

Immunotherapy of Hematologic Malignancies: The Road to the Future

Since the early days of cancer therapy, the treatment of hematologic tumors has been at the forefront of innovative approaches leading to better cancer treatment. Indeed, strategies such as combination chemotherapy using non-cross-resistant drugs and the concept of “dose intensification” initially applied with success in the treatment of hematologic malignancies were rapidly expanded to manage tumors of nonhematologic origin. Similarly, the successes achieved with high-dose therapy in the treatment of hematologic tumors led to application of this modality in the management of solid malignancies, a field recently revived due to the promising results obtained with “mini-allogeneic” bone marrow transplant for patients with melanoma and renal cell carcinoma. More recently, the successful application and impressive results achieved with molecular-targeted therapy for patients with chronic myelogenous leukemia (CML) have expanded this strategy beyond the field of hematologic malignancies.

Continuing with this impressive “track record,” the use of immune-based strategies in the treatment of tumors of hematologic origin is now paving the road to a better cancer treatment. During the past several years, the critical role of the immune system in the treatment of hematologic malignancies has been highlighted in a variety of settings. Indeed, the significant clinical effects observed by the withdrawal of immunosuppression in patients with posttransplant lymphoproliferative disorders, the reduced relapse rates in the allogeneic transplant setting compared to autologous transplants, and the ability to reinduce remissions with only donor lymphocyte infusions (DLIs) in a substantial number of patients all point to a major role of immune-mediated mechanisms in the control and destruction of malignant cells in patients with hematologic tumors. These observations, coupled with the increased understanding of the immune factors regulating host-tumor interactions and the demonstration that immune-effector mechanisms may efficiently destroy chemotherapy-resistant hematologic tumors has led to the development of novel immunotherapeutic strategies against these diseases. The recent successes of antibody-based therapies in the treatment of lymphomas and leukemias have not only dramatically changed the management of these malignan-

cies, but also prompted — once again — the development of similar strategies for tumors of nonhematologic origin. Antibody-based therapy has provided us with the long-elusive “proof of principle” needed to convince many skeptics of the value of immunotherapy as an effective modality of cancer treatment. In light of the evolving role of immunotherapy in the treatment of hematologic malignancies, this issue of *Cancer Control* highlights the recent advances in antibody-based therapy as well as cellular immunotherapy of hematologic tumors.

A hallmark in the history of treatment of B-cell lymphomas occurred almost 10 years ago with the first-time use of the chimeric anti-CD20 monoclonal antibody (MAb) in the treatment of a patient with low-grade B-cell lymphoma. Since then, this MAb and others recently developed have been used in several clinical trials either alone or in combination with chemotherapy in the treatment of a large number of patients with B-cell malignancies. Although major therapeutic successes have been achieved with some of these strategies, clinical trials have also unveiled the limitations associated with MAb-based therapy. Therefore, at this point, it is important not only to develop new strategies and find new targets, but also to explore new settings in which the therapeutic efficacy of MAbs can be further enhanced. In this issue of *Cancer Control*, Ivan Aksentijevich, MD, and Ian W. Flinn, MD, PhD, review the integration of MAb therapy with autologous bone marrow transplantation for patients with non-Hodgkin's lymphoma. They discuss the rationale as well as the promising therapeutic benefit associated with this approach. In addition, they address the issue of *in vivo* purging with either naked or radiolabeled MAbs in the autologous transplant setting. In spite of the feasibility of this combination and the promising results obtained in early clinical trials, the authors report that issues such as naked vs radiolabeled antibody, choice of isotope, and/or the timing of MAb administration need to be resolved in controlled clinical trials before a specific role for this strategy can be defined.

John M. Burke, MD, and coauthors summarize the role of radioimmunotherapy with MAbs in the treatment of leukemias. Due to the emerging limitations of naked MAbs, the use of radioimmunoconjugates to specifically

deliver radioisotopes to malignant cells has become a promising strategy in the management of leukemia. The authors present a concise yet thorough review of the properties, benefits, and limitations of the radioimmunoconjugates used in clinical trials for patients with leukemia. While radioimmunotherapy with β particle-emitters is more effective for bulky disease or as part of a conditioning regimen for stem cell transplant, the authors conclude that radioimmunotherapy with α particle-emitters would be better suited for the treatment of small-volume or minimal residual disease. Recently completed phase I and II clinical trials have shown the feasibility and antileukemic activity of radioimmunoconjugates. Therefore, phase III clinical trials will determine whether this strategy will positively impact the outcome of patients with leukemia.

The important role of T cells in mediating clinically significant antitumor effect has been highlighted by the demonstration that these cells are critical in the immunologically mediated graft-vs-leukemia (GVL) effect that accompanies allogeneic bone marrow transplant. Stanley Riddell, MD, and collaborators from the Fred Hutchinson Cancer Research Center place the field of T-cell adoptive immunotherapy in perspective with their review of T-cell therapy of leukemia. In addition to their discussion of the effector mechanisms mediating GVL effect, the authors review the candidate target antigens for immunotherapy of leukemia in transplant and nontransplant patients. The identification of minor histocompatibility antigens expressed on hematopoietic cells including leukemic cells, but not on non-hematopoietic tissues, has provided the investigators with an opportunity to separate GVL from graft-vs-host effect after allogeneic stem cell transplant. The promising results of preclinical studies using adoptive therapy with antigen-specific T-cell clones have led to the evaluation of this modality in recently initiated clinical trials.

Definitive evidence for a major role of cellular immunotherapy in the treatment of hematologic tumors was provided when patients with CML in relapse after allogeneic bone marrow transplant were effectively treated with DLI. Leo Luznik, MD, and Ephraim Fuchs, MD, review the clinical results as well as the advantages, complications, and limitations of DLI in the treatment of a variety of hematologic malignancies in relapse after allogeneic blood or marrow transplantation. Despite the ability of DLI to induce sustained complete remissions in more than 60% of patients with CML in early relapse, only a minority of patients (less than 20%) with acute leukemia, multiple myeloma, and lymphoma respond to this treatment. The authors discuss strategies to augment the antitumor efficacy of DLI while trying to minimize graft-vs-host disease.

The advances in the identification of antigens expressed by hematologic tumors, together with our better understanding of the mechanisms regulating anti-

tumor immune responses, have justified the study and use of cancer vaccines as a strategy to enhance the anti-tumor responses of both the humoral and cellular arms of the immune system. Ivan Borrello, MD, and Eduardo Sotomayor, MD, present a review of vaccine studies in experimental models as well as the results of clinical trials using this strategy in patients with hematologic tumors. In addition, they discuss issues such as the effect of immune tolerance and tumor burden in limiting the efficacy of active immunotherapy with either antigen-specific vaccine strategies or tumor cell-based vaccine approaches. Finally, they comment on new vaccine formulations, targets as well as settings (eg, integration of vaccines with autologous stem cell transplant) that may help validate the encouraging results obtained in recently completed clinical trials using cancer vaccines in patients with tumors of hematologic origin.

Mitchell Reff, PhD, and colleagues describe where the road to the future may lead in the management of hematologic tumors (and by extension, in the treatment of solid malignancies). The authors review basic preclinical developments in antibody modifications that may result in better therapeutic antibodies than those currently used in clinical practice. The significant improvement in genetic engineering techniques is allowing the generation of MAbs with reduced immunogenicity, enhanced affinity, altered half-life, and biodistribution as well as enhanced tumor targeting properties. Furthermore, as discussed by the authors, the improvements in radiolabeled antibodies, immunotoxins, and antibodies carrying cytotoxic drugs, coupled with better methodologies to deliver a more effective MAb dose at the tumor site, are likely to have a powerful impact in the management of hematologic tumors in the years to come.

As you will gather from reading the articles presented in this issue of *Cancer Control*, these are exciting times for the field of hematologic malignancies. Novel therapies are rapidly increasing our armamentarium against these diseases. The significant advances made in the last 10 years in immunotherapy of hematologic tumors represent just the beginning of a promising road to the future that ultimately will lead us to better cancer treatment.

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