Cytokines/immunobiology/ immunotherapy

Poster presentations (Mon, 31 Oct)
Cytokines/immunobiology/immunotherapy

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Phase 1 dose-escalation study of intravenous recombinant human Interleukin-21 (IL-21) in patients with metastatic melanoma: preliminary results of tolerability and effect on immunologic biomarkers

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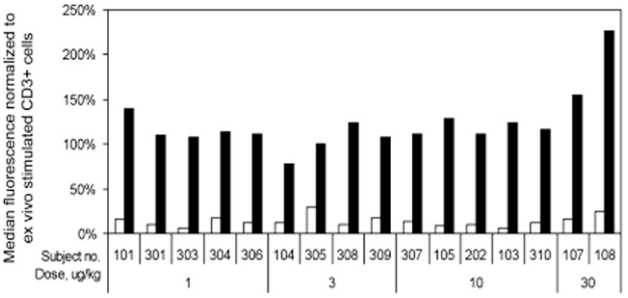
Background: Interleukin-21 (IL-21), a pleiotropic class I cytokine, has significant anti-tumor activity in several preclinical tumor models including metastatic melanoma.
Material and methods: In an ongoing phase 1 dose-escalation study, IL-21 is administered intravenously to patients with AJCC stage IV metastatic melanoma using two different dose regimens. At each dose level in the planned dose range of 1 μg/kg to 1 mg/kg, cohorts of two patients are being treated with IL-21 either thrice weekly for 6 weeks ('3×/week') or with 3 cycles of daily dosing for 5 days followed by 9 days of rest ('5+9'). The objectives are to estimate the maximum tolerated dose of the two dose regimens, to estimate the minimum biologically effective dose, and to optimize the dose regimen for future studies.
Results: Seven cohorts of two patients each have been enrolled in the 3x/week regimen at dose levels of 1, 3 10, and 30 μg/kg or the 5+9 regimen at dose levels of 1, 3 and 10 μg/kg. No dose limiting toxicity (DLT) has been reported so far. All patients experienced one or more adverse events, but no drug-related serious adverse events have been observed among the 11 completed patients. By RECIST criteria, one patient at each dose level of 1, 3 and 10 μg/kg had stable disease at the week 8 assessment. Dose- and dosing regimen-related effects on pharmacodynamic and immunologic biomarkers have been observed. Preliminary analyses have shown that increased levels of sCD25, phosphorylated STAT3 (pSTAT3), and perforin/granzyme B mRNA after IL-21 treatment. The figure shows the relative levels of pSTAT3 in $CD3^+$ lymphocytes from 16 patients isolated before and 15 minutes after dosing. The data are expressed as percent of the pSTAT3 level in $CD3^+$ lymphocytes from patient blood stimulated ex vivo with 10 ng/ml IL-21.



Conclusions: This ongoing study has shown that IL-21 administered in either of two dose regimens at doses up to 30 and 10 μg/kg respectively has been well-tolerated. Preliminary evidence of biological activity has been observed, even at doses as low as 1 μg/kg.

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IL-1 RA expression in ascites of advanced ovarian cancer patients influences the overall survival

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Background: Interleukin-1β (IL-1β) and IL-1 RA are known to be critically involved in ovarian carcinogenesis. There are limited data on expression of IL-1β and RA in ascites in patients with ovarian cancer. The aim of this study was to determine whether expression of IL-1β and RA in ascites may influence the prognostic of ovarian cancer.
Methods: In a prospective study from 2001 to 2003, 33 patients with primary ovarian cancer and 20 with recurrence and 50 women with benign gynaecological diseases as a control group were enrolled. IL-1β and RA levels in ascites were analysed with ELISA technique.
Results: The median age of the patients was 55.6 years (range 19–80) in the ovarian cancer group and 40 years (range 15–89) in control group. The median follow-up period was 26 (0–42) months. The concentrations of IL-1β and IL-1 RA in ascites were significantly increased in patients with ovarian cancer in comparison to control group, for both cytokines ($p < 0.0001$). The IL-1β level in ascites correlated significantly with the histopatological grading ($p = 0.038$). IL-1 RA level in ascites was correlated with FIGO stage ($p = 0.049$).
Using Kaplan-Meier method and long-rank test was showed that patients with low level of IL-1 RA in ascites had a significant longer overall survival (34.6 vs. 17 months, $p = 0.01$) and progression free survival (24.6 vs.12.8 months, $p = 0.008$) in comparison with patients with high level of IL-1 RA in ascites. Application of multivariate Cox regression analysis showed IL-1 RA expression in ascites to be an independent prognostic factor for overall survival ($p = 0.04$).
Conclusions: The data suggest that lower expression of IL-1 RA in ascites correlated significant with improved clinical outcome in patients with ovarian cancer. IL-1 RA may have important roles in the growth and development of ovarian cancer and shows a prognostic relevance.

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Autologous large multivalent immunogen vaccine for the treatment of stage IV malignant melanoma and stage IV renal cell carcinoma

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Renal cell carcinoma is the sixth leading cause of cancer death with a survival rate of 11% for stage IV cancer. More than a million skin cancer cases occur each year globally with a 5 year survival rate of 7–9% and 10 year survival rate of 3–6% for stage IV melanoma. These survival statistics have remained essentially unchanged for several decades. Although immune stimulation with high doses of interleukin-2 has demonstrated efficacy in the treatment of malignant melanoma or renal cell carcinoma, it can be applied only to limited groups of patients. Vaccination has also been explored as a means to boost antitumor T cell responses, which results in the specific killing of malignant cells. We have developed a novel approach of vaccine-induced augmentation of tumor-specific cytotoxic T lymphocyte (CTL) responses using (5 m diameter) latex or silica beads.
Methods: 61 patients with diagnosis of malignant melanoma or renal cell carcinoma were randomized to the following treatment arms: large multivalent immunogen (LMI) vaccine alone, Cyclophosphamide 300 mg/m^2 and LMI vaccine, and Cyclophosphamide 300 mg/m^2, LMI vaccine and subcutaneous IL-2 at 1.75×10^6 IU/m^2 for 1 week starting on day 5 after LMI vaccine.
Results: No grade 4 toxicities (by NCI CTC v3.0) were observed in either arm. For patients with malignant melanoma: median and 12 months survival were 8.78 months (95%CI: 7 months, NA) and 46.1% (95%CI: 23.4%, 68.8%), respectively, and median time to disease progression was 2.76 months (95%CI: 1.88, 6.25). For renal cell carcinoma patients: at median follow-up of 12 (range 0.4–30.4) months overall survival was 75.7% (95%CI: 59.9, 91.4%) and time to disease progression was 12.2 months (95%CI: 6.41 months, NA). One patient with melanoma and one patient with renal cell carcinoma have documented partial response (by RECIST criteria).
Conclusion: LMI vaccine has activity in malignant melanoma as documented by clinical responses and has activity in renal cell carcinoma as measured by prolonged time to disease progression. Phase II study of allogeneic vaccine is now in progress for patients with malignant melanoma to confirm feasibility of LMI strategy in this setting. Phase II study of autologous vaccine in patients with renal cell carcinoma is now in preparation to confirm prolonged time to disease progression observed in this group of patients.

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Association of Electrochemotherapy and CpG DNA: toward a new vaccination approach for cancers with cutaneous localizations

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Introduction: electrochemotherapy (ECT) is a new therapeutic approach for tumor reduction, effective on cutaneous and subcutaneous cancers. Its local efficacy and the absence of systemic side-effect have been