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A RANDOMIZED TRIAL OF IFNα AND IL-2 ± CISPLATINUM IN ADVANCED MELANOMA - A PRELIMINARY ANALYSIS.

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Within the EORTC Melanoma Cooperative Group, a randomized multicenter-trial comparing immunotherapy with IFNα and IL-2 versus chemo-immunotherapy with cisplatinum (CDDP) and IFNα/IL-2 was performed in 124 patients to determine the impact of CDDP on survival. Arm A contained 100 mg/m^2 CDDP on day 1, 10 x 10^6 U/m^2/day IFNα (Roferon) days 1 to 5 and high dose IL-2 (Proleukin) on days 3 to 8 with a decrescendo regimen (1mg/m^2 per 6 hours, followed by 1mg/m^2 per 12 hours, 1 mg/m^2 per 24 hours, and a maintenance dose of 0.25mg/m^2 per 24 hours for 3 x 24 hours). Arm B contained the same treatment without CDDP. Cycles were repeated on day 28 to a maximum of four cycles. Patients were stratified into two strata: favourable prognosis with normal serum LDH and a tumor surface area < 30 cm^2 and unfavourable prognosis with elevated LDH or tumor surface area > 30 cm^2. An interim analysis was performed at the time when response assessment of the initial 83 patients was available. In addition to the usual toxicity of this regimen of IFNa and high dose IL-2, CDDP was associated with a higher degree of hepatic toxicity in patients with liver metastases, some increase in renal toxicity, and sometimes severe nausea. In the arm with immunotherapy only, the response rate was 17% (22% in the stratum with favourable prognosis and 11% in the stratum with unfavourable prognosis). In the arm with CDDP and immunotherapy, the response rate was 32% (35% in the stratum with favourable prognosis and 27% in the stratum with unfavourable prognosis). 6 patients with PR have been converted into CR by subsequent surgery.

The doubling of the response rate achieved by the addition of CDDP (at the cost of higher toxicity) in both patient strata will permit a meaningful analysis of the influence of CDDP on survival.

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4-YEAR SURVIVAL DATA OF PATIENTS WITH ADVANCED RENAL CELL CARCINOMA TREATED WITH AUTOLOGOUS TUMOR VACCINE AND SUBCUTANEOUS ADMINISTRATION OF RECOMBINANT INTERLEUKIN-2 AND INTERFERON-ALPHA $_{2b}$

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40 patients with advanced renal cell carcinoma (RCC), all with distant metastases in at least one organ, were entered after nephrectomy into a protocol involving vaccination with Newcastle disease virus (NDV)-modified autologous tumour material, with a subsequent induction week and repetitive 3 bi-weekly cycles of interleukin-2 (rIL-2) and interferon-alpha$_{2b}$/rIFN-alpha$_2$ at a lower s.c. dose (1,5 million Cetus units m^{-2} day^{-1} and 3 million IU/m^2 once a day resp. Of the 40 evaluable RCC patients 5 exhibited a complete response and 6 displayed partial remission, 12 showed stable disease (median 25 months), and progression was seen in 17. Survival distribution analysis predicted for all patients displaying objective response a median survival of 31 months. These patients appear to have a survival advantage over those patients experiencing progressive disease during the treatment period and over a historic reference group. This correlation was significant. In this study number of metastatic sites was predictive of survival characteristics, the correlation being significant for number of sites. A marked increase of DTH reactivity predicted a survival advantage (35 vs 14 months), a correlation that was significant by Wilcoxon test. We conclude that vaccination with autologous tumour material combined with s.c. rIL-2 and rIFN-alpha$_{2b}$ administration can induce survival benefit patients with advanced RCC and that even in non-responding patients a more favourable course of the disease can be achieved.

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IMMUNIZATION WITH ANTI-IDIOTYPE VACCINE SCV 106 PROLONGS SURVIVAL TIME OF CANCER PATIENTS WITH METASTATIC COLORECTAL CANCER: A RANDOMIZED DOUBLE BLIND CLINICAL TRIAL

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Active specific immunotherapies of colorectal carcinoma (CRC) may offer attractive alternatives to still unsatisfying conventional treatment modalities. An unique strategy to elicit a tumor specific immune response makes use of anti-idiotypic antibodies bearing the internal image of tumor antigens. A controlled double blind clinical trial in metastatic colorectal carcinoma patients was initiated to evaluate efficacy and tolerability of multiple immunizations with a polyclonal goat IgG anti-idiotype vaccine (SCV 106; 21 patients) versus unspecific goat IgG as control (21 patients). SCV 106 is a surrogate of the 17-1A glycoprotein antigen associated with CRC. 39 of the 42 entered patients were evaluable for efficacy. Treatment in both groups was well tolerated. Tumor responses according to UICC criteria were not observed. However, survival analysis revealed a borderline significant survival advantage for the SCV 106 group (mean 55 vs 37 weeks; p = 0,0409). Efficacy of active immunotherapy is based on immunological responsiveness. 11 immunological non-responders (no antibodies to goat IgG) were identified (SCV 106: 7; control: 4). Survival analysis of immunological responders in both groups showed a highly significant survival prolongation of patients vaccinated with SCV 106 (mean 73 vs 39 weeks; p = 0.0054). Non-responders in both groups had significant shorter survival times than responders (p = 0,001). In conclusion, vaccination of immunologically responsive metastatic CRC-patients with SCV 106 led to a significant survival benefit. Immunocompromised patients regardless of treatment showed a clear survival disadvantage.

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Gene transfer-mediated expression of costimulatory molecules to enhance the immunogenicity of human tumor cells

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Activation of T lymphocytes requires the interaction with specific antigen and, in addition, secondary signals provided by costimulatory molecules. Since expression of costimulatory molecules is reduced or absent on tumor cells, we tested whether tumor cell-induced T cell activation can be improved by expressing costimulatory molecules via somatic gene transfer. This may yield immunogenic tumor cell variants which could be used for vaccination of tumor patients in autologous or, alternatively, allogeneic situations. We used allogeneic mixed lymphocyte tumor cell cultures to analyse T cell activation promoted by tumor cells. Expression of CD80 (B7.1), CD86 (B7.2) or coexpression of CD80 and CD86 following transfection with plasmid vectors resulted in augmented T cell proliferation against a melanoma cell line (SkMel63). T lymphocytes activated by CD80$^+$ SkMel63 cells were found to express CD8 and to exhibit class I MHC-restricted cytolytic activity. However, expression of CD80, CD86, and CD80/CD86 in two colorectal carcinoma cell lines (SW480, SW707) was ineffective in inducing proliferative responses. Exogenous cytokines like Il-2, Il-4, γ-IFN, and α-TNF, respectively, did not alter the low stimulatory capacity of the colorectal carcinoma cells, even following CD80 expression. Since both colorectal carcinoma cells, in contrast to SkMel63, did not express CD54 and class II MHC molecules, we expressed CD54 and one class II MHC allele (HLA-DR3) in CD80-negative and positive SW480 cells. SW480 cells positive for, respectively, CD54 and HLA-DR3, either alone or in combination with CD80, did not stimulate T cell proliferation. Using submitogenic concentrations of a CD3 mAb we were able to demonstrate the costimulatory function of the transfected molecules. We conclude that expression of additional costimulatory molecules is needed for colorectal carcinoma cells like SW480 to induce T lymphocyte activtion *in vitro*. Whether the ability of tumor cells to provide an antigen-dependent first signal has to be improved in addition to providing costimulatory molecules needs to be investigated.

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