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TALL-104 adoptive immunotherapy in breast cancer

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Keywords

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Introduction

The goal of adoptive immunotherapy is to boost host immune response to malignant cells using cells and/or cytokines that are either themselves tumoricidal, or that stimulate the host's own immune-mediated tumoricidal machinery. This strategy can be of potential value given singly or in combination with chemotherapy, and in many cases has the advantage of limited toxicity. Numerous therapies, including interleukin (IL)-2 and interferon (IFN), have been explored clinically with modest benefits to date. TALL-104 is a designer human histocompatibility complex non-restricted killer cell line with anti-tumor efficacy in mammary xenograft models. This phase I trial explored its tolerability and efficacy in patients with refractory MBC.

Aims

To determine the dose limiting toxicity and appropriate recommended dose of TALL-104 cells in refractory MBC patients. To correlate changes in levels of cytokines and immune activity with *in vivo* and *in vitro*anti-tumor effects in post-treatment patient sera.

Comments

Particularly noteworthy in this phase I of adoptive immunotherapy in metastatic breast cancer are the parallel laboratory studies which examined the effect of TALL-104 cell line infusions on host cytokine production and tumoricidal activity. Investigators combined traditional phase I trial elements of tolerability and dose finding with laboratory models in order to better understand the *in vivo*cytotoxic mechanisms of the TALL-104 cell line.

Methods

Adult women with performance status of 0-1 who did not require corticosteroid therapy (which could dampen immune response), and who had failed at least two prior chemotherapy regimens for MBC were eligible. Five dose levels of lethally irradiated TALL-104 cell infusions (106, 3 x 106, 107, 3 x 107, 108 cells). Patients who did not progress after the first 5-day infusion received monthly booster injections. Patient sera were tested before and at several time points after infusion for levels of IFN-γ, tumor necrosis factor (TNF)-α, TNF-β, granulocyte macrophage-colony stimulating factor (GM-CSF), IL-10, and the presence of TALL-104 cellular DNA. Tumor cells from biopsies from five patients were incubated with their post infusion sera to determine cytocidal activity. These tumor cells were subsequently injected into severe combined immunodeficient (SCID) mice to determine the inhibitory capacity of this treatment on xenograft tumor development.

Results

Fifteen patients were enrolled: nine progressed within 1 month and five had disease stabilization of 2-6 months; one had significant necrosis of hepatic metastases but withdrew consent and one experienced significant relief of bone pain. Grade IV nausea, vomiting, and fever occurred in the patient with hepatic metastasis necrosis, but there were no other grade III/IV toxicities and only two grade II toxicities (one leucopenia and one hyperglycemia). Haematologic toxicity was one grade I neutropenia, and one each of grade I and grade II leucopenia, all reversible. Laboratory studies demonstrated the presence of TALL-104 DNA in patient sera throughout the infusion with complete clearance by day 7. Only one patient developed anti-TALL-104 antibodies. In four of five patients, post-treatment sera demonstrated *in vitro* lysis of biopsies from their own tumors; all five had detectable cytokine levels. A sample of these post-treatment biopsies was implanted into SCID mice: mammary tumor grew in two mice inoculated with cells from the same patient after 6 months; the remaining 17 mice remained tumor free with 6-18 months follow-up. Pre- and postinfusion sera had no significant detectable levels of TNF-α, TNF-β, or GM-CSF; IFN-γ and IL-10 levels increased by >20% in five and seven patients, respectively. Levels of sIL-2R and sICAM-1, markers of nonspecific immune activation, increased during infusion and returned to baseline by day 5.

Discussion

Possible explanations for the lack of substantial change in cytokines after TALL-104 infusions include, an insufficient cell number (dose) infused to provoke an immune response, other mediators/ mechanisms responsible for the major cytotoxic activity, a relatively immune-deficient state of these patients due to numerous prior therapies, and finally, that this cell line has limited immune-stimulatory capacity in humans. If the immune stimulation proves better in more immune-competent patients, there

is also a risk that more will develop anti-TALL-104 antibodies, which would limit efficacy. Given that nine patients progressed immediately and the duration of disease stabilization was relatively short for the other five, it is difficult to speculate whether or not cytokine levels correlate with tumor response, as was observed in previous studies on dogs. The fact that transplanted tumors exposed to treated patient sera were unable to generate tumors in the majority of injected SCID mice suggests that the anti-tumor effects may be long lasting. Excellent tolerability at the doses tested coupled with visible metastasis necrosis in one patient, symptom relief in another, and modest disease stabilization in five suggest that the potential efficacy of TALL-104 cell infusions is worth exploring further. A less heavily pretreated patient population may be a better target for immune-modulating therapies such as this. The addition of similar parallel laboratory assays in subsequent studies is attractive, as they would allow a better understanding of the specific immune changes that are induced by TALL-104 cell therapy.

References

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