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Stage C or not stage C...?

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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 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.

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REFERENCES

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**Tregs served sunny-side up**

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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.1 Photodepletion of these alloreactive lymphocytes concomitantly preserves and expands Tregs, which when reinfused 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).2 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).3 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.3-5

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.6 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).3 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
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