Meeting Report on the Ninth Conference on Cancer Therapy with Antibodies and Immunoconjugates

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Abstract

This conference, held biennially for the past 12 years, provides a forum where investigators from throughout the world can gather and discuss how monoclonal antibodies can be used to improve the treatment of cancer. As in the past, this meeting focused primarily on the use of radiolabeled antibodies in cancer treatment, but this year there were many additional contributions on the use of unconjugated “naked” antibodies for the treatment of cancer, reflecting a growing understanding that antibodies not only can be used to direct isotopes and drugs to tumors but can also be effective agents in themselves. Preclinical studies using immunoconjugates prepared with toxins, drugs, or other agents were also reported to be highly effective therapeutic agents. Some of these are now showing efficacy in clinical trials. In addition, presentations focused on a variety of approaches, including pretargeting, regional delivery, and combinations with other standard treatment regimens designed to optimize antibody-targeted treatment strategies. Although the most efficacious treatments were reported in a variety of hematological malignancies, there were a number of presentations, primarily in early preclinical development, that provided evidence for potential future improvements in the treatment of solid tumors.

Introduction

Overall, the central theme of this conference remains one where the translational application of antibodies in the treatment of hematological and nonhematological malignancies is highlighted in a series of presentations that focus on the preclinical development and ultimate clinical application of these treatment strategies. Since the inception of this conference in 1978 (1) to highlight the advances made in using radiolabeled antibodies for cancer detection, antibody-directed targeting agents, as well as antibodies that are unlabeled, have steadily been making their way into clinical practice. Indeed, early preclinical and clinical testing of a number of now Food and Drug Administration-approved agents has been discussed over the years at this conference. This year’s meeting was chaired by David M. Goldenberg (Center for Molecular Medicine and Immunology and GSCC, Belleville, NJ), Ralph A. Reisfeld (The Scripps Research Institute, San Diego, CA), and Edward A. Sausville (NCI, Bethesda, MD) and attended by almost 200 scientists and clinicians from both academia and industry, specializing in immunology, pharmacology, oncology, radiation oncology, nuclear medicine, medical physics, and chemistry, and presenting almost 60 papers. Keynote speakers briefly highlighted several topics, but perhaps one of the key features of a focused forum such as this was the number of succinct presentations that enabled attendees to listen and ask questions of prominent and young investigators alike.

Immunoconjugates

Dr. Ira Pastan (NCI) provided an overview of the development of an immunoconjugate for the treatment of CD22-expressing hematological malignancies, including hairy cell leukemia, NHL, and chronic lymphocytic leukemia. Dr. Pastan highlighted a number of important considerations that made it possible to develop the BL22 anti-CD22 single-chain, Pseudomonas exotoxin A, fusion protein for clinical studies, including antibody specificity and ability to internalize appropriately, and the importance of appropriate molecular engineering for both the toxin and the MAb to optimize performance. Clinical studies with this new agent led to new discoveries, such as how to better manage some of the side effects associated with this treatment and the determination that a higher response rate in patients was linked with higher levels of antigen expression. This subsequently led investigators to select a new affinity-enhanced version of the single-chain antibody that they plan to test clinically in the future. However, promising antitumor effects have already been seen in drug-resistant hairy cell leukemia with the initial BL22 construct, with 11 of 12 patients having a complete response to the treatment with durations >1 year. Dr. M. Jules Mattes (GSCC) also spoke of the importance of MAb internalization. He showed data that even MAbs not noted for internalization are taken into cells, possibly due to membrane turnover in tumor cells. In this regard, Dr. Mattes described the internalization properties of a MAb directed to the CD20 antigen (1F5), which was not considered to be an antibody that internalized after binding to human lymphoma cell lines. His work also highlighted the trafficking of the anti-CD20 MAb into the endocytic recycling compartment rather than a lysosomal compartment. Radioconjugates that residualize inside the cell would be advantageous irrespective of the trafficking mechanism, but different patterns of trafficking will also likely impact on the efficacy of other immunoconjugates. Dr. Raya Mandler (NCI) showed some very promising preclinical data with a geldanamycin conjugate to an anti-HER2 MAb (Herceptin, trastuzumab). Both in vitro and in vivo data supported highly specific targeting and improved therapeutic outcome in HER2-overexpressing cell line and xenografts of human breast and gastric cancers when compared with the MAb alone. Dr. Hu (University of Southern California Keck School of Medicine, Los Angeles, CA) described studies using a fusion protein between two MAbs, one that binds to tumor vascular tissues, and another that binds to tissue factor (TF), a cell membrane receptor protein that initiates the extrinsic pathway of blood coagulation. These fusion proteins caused microregional thrombosis in tumor xenografts, suggesting a possible future role for appropriate constructs to inhibit or block the tumor blood

Received 4/7/03; revised 8/28/03; accepted 9/2/03.

Grant support: The conference was gratefully supported by a conference grant from the National Cancer Institute and the New Jersey Commission on Cancer Research, as well as grants from Abgenix, Amgen, Bristol-Myers Squibb Oncology, Genentech Bio- oncology, GlaxoSmithKline, IDEC Pharmaceuticals, and Imedex Systems. Imedex provided logistical support as the conference organizer. The Ninth Conference on Cancer Therapy with Antibodies and Immunoconjugates was held October 24–26, 2002, in Princeton, New Jersey.

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1 The abbreviations used are: NCI, National Cancer Institute; GSCC, Garden State Cancer Center; MAb, monoclonal antibody; NHL, non-Hodgkin’s lymphoma.
supply. Overall, the presentations illustrated how diverse, effective immunoconjugates can be developed.

“Naked” Antibodies

With the advent of the successful treatment of NHL using a chimeric MAb to the CD20 antigen (rituximab) and an anti-HER2 antibody (trastuzumab) for the treatment of breast cancer with minimal side effects, there has been considerable interest in the use of naked antibodies for the treatment of a variety of malignancies. Dr. Stephen Schuster (Hospital of the University of Pennsylvania, Philadelphia, PA) provided a brief overview of the treatment of NHL with rituximab and, importantly, highlighted the utility for using rituximab as a form of maintenance therapy for this indication. When used in this manner, complete response rates were increased, and duration of responses was extended. Dr. Morton Coleman (Weill Medical College of Cornell University and New York Presbyterian Hospital, New York, NY) further expanded on the possibility of using an anti-CD22 MAb (epratuzumab) that alone, in early Phase I/II trials, showed efficacy in NHL, but he also provided data from early clinical testing that suggest that the combination of anti-CD22 and anti-CD20 (rituximab) antibodies will improve efficacy in NHL. Dr. Alessandra Cesano (Amgen, Thousand Oaks, CA) provided an overview of preclinical studies directed toward understanding the potential mechanism(s) of action and explanation of the antitumor responses seen with epratuzumab. Dr. Mitchell Cairo (Columbia University, New York, NY) reported some promising early clinical results using rituximab in combination with chemotherapy to improve the treatment of post-transplant lymphoproliferative disorder. Other studies showed promising new approaches for naked antibody therapy, including preclinical studies on the use of hMN-14, a humanized anti-carcinoembryonic antigen MAb, 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. Dr. F. Modrak, GSCC). Dr. Ken Foon (Abgenix, Fremont, CA) discussed the development of a high-affinity, fully human anti-epidermal growth factor receptor MAb (ABX-EGF) that has begun clinical testing. Early results from the trial have indicated some antitumor activity without 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 (Dr. David Gold, GSCC). Dr. D. Blumenthal (Cambridge Antibody Technology, Cambridge, United Kingdom) described their work using phage display to develop single-chain MAbs to tumor necrosis factor-related apoptosis-inducing ligand receptor 1. Early in vitro studies have identified several candidates that induce apoptosis. Thus, there is renewed interest in naked antibody approaches for treating cancer and other diseases as ultimately new targets are discovered and mechanisms of action are elucidated.

Radiolabeled Antibodies

The largest number of presentations involved the use of radiolabeled antibodies for the treatment of cancer. In this year’s meeting, there were a larger number of presentations using antibodies combined with a variety of α-emitters, including bismuth-213, astatine-211, and actinium-225. Dr. Senekowitsch-Schmidle (Universität München, Munich, Germany) presented data for a new MAb that is directed to a mutated, tumor-specific E-cadherin. The MAb specifically reacted with exon 8- or exon 9-deleted E-cadherin and not the wild type, making the reactivity of this MAb highly unique in its specificity for patients with gastric cancers, which express this mutated form of E-cadherin. This antibody (d9MAb) radiolabeled with bismuth-213 and 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. Whereas others discussed the use of α-emitter antibody conjugates, liposomally entrapped, and modified polylysine for targeting α-emitters in the treatment of locoregional disease, Dr. Greg Adams (Fox Chase Cancer Center, Philadelphia, PA) showed that an i.v. injected diabody to HER2/new (C6.5) radiolabeled with astatine-211 was better than the same antibody radiolabeled with yttrium-90 for the treatment of a s.c. breast cancer xenograft. This study was particularly interesting because α-emitters have been considered primarily for use in micrometastatic disease, but in this case, it is possible that the pharmacokinetics and other targeting properties of the antibody are well matched for this use with astatine-211. Other potential applications of α-emitter therapy were in myeloid leukemia, where clinical studies presented by Dr. John Burke (Memorial Sloan-Kettering Cancer Center, New York, NY) showed the efficacy of fractionated injections of a bismuth-213-labeled anti-CD33 MAb (HuM195) with minimal side effects.

Other presentations focused on improving chelation of radioisotopes and appropriate selection of radioconjugates for matching to the internalization or pharmacokinetic properties of the MAb. Dr. Gerald DeNardo (University of California Davis, Sacramento, CA) showed how designing chelates that can be selectively degraded by liver enzymes could reduce the hepatic uptake of chelated radiometals, and Dr. Sally DeNardo (University of California Davis) presented results comparing traditionally conjugated chelates with cathepsin-sensitive chelates, indicating that a similar reduction in hepatic uptake could be achieved clinically. Another topic of interest was the potential for combining radiolabeled antibodies with chemotherapy. Dr. Rosalyn D. Blumenthal (GSCC) gave a detailed account of in vitro studies directed at developing an approach to rationally select agents and how they might be used in combination with a radiolabeled MAb. One unexpected finding was that certain combinations could potentially be antagonistic, whereas using it in a different manner could provide additive antiproliferative effects. Dr. David V. Gold (GSCC) showed in a human pancreatic cancer animal xenograft model that a yttrium-labeled MAb to pancreatic cancer (PAM4) 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. Clinically, therapeutic studies with radiolabeled antibodies focused primarily on the use of a humanized anti-CD22 MAb, epratuzumab, in the treatment of NHL. These studies included the use of yttrium-90- and rhenium-186-labeled antibodies, both of which have shown antitumor activity in Phase I trials.

Pretargeting approaches were also discussed at the meeting, focusing primarily on the use of bispecific antibodies. Dr. Robert M. Sharkey (GSCC) gave an overview presentation that illustrated the importance of the bispecific antibody pharmacokinetics and other factors to optimize this type of pretargeting approach. Dr. Edmund Rossi (IBC Pharmaceuticals, Inc., Morris Plains, NJ) presented data with a series of molecularly engineered, recombinant, bispecific antibodies, showing how such constructs could significantly improve targeting by having highly favorable binding and pharmacokinetic properties. Pretargeting studies in animal models illustrated the potential advantage of pretargeting radiolabeled peptides using a novel anti-hapten antibody system. Early clinical studies designed to optimize a bispecific pretargeting approach also were presented (Dr. Jacques Barbet, INSERM, Nantes, France). The data indicated excel-
lent targeting ratios, but full optimization of the procedure was not yet achieved.

**Summary**

The conference in some sense represented a real milestone for this field. The past year has marked the regulatory approval for marketing of two radiolabeled anti-CD20 MAbs (Zevalin and Bexxar). These reflected the documentation of clinical activity with perceived benefit in a variety of indications, including indolent and transformed, chemo-refractory lymphomas, as well as post-transplant lymphoproliferative disorder. Manageable toxicities were associated with these treatments. The diversity of approaches illustrated that the field supports several innovative technologies, particularly the engineering of novel forms of targeting agents, including “diabodies,” “minibodies,” and the like. New targets are clearly being addressed with these strategies.

However, a number of issues remain, and challenges to the radioimmunotherapeutic field in general were clearly apparent in the discussions of the meeting. First, the “challenge” of solid tumors must be acknowledged. Indeed, the sense emerged that the ongoing dosimetric evaluations reinforce the likely continued reliable delivery of radiation doses concordant with sterilization of hematopoietic tumors. But real concern about the doses possible with various delivery strategies in relation to the known sensitivity of epithelial tumors must be considered further by investigators in this field. Second, delivery of MAb-based approaches to solid tumor masses remains a challenge and reinforces the need for focus on 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.

In the case of non-labeled MAbs, one must further be concerned that without a better understanding of the biology underlying the basis of responding tumors or eliciting novel target antigens that engage complementary pathways, a potential limit to the value of the current agents may be expected. 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 would attempt to develop intoxicating mechanisms distinct from the protein synthesis poisons represented by *Pseudomonas* constructs. These would specifically be chosen and optimized to minimize the now almost stereotypical toxicities expected from these constructs that could be potentially problematic in projecting to more widespread clinical use, except perhaps in patients with circulating tumor cells or bulky disease.

The recognition of these prospects and issues should actually be regarded as quite a healthy set of actual opportunities. Whereas one cheers when a “Gleevec” bursts upon the clinical scene, there is frequently very little that can easily be done to re-engineer such a molecule to address limitations of its use. In contrast, the confluence of advances and ingenuity in protein engineering, biology, and the accumulating evidence of clinical benefit will assure continued vigorous growth and innovation in antibody-based approaches in the coming years.

**Acknowledgments**

We appreciate the assistance of Dr. Gerald D. DeNardo in publishing the abstracts of the presentations in *Cancer Biotherapy & Radiopharmaceuticals, 17*: 465–492, 2002. The proceedings of this conference appear as a supplement to the September 2003 issue of *Clinical Cancer Research*.

**Reference**

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