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THROMBOSIS AND HEMOSTASIS

Comment on *Burdett et al*, page 1322

Summiting thrombotic hazards in glioma

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In this issue of *Blood*, Burdett and colleagues describe the first venous thromboembolism (VTE) prediction model following surgical resection of grade 2 to 4, molecularly defined, adult-type diffuse gliomas.¹

About 10% to 30% of patients with glioma experience a VTE event over the course of their disease.² The majority of VTEs in glioma arise in association with surgical resection or while receiving adjuvant therapy.³ Advanced age, large tumor size, leg paresis, prior VTE, A or AB blood type, and the presence of intratumoral thrombosis have all been identified as thrombotic risk factors.⁴ The proposed mechanisms of thrombogenesis in glioma center on tumor production of tissue factor, procoagulant tumor microvesicles (MVs), and podoplanin, a transmembrane sialoglycoprotein believed to increase platelet activation in glioma.⁵ Gliomas with mutated *IDH1* status have lower levels of tissue factor expression and may be associated with a lower risk of VTE than gliomas with wild-type *IDH1*—an observation first reported in 2016 by the authors of the present study.⁶ Podoplanin production by glioma cells is also downregulated in the presence of mutated *IDH1*.⁷

Despite the strong association of glioma with VTE, no VTE prediction tools are available that accurately gauge VTE risk in this disease. The Khorana score, the most widely used clinical prediction tool for VTE in cancer, did not include sufficient numbers of patients with glioma in

its original study design, although modifications to the Khorana score to incorporate glioma have been devised.^{8,9} In the absence of accurate VTE prediction tools in glioma, the potential utility of prophylactic anticoagulation in these patients is uncertain, as concerns about hemorrhagic risks from anticoagulation have long dissuaded most practitioners from its use in patients with glioma despite their high VTE risk.^{3,10}

In the current prospective, observational study, Burdett and colleagues have developed the first risk prediction model of incident VTE in glioma by analyzing 3 separate cohorts of patients with glioma: a discovery cohort of 393 patients with newly diagnosed or recurrent glioma treated at Northwestern Memorial Hospital in Chicago and 2 validation cohorts from Duke University (157 patients) and UCLA (68 patients). Using their discovery cohort, the authors employed lasso regression to identify 10 risk factors for incident VTE in patients with glioma in their initial discovery cohort. The identified risk factors, in no specific order, included: (1) IDH mutation status, (2) MGMT promoter methylation, (3) glioma grade, (4) prior history of VTE, (5) hypothyroidism, (6) asthma, (7) hypertension, (8) leukocyte count, (9) body mass index, and (10) patient age. These risk factors

then in turn informed their Cox proportional hazards model with the continuous outcome of time-to-incident-VTE diagnosis, in the context of a mean follow-up period of 20.5 months across all cohorts. The model was then utilized to evaluate predictive ability for the outcome of interest in the 2 external cohorts. In all, the areas under the receiver operating characteristic curves for each external cohort, aiming to find an ideal balance of the highest specificity and sensitivity, were 0.79 to 0.84 in the discovery cohort and 0.63 to 0.68 and 0.70 to 0.73 in the 2 external cohorts. This is a respectable output in the context of clinical medicine (by comparison, this statistic was 0.7 for the Khorana score as originally reported in 2008). The model is available as an R Shiny application at <https://kbellburdett.shinyapps.io/GliomaPredictVTE/>.

In addition to the VTE prediction model, the authors also report a number of interesting pathophysiologic insights on VTE development in glioma. In their analysis, patients with wild-type *IDH1/IDH2* showed a trend toward higher levels of circulating tissue factor on tumor MV (TF-MV). Patients with the highest levels of TF-MV activity had the fastest time to VTE and highest cumulative incidence of VTE. Tumor podoplanin had a significant association with development of VTE while circulating podoplanin did not. In a murine inferior vena cava stenosis model of thrombosis, mice with wild-type *IDH1* and high tissue factor expression developed larger thrombi than mice with mutated *IDH1* and low tissue factor expression.

In all, the new established model by Burdett and colleagues, and the pathophysiologic insights they report, represent major steps forward in the field of cancer-associated thrombosis and in the study of patients with glioma. As has been the case with nearly every VTE risk prediction model, future modifications of Burdett's model may be expected by centers across the globe. In particular, a reevaluation of the model in the context of a competing risk framework might improve its performance, as patients without VTE in the current model were censored at last follow-up, inclusive of a possibility of having died; this would constitute a competing risk preventing full capture of VTE events

that theoretically may have otherwise developed. Another consideration in interpreting the study findings is that only VTE events that occurred either after surgical resection for newly diagnosed glioma or prior to surgical resection of recurrent glioma were included in the analysis, which could in principle represent 2 distinct clinical scenarios for the development of VTE.

How might these findings be translated into clinical practice? One application could be the targeted use of prophylactic anticoagulation specifically in patients with a high VTE risk score calculation and *IDH1/IDH2* wild-type disease, which might in principle offset some of the hemorrhagic risk from anticoagulation by selecting for patients predicted to have high levels of circulating tissue factor. Mechanistically, the impact of *IDH* mutation status on podoplanin production, differences in the potential roles of tumor-derived versus circulating podoplanin, and the effects of these variables on circulating TF-MV all raise exciting new questions about the pathophysiology of VTE in glioma, as well as the greater context of cancer-associated thrombosis. Through the incorporation of state-of-the-art clinical, pathologic, and molecular data, the incident VTE risk prediction model created by Burdett and colleagues represents a landmark advance with tremendous potential to transform the clinical care of patients with adult-type diffuse gliomas.

Conflict-of-interest disclosure: The authors declare no competing financial interests. ■

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TRANSPLANTATION

Comment on *Ramos et al*, page 1337

GVHD prophylaxis: use an ortho IL-2/IL-2R β Treg system!

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In this issue of *Blood*, Ramos et al demonstrate that the orthogonal interleukin-2 (IL-2)/IL-2 receptor β (IL-2R β) system selectively expands adoptively transferred regulatory T cells (Tregs) in vivo, leading to the amelioration of acute graft-versus-host disease (GVHD) without compromising the graft-versus-leukemia (GVL) effect in a mouse major histocompatibility complex (MHC) mismatch model.¹

Allogeneic hematopoietic stem cell transplantation (allo-HSCT) is a potentially curative therapy for hematologic malignancies due to the graft-versus-tumor (GVT) effect. However, its success is limited by the occurrence of GVHD. Acute GVHD (aGVHD) is caused by alloreactive donor T cells recognizing and destroying host tissues.² With GVHD being a major cause of nonrelapse mortality post-allo-HSCT, there remains a need to develop novel prophylaxis options that improve survival without relapse.

One emerging and promising prophylactic strategy is the use of Treg therapy. Preclinical models and early clinical trials showed that adoptive transfer of polyclonal Tregs efficiently ameliorate aGVHD while maintaining the GVT effect if used at high Treg to conventional T cell (Tcon) ratios (1:1).^{3,4} The limiting factor for a broader clinical application of Treg therapies is the low Treg numbers in the graft and the necessity of expansion for clinical use. The IL-2 dependence of Tregs for their homeostasis makes this cytokine an attractive target

for in vivo Treg manipulation, and low-dose IL-2 has been used clinically to treat chronic GVHD.⁵ Notably, its pleiotropic nature affects different cell subsets in a dose-dependent manner, and at high doses, it can stimulate effector cells and potentially worsen alloimmune responses driving GVHD. The recently described orthogonal IL-2/IL-2R β system^{6,7} applied here reduces the need for extensive ex vivo Treg expansion and virtually eliminates IL-2 off-target effects.

In this study, the authors evaluated genetically engineered Tregs, which can be selectively expanded in vivo as a novel, innovative method for aGVHD prophylaxis. Using a mouse MHC mismatch model for HSCT, they demonstrated that early adoptive transfer of Tregs expressing the orthogonal IL-2R β (oIL-2R β) enables their effective and selective expansion in vivo after administration of oIL-2. This expansion of oIL-2R β -expressing Tregs led to a near complete protection from lethal aGVHD at high Treg to Tcon (1:1) ratios and improved survival at suboptimal ratios (1:5) (see figure). The ability to significantly reduce the Treg numbers needed in the