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Enhanced activity of anti-Lewis^{y}humanised 3S193 when combined with Taxol

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Keywords

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Introduction

Monoclonal antibody (mAB) therapy is a potential new treatment option that selectively targets tumours and produces a therapeutic effect via the delivery of radiation or other toxins directly to tumour cells, or by producing an intrinsic immune inflammatory response. The Lewis^{y} antigen (Le^{y}) is a difucosylated oligosaccharide expressed on the surface of up to 60% of breast cancer cells, whilst rarely expressed on normal tissues. The humanised murine antibody, hu35193 has been shown to have high specificity for Le^{y}.

Aims

To examine the antitumour effect of ^{131}I-labelled hu3S193 in an MCF-7 xenografted BALB/c nude mouse breast cancer model compared with that of placebo and radiolabelled huA33 control antibody. To examine the synergy between radioimmunotherapy and chemotherapy using a combination of ^{131}I-labelled hu3S193 and Taxol.

Comments

This study was well conceived and performed, and produced interesting results. The use of, and research into, so called targeted therapies has accelerated over the past 5 years, particularly following the successful development of Herceptin for the treatment of HER2-neu overexpressing breast cancers. The promise of a therapy with a greater therapeutic index (ie higher efficacy with lower toxicity) is certainly attractive; however determining exactly where it might fit into current treatment strategies remains problematical. The Lewis^{y} antibody appears to be specific, delivers radioactivity to the desired

tissues, and appears to have definite antitumour efficacy. How this translates into the human setting is obviously the next key question to be answered. Hopefully, with well planned and conducted clinical trials the answer will rapidly become known, with the Lewis^{y} antibody becoming another option for the treatment of highly expressing cancers.

Methods

mABs were produced using standard hybridoma techniques and then humanised. MCF-7 cells were used as the tumour target, and SW1222, a Le^{Y} negative colonic cancer cell line was used as control. Tumour cells were injected into the left inguinal mammary line of 5-6 week old BALB/c nude mice and supported by slow release oestrogen pellets. Antibodies were radiolabelled the day of injection. In the first part of the study, antibody with escalating doses of iodine (50, 100, 200 and 300 μCi) was injected 22 days after tumour inoculation and effect on tumour volume measured. In the second part of the study, the determined dose of iodine-labelled antibody was injected with or without intraperitoneal Taxol. This component of the study incorporated nine different treatment groups (some acting as controls).

Results

The maximum tolerated dose of ^{131}I-labelled antibody was 200 μCi/mouse. At this dose level three out of six mice receiving ^{131}I-hu3S193 had a partial tumour response and two out of six had a minor response. There were no responses in the comparable ^{131}I-huA33 control treatment arm. A significant dose-response relationship was seen for ^{131}I-hu3S193. Unlabelled antibody had little impact upon tumour growth. In the combination part of the study, the combination of 600 μg Taxol and 100 μCi ^{131}I-hu3S193 produced partial tumour inhibition in 80% of mice, while no significant responses were seen with either treatment modality alone or the combination of Taxol and ^{131}I-huA33.

Discussion

These results confirm that specifically targeted radiolabelled antibody can effectively slow tumour growth in a murine model. In addition, combining the antibody with a chemotherapeutic agent increased the antitumour efficacy. Thus, the study indicates a potential therapeutic role for radiolabelled hu3S193 in the management of breast cancer, either as a single agent or in combination with Taxol, and warrants further investigation of this new agent.

References

1. Clarke K, Lee F-T, Brechbiel MW, Smyth FE, Old LJ, Scott AM: Therapeutic efficacy of anti-Lewis^{y}humanised 3S193 radioimmunotherapy in a breast cancer model: enhanced activity when combined with Taxol chemotherapy. Clin Cancer Res. 2000, 6: 3621-3628.

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