Rationale for an ISTH SCC guidance document on:

CAR-T Associated Bleeding and Thrombosis

Participating SSC

Hemostasis & Malignancy (Zwicker)

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Statement of Purpose

Chimeric antigen receptor T (CAR T) cell therapy utilizes genetically manipulated autologous T cells that are activated in an MHC-independent manner upon binding to their target antigen on the tumor cell. This results in the lysis of the targeted tumor cell. CD19-directed CAR T-cell therapy has been approved for B cell malignancies and more recently, B-cell maturation antigen (BCMA) directed CAR T-cell therapy has also been approved for the management of multiple myeloma. With increasing access and experience with this therapy, our understanding of associated toxicities is also expanding. Hematological toxicities including cytopenias and impaired immune reconstitution have been well described. Hypofibrinogenemia and abnormalities in other coagulation laboratory parameters are also commonly observed[1,2,3] but the clinical consequences of abnormal hemostasis after CAR T-cell therapy are not well understood. Original studies have reported an increased incidence of bleeding events[4] within the first 30 days and thrombosis events within the first 100 days[5] after infusion of CAR T-cell therapy. We postulated that this sub-group may benefit from consensus guidelines for diagnosis and management of coagulation disorders.

We plan develop a set of expert guidance statements related to the bleeding and thrombotic manifestations following CAR-T cell therapy, focusing on laboratory monitoring, thromboprophylaxis and fibrinogen repletion. Prior to developing guidance statements, we will perform a systematic review and meta-analysis of available data and by pooling incidence rates of thrombosis and bleeding in patients who received CAR T-cell therapy for an underlying hematologic malignancy stratified based on baseline characteristics and type of CAR T-cell therapy. The objectives of the systematic review and meta-analysis are to a) assess the bleeding and thrombosis risk associated with CAR T-cell therapy, b) assess the impact of cytokine release syndrome and neurotoxicity on coagulopathy and hemorrhagic risk, and c) assess the safety of anticoagulant/antiplatelet use in the period following treatment with CAR T-cell therapy

The guidance statements will be generated by consensus of the subcommittee members following the systematic review and meta-analysis. In keeping with prior ISTH guidance documents, “recommend” will be used to reflect strong guidance statements supported by high-quality evidence from clinical trials. “We suggest” reflects weaker guidance statements based on low-quality evidence or expert opinion. The voting of the participating members will be recorded and reflected within the context of each guidance statement.

Content Outline

a) Systematic review and meta-analysis of CAR-T therapy for management of hematologic malignancies

Inclusion studies: Randomized controlled trials, retrospective and prospective observational studie, case series, post-hoc analysis

Exclusion studies: Commentaries, editorials, case reports

Main outcomes: 1) pooled thrombosis rates; 2) pooled bleeding rates, 3) rate of abnormal hematologic laboratory parameters (i.e. d-dimer fibrinogen, PTT/PTT) and relative risk of bleeding or thrombotic event (and cytokine release syndrome)

b) Guidance statements
    i. Laboratory monitoring of coagulation indices with or without cytokine release syndrome
    ii. Measures to prevent or manage bleeding including routine repletion of fibrinogen, platelet transfusion, correction of coagulopathy
    iii. Thromboprophylaxis with or without cytokine release syndrome

Expected Timeline:

- Feb-April – literature review
- April/May – meeting to discuss findings and discuss guidance statements
- June-July – Manuscript draft

Expected Outcomes:

SSC Guidance Publication in JTH

References
References

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2. Jiang H, Liu L, Guo T, et al. Improving the safety of CAR-T cell therapy by controlling CRS-related coagulopathy. Ann Hematol 2019;98(7):1721–32.

3. Wang Y, Qi K, Cheng H, et al. Coagulation Disorders after Chimeric Antigen Receptor T Cell Therapy: Analysis of 100 Patients with Relapsed and Refractory Hematologic Malignancies. Biology of Blood and Marrow Transplantation 2020;26(5):865–75.

4. Johnsrud A, Craig J, Baird J, et al. Incidence and risk factors associated with bleeding and thrombosis following chimeric antigen receptor T-cell therapy. Blood Advances 2021;5(21):4465–75.

5. Hashmi H, Mirza A-S, Darwin A, et al. Venous thromboembolism associated with CD19-directed CAR T-cell therapy in large B-cell lymphoma. Blood Adv 2020;4(17):4086–90.