Hope for Orphan Lymphoproliferative and Histiocytic Diseases on the Horizon?

Orphan diseases are conditions with low prevalences in the population, and the rarity of these diseases has been a major obstacle for experimental and clinical investigations. The recent advent of new high-throughput molecular biology techniques (eg, next-generation sequencing) has accelerated our understanding of these diseases as well as the identification of new target molecules, which have substantially facilitated drug discovery. Although our understanding of the pathobiology of these rare diseases is far from satisfactory, progress has been made in the diagnosis and management of several rare lymphoproliferative and histiocytic disorders discussed in this issue of Cancer Control.

The first article in this issue is by Dr Soumerai and colleagues and is devoted to Castleman disease. The majority of patients with the unicentric, hyaline-vascular subtype of Castleman disease can be cured with complete surgical resection of the enlarged lymph nodes; by contrast, the multicentric plasma cell variant of Castleman disease typically has a more aggressive course of disease. Results from a recent, randomized phase 3 study of an anti-interleukin 6 monoclonal antibody led the US Food and Drug Administration to approve the agent as a therapeutic option for the multicentric plasma cell variant of Castleman disease in patients negative for both HIV and human herpesvirus 8 infections.

Dr Riaz and others discuss a rare aggressive malignancy called blastic plasmacytoid dendritic cell neoplasm, a disease initially believed to arise from immature natural killer cells; however, more recently, a plasmacytoid dendritic cell origin has been suggested. Whole genome sequencing revealed somatic gene mutations similar to those identified in myelodysplastic syndrome, acute myeloid leukemia, and some lymphoproliferative disorders. The strong expression of interleukin 3α receptor (CD123) on blastic plasmacytoid dendritic cell neoplasm cells became a target for novel biological therapy. Recent data from an early phase 1/2 study of an anti-CD123 antibody conjugate are very promising.

Dr Dalia and coauthors review rare dendritic and histiocytic cell sarcomas, which make up a clinically and histopathologically heterogeneous group of malignant diseases derived from mature dendritic cells or histiocytes. Patients with localized disease can benefit from a complete resection of the tumor mass. However, the standard of care has not been established for patients with disseminated disease; therefore, such patients should be referred to tertiary centers for diagnostic confirmation and for the design of a therapeutic plan.

Dr Zhang and colleagues review hemophagocytic lymphohistiocytosis in the next article. Within the last decade significant progress has been made in the diagnosis and management of familial hemophagocytic lymphohistiocytosis. Several causative germinal mutations have been identified in families with this disorder. Patient outcomes have improved following the introduction of allogeneic stem cell transplantation; however, patients with secondary hemophagocytic lymphohistiocytosis due to malignancies, viral infection, or autoimmune diseases have a worse prognosis. The mortality rate is high, particularly in patients who develop multiple organ failure; therefore, early diagnosis is essential for better outcomes.

Dr Deaver and others discuss Kikuchi–Fujimoto disease, which is a rare histiocytic disorder. This idioopathic condition frequently manifests with the rapid and painful enlargement of cervical lymph nodes and systemic B symptoms in young women of Asian descent. Clinical symptomatology and high fluorodeoxyglucose uptake using positron emission tomography/computed tomography may clinically mimic malignant lymphoma. Typically, excisional or core needle biopsy of the enlarged lymph nodes and a careful histology and immunohistochemistry evaluation by an experienced hematopathologist are sufficient for diagnosis. The disease is self-limiting and rarely requires treatment.

In their article, Dr Dalia and colleagues describe Rosai–Dorfman disease, a rare histiocytic disorder that involves various organs and systems (eg, central nervous system, skin, lymph nodes). Surgical resection of the tumor mass in patients with localized disease is considered the most effective frontline therapy, although some patients with more advanced or unresectable disease can benefit from radiation therapy. The use of systemic chemotherapy or immunotherapy is based on case reports alone.

Dr Grana reviews the diagnosis and management of Langerhans cell histiocytosis in children and adults. This disease can aggressively manifest in infants and young children as Letter–Siwe disease or Hand–Schüller–Christian disease, respectively, and
may require intensive systemic therapy. A less acute course of the disease is often observed in adults who present with localized eosinophilic granuloma that commonly involves the bones and the lungs. Smoking has been implicated in the pathogenesis of Langerhans cell histiocytosis when the lungs are involved. Smoking cessation can result in the spontaneous regression of the disease. The discovery of the BRAF V600E gene mutation in patients with Langerhans cell histiocytosis has offered the possibility of novel targeted therapy using BRAF inhibitors.

Dr Cruz-Chacon and coauthors provide a comprehensive review about the utility of hematopoietic stem cell transplantation in patients with rare lymphoproliferative and histiocytic disorders. Some of these diseases are aggressive and have short-lived responses to conventional chemotherapy regimens. Consolidation with high-dose chemotherapy followed by hematopoietic stem cell transplantation during the first remission or in patients with chemosensitive disease can be curative in selected patients.

In 2 Special Reports included in this issue, Dr Harvey and coauthors review the medical literature dealing with the social determinants of racial and ethnic disparities in cutaneous melanoma outcomes, and Dr Tayyem and colleagues compare fruit and vegetable intake between 2 groups of Jordanians in a case-control study of colorectal cancer.

I hope that our series of articles dealing with rare lymphoproliferative and histiocytic disorders as well as the Special Reports in this issue will be useful for busy hematology practitioners and other medical professionals interested in this field.

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