Immunotherapy is an exciting approach that can result in the regression of bulky, invasive cancer in some patients. Much progress has been made in our understanding of the role of the host immune response in affecting tumor progression and response to various treatments. Through these advances, novel immunotherapies have been introduced into the clinic.

In this issue of Cancer Control, experts review the latest clinical and therapeutic aspects of emerging immunotherapies for numerous disease sites.

We have seen a recent explosion of agents for metastatic castrate-resistant prostate cancer. In the lead article, Dr Shore and colleagues review data relating to the potential pharmacodynamic biomarkers associated with the immunotherapy sipuleucel-T, as well as considerations for patient selection and for sequencing this agent with other prostate cancer treatments. Indeed, sipuleucel-T is the first autologous cellular immunotherapy approved by the US Food and Drug Administration for the treatment of asymptomatic or minimally symptomatic metastatic castration-resistant prostate cancer. In this platform, peripheral blood mononuclear cells (antigen-presenting cells and T cells) are obtained from each patient via leukapheresis and treated ex vivo with PA2024, a fusion protein consisting of prostatic acid phosphatase/ granulocyte-macrophage colony-stimulating factor antigen. In three phase III trials, sipuleucel-T showed improvement in overall survival. This sets the stage for further approval of novel immune-modulating approaches. There are numerous possible directions for future development, including treatment of less advanced prostate cancer populations, combination treatment, and immune modulation.

In the second article in this issue, Dr Soliman provides an overview of the available data of breast cancer regarding the immune-modulating effects of both current and novel treatments. With respect to breast cancer, there is increasing evidence to support the theory that some breast tumors may be more immunogenic than others; tumors that elicit more potent cytotoxic T-cell responses appear to have a more favorable prognosis and respond better to chemotherapy than do less immunogenic tumors. This is coupled with a realization that standard treatments rely in part on their immunogenic effects for their success in eliminating lesions. New immunomodulatory agents and vaccines that can reverse underlying immunosuppression caused by established tumors are currently in development. Combining these novel agents for breast cancer with current therapies may boost their efficacy.

Lung cancer presents a difficult problem as the most common cause of cancer-related deaths in the United States. It is without perfect solutions as traditional chemotherapy fails to provide long-term benefit for many patients. New innovative approaches are desperately needed to improve overall survival beyond the current standard of care. Dr Hall and colleagues review the most recent clinical trials using immunotherapy techniques to treat both non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC). For NSCLC, phase II clinical trials have examined allogeneic vaccines that target various epitopes including but not limited to mucin 1, epidermal growth factor, and melanoma-associated antigen 3. Vaccine approaches against these antigens are undergoing phase III trials. In addition, autologous cellular therapy approaches directed against transforming growth factor beta-2 and a recombinant protein with antitumor properties have also shown promise in prolonging survival in NSCLC in phase II trials. The monoclonal antibodies ipilimumab, BMS-936558 (anti-PD-1), and BMS-936559 (anti-PD-L1) have appeared to lead to enhanced T-cell–mediated antitumor effects with objective responses in early-phase clinical trials. Studies for SCLC have been more limited.

Esophageal, gastroesophageal, gastric, liver, pancreatic, and colorectal gastrointestinal malignancies have been targeted for immune treatment as these sites represent the highest incidence among human cancers worldwide. The majority of gastrointestinal cancers are frequently unresectable at the time of diagnosis; there have only been modest improvements in survival in this setting with the addition of traditional modalities such as chemotherapy and radiation therapy. Dr Toomey and associates review current immunotherapeutic strategies to improve outcomes. To date, monoclonal antibody therapy is the only immunotherapy approved by the US Food and Drug Administration for gastrointestinal cancers. Initial trials validating novel immunotherapeutic approaches for gastrointestinal malignancies, including vaccination-based and adoptive cell therapy strategies, have adequately demonstrated safety and the induction of antitumor immune responses.

The next article focuses on brain cancer. Despite improvements in surgical technique, radiation therapy delivery, and options for systemic cytotoxic therapy, the median survival for newly diagnosed glioblastoma multiforme patients remains poor at 15 months with trimodality therapy. As Dr Marsh and colleagues review, antitumor vaccines (dendritic and formalin-fixed) have demonstrated clinical efficacy in phase I and II trials with mild toxicity, suggesting that innate immune responses can be amplified and directed...
against these tumors. An alternative approach using suicide gene therapy (gene-mediated cytotoxic therapy) employing viral vectors has also shown efficacy in completed phase I and ongoing phase II trials; neural stem cells are also being investigated as vectors. Thus, the phase I and II data suggest that immunologic therapies can produce meaningful and sometimes durable responses in the treatment of glioblastoma multiforme with mild toxicity compared to other standard therapies.

In the current treatment paradigms for leukemias, hematopoietic stem cell transplant (HSCT) is considered the best option with a curative potential. Dr. Brayer and associates summarize the recent advances in the field of immunotherapy for leukemia. With respect to passive immunotherapy, recent improvements in chimeric T-cell antigen receptor technology have been employed. In active immunotherapy, various clinical studies of peptide vaccination strategies focusing on molecular targets such as the Wilms’ tumor gene 1 (WT1), proteinase 3 (PR3), and receptor for hyaluronan acid-mediated motility (RHAMM) suggest the immune system has the capacity to recognize and react to leukemia cells mounting inflammatory and CD4 T-cell responses to complement and support cytotoxic activity.

Finally, we discuss radioimmunotherapy. This approach has been approved for the treatment of B-cell non-Hodgkin lymphomas in the United States for over a decade. Development of radioimmunotherapy agents for advanced-stage solid malignancies has engendered renewed interest. Dr. Tomblyn and coauthors examine available evidence for the preclinical and clinical development of these agents for a variety of solid tumors, including colorectal, breast, prostate, ovarian, pancreatic, hepatocellular, and primary brain tumors. Novel radioimmunotherapy agents are in active clinical investigation, either as single agents or combined with radiosensitizing chemotherapy or with external beam radiotherapy. Antibody (and antibody fragment) design and availability have improved, with fewer side effects than more traditional cytotoxic systemic therapy. Radionuclides such as alpha-emitters offer increased antitumor potency with reduced toxicity.

In summary, immunotherapeutic options for cancer are rapidly expanding. Our improved understanding of immune biology has resulted in an explosion of novel agents over the last few years. The exciting display of ongoing clinical trials and investigational drugs in immunotherapy, many of which have a novel mechanism of action, may shift the landscape of current cancer care. These new immunotherapies, used alone or in combination with other standard modalities such as radiation\textsuperscript{1,2} or chemotherapy,\textsuperscript{3} may lead to less toxic regimens for more patients. Optimal immunotherapeutic management requires a personalized approach tailored to the unique clinical status of each patient. Coordination of care using a multidisciplinary approach involves immunotherapists, medical oncologists, radiation oncologists, surgeons, and radiologists to achieve maximal therapeutic benefits. In this way, we will continue building immunotherapeutic bridges from the bench to bedside.

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References