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Adoptive T cell therapy using antigen-specific CD8+ T cells for the treatment of patients with metastatic melanoma: a phase I clinical study

N Meidenbauer, S Vogl, M Laumer, J Heymann, R Andreesen and A Mackensen*

Address: Department of Hematology/Oncology, University of Regensburg, D-93042 Regensburg, Germany

Email: A Mackensen* - andreas.mackensen@klinik.uni-regensburg.de

* Corresponding author

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The adoptive transfer of *in vitro* induced and expanded tumor antigen-specific cytotoxic T lymphocytes (CTL) provides a promising approach to the immunotherpy of cancer. We have previously shown that Melan-A-specific CTL can be generated from HLA-A2.1+ melanoma patients by 4 rounds of *in vitro* stimulation of purified CD8+ T cells with autologous dendritic cells pulsed with a mutated HLA-A2 binding Melan-A (ELAGIGILTV) peptide. Based on these results we have initiated a pilot study of adoptive T cell therapy in advanced melanoma patients demonstrating that *in vitro* generated Melan-A specific CTL survive intact *in vivo* for several weeks and localize preferentially to tumor (Meidenbauer *et al., J Immunol* 2003, **170:**2161, 2003). Here we report on the clinical results of a phase I study of 12 HLA-A2+ melanoma patients that received at least three i.v. infusions of Melan-A-specific CTL i.v. at 2-week intervals. Each T cell infusion was accompanied by a 6-day course of s.c. IL-2 (3×10^6 IU daily). A total of 51 T-cell infusions were administered, averaging 1.48×10^8 Melan-A multimer+ T cells per infusion, with a range from $0.11–6.58 \times 10^8$ Melan-A-specific T cells per infusion. Clinical side effects were mild and consisted of chills and low-grade fever (WHO grade I-II) in 8 out of 12 patients that typically occurred within 6 to 8 h post infusion. Hematological effects, observed after T cell transfer, consisted of an increase in eosinophils up to 30% in 7 out of 12 patients, peaking 24 h post transfer. Clinical and immunological responses consisted of anti-tumor responses in 3 out of 12 patients (2 PR, 1 mixed response), an elevated frequency of circulating Melan-A multimer+ T cells up to 2% of total CD8+ T cells up to 14 days post transfer, suggesting long-term survival and/or proliferation of transferred CTL, and a complete loss of Melan-A expression in lymph node metastases of 2 patients after T cell transfer. Our data indicate that the adoptive transfer of antigen-specific T cells in melanoma patients is capable of inducing clinical and systemic tumor-specific immune responses without provoking major side effects.