Phase 1 Trial of Retroviral-Mediated Transfer of the Human MDR-1 in Patients Undergoing High-Dose Chemotherapy and Autologous Stem Cell Transplantation

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Summary. Normal bone marrow cells have little or no expression of the MDR p-glycoprotein product and are, therefore, particularly susceptible to killing by MDR-sensitive drugs such as the vinca alkaloids, anthracyclines, podophyllotoxins, and taxanes. In this report of a phase 1 clinical study performed at the Columbia-Presbyterian Medical Center, we demonstrate the safety and efficacy of transfer of the human multiple drug resistance (MDR) gene into hematopoietic stem cells and progenitors in bone marrow as a means of providing resistance of these cells to the toxic effects of cancer chemotherapy. One-third of the cells harvested from patients undergoing autologous bone marrow transplantation as part of high-dose chemotherapy treatment for advanced cancer were transduced with an MDR cDNA-containing retrovirus; these transduced cells were reinfused together with unmanipulated cells following the administration of the high-dose chemotherapy. High-level MDR transduction of BFU-E and CFU-GM derived from transduced CD34+ cells was demonstrated posttransduction and prereinfusion. However, only two of the five patients showed evidence of MDR transduction of their marrow at a low level at 10 weeks and 3 weeks, respectively, post transplantation. This relatively unexpected low level of efficiency of transduction was thought to be because the unmanipulated cells, infused at the same time as the transduced cells, might compete with the cytokine-stimulated transduced cells in repopulating the marrow. The MDR retroviral supernatant used was shown to be free of replication-competent retrovirus (RCR) before use, and all tests of patient samples post transplantation were negative for RCR. In addition, no adverse events with respect to marrow engraftment or other problems related
to marrow transplantation were encountered. This study does indicate the feasibility and safety of bone marrow gene therapy with a potentially therapeutic gene, the MDR gene.

**Key words.** Gene therapy, MDR, Retrovirus, Advanced malignancies

**Introduction**

High-dose chemotherapy followed by autologous marrow or peripheral blood progenitor cell transplantation has become an accepted therapy for selected patients with various malignancies who have a low probability of cure with conventional therapy. In the laboratory, a linear increase in the dose of various chemotherapeutic agents causes a log increase in the death rate of cancer cells [1]. The myeloablative effect of increasing doses of chemotherapy can be ameliorated by the reinfusion of hematopoietic progenitor cells harvested before the administration of chemotherapy from either marrow or peripheral blood. In retrospective analyses, the administration of the full planned dose of chemotherapy, in comparison with patients for whom doses were attenuated for various reasons, results in an improved disease-free and overall survival [2,3]. In small randomized trials in myeloma, relapsed non-Hodgkin's lymphoma, and breast cancer, high-dose chemotherapy with hematopoietic stem cell support has increased the disease-free survival rate over conventional dose therapy [4-6].

An increased number of cycles of high-dose chemotherapy might further improve survival rates, but are often limited by repeated pancytopenia with associated life-threatening infection or hemorrhage. To resolve this problem, gene transfer strategies aimed at making hematopoietic stem cells and progenitor cells resistant to specific chemotherapy drugs have been devised and tested in animal models and in human hematopoietic progenitor and stem cells (HPC) in vitro [7-11]. We report here our first clinical trial with retroviral transduction of the human multiple drug resistance (MDR-1, MDR) gene into marrow- or blood-derived progenitor cells as a potential means of protecting these cells from the myelotoxic effects of chemotherapy [12]. The MDR gene is normally expressed at low levels in HPC, and thus these cells are particularly susceptible to the myelotoxic effects of many anticancer drugs including the vinca alkaloids, anthracyclines, podophyllins, and paclitaxel and its congeners, all of which require the MDR gene product, p-glycoprotein, for their removal from the cells. The aim of this phase I study is to evaluate the feasibility and toxicity associated with the transduction of the MDR gene into HPC for patients with solid tumors undergoing high-dose chemotherapy with hematopoietic stem cell support.