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IMMUNOBIOLOGY AND IMMUNOTHERAPY

Comment on Rejeski et al, page 865

A road map for navigating CAR T hematotoxicity

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In this issue of *Blood*, Rejeski et al, representing an international panel of experts from the European Hematology Association (EHA) and the European Society for Blood and Marrow Transplantation (EBMT), review available data on chimeric antigen receptor (CAR) T cell–associated cytopenias, which they define as immune effector cell–associated hematotoxicity (ICAHT), and assemble recommendations on grading, predicting, preventing, evaluating, and managing ICAHT.[1]

This is the first such guideline by a major organization and is a much-needed development for the management of this important CAR T cell–associated toxicity. Neutropenia is the most common toxicity observed after CAR T therapy. Infections are the most common cause of non-relapse mortality in CAR T recipients, more frequently observed than cytokine release syndrome (CRS) or deaths related to immune effector cell–associated neurotoxicity (ICANS), and they are often observed in the setting of severe and prolonged neutropenia.[2,3] Whereas other CAR T cell–associated toxicities such as CRS and ICANS have been heavily studied with robust guidelines, post–CAR T therapy cytopenias are less understood, despite their clinical significance.

It is important to note that the cytopenias seen after CAR T therapy are distinct from standard chemotherapy-associated cytopenias. A neutropenia-predominant, biphasic presentation is commonly seen, with early cytopenias within the first 2 weeks of CAR T therapy and a late recurrence often more than 30 days after treatment.[4,5] A small subset of patients suffer persistent, severe neutropenia, with associated high risk of severe infection. Although lymphodepleting chemotherapy and acute inflammation related to cytokine release provide ready explanations for early cytopenias, the pathophysiology of late hematotoxicity remains poorly understood. There are likely a combination of factors at play in late ICAHT, including limited marrow reserve, immune-driven suppression, and marrow microenvironmental changes, along with other potential factors in subsets of patients such as hemophagocytic lymphohistiocystosis/macrophage activation syndrome, clonal hematopoiesis of indeterminate potential, and secondary malignancies.[6]

Perhaps most importantly, this work defines the problem specifically and provides a novel grading system that can be implemented in studies and clinical trials (see figure). The system is feasible, relying only on absolute neutrophil count and timing. The grading scale distinguishes "early" ICAHT within 30 days of CAR T administration and "late" ICAHT, occurring more than 30 days after CAR T therapy. These classifications better capture the biphasic physiology of post–CAR T therapy cytopenias, which is often observed, and offers an improvement over conventional grading scales such as the Common Terminology Criteria for Adverse Events,[7] which only captures the depth of neutropenia without regard for timing or duration.

The authors also highlight the use of the CAR-HEMATOTOX prognostic score, which uses easily measurable lab values obtained prior to lymphodepletion to estimate a patient's risk of experiencing prolonged neutropenia.[3,5] The CAR-HEMATOTOX score has been validated in large B-cell lymphoma, mantle cell lymphoma, and multiple myeloma, although further study is needed to confirm whether it is prognostic in indolent non-Hodgkin lymphoma or acute lymphoblastic leukemia. The scoring system has shown high sensitivity but lower specificity for predicting patients with severe and prolonged neutropenia after CAR T therapy; nearly all patients with severe, prolonged neutropenia were identified as being at high risk, but many patients identified as high risk did not have prolonged neutropenia, whereas low-risk patients have minimal risk of prolonged neutropenia. Further study is needed to determine how best to leverage this score and whether preventative strategies, such as earlier colony-stimulating factor use, more aggressive antibiotic prophylaxis, immunomodulating therapies, or stem cell collection prior to CAR T therapy for subsequent stem cell boost, are effective approaches.

Important approaches to the management of ICAHT are covered, including the use of prophylactic antibiotics, colony-stimulating factors, and transfusions. One of the most challenging scenarios in ICAHT remains that of late, aplastic disease, with persistent cytopenias sometimes lasting months after treatment. A reflection of this is their stated "ultima ratio," their last resort: the use of allogeneic transplant. The authors recommend initiation of a donor search if grade 4 ICAHT persists beyond day 30,

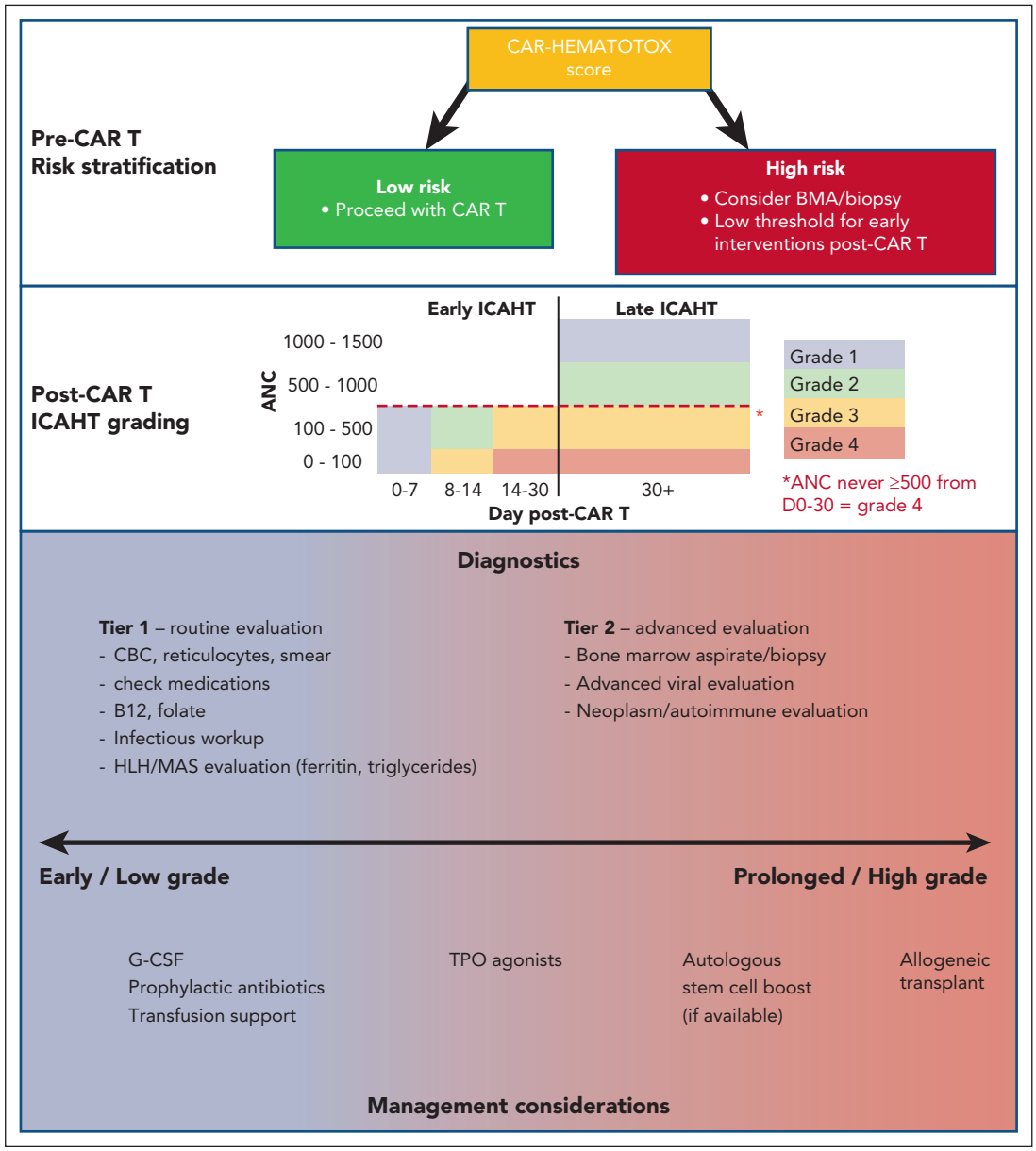

Diagram illustrating broad recommendations from the EHA/EBMT on evaluation and management of ICAHT. Highlighted components include the use of CAR-HEMATOTOX prior to leukapheresis to determine risk of ICAHT, a new grading system for ICAHT, and diagnostic and therapeutic measures based on the duration and severity of cytopenias. ANC, absolute neutrophil count; BMA, bone marrow aspirate; CBC, complete blood count; G-CSF, granulocyte colony stimulating factor; HLH, hemophagocytic lymphohistiocytosis; MAS, macrophage activation syndrome; TPO, thrombopoetin.

with a time frame between months 3 to 6 post–CAR T therapy deemed reasonable to consider transplant. They point out that this is a highly individualized decision based on donor availability, patient fitness, comorbidities, and disease status. We agree that this is a difficult decision, given the high risks of mortality associated with allogeneic transplant; our practice has generally been to defer transplant to 6 or more months post–CAR T therapy, based on our own experience and data suggesting that late recoveries between 3 and 6 months still commonly occur.[8]

While providing comprehensive recommendations for ICAHT, the EHA/EBMT guidelines also highlight important gaps in our current knowledge of ICAHT, which are significant. This is not the destination but an early road map, offering standardized approaches to ICAHT, which will hopefully lead to subsequent preclinical and clinical research to further our understanding and improve outcomes for CAR T recipients.

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CLINICAL TRIALS AND OBSERVATIONS

Comment on Armand et al, page 878

Pembrolizumab: a key for some, but not all, HL

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In this issue of *Blood*, Armand et al describe the long-term outcomes of a phase 2 study of the immune checkpoint inhibitor pembrolizumab in patients with relapsed/refractory classic Hodgkin lymphoma (HL).[1]

Although most patients with HL are cured with multiagent chemotherapy, a substantial minority remain in need of other therapies. Fortunately, the discovery and subsequent therapeutic exploitation of the programmed cell death 1 pathway has led to agents such as pembrolizumab becoming available for patients with a variety of cancers, including HL. In the initial report, with a median follow-up of 10.1 months, the objective response rate (ORR) was 69.7% (complete response [CR], 22.7%).[2] Response rates were similar regardless of prior autologous stem cell transplant (ASCT) and/or brentuximab vedotin exposure, and were consistent among the one-third of patients with primary refractory disease.[3] Many patients with HL are young adults (the median age of KEYNOTE-087 participants was 35 years at enrollment) and often deal with relapsed lymphoma in the face of other major life events, such as marriage, parenthood, or establishing careers. For such patients, when their lymphoma does not respond to chemotherapy, understanding long-term outcomes from pembrolizumab provides important context for decision-making.

Now with a median observation period exceeding 5 years, the median duration of response (DOR) remained steady at 16.6 months, and the 5-year progression-free survival (PFS) and overall survival rates were 14.2% and 70.7%, respectively. Unsurprisingly, the 58 patients who achieved CR to pembrolizumab had the most favorable outcomes, with median DOR not reached. A key question for patients with HL achieving CR following pembrolizumab in this setting is whether to proceed to stem cell transplant. This question is challenging to study prospectively, and observations from studies such as this can be informative (with the caveat that the study was neither designed nor appropriately powered to provide definitive answers). Of the 58 patients who achieved CR, 10 ultimately underwent allogeneic stem cell transplant (5 proceeding directly to transplant, and the others requiring further therapy for relapsed disease), and the median DOR and PFS were 13.6 and 36.9 months, respectively. Among the 48 patients who did not proceed to transplant, the median DOR was not reached, and the median PFS was 56.5 months. Although allocation to transplant was nonrandomized, the favorable outcomes observed among the patients who did not undergo allogeneic stem cell transplant are encouraging and suggest that observation of patients achieving CR may be reasonable.

The data set also provides useful data regarding pembrolizumab retreatment. Per protocol, patients who achieved CR and received ≥6 months of therapy and ≥2 doses after CR were allowed to discontinue treatment before 2 years, with those who experienced subsequent disease progression able to receive retreatment for up to an additional 17 cycles. Among 20 such patients, the ORR (73.7%) and CR (36.8%) rates following retreatment were similar to those observed with initial treatment in the overall population, and the median PFS was 17.2 months, with no new safety signals observed.

Important unanswered questions remain, such as the role of ASCT following checkpoint inhibitor therapy. Observational series suggest a potential chemosensitization effect from checkpoint inhibitors, with a US academic collaborative group reporting favorable outcomes for patients undergoing ASCT after checkpoint inhibitor use.[4] The 18-month PFS was 86%, and prior response to checkpoint inhibitor appeared to be a better predictor of outcome than positron emission tomography status before transplant. The role of allogeneic stem cell transplant after checkpoint inhibitors (and vice versa) also remains an open question. In a pooled analysis of allogeneic stem cell transplant after checkpoint inhibitor, rates of grade 3 to 4 acute graft-versus-host disease were increased, but chronic graft-versus-host disease and nonrelapse mortality rates were similar.[5] However, the use of posttransplant cyclophosphamide may mitigate some of the immune activation from checkpoint inhibitors and improve their safety in this setting.[6] Conversely, the use of checkpoint inhibitors after allogeneic stem cell transplant, although effective, does appear to result in