Immune-based interventions are steadily broadening the range of choices among cancer prevention and treatment modalities. Recent major advances in the therapy of lymphoid malignancies and prevention of cervical cancer (to name a few) fuel the interest of investigators and clinicians who tried for decades to exploit the potential of the immune system to control the disease. Lung cancer presents a more challenging group of diseases, where major breakthroughs in immunotherapy or vaccination are yet to be seen. The following update may elicit cautious optimism for some areas of this endeavor.

Dr. Scott Antonia summarized the essential processes by which the immune system recognizes and responds to tumor-associated antigens (TAAs) on tumor cells. From the MHC Class I antigen processing pathway, dendritic cell-based activation to cytotoxic T lymphocytes (CTLs) to the list of various types of tumor-associated antigens and evidence of the presence of specific CTLs for individual TAAs; experimental and clinical data provide the rationale for the development of tumor vaccines (Table 1).

Nevertheless, once vaccines are tested in clinics, there is a “glass ceiling” with a tumor response rate of 5 to 10%. Efficacy can only be improved by developing combination immunotherapy with the use of (1) immunomodulatory agents (T-cell growth factors, anticheckpoint, or costimulatory agents); (2) elimination of suppressive cells; (3) inactivation of suppressive cytokines and factors in the tumor microenvironment; and (4) sequencing with chemotherapy.

**Summary of Presentations**

**p53 Vaccine**

A good example of a dendritic cell vaccine was the use of p53 as antigenic target in small cell lung cancer (SCLC). Patient-derived dendritic cells were infected with an adenoviral vector containing the p53 gene (Ad.p53-DC) and administered back to patients. Of 31 subjects, 16 (52%) showed specific responses with three (10%) reaching a complete response. The treatment caused no significant toxicities. A randomized phase II trial testing salvage chemotherapy in extensive stage SCLC patients after the Ad.p53-DC vaccine is planned.1

**MAGE-A3 Vaccine**

Melanoma-associated antigen 3 is a tumor-specific antigen that in humans is encoded by the MAGEA3 gene. It is present in 30 to 50% of NSCLC. The MAGE-A3 vaccine is made of the ProtD-A3/His recombination fusion protein with a sequence of histidine residues produced in Escherichia coli and combined with the adjuvant ASO2B. Dr. Ramaswamy Govindan presented results of a randomized phase II trial in stage IB or II NSCLC with active vaccination versus placebo that yielded enough enthusiasm to design the four-arm MAGRIT phase III study in resected MAGE-A3-positive NSCLC.2 Patients can receive platinum-based chemotherapy or not (clinical decision) and both groups are randomized to MAGE-A3 or placebo. Disease-free survival is the primary objective. As of January 2011, 9726 patients were screened and 1547 randomized in 34 participating countries over the world.

**MUC1 (Stimuvax)**

Another TAA presented by Dr. Govindan, is Mucin 1 (MUC1), a mucinous glycoprotein overexpressed in several human malignancies. A peptide vaccine L-BLP25 (Stimuvax) against the exposed core peptide of MUC1 induced cellular immune response in preclinical studies. In a phase IIB study, Stimuvax with best supportive care showed superior overall survival in stage IIIIB patients against best supportive care only (3-year survival 49 versus 27%). The phase III study randomized against placebo and best supportive care was halted because of a single case of encephalitis but was reopened in June 2010.3

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MUC1 (TG4010-MVA MUC1-IL2)

Dr. Jean-Marc Limacher introduced TG4010, a targeted immunotherapy agent containing a modified Vaccinia virus strain Ankara coding for MUC1 and interleukin 2. So far, two phase I and five Phase II trials yielded a good safety profile with proof of activity in prostate cancer and cellular immunogenicity against MUC1. A phase IIB study randomized 148 advanced, MUC1-positive NSCLC patients to a cisplatin/gemcitabine regimen with or without a weekly subcutaneous injection of TG4101 for 6 weeks and then once every 3 weeks until progressive disease. There was a trend of a better response in TG4010-treated patients. A significantly increased overall survival was seen in TG4010-treated patients with normal levels of activated natural killer (NK) cells at baseline. The opposite result came out in patients with high level activated NK cells that may kill cytotoxic T cells. Phase IIB/3 study will be launched in the second half of 2011.4

Talactoferrin Alfa

Talactoferrin alfa (TLF) is a unique recombinant human lactoferrin with immunomodulatory properties. Oral TLF mediates its anticancer activity by the activation of tumor antigen-bearing dendritic cells in gut-associated lymphoid tissue. Dr. Giuseppe Giaccone reported the promising results of the phase II study of TLF versus best supportive care (LF-0201), where overall survival benefit of a well-tolerated treatment was seen in non-SCLC (NSCLC) patients.5 Two phase III studies are currently in progress: Fortis-M is a randomized, double-blinded, placebo-controlled study of oral talactoferrin in addition to best supportive care in patients with NSCLC who have failed two or more previous regimens and Fortis-C, a randomized, double-blinded, placebo-controlled study of oral talactoferrin in combination with carboplatin and paclitaxel as first-line therapy in patients with locally advanced or metastatic NSCLC.

Anti-CTLA-4 (Ipilimumab)

Targeting of the immunosuppressive immunoglobulin CTLA4 expressed on T cells has shown anticancer activity in melanoma, brain metastases, prostate, renal, pancreatic, lung cancers, and lymphoma. In March 2011, the US Food and Drug Administration (FDA) approved ipilimumab (Yervoy), the antibody against CTLA4, for treatment of patients with late-stage melanoma. Dr. Joel Neal presented a lung cancer phase II trial (BMS CA 184-041) where phased ipilimumab in combination with paclitaxel/carboplatin extended progression-free survival of advanced stage NSCLC and extensive stage SCLC patients. A statistically nonsignificant numerical improvement in overall survival was observed in the phased schedule. The safety profile was comparable with other ipilimumab studies. A fatal (grade 5) toxic epidermal necrolysis (TEN) was observed in one patient in the arm where ipilimumab was concurrently administered with chemotherapy. A phase III study in 800 patients with squamous NSCLC is planned that will compare carboplatin/paclitaxel ± ipilimumab.6

Anti-PD-1 (BMS-936558/MDX1106/ONO-4538)

The cell surface protein Programmed Death 1 (PD-1) is a member of the extended CD28/CTLA-4 family of T cell regulators. Similar to CTLA4, it also regulates negatively the activity of memory and regulatory T cells to tumors. Dr. Julie Brahmer reported that the ligand of PD-1, PD-L1/B7H1 is more expressed in adenocarcinoma than in squamous cell lung cancer and indicates worse prognosis. An IgG4 PD-1-blocking antibody (BMS-936558) with no antibody or complement dependent cellular cytotoxicity activity is currently in clinical testing. A phase I single-agent/dose study showed responses in melanoma, renal and colorectal cancers, and a mixed response in NSCLC. The agent was well tolerated and the receptor occupancy lasted for 3 months.7 A multidose/single-agent phase I study (once every 2 weeks, doses 1, 3, or 10 mg/kg) generated durable responses with manageable adverse events (only 5.7% subjects experienced grade 3 or 4 events). One partial response, five cases of stable disease, and five of progressive disease in NSCLC were observed. Therapy with BMS-936558 to enhance endogenous antitumor immunity, either alone or in combination with other therapeutic modalities, warrants further study.

PD-1-Ligand (AMP-224)

The natural ligand for PD-1, B7-DC is expressed on dendritic cells and macrophages. AMP-224 is a B7-DC Fc fusion molecule that restores immune function and has antitumor activities. Dr. Sol Langermann shared the results from preclinical studies with AMP-224 in a CT26 tumor model. Besides eradication of the tumor, the agent promoted the establishment of long-term antitumor activity through multiple mechanisms of action. First-in-human study is to be initiated in 2011.

Picornavirus SVV-001

This serendipitously discovered virus has a selective tropism for tumors with neuroendocrine features. Dr. Charles Rudin summarized the preclinical work that demonstrated efficacy in xenograft, syngeneic, orthotopic, and metastatic models of SCLC. Intravenous SVV-001 administration in a phase I trial was well tolerated at doses up to 1011 vp/kg, with predictable viral clearance kinetics, intratumoral viral replication, and evidence of antitumor activity in patients with small cell lung cancer.8 Phase II clinical evaluation in small cell lung cancer has been initiated.

Future Directions

The success of immunotherapy in lung cancer will depend on the careful selection of patients responsive to this modality. Further refinement of the interventions together with favorable combinations regimens may lead to positive long-term results, a hallmark often seen in preclinical immunotherapy models.

REFERENCES


