annual Report for 2007 of the Israeli National Cancer Registry is 13.54 per 100,000. The risk of second primary malignancy in cutaneous T-cell lymphoma [CTCL], including non-melanoma skin cancer, has been well documented. However, reports of malignant melanoma [MM] as second primary malignancy in CTCL are rare.
Patients and Methods: The National Cancer Registry and the Rambam Health Care Campus databases were queried to identify second primary malignant melanoma in CTCL patients. As a result, a database of 200 patients was developed, encompassing the period from 1950 until June 2010.
Results: Seven mycosis fungoides [MF] cases associated with MM were identified. Five had been treated with total skin electron irradiation [TSEI], one with involved field skin electron irradiation, and one had no irradiation treatment. Two patients were treated with PUVA or MN topically and one received total body irradiation. The patients had early stages (IA-IB) of MF.
Conclusions: In CTCL patients, we found the incidence to be 7 per 199. The mechanisms of the phenomena may lay in host immunomodulation that results in CTCL pathogenesis and/or in the negative influence of electron beam treatment of susceptible persons with MF.

9316 POSTER

Near-Infrared Guided Indocyanine Green (ICG) and Indocyanine Green With Human Serum Albumin (ICG:HAS) Sentinel Lymph Node Biopsy in Melanoma Patients

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Introduction: For a number of years now, the 'gold standard' in assessment of regional lymph node status in cutaneous melanoma has been sentinel lymph node biopsy (SLNB) using markers such as radioactive technetium and/or methylene blue. However, with the recent advent in near infrared (NIR) technology, a novel fluorophore Indocyanine Green (ICG) has been proposed as a promising alternative.
The aim of this study was to assess the usage of ICG and ICG in combination with human serum albumin (ICG: HSA) in performing SLNB of patients with cutaneous melanoma.
Material and Methods: All 10 patients with cutaneous melanoma after initial surgical resection of the tumour underwent SLNB. In five patients, ICG alone was used and the other five, a combination ICG:HSA was used. NIR PDE (Hamamatsu, Japan) camera was used to detect the lymphatic flow of ICG and ICG:HSA and to perform real time exploration. In all patients, technetium radiocolloid was used as a standard marker for SLNB.
Results: After the injection of ICG and ICG:HSA, real time lymphatic flow using PDE camera was observed in 8 out of 10 patients. In the group of patients where SLNBs were performed with ICG, total of 13 SLNs (mean 2.16) and 10 SLNs (mean 1.67) were detected with ICG and radiocolloids respectively. In the group of patients where SLNBs were performed with ICG:HSA, total of 11 SLNs (mean 1.83) and 10 (mean 1.67) were detected with ICG:HSA and radiocolloids respectively. No difference in number of lymph nodes found during biopsy between radiocolloid and fluorophores was seen $p = 0.59$.
Conclusion: SLNB with NIR guided ICG and ICG:HSA seems to be an effective alternative to radiocolloid method. Although further research is indicated for routine implementation of this method, the future holds much potential and promises.

9317 POSTER

MIPI-TURK – Multicentric Ipilimumab Experience in Turkish Patients With Metastatic Melanoma

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Background: Ipilimumab, an anti-CTLA-4 (cytotoxic T lymphocyte-associated antigen) monoclonal antibody has been shown to enhance immune responses and induce durable clinical responses in patients with metastatic melanoma. The authors report retrospectively on metastatic melanoma patients treated under compassionate use program in Turkey among 12 centers.
Methods: Patients with metastatic melanoma were treated with ipilimumab 3 mg/kg for 4 doses on weeks 1, 4, 7, 10 as induction. Response evaluation was done on week 12. Patients with complete response (CR), partial response (PR) and stable disease (SD) at week 12 were eligible for reinduction treatment.
Results: A total of 27 patients enrolled with 23 evaluable. Ipilumumab treatment was given as 2nd, 3rd and 4th line in 21.7%, 60.9% and 17.4% of patients respectively. The numbers of patients receiving ipilimumab for 1, 2, 3 and 4 doses were 3, 2, 3, 15 respectively. Three of 23 patients were eligible for reinduction. G1/2 adverse events were reported in 43.4% of patients. G3/4 was reported in 10% of patients as skin rash and diarrhea. The most common G1/2 immune related adverse events were muscle weakness (30%) and gastrointestinal (15%). Fifteen of 23 patients completing 4 doses of ipilimumab treatment were available for response evaluation. There was no CR. The overall response rate was 40% (6/15): total of PR: 13.3% (2/15) and SD 26.7% (4/15). Median time to progression was 3.2 months (95% CI: 2.4−3.9 months). Median overall survival was not reached with 59.8% of patients are surviving within 12 months of follow up period.
Conclusions: Ipilimumab treatment is safe and effective for metastatic melanoma patients with tolerable immune related adverse events according to the accessible data so far.

9318 POSTER

Phase 3 Randomized Study of Ipilimumab (IPI) Plus Dacarbazine (DTIC) Vs DTIC Alone as First Line Treatment in Patients With Unresectable Stage III or IV Melanoma

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Background: IPI monotherapy (3 mg/kg) improved overall survival (OS) in a phase 3 study of previously treated, unresectable or metastatic melanoma patients (pts). Current study evaluates DTIC, a global standard of care, plus IPI in first line metastatic melanoma.
Material and Methods: In this double-blind phase 3 study, pts with metastatic melanoma, ECOG PS 0/1, and no prior therapy for advanced disease, were randomized 1:1 to IPI (10 mg/kg) + DTIC (850 mg/m^2) or placebo + DTIC (850 mg/m^2) at Wks 1, 4, 7, 10 followed by DTIC q3 wks through Wk 22 (induction). Eligible pts received IPI or placebo q12 wks as maintenance. Primary endpoint was OS; 2-sided log-rank test was performed, stratified by M stage and ECOG PS at randomization.
Results: Of 502 (IPI + DTIC=250; DTIC alone=252) pts, 60% were male, 68% were <65 yrs; 71% had ECOG PS 0, 56% had M1c disease, 40% had elevated lactate dehydrogenase (LDH), and 26% received adjuvant therapy. 37% in IPI + DTIC and 65% in DTIC alone arms received 4 induction doses. A significant improvement in OS [11.2 vs 9.1 mo; HR = 0.72; P = 0.0009] with higher estimated survival rates at 1 yr (47.3 vs 36.3%), 2 yr (28.5 vs 17.9%) and 3 yr (20.8 vs 12.2%) were seen in IPI + DTIC vs DTIC alone. OS results were consistent with primary endpoint for subgroups of ECOG-PS, LDH and M stage. In IPI+DTIC vs DTIC alone arms, median progression-free survival (first assessed at ~3 mo) was 2.8 vs 2.6 mo (HR = 0.76; P = 0.006); best overall response rate was 15.2% vs 10.3%; and median response duration was 19.3 vs 8.1 mo. Grade 3/4 adverse events (AEs, regardless of attribution) were noted in 56% in IPI +DTIC (n = 247) and 27% pts in DTIC alone (n = 251) arms, including: elevated ALT (22% vs 1%); diarrhea (4% vs 0%); rash (1% vs 0%). There were no drug-related deaths in IPI + DTIC and 1 due to gastrointestinal (GI) hemorrhage in DTIC alone arm.
Conclusions: A significant improvement in OS was seen in first line metastatic melanoma pts with IPI (10 mg/kg) + DTIC vs DTIC alone and was consistent across the subgroups of ECOG-PS, LDH and M stage. Durable survival and objective responses were noted in some pts after follow-up for up to 4 yrs. Types of AEs were generally consistent with prior IPI studies; however, frequencies of some AEs differed in this study with higher transaminitis and lower diarrhea/colitis/GI perforation rates

than expected. This study confirms OS benefit of IPI in treatment-naïve metastatic melanoma.
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9319 POSTER

A Regional Review of Outcomes of Systemic Therapy in Patients With Metastatic Malignant Melanoma

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Background: The incidence of malignant melanoma (MM) has risen steadily over recent decades. NCI data from 2005–2007 have suggested that 1.93% of individuals born today in the US will develop melanoma at some stage [1]. Approximately 15% of patients with MM either present with metastatic disease or develop metastases during the course of their illness. Unfortunately, metastatic MM remains a challenge with limited treatment options and median overall survival (OS) reported as 6−9 months. Dacarbazine (DTIC) remains the standard first line treatment with published response rates of less than 10% and infrequent durable responses. We reviewed our data for the treatment of metastatic MM over a period of four years.
Material and Methods: Data from all patients with metastatic MM treated with systemic therapy outwith clinical trials from 2006 to 2009 were reviewed. Response rate was determined as per RECIST criteria.
Results: Sixty-four patients were treated with one or more lines of cytotoxic therapy. Median age was 62 years (range 23−82 years) with 53% males. Primary site of disease was skin in 75%, mucosal in 12.5%, ocular in 9.3% and nodal with occult primary in 3.1%. Visceral metastases were present in 75% of patients at the start of treatment, including pulmonary (39.6%) and hepatic (34.4%). All patients were screened for brain metastases: these were present in 26.5% of patients. ECOG performance status (PS) was 0 in 7.8%, 1 in 68.7%, 2 in 9.4% and undocumented in the remaining 14%. Patients without brain metastases received single agent DTIC first-line; those with brain metastases received temozolomide. Response rate was 7% for DTIC and 28% for temozolomide, with median progression free survival (PFS) of 2.1 and 2.4 months respectively. Seven patients who received DTIC are alive on follow-up, 2 have ongoing stable disease post-DTIC at 41 months and 18 months respectively. Second line therapy with vinblastine was given to 21 patients (32%), with a response rate of 9.5% and median PFS of 3.4 months. Median OS from initiation of therapy was 7.7 months for DTIC and 3.6 months for patients with brain metastases receiving temozolomide. PS of 2 was associated with shorter median OS (2.0 months).
Conclusions: Our results are comparable to those in published data [2]. MM is a disease with rising incidence and limited treatment options. These patients are best treated in the context of clinical trials as new targeted therapies are promising as future strategies.

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9320 POSTER

PolyMEL, a Polyepitope DNA Vaccine − Results From a Phase 1 Study for Metastatic Melanoma

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Background: Metastatic melanoma carries a poor prognosis. Although promising therapies are emerging, new approaches are still needed.
Materials and Methods: A phase I dose escalation study with PolyMEL, a DNA polyepitope vaccine encoding 8 nine-amino acid epitopes derived from 45 shared melanoma antigens, was devised. The objectives of this study were to establish the safety and feasibility of DNA vaccination with polyMEL, to determine the maximum tolerated dose, and to see whether polyMEL vaccination elicits a clinical anti-tumour response. Cohorts of 3 patients with stage IV melanoma who were either HLA-A1 or -A2 positive received 3 intramuscular injections of increasing doses of polyMEL DNA vaccination: 30 μg, 100 μg, 300 μg or 1000 μg/ injection.
Results: 15 patients were entered into the trial between October 2003 and September 2008. Two patients withdrew early from the study with clinical deterioration and were replaced, and a third was found to have brain metastases at baseline and did not receive study drug. 12 patients were therefore assessable for response, and 14 were assessable for toxicity. Nine patients had cutaneous melanoma and five had ocular melanoma. The vaccine was well tolerated, with no haematological or biochemical toxicity, and mainly grade 1 or 2 non-haematological toxicity. All 9 patients with cutaneous melanoma had progressive disease at the end of the study protocol. By contrast, 3 of the 5 patients with ocular melanoma had stable disease at the end of the study protocol (60% disease control rate), and 2 had progressive disease. Median progression-free survival was 64 and 102 days for patients with cutaneous or ocular primary melanoma respectively, and the respective median overall survival was 182 and 336 days.
Conclusions: Administration of polyMEL polyepitope vaccine at doses ranging from 30 μg to 1000 μg, given every 2 weeks to a total of 3 injections, is safe and associated with minimal toxicity. The tolerability of polyMEL should allow its combination with established or experimental agents in future studies. Patients with ocular melanoma had better outcomes compared with patients with metastatic cutaneous melanoma. This agent may therefore be of particular interest for patients with metastatic ocular melanoma, for whom no effective treatment exists.

9321 POSTER

Prognostic Factors in a Cohort of Dacarbazine Treated Patients for Metastatic Melanoma

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Background: Incidence and mortality of melanoma in Europe is increasing. Metastatic melanoma (mM) has poor prognosis with 5-year survival rates of 15%. Dacarbazine (DTIC) is considered a standard treatment for mM despite response rates of 10−20% and median response duration 3−6 months. Our purpose was to identify prognostic factors associated with improved survival in mM patients (pts) treated with DTIC.
Methods: Retrospective cohort study, in a Portuguese cancer centre, of mM pts treated with DTIC as 1st line systemic treatment. Survival time was defined as a difference between the start date of DTIC and death. Pts alive were censored on the date they were last seen in the clinic. Potential prognostic variables were assessed in univariate analysis with a log rank test and in multivariate analysis through a Cox proportional hazards model.
Results: From 2005 through 2009, 109 pts with mM were treated with DTIC in our centre. Median age was 58 years (range 20−77), 45% were male and 60% had an ECOG performance status of 0. Visceral metastases were present in 66% of pts.
Half of the patients completed at least 4 cycles of DTIC and 27% completed $\geqslant$ 6 cycles. A relative dose-intensity of DTIC $\geqslant$90% was achieved in 77%. Main reason for treatment interruption was disease progression (68%). Serious adverse events occurred in 19% and 2 pts died on treatment due to unknown causes. Overall response rate was 32% and median duration of response was 3 months (m). Median overall survival was 6 m (95CI: 4.1−7.9).
In univariate analysis, normal LDH was associated with improved survival (median survival: 9 m *vs* 4 m; $p = 0.005$) as was ECOG status 0 *vs* $\geqslant$ 1 (median survival: 8 m *vs* 4 m; $p = 0.013$). Patients with visceral metastases tended to have a worst prognosis (median survival 5 m *vs* 7 m), however this was not statistically significant ($p \geqslant 0.05$). Age and gender had no impact on survival. In multivariate analysis, normal LDH was the only factor associated with increased survival (HR, 0.50; [95CI, 0.28–0.93]).
Conclusion: Of the known prognostic factors in metastatic melanoma only LDH had a significant impact on survival. The small sample size limits the power of our study which may explain our inability to identify other probably less discriminating prognostic factors. The strong prognostic information conveyed by LDH should be incorporated in patient stratification in trials of new treatment for metastatic melanoma.

9322 POSTER

Immunological and Biological Changes and Their Correlation With Clinical Response and Survival During Ipilimumab in Metastatic Melanoma Compassionate Use Program

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Background: Recentely FDA has approved ipilimumab at 3 mg/kg as first and second line of therapy in patients with metastatic melanoma. This is sustained by an impact on overall survival in this setting of patients of 10.1 months. Anyway no clinical parameter has been consistentely found to be a surrogate or a predictive marker for response to ipilimumab therapy