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

Vaccination of breast cancer patients with MUC1 keyhole limpet hemocyanin conjugate plus QS-21

ArticleInfo		
ArticleID	:	3749
ArticleDOI	:	10.1186/bcr-2000-66712
ArticleCitationID	:	66712
ArticleSequenceNumber	:	21
ArticleCategory	:	Paper Report
ArticleFirstPage	:	1
ArticleLastPage	:	4
ArticleHistory	:	RegistrationDate : 2000–8–10 OnlineDate : 2000–8–10
ArticleCopyright	:	Current Science Ltd2000
ArticleGrants	:	
ArticleContext	:	1305833

Richard de Boer,[Aff1]

Aff1 Austin and Repatriation Medical Centre, Victoria, Australia

Keywords

Immunotherapy, KLH, mucin-1

Introduction

Immunotherapeutic approaches to the management of solid tumours have been an area of active research in recent years. Approaches have been particularly advanced for melanoma, for which a number of distinct tumour antigens have been identified. A number of differentiation antigens have also been identified on breast cancer cells. One of these is MUC1, which is a transmembrane glycoprotein. MUC1 has been identified on a number of different tumour types a variety of normal epithelial cells. There are differences in MUC1 expression, with greater exposure of MUC1 epitopes to the immune system in tumours due to altered tissue structure leading to MUC1 expression on multiple cell surfaces, and also due to changed structure with abnormal glycosylation. Cloning and sequencing of MUC1 has led to the development of various synthetic peptides for use in vaccines. These peptides elicit both humoral and cellular immune responses in animal models. The lack of development of intrinsic immune responses against endogenous MUC1 on tumour cells suggests that there is low tumour immunogenicity. This may be overcome by conjugating the MUC1 peptide with a protein carrier and with an immune adjuvant. Keyhole limpet hemocyanin (KLH) is one such protein carrier obtained from the blood of the keyhole limpet, and QS-21 is an immune adjuvant obtained from the bark of a South American tree. This combination of KLH and QS-21 has been shown to be effective in inducing antibody responses.

Aims

To determine whether an immune response can be generated against synthetic MUC1 peptide and against tumour cell MUC1 after vaccination with MUC1-KLH conjugate plus QS-21 in breast cancer patients who have a high risk of relapse.

Comments

This is an important study. Vaccine approaches are particularly interesting in that they hold out the promise of targeted therapy with minimal toxicity. Unfortunately there have been few vaccine studies in the field of breast cancer; this study goes some way towards rectifying this. MUC1 has been identified as a potential target in a number of tumour types and certainly appears to be a reasonable target in breast cancer patients. There are a number of possible peptides of differing length available and a great deal of preliminary work is still required to determine the most appropriate length of polypeptide (eg 30 amino acids (aa) vs 32 aa vs 106 aa), and the most appropriate treatment schedules. An important issue is which patients to treat; there is certainly some evidence suggesting that patients with minimal residual disease and a high risk of relapse may be the ideal candidates. Once these issues are resolved, then larger phase II and phase III studies can be performed in breast cancer patients.

Methods

Patients with a history of breast cancer, but without evidence of disease, were eligible. In particular, patients with advanced disease who had been rendered disease free by therapy, or patients with earlier stage disease but with rising levels of tumour markers were recruited. Patients were administered MUC1-KLH conjugate plus QS-21, containing 100 μg of MUC1 and 100 μg of QS-21 via subcutaneous vaccination. Doses were delivered at weeks 1, 2, 3, 7, and 19 at rotating sites. Standard patient antitumour assessments were made at regular intervals. Peripheral blood was drawn at frequent intervals to assess antibody titres (antibody production against MUC1 was assessed using ELISAs). Skin tests were performed at weeks 1, 3, 9, and 21 to determine delayed-type hypersensitivity reactions. Cell-mediated immunity was assessed using limiting dilution chromium release assays.

Results

Of the nine patients who entered the trial, eight patients had previously documented metastatic disease and eight had been treated with prior chemotherapy. Common toxicities included a local skin reaction at the site of the vaccine, usually of 4-5 days duration, and mild flu-like symptoms of shorter duration. Erythema of ≥15 cm was commonly observed at the vaccination site. There was no clinical evidence of an autoimmune reaction as determined by clinical or laboratory findings. High immunoglobulin (Ig)M and IgG antibody titres against synthetic MUC1 were detected in all patients. IgG antibody titres remained elevated for a minimum of 106-137 weeks after the first vaccination. Binding of IgM antibody to MCF-7 tumour cells (which express MUC1) was observed in seven patients, although there was minimal binding of IgG antibody. No delayed-type hypersensitivity reactions against MUC1 were detected. There was no evidence of T-cell activation.

Discussion

Vaccine studies in breast cancer have been infrequent and subject to design flaws or limitations secondary to the immune agents used. This study demonstrated that this particular MUC1-KLH conjugate plus QS-21 was well tolerated with minimal toxicities in breast cancer patients and no evidence of autoimmune reactions against normal epithelial cells. The vaccine also proved to be immunogenic, with the production of both IgM and IgG antibodies, although T cell activation was not seen. Additional trials are ongoing to determine the optimal MUC1 peptide for use in larger clinical trials. Further investigation of vaccine therapy in high-risk breast cancer appears warranted.

References

1. Gilewski T, Adluri S, Ragupathi G, Zhang S, Yao T-J, Panageas K, Moynahan M, Houghton A, Norton L, Livingston PO: Vaccination of high-risk breast cancer patients with mucin-1 (MUC1) keyhole limpet hemocyanin conjugate plus QS-21. Cancer Res. 2000, 60: 2660-2665.