Population-based external validation of the CAR-HEMATOTOX score to predict CAR T-cell related toxicity and outcome in R/R LBCL patients

JW de Boer[1], K Keijzer[1,2], S van Dorp[3], PGNJ Mutsaers[4], AGH Niezink[2], JA van Doesum[1], YIM Serroukh[4], LW Muntendam[5], AE Pulles[5], EJ Kret[6], A Sijs-Szabo[6], J Oomen[3], AMP Demandt[7], WBC Stevens[3], MT Kuipers[8], ERA Pennings[9-12], AM Spanjaart[9-11], MJ Kersten[9-11], M Jak[5], LV van Dijk[2], MWM van der Poel[7], JSP Vermaat[6], T van Meerten[1]

[1] Department of Hematology, University Medical Center Groningen, University of Groningen, Groningen, the Netherlands
[2] Department of Radiation Oncology, University Medical Center Groningen, University of Groningen, Groningen, the Netherlands.
[3] Department of Hematology, Radboud University Medical Center, Nijmegen, The Netherlands
[4] Department of Hematology, Erasmus MC Cancer Institute, University Medical Center Rotterdam, Rotterdam, The Netherlands
[5] Department of Hematology, University Medical Center Utrecht, Utrecht, The Netherlands
[6] Department of Hematology, Leiden University Medical Center, Leiden, The Netherlands
[7] Department of Internal Medicine, Division of Hematology, GROW school for Oncology and Developmental Biology, Maastricht University Medical Center, Maastricht, The Netherlands
[8] Department of Hematology, Amsterdam UMC location Vrije Universiteit Amsterdam, Amsterdam, The Netherlands
[9] Cancer Center Amsterdam, Amsterdam, The Netherlands
[10] Department of Hematology, Amsterdam UMC location University of Amsterdam, Amsterdam, The Netherlands
[11] LYMMCARE (Lymphoma and Myeloma Center Amsterdam), Amsterdam, The Netherlands
[12] Erasmus School of Health Policy and Management, Erasmus University Rotterdam, Rotterdam, The Netherlands

Early identification of patients with an increased risk for immune effector cell-associated hematotoxicity (ICAHT) is crucial for early intervention and thereby minimizing non-relapse mortality due to toxicities and infections. Therefore, the CAR-HEMATOTOX (HT) score has been proposed as a risk-stratification tool for ICAHT, infections and outcome in patients with relapsed or refractory large B-cell lymphoma (R/R LBCL) treated with CAR T cell therapy (CART) (Rejeski et al. Blood 2021; Rejeski et al. JITC 2022). This easy-to-use score is widely implemented and recommended by EHA/EBMT as prediction score for ICAHT with subsequent treatment advices (Rejeski et al. Blood adv 2023). Although the HT score was validated in the HT defining study, it was developed in a rather small cohort (n=55), with a low positive predictive value. As no fully external multicenter validation has been performed, a comprehensive independent validation study is warranted. This study aims to externally validate the HT-score in an independent population-based real-world LBCL CART cohort.

Adults with R/R LBCL after ≥2 lines of systemic therapy who received CART as standard of care between May 2020 and December 2023 across all 7 Dutch CART centers were included. HT score was calculated per the original report, including absolute neutrophil count (ANC), hemoglobin (Hb), platelet count, C-reactive protein (CRP) and ferritin, determined prior to lymphodepleting chemotherapy. A high HT score was defined as HT score ≥2 (HT^{high}/HT^{low}). Patients with at least 3 out of 5 laboratory parameters were included. Missing laboratory values were imputed with predictive mean matching and pooled results are reported. Endpoints included clinically significant neutropenia (ANC <500/µl, ≥14 days, between day 0-60), severe infections, progression free survival (PFS) and overall survival (OS). Infections between infusion and day +90 were graded severe (grade ≥3) when requiring intravenous anti-infective agents and/or hospitalization.

Of the 244 identified patients, 239 patients had ≥3 laboratory parameters available, with 141 complete cases. The median age was 62 [20-84] years. The majority of patients were diagnosed with LBCL (52%), followed by transformed Follicular Lymphoma (31%). Median number of prior lines of therapy was 2 (range 2-6) and 29% received a previous stem cell transplantation. Median HT score was 2 (IQR 1-3], with 163 patients (68%) classified as HT^{high}.

Severe neutropenia (ANC <500/µl) after CART was common (n = 202/239, 85%), but only 50 patients (21%) experienced a duration of ≥14 days. Granulocyte colony-stimulating factor (G-CSF) was administered in 113 patients (47%). A higher HT score was associated with a higher risk of clinically significant neutropenia (continuous HT: OR 1.61; 95% CI [1.24 – 2.08]; $p < 0.01$), and had a fair predictive performance (AUC 0.70). This increased risk was also observed in HT^{high} patients (binary HT: OR 2.39; 95% CI [1.10 – 5.20]; $p = 0.03$).

Any grade infection was seen in 73/193 patients (38%), with severe infections in 38 patients (20%). Incidence was comparable to previous reports. Both the continuous and the binary HT score were not associated with severe infections in our cohort ($p = 0.10$ and $p = 0.46$, respectively). CRS and ICANS grade ≥2 were apparent in 118/239 patients (49%) and 96/239 patients (40%), respectively. HT score was not associated with developing CRS or ICANS grade ≥2 ($p = 0.38$ and $p = 0.16$, respectively).

Nevertheless, HT score was significantly associated with OS and PFS (HR 1.55; 95% CI [1.32 – 1.81]; $p < 0.01$ and HR 1.33; 95% CI [1.16 – 1.51]; $p < 0.01$, respectively). In detail, Hb, ferritin and CRP were univariably associated with survival (all p<0.01), suggesting the potential adverse prognostic effect of a limited bone marrow reserve and high baseline inflammation. Additionally, patients classified as

HT^{high} had a nearly 3-fold increased risk of death compared to HT^{low} patients (OS: HR 2.83; 95% CI [1.64 – 4.90]; $p < 0.01$ and PFS: HR 1.82; 95% CI [1.09 – 3.04]; $p = 0.02$)).

In conclusion, higher HT scores identify patients at risk for severe neutropenia and reduced survival, but not for severe infections after CART in this population-based, real-world cohort. This study underscores the potential of the HT score, yet emphasizes the need for further optimalization before broad implementation and guidance of antibiotic prophylaxis strategies.

Conflicts of interest

A.G.H.N. discloses conflicts of interest all outside of the submitted work with: Siemens and Genentech. M.T.K. has a consulting/advisory role for CellPoint. M.J. received honoraria from Kite/Gilead and BMS/Celgene, has a consult- ing/advisory role for Janssen and received research funding from Novartis. M.W.M.v.d.P. received honoraria from Kite/Gilead and Takeda. M.J.K. received honoraria from and performed in a consulting/advisory role for BMS/Celgene, Kite, a Gilead Company, Miltenyi Biotec, Novartis and Roche, as well as receiving research funding from Kite, a Gilead Company, Roche, Takeda, and Celgene and travel support from Kite, a Gilead Company, Miltenyi Biotec, Novartis, and Roche (all to institutions). L.V.v.D. received funding and salary support from unrelated to this project from NOW ZonMw via the VENI (NWO-09150162010173) Individual career development grant and KWF Dutch Cancer Society Young Investigator Grant (KWF-13529). T.v.M. has served on the advisory boards of Kite/Gilead, Celgene/BMS, Jansen and Lilly and received research funding from Kite/Gilead, Celgene/BMS, Genentech and Siemens. J.W.d.B, K.K., S.v.D., P.G.N.J.M., J.A.v.D., Y.I.M.S., L.sW.M., A.E.P., J.O., A.M.P.D., W.S., A.S.-S., A.M.S., E.R.A.P., and J.S.P.V. declare no conflicts of interest.