PublisherInfo		
PublisherName	:	BioMed Central
PublisherLocation	:	London
PublisherImprintName	:	BioMed Central

Autologous stem-cell transplantation of hematopoietic cells containing the MDR1 cDNA

ArticleInfo		
ArticleID	:	3626
ArticleDOI	:	10.1186/bcr-1999-66604
ArticleCitationID	:	66604
ArticleSequenceNumber	:	46
ArticleCategory	:	Paper Report
ArticleFirstPage	:	1
ArticleLastPage	:	4
ArticleHistory	:	RegistrationDate : 1999–8–16 OnlineDate : 1999–8–16
ArticleCopyright	:	Current Science Ltd1999
ArticleGrants	:	
ArticleContext	:	1305811

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Keywords

Multidrug resistance gene, breast cancer, retroviral induction, autologous stem cell transplant

Introduction

The use of high-dose chemotherapy requires rapid hematopoietic reconstitution to avoid the problems associated with prolonged pancytopenia. This reconstitution can be achieved by either using harvested bone marrow, or by reinfusing collected hematopoietic stem cells (HSCs). Previous studies have demonstrated that human HSCs can be transduced *ex vivo* with retroviral vectors and then be detected in the blood or bone marrow for a considerable time following infusion. This opens up a potential therapeutic strategy of transducing HSCs with genes conferring certain important biological properties, reinfusing them into a patient after high-dose therapy, and then, following reconstitution of the hematopoietic system by these transduced cells, taking advantage of these properties. The *MDR1* multidrug resistance gene confers resistance to natural-product anticancer drugs, including paclitaxel. Although tumor cells containing this gene cause problems of resistance, if normal hematopoietic cells contained this gene, then, theoretically these cells would be resistant to the effects of those anticancer drugs. If a patient's hematopoetic system was reconstituted using cells containing this gene, then there is the potential to further treat the patient with drugs such as paclitaxel without causing significant hematopoietic toxicity.

Aims

To determine whether retrovirus-mediated transfer of *MDR1* to human hematopoietic cells would result in their stable engraftment and possibly their expansion, and to study the effects on this population of cells of treatment with myelosuppressive doses of paclitaxel.

Comments

This study describes a new technique to improve transfer systems of *MDR1*. However, with only four fully treated patients, any conclusions reached are tentative. Nevertheless, the study raises many interesting questions, and provides a tantalizing hint that this technique can result in the engraftment of

cells with added beneficial biological properties. Whether high-dose chemotherapy is in fact a reasonable option in the treatment of breast cancer remains to be seen (although if this technique can be refined it could provide a further rationale for high-dose therapy in breast cancer). Nevertheless, high dose therapy with reinfusion of HSCs is commonly used in the hematopoietic malignancies, and if the transduction efficiency can be improved then the therapeutic possibilities are great, limited only by the number of useful genes available.

Methods

Metastatic breast cancer patients achieving a complete or partial remission after standard chemotherapy were eligible for the study. HSCs were mobilized with a single dose of cyclophosphamide (4 g/m^2) and daily Granulocyte colony-simulating factor (G-SCF[filgrastim 10 μg/kg/day]), and then collected from both the peripheral blood and bone marrow harvest. After enrichment for CD34$^+$ cells, two-thirds of the cells were stored without further manipulation. The other one-third of each collection was incubated *ex vivo* for 72 h with a replication-incompetent retrovirus containing the *MDR1* gene (G1MD). Also present were stem-cell factor, interleukin 3, and interleukin 6. Following treatment with the high dose regimen of ifosfamide, carboplatin, and etoposide, all of the stored CD34$^+$ cells (manipulated and nonmanipulated) were reinfused for hematopoietic rescue. After hematopoietic recovery, patients received six cycles of paclitaxel (175 mg/m^2 every three weeks). A PCR assay was used to determine the presence of the *MDR1* transgene in bone marrow and serial peripheral blood samples.

Results

Six patients were enrolled in the study, four of whom received infusion of genetically altered cells (one patient mobilized insufficient HSCs, and the other developed early progressive disease). The *ex vivo* transduction efficiency, estimated by the PCR assay, ranged from 0.1% to 0.5%. Following high-dose chemotherapy, three of the four patients demonstrated engraftment of cells containing the *MDR1* transgene. In these three patients, the estimated percentage of circulating granulocytes containing the *MDR1* transgene ranged from a maximum of 9% down to the limit of detection of 0.01%. One patient remained positive for the *MDR1* transgene throughout all six cycles of paclitaxel therapy (the patient having the highest percentage of cells containing the transgene), whereas the other two patients showed a decrease in the number of cells containing the transgene to undetectable levels. Despite the low level of engraftment of *MDR1*-marked cells, there did appear to be a correlation between the granulocyte nadir after paclitaxel therapy and the relative number of granulocytes containing the *MDR1* transgene. There were no specific adverse reactions to the genetic manipulation procedures, and there was no evidence of myeloproliferative disorders in the patients following engraftment with *MDR1*-transduced cells.

Discussion

This study shows that engraftment of human HSCs transduced with *MDR1* can be achieved; however, the overall transduction efficiency was low (0.1-0.5%) and this may have been related to the choice and availability of the vector used. Despite low transduction efficiency, and therefore the infusion of a relatively small number of *MDR1* gene-carrying cells, engraftment of these cells occurred in three of four patients; in particular, one patient demonstrated a high level of gene-carrying cells (9%). This raises the possibility that gene-modified HSCs may have an engrafting or a survival advantage. Although the numbers are small, there was some evidence that engraftment with cells carrying the *MDR1* gene resulted in a degree of myelo-protection following paclitaxel administration. In conclusion, although feasible, this technique of infusion of gene-modified HSCs must be improved before *MDR1* gene therapy followed by *in vivo*selection with specific anticancer drugs can be reliably used to protect cancer patients from drug-related hematopoietic toxicity.

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