Concluding Remarks: Ninth Conference on Cancer Therapy with Antibodies and Immunoconjugates

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Introduction

The papers presented at this conference represent the maturation of a number of important themes in the development of antibody-targeted therapies. In sequence, the following general areas were touched on in the presentations at the conference, although not all are included in the proceedings.

Design Strategies

Monoclonal antibody technology, first defined by Köhler and Milstein in the 1960s and 1970s, had advanced to initial clinical application by the mid-1980s. However, the essentially negative results of many trials, and the marginal and inconsistently reproduced work of most others, led several observers to question in the early 1990s whether antibody-based therapeutics would ever be of value. Among the major issues bedeviling their development outside very specialized circumstances were the presence of human antimouse responses, uncertainty about which types of antigens would make the best targets, and whether "naked" antibodies (as opposed to various types of "armed" agents) would be of value.

The development and rapid application of "humanization" strategies clearly has revolutionized the practical application of monoclonal antibodies and has considerably diminished the first of these concerns. However, questions remain as to the best type of reagent to produce and how to administer the agent. "Naked" antibodies were the focus of several presentations. Although initial clinical studies focus on single antibodies to address hematological neoplasms (Schuster), the strategy of extending administration for "maintenance" effects emerged as a promising lead to extend the duration and increase the magnitude of the response rate. Several approaches emphasized the evolution of the field by considering strategies that combined anti-CD22 plus anti-CD20 antibodies (Coleman) or antibodies with chemotherapy (Cairo). Naked antibodies addressing nonhematological targets include carcinoembryonic antigen antibodies in medullary thyroid cancer in combination with chemotherapy and a bispecific antibody directed to carcinoembryonic antigen and p-glycoprotein for more selective inhibition of p-glycoprotein in hopes of reducing multidrug resistance (Modrak). A new high-affinity, fully human antiepidermal growth factor receptor antibody has begun clinical testing. Early results from the trial have indicated some antitumor activity without the development of antiantibody responses, suggesting that repeated cycles can be given (Foon). Amyloid deposition was targetable with an antibody reactive with amyloid fibers. In mice, it enhanced the removal of human light chain-associated amyloidomas by activating an Fc-mediated immune response. These data suggest that a similar approach might be developed for other forms of amyloid-associated diseases (Solomon). Efforts to develop reagents directed against ligands important in tumor cell biology included antibodies to tumor necrosis factor-related apoptosis-inducing ligand receptor 1. Early *in vitro* studies have identified several candidates that induce apoptosis (Dobson).

Pretargeting approaches were also discussed at the meeting, focusing primarily on the use of bispecific antibodies (Sharkey). The superior binding and pharmacokinetic properties of such constructs were also highlighted (Rossi), as well as initial efforts to bring these concepts to the clinic (Barbet). The data indicated excellent targeting ratios, but full optimization of the procedure was not yet achieved. Other design features considered were the nature and internalizing potential of the antibody, *e.g.*, even classically "noninternalizing" antigens, such as CD20, might traffic repeatedly to a compartment that would allow "residualizing" of delivered isotope or toxin (Mattes).

Conjugation Strategies

The rational series of modifications leading to an anti-CD22 immunotoxin based on *Pseudomonas* toxin was highlighted (Pastan). Promising antitumor effects have already been seen in drug resistant hairy cell leukemia, with 11 of 12 patients having a complete response to the treatment with durations >1 year. Other types of novel conjugation strategies included promising preclinical data with a geldanamycin conjugate to an anti-HER2 antibody. Both *in vitro* and *in vivo* data supported highly specific targeting and improved therapeutic outcome in HER2 overexpressing cell lines and xenografts of human breast and gastric cancers, when compared with the antibody alone (Mandler). Antibody-based targeting of tumor vascular tissue and tissue factor, a cell membrane receptor protein that initiates the extrinsic pathway of blood coagulation, resulted in thrombosis in tumor xenografts, suggesting a possible future role for appropriate constructs to inhibit or block the tumor blood supply (Hu). Overall, the presentations illustrated how diverse, effective immunoconjugates can be developed.

Radiolabeled Antibody Strategies

An antibody selective for a mutated E-cadherin, radiolabeled with Bi-213, was presented (Senekowitsch-Schmidtke). This reagent, when injected i.p., was shown in an animal model mimicking peritoneal carcinomatosis to be highly effective in preventing the growth of the human tumor xenograft. A "diabody" directed against HER2/*neu* radiolabeled with astatine-211 was better than a same antibody radiolabeled with yttrium-90 for the treatment of an s.c. breast cancer xenograft (Adams). A

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bismuth-213-labeled anti-CD33 antibody for therapy of myeloid leukemia showed the efficacy of fractionated injections with minimal side effects (Burke).

Chelates were described that showed selective degradation by liver enzymes and therefore reduced hepatic uptake (G. DeNardo). A comparison of traditionally conjugated chelates to cathepsin-sensitive chelates was given, indicating that a similar reduction in hepatic uptake could be achieved clinically (S. DeNardo). A potential concern about combining radio-conjugates with chemotherapy was apparent in that some studies revealed antagonism between the two therapies (Blumenthal). On the other hand, a human pancreatic cancer animal xenograft model showed that a yttrium-labeled antibody to pancreatic cancer could significantly improve the therapeutic response seen with gemcitabine, even when it was given at very low doses along with a standard dose regimen of gemcitabine (Gold).

Issues and Challenges

The conference was also of importance for its recognition of general challenges to the field. First and foremost, solid tumors remain a "problem." Ongoing dosimetric evaluations raised real concern about the radiation doses possible with various delivery strategies in relation to the known sensitivity of epithelial tumors. This is in comparison to hematopoetic neoplasms, where continuing evidence mounted that effective doses were possible with current technology. Second, delivery of antibody-based approaches to solid tumor masses remains a challenge and reinforces the need for focus in solid tumors in adjuvant or minimal disease settings, with manipulation of pharmacology, antibody affinity, or "loading" of labeled constructs to optimize delivery of radiation. A better understanding of the determinants of the tumor microcirculation would go hand-in-hand with the generation of novel approaches.

When using nonlabeled antibodies, why one tumor may respond and another is resistant is not clear. Greater effort must be made to better understand the biology underlying responding tumors or enable engagement of complementary pathways. With regard to current versions of immunotoxins, although strategies to manage vascular leak syndrome have been zealously pursued, full optimization of the potential value of these approaches should attempt to develop intoxicating mechanisms distinct from the protein synthesis poisons represented by *Pseudomonas* constructs. These would be chosen to minimize the vascular leak toxicities expected from these constructs.

The recognition of these prospects and issues should actually be regarded as quite a healthy set of actual opportunities. The design ingenuity of the investigators and papers at this meeting point to continued vigorous growth and innovation in antibody-based approaches in the coming years.