Chemoprotection of normal tissues by transfer of drug resistance genes

J.A. Rafferty1, I. Hickson1,2, N. Chinnasamy1,2, L.S. Lashford2, G.P. Margison1, T.M. Dexter2 and L.J. Fairbairn2
CRC Departments of 1 Carcinogenesis and 2 Experimental Haematology, Paterson Institute for Cancer Research, Christie Hospital (NHS)-Trust, Manchester M20 9BX, UK

Key words: myelosuppression, therapy-related malignancy, chemoprotection, MDR-1, ATase, retrovirus

Abstract

The effectiveness of many types of antitumour agent is limited by (i) acute dose limiting cytotoxicity, principally myelosuppression but also lung, liver and gastrointestinal tract toxicity, (ii) the risk of therapy related secondary malignancy and (iii) the inherent or acquired drug-resistance of tumour cells. As the management of the acute toxic effects improve, the more insidious effects, and particularly haematological malignancies, are anticipated to increase. Furthermore, attempts to overcome tumour cell resistance to treatment can lead to increased collateral damage in normal tissues.

One approach to circumventing both the acute toxic and chronic carcinogenic effects of chemotherapy would be to use gene therapy to achieve high levels of expression of drug resistance proteins in otherwise drug-sensitive tissues. To date the products of the multi-drug resistance (MDR-1) and the human O6-alkylguanine-DNA-alkyltransferase (ATase) gene have been used in preclinical experiments to demonstrate proof of principle, and the former of these is now being tested in a clinical situation.

Here we discuss the potential of drug-resistance gene therapy to provide chemoprotection to normal tissues and examine the prospects for a dual approach which combines this with pharmacological sensitisation of tumours to chemotherapeutic agents.

Introduction

Systemic chemotherapy is currently one of the most widely used forms of cancer treatment. A large number of agents have been developed which either alone or in combination can effectively kill tumour cells in situ in a dose dependent manner. However, this cytotoxic effect is not confined to the tumour. Significant toxicity is often manifest in normal tissues, particularly those with a high proliferative index such as the haemopoietic system and gut. These secondary toxicities can often lead to limitations in the doses of agent used, resulting in inadequate tumour cell kill and failure to reach disease free remission. Severe side effects experienced by patients during treatment may necessitate a reduction in either the dose of chemotherapy, its frequency of administration or in extreme cases cessation of therapy. Such treatment modifications can compromise the chance of cure either through inadequate cytodestruction of the malignant clone or through selection of a drug-resistant tumour population. In an attempt to maintain the intensity and duration of treatment, supportive care is always initiated early. This includes the rapid use of broad spectrum antibiotics in cases of fibrile neutropenia as well as the use of blood products and nutritional support during episodes of bleeding and mucositis. Whilst these measures are often successful in sustaining patients through repeated courses of chemotherapy, treatment delays and dose reductions remain a regular feature of any intensive chemotherapy regimen.

Chemotherapeutic agents usually manifest their
Sequential rounds of chemotherapy

Figure 1. Strategies to overcome dose limiting myelotoxicity. a) In the absence of myelosupportive or myeloprotective therapy, bone marrow toxicity and recovery may mirror tumour kill and recovery and dose limitation due to myelotoxicity may occur, compromising the chances of cure. b) The administration of growth factors such as G-CSF between successive rounds of chemotherapy can increase the recovery of the bone marrow, facilitating more intense chemotherapy and leading to disease cure. c) In the ideal situation, the normal tissue(s) would be resistant to the toxic effects of the chemotherapeutic agents. This might be the outcome of drug resistance gene therapy.

effect via genotoxicity and sub-lethal genetic damage in normal tissues can lead to undesirable long term effects exemplified by the emergence of therapy related malignancies of the haemopoietic system. While strategies are emerging to address the acute toxicities, effective management of the more insidious side effects of systemic chemotherapy has not been possible. Here we describe some of the current approaches to managing the acute effects of collateral damage and examine the potential of gene therapy to address both the acute and long term complications of antitumour treatments. We concentrate principally on means of overcoming damage in the haemopoietic system since this tissue is the main focus of gene therapy research at the moment. However, protection of haemopoietic stem cells should be seen as a paradigm for the protection of at-risk stem cells in other drug sensitive tissues.

**Current approaches to managing acute collateral bone marrow toxicity**

In terms of haematotoxicity, support measures are frequently taken and these may make use of growth factors and cytokines to which haemopoietic stem cells and progenitors are responsive. Alternatively, haemopoiesis may be supported using autologous sources of stem and progenitor cells.

**Growth factor stimulation of haemopoiesis following chemotherapy**

Recently, one of the most successful methods for supporting haemopoiesis during cancer treatment has been the stimulation of myelopoiesis, following chemotherapy, using recombinant haemopoietic growth factors to induce accelerated recovery of bone marrow progenitors and their mature progeny (illustrated in Figure 1). Perhaps the best example of growth factor support to date has been the use of recombinant human Granulocyte Colony Stimulating Factor (G-CSF) in facilitating myelopoietic recovery. The use of G-CSF can reduce the severity and extent of neutropenia in patients undergoing cytotoxic drug treatment (e.g. see references [1–3]), hence reducing the incidence of secondary infections and allowing patients to stay at home rather than in hospital. Growth factors acting on the eryth-