Stage C or not stage C…?

Claire Dearden THE ROYAL MARSDEN HOSPITAL AND THE INSTITUTE OF CANCER RESEARCH

In this issue of Blood, Moreno and colleagues report that autoimmune cytopenias in CLL are associated with poor prognostic markers, but not with the poor survival expected for patients with cytopenias due to bone marrow infiltration.1 Since the 1970s, clinicians treating patients with chronic lymphocytic leukemia (CLL) have relied on a staging system that defines the poorest risk disease as that characterized by the presence of anemia, thrombocytopenia, or both (Rai stages III and IV; Binet stage C).2,3 These staging systems have been endorsed in the recent guidelines for the diagnosis and treatment of CLL produced by the International Workshop on CLL,4 and remain standard practice worldwide. CLL patients with Binet stage C or Rai III/IV disease have shown consistently poorer response to treatment and shorter overall survival in clinical trials.5 In neither staging system is the origin of the cytopenia specified. In their article, Moreno et al have redefined the advanced clinical stage (Binet stage C) as “immune” or “infiltrative” based on the cause of the anemia or thrombocytopenia. In their series of 960 patients with CLL, those with advanced clinical stage due to an immune mechanism (n = 19) had significantly better survival (median 7.4 years vs 3.7 years) than those in whom the advanced stage was due to heavy bone marrow infiltration (n = 54). Patients with stage C “immune” were more likely to revert to normal counts after therapy, usually only with steroids, than those with stage C “infiltrative,” explaining in part their superior outcome. However, patients with stage C “immune” still had shorter survival compared with uncomplicated early stage A patients, suggesting that autoimmune cytopenias may be a marker of a more aggressive CLL (see figure). This is likely, given the association with other poor prognostic variables such as short lymphocyte doubling time and high B2M, ZAP70+, CD38+, and unmutated IGHV genes, as shown in this and other studies.6

Despite the relatively common occurrence of autoimmune cytopenias in patients with CLL (7% in the report by Moreno et al), the pathogenesis, treatment, and clinical outcomes of this complication are still poorly understood. Whether autoimmune hemolytic anemia (AIHA) or immune thrombocytopenia (ITP) are associated with poorer patient outcomes remains controversial and Moreno et al discuss the conflicting reports, mostly from single institution retrospective studies. A prospective randomized controlled trial of previously untreated CLL patients showed that, in multivariate analysis, development of AIHA was associated with poorer 5-year survival.7 This was in a group of patients selected by their requirement for therapy; the poorer outcome may have been partly related to the fact that these patients received less CLL therapy because it was discontinued after development of AIHA. Some of the conflicting results may also be explained by the specific patient cohorts studied and the distribution between early stage A patients who have a very favorable outcome and in whom an autoimmune complication may have less impact on survival and those who develop autoimmune cytopenias in association with disease progression.

Another long-standing issue in relation to autoimmune cytopenias is whether exposure to certain treatments, notably purine analogs, poses a greater risk for development of this complication. Moreno et al found that the incidence of AIHA was slightly lower after fludarabine-based therapy (4%) than after chlorambucil treatment (5%), in agreement with other studies.8 There is thus no increased risk for a patient of developing hemolysis on fludarabine-combination therapy and no contraindication to its use in patients who have a history of autoimmune complications. However, not all patients presenting with autoimmune cytopenias will necessarily require treatment for the underlying CLL. After successful treatment with corticosteroids patients with stage C “immune” may be “down-staged” to Binet stage A and thus no longer fulfill the criteria for initiation of treatment for CLL. This makes a clear understanding of the origin of cytopenia in a patient with CLL even more important before a decision about treatment is made.

The definition of stage C “immune” therefore provides us with a new clinical prognostic group in CLL that needs to be distinguished from stage C “infiltrative” to appropriately guide treatment decisions and inform prognosis. Indeed, should we call this stage C at all? That is the question.

Conflict-of-interest disclosure: The author declares no competing financial interests.

REFERENCES


Comment on Bastien et al, page 4859

Tregs served sunny-side up

Brian C. Betts and James W. Young
MEMORIAL SLOAN-KETTERING CANCER CENTER/WEILL-CORNELL MEDICAL COLLEGE

In this issue of Blood, Bastien and colleagues demonstrate that photopheresis purges donor T cells proliferating against host alloantigens in patients with GVHD after HSCT. Photodepletion of these alloreactive lymphocytes concomitantly preserves and expands Tregs, which when rein infused into patients with treatment-refractory chronic GVHD, survive in vivo and correlate with positive clinical responses.

This group previously demonstrated that infusion of photodepleted donor lymphocytes after haploidentical, allogeneic hematopoietic stem cell transplantation (HSCT) reduced posttransplantation infectious complications, but did not induce graft-versus-host disease (GVHD). They now raise the bar and successfully explore mechanisms and treatment of patients with established chronic GVHD, using donor lymphocytes depleted of alloreactive CD4+ effector T cells and enriched for regulatory T cells (Tregs). Clinical trials of extracorporeal photopheresis (ECP) for refractory chronic GVHD have yielded some encouraging results, yet conclusive immune mechanisms to account for the observed effects have not emerged.

Unlike conventional photodepletion, Bastien and colleagues performed ECP using the rhodamine-derived photosensitizing agent, TH9402. Rhodamine-derived photosensitizers differ from standard psoralen-based compounds, as they are activated by visible light, instead of nonionizing ultraviolet (UV) radiation. TH9402-based photodepletion involves the collection of patient lymphocytes, treatment of the cells ex vivo with TH9402, followed by exposure of the lymphocytes to a visible light source. The photodepleted cells are then reinfused into the patient host with autologous serum. Previously, this group used healthy donor peripheral blood mononuclear cells (PBMCs) and showed that TH9402 induces mitochondrial oxidative damage and cell death in proliferating CD4+ and CD8+ T cells. Resting T cells are spared from the effects of photodepletion, as they can eliminate TH9402 through a P-glycoprotein–dependent mechanism. This drug efflux mechanism is regulated by multidrug-resistance-1 (MDR1) gene expression, which is inactive in proliferating T cells.

Bastien et al again “up the ante” by demonstrating in a human study that ECP eliminates proliferating donor T cells not only in healthy donor samples, but also from patients with chronic GVHD (see figure). Their current analysis advances our understanding of ECP in chronic GVHD by demonstrating that photodepletion with TH9402 preserves the immunosuppressive capacity of Tregs and allows for their expansion. Photodepletion resulted in a doubling of Foxp3+ cells among the treated PBMCs. Treg proliferation per se did not account for their proportional increase among photodepleted compared with untreated...
Stage C or not stage C…?

Claire Dearden