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 Abstract:

Soft tissue sarcomas are mesenchymal tumors which respond poorly to systemic therapy. Recent studies suggest a higher response rate with an increased doxorubicin dosage. However, this was parallel with a profound hematotoxicity in 75% of patients. Transfer of the human multidrug resistance 1 (MDR1) gene to normal hematopoietic stem cells and transplantation may significantly reduce the hematotoxicity of anthracyclin-based chemotherapy. To test this concept of supportive gene therapy in advance of a clinical study, we transduced mobilized peripheral blood progenitor cells (PBPC) with the retroviral vector SF91m3 containing the human MDR1 gene, transplanted these cells to immune-deficient mice, allowed 6 weeks for engraftment to occur and treated the animals with MDR1-based chemotherapy. In the MDR1-transduced group the human leukocytes were significantly protected from the toxicity of chemotherapy (p 90%) while other tumor cell lines and primary human PBPC were less susceptible. The thymidine kinase (TK) suicide gene was cloned into an AAV-2 vector and a complete kill of TK-transduced HS-1 and HT1080 cells was observed following exposure to aciclovir or ganciclovir (GCV), while >90% of mock-transduced HS-1 cells survived at these dosages. Transplantation of
those sarcoma cells to nonobese diabetic (NOD)/LtSz-severe-combined immunodeficient (scid)/scid (NOD/SCID) mice resulted in a survival of >5 months in the AAV-TK-transduced/GCV-treated group, while the mice in the mock-transduced/GCV-treated group had died after 3 weeks. These data show that soft tissue sarcomas are a particularly suitable model system for the development and clinical testing of new gene therapeutic concepts.

Stichworte:
- Sarcoma
- Myeloprotective gene transfer
- Multidrug resistance 1 gene
- Retroviral vector
- Suicide gene transfer
- Thymidine kinase gene
- Adenoassociated virus-2 vector

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