from the daily arm, 28 patients had a decrease in ANC post-treatment; with the neutrophil-fall being 3.62 (+2.64) cells/μl and a mean SF of 42% (2–87%). The mean, observed days to neutrophil and platelet nadir are 18 days.
Conclusion: Half of patients with AUCs above 750 (4 of 8) had neutrophil SF of less than 25% (3 of which were the only neutropenic DLTs); as well as platelet SF of less than 35%. With in vitro evidence suggesting B-ol toxicity to be 40−49% that of B in glioma cell lines, further study of hematologic toxicities linked to both B and B-ol PK parameters is warranted and ongoing.

Vaccines

601 POSTER

Cross-trial analysis of immunological and clinical data resulting from phase I and II trials of MVA-5T4 (TroVax®) in colorectal, renal and prostate cancer patients

R. Harrop[1], W.H. Shingler[1], N. Drury[1], M. Goonewardena[1], J. de Belin[1], S. Naylor[1], P. Treasure[2]. *[1]Oxford Biomedica, Clinical Immunology, Oxford, United Kingdom; [2]Peter Treasure Statistical Services Ltd, NA, Cambridge, United Kingdom*

Background: The attenuated vaccinia virus MVA has been engineered to deliver the tumour antigen 5T4 (MVA-5T4; TroVax®). 5T4 is a surface glycoprotein expressed by most solid tumours. MVA-5T4 has been tested in two phase I/II and seven phase II clinical trials in colorectal (4 trials), renal (4 trials) and prostate (1 trial) cancer patients. All trials demonstrated that MVA-5T4 was well tolerated when administered alone (2 trials) or in combination with cytokines (5 trials) or chemotherapies (2 trials). Antibody and/or cellular responses specific for 5T4 were induced in the majority of patients and these responses were associated with clinical benefit in each of 6 trials. We have now collated data from all nine TroVax trials and investigated the incidence and kinetics of immune responses across trials and looked for associations with improved survival.
Methods: Antibody responses specific for the 5T4 tumour antigen and the MVA viral vector were monitored by ELISA. Survival data were collated from each hospital site. Immunological and survival data were analysed using proportional hazards regression adjusting for age and gender.
Results: Both survival and immunological response data were available for 189 patients (median age 62), with colorectal (n = 73), renal (n = 89) and prostate (n = 27) cancer. The median number of TroVax vaccinations received was 5 (range 1–12). TroVax was safe and well tolerated across trials and in combination with both chemo- and cytokine-therapies. Of 189 patients analysed prior to treatment with TroVax, 20 (10.5%) had weak positive 5T4-specific antibody responses and 23 (12%) had MVA-specific antibodies. Of 180 patients tested for antibody responses post-vaccination, 159 (88%) and 176 (98%) showed positive responses for 5T4 and MVA respectively. Peak median antibody titres were detected following 2 vaccinations for MVA and 4 vaccinations for 5T4. Exploratory analyses demonstrated significant associations between immune responses and overall survival across trials in patients with colorectal cancer alone (4 trials), renal cancer alone (4 trials) or colorectal, renal or prostate cancer (9 trials).
Conclusions: MVA-5T4 induced 5T4-specific immune responses in the majority of patients irrespective of cancer type or the addition of co-meds. Generally, two to three vaccinations were required to induce 5T4-specific antibody responses in most patients. Although the studies described here were uncontrolled, there were encouraging signs of activity which associated with the presence of 5T4-specific immune responses. These observations will be tested more thoroughly in an ongoing randomized, placebo-controlled phase III trial in renal cancer patients.

602 POSTER

An anti-idiotypic HER2 vaccine can reverse immunological tolerance to HER2 and induce anti-tumor immunity in huHER2 female transgenic mice

M.Z. Ladjemi[1], S. Corgnac[1], S. Morisseau[1], B. Robert[1], C. Mollevi[2], T. Charès[1], W. Jacot[3], A. Pèlegrin[1], I. Navarro-Teulon[1]. *[1]Institut de Recherche en Cancérologie de Montpellier, Immunociblage et Radiobiologie en Oncologie, Montpellier, France; [2]Centre de Recherche et de Lutte contre le Cancer de Montpellier, Biostatistiques, Montpellier, France; [3]Centre de Recherche et de Lutte contre le Cancer de Montpellier, Oncologie médicale, Montpellier, France*

Background: Breast cancer is a widely spread women's disease. Inspite of progress in the field of surgery and adjuvant therapies, the risk of breast cancer metastatic relapses remains high. Thus, it is important to develop adjuvant therapies to decrease mortality related to this type of cancer. In this context, the development of antitumor vaccines takes an important place. The oncoprotein HER2, which is an over-expressed antigen for different human carcinomas, represents a valuable target for the design of such a vaccine. However, an immunological tolerance against HER2 antigen exists representing a barrier to effective vaccination against this oncoprotein. We have selected two human ScFv antibody fragments (named ScFv 40 and ScFv 69) able to mimick the human HER2 antigen and to induce an anti-HER2 response in sera of immunized BALB/c mice (1).
Material and Methods: Production, purification and characterization of anti-Id ScFv 40 and ScFv 69 have been described. The huHER2-Transgenic mice FVB-MMTV.f.huHER2(Fo5) were obtained from Genentech and have been decribed (2). These mice overexpress human HER2 (huHER2) under the murine mammary tumor virus promoter and were used as a model of huHER2-overexpressing breast cancer. The anti-Id scFv vaccines were injected subcutanously (s.c.) after emulsion with Complete Freund Adjuvant (CFA). This injection was followed 2 weeks later by a second s.c. administration with Incomplete Freund Adjuvant (IFA). Two additional injections were given, in combination with IFA, intraperitonally (i.p.) at 21 and 35 days after the initial immunization.
Results: We demonstrated that the sera of immunized BALB/c mice are able to inhibit in vitro and in vivo the growth of human HER2-overexpressing cancer cells. Furthermore, following our vaccination schedule, all the transgenic FVB-MMTV.f.huHER2(Fo5) mice immunized with ScFv 69 were protected from the developpement of spontaneous mammary tumors whereas all control mice immunized with PBS and CFA/IFA developed tumors.
Conclusion: Our results demonstrated the remarkable efficacy of the ScFv vaccine candidate in protecting mice from the developpement of HER2-positive mammary tumors and allow us to consider that ScFv 69 fragment could be used as an anti-idiotype based vaccine for adjuvant therapy for patients bearing HER2 positive tumors.

References

[1] Coelho M, Gauthier P, Pugniere M, Roquet F, Pèlegrin A, Navarro-Teulon I. Isolation and characterisation of a human anti-idiotypic scFv used as a surrogate tumour antigen to elicit an anti-HER-2/neu humoral response in mice. Brit J Cancer 2004; 90: 2032−41.
[2] Finkle D, Quan ZR, Asghari V, et al. HER2-targeted therapy reduces incidence and progression of midlife mammary tumors in female murine mammary tumor virus huHER2-transgenic mice. Clin Cancer Res 2004; 10(7): 2499–511.