sia.[9,11,12] It is highly probable that the inferior outcome of t-ALL patients may be attributable to the high-risk of cytogenetic abnormalities in these patients rather than the antecedent cancer itself even after considering the possible relapse of the neoplasia after the ALL treatment. In Ph-positive t-ALL the combination of tyrosine kinase inhibitors and chemotherapy, generally followed by alloHSCT, yields similar results to those observed in *de novo* Ph-positive ALL.[16] The presence of ACA to the Ph chromosome does not seem to have an impact on prognosis, but the low number of cases cannot drive solid conclusions.

The current information of t-ALL is based on retrospective studies of patients treated with chemotherapy followed, when possible, by alloHSCT in first CR. The latter decision is based on the assumption of their poor prognosis, mirroring what occurs in t-AML or t-MDS. Deep molecular studies as well as the systematic use of MRD in newly diagnosed patients with t-ALL are required in order to increase the knowledge of the precise mechanisms of leukemogenesis and to make an adequate choice of the post-remission therapy. Given the scarce frequency of t-ALL, the response of the relapsed or refractory patients to the modern immunotherapeutic or targeted therapy approaches is largely unknown, and their possible use in first-line therapy has not been evaluated to date. Finally, the identification of prognostic factors, especially genetic biomarkers, predictive for t-ALL or s-ALL in patients with primary malignancies should be pursued in order to prevent or anticipate the occurrence of this disease.

References

1. Aldoss I, Stiller T, Tsai NC, et al. Therapy-related acute lymphoblastic leukemia has distinct clinical and cytogenetic features compared to de novo acute lymphoblastic leukemia, but outcomes are comparable in transplanted patients. Haematologica. 2018. doi: 10.3324/haematol.2018.193599.
2. Bagg A. Therapy-associated lymphoid proliferations. Adv Anat Pathol. 2011;18(3):199-205.
3. Pagano L, Pulsoni A, Tosti ME, et al. Acute lymphoblastic leukaemia occurring as second malignancy: report of the GIMEMA archive of adult acute leukaemia. Gruppo Italiano Malattie Ematologiche Maligne dell'Adulto. Br J Haematol. 1999;106(4):1037-1040.
4. Shivakumar R, Tan W, Wilding GE, Wang ES, Wetzler M. Biologic features and treatment outcome of secondary acute lymphoblastic leukemia--a review of 101 cases. Ann Oncol. 2008;19(9):1634-1638.
5. Tang G, Zuo Z, Thomas DA, et al. Precursor B-acute lymphoblastic leukemia occurring in patients with a history of prior malignancies: is it therapy-related? Haematologica. 2012;97(6):919-925.
6. Abdulwahab A, Sykes J, Kamel-Reid S, et al. Therapy-related acute lymphoblastic leukemia is more frequent than previously recognized and has a poor prognosis. Cancer. 2012;118(16):3962-3967.
7. Ganzel C, Devlin S, Douer D, et al. Secondary acute lymphoblastic leukaemia is constitutional and probably not related to prior therapy. Br J Haematol. 2015;170(1):50-55.
8. Matnani R, Parekh V, Borate U, Brazelton J, Reddy V, Peker D. Therapy-related B-lymphoblastic leukemia associated with Philadelphia chromosome and MLL rearrangement: Single institution experience and the review of the literature. Pathol Int. 2015;65(10):536-540.
9. Giri S, Chi M, Johnson B, et al. Secondary acute lymphoblastic leukemia is an independent predictor of poor prognosis. Leuk Res. 2015;39(12):1342-1346.
10. Kelleher N, Gallardo D, Gonzalez-Campos J, et al. Incidence, clinical and biological characteristics and outcome of secondary acute lymphoblastic leukemia after solid organ or hematologic malignancy. Leuk Lymphoma. 2016;57(1):86-91.
11. Rosenberg AS, Brunson A, Paulus JK, et al. Secondary acute lymphoblastic leukemia is a distinct clinical entity with prognostic significance. Blood Cancer J. 2017;7(9):e605.
12. Swaika A, Frank RD, Yang D, et al. Second primary acute lymphoblastic leukemia in adults: a SEER analysis of incidence and outcomes. Cancer Med. 2018;7(2):499-507.
13. Kurt H, Zheng L, Kantarjian HM, et al. Secondary Philadelphia chromosome acquired during therapy of acute leukemia and myelodysplastic syndrome. Mod Pathol. 2018;31(7):1141-1154.
14. Imamura T, Taga T, Takagi M, et al. Leukemia/Lymphoma Committee; Japanese Society of Pediatric Hematology Oncology (JSPHO). Nationwide survey of therapy-related leukemia in childhood in Japan. Int J Hematol. 2018;108(1):91-97.
15. Aldoss I, Dagis A, Palmer J, et al. Therapy-related ALL: cytogenetic features and hematopoietic cell transplantation outcome. Bone Marrow Transplant. 2015;50(5):746-748.
16. Aldoss I, Stiller T, Song J, et al. Philadelphia chromosome as a recurrent event among therapy-related acute leukemia. Am J Hematol. 2017;92(2):E18-E19.

eGVHD App: a new tool to improve graft-*versus*-host disease assessment

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Accurately diagnosing and scoring acute and chronic graft-*versus*-host disease (GvHD) remain challenging for many hematologists. Inconsistency between bone marrow transplant centers has been recognized in this field, in particular because of problems in following the latest recommended guidelines.[1-3] In this regard, Schoemans *et al.* present a new electronic tool, the eGVHD application (eGVHD App), designed to improve and harmonize GvHD assessment.[4]

The eGVHD app was developed by the UZ Leuven (Belgium) in collaboration with the European Society for Blood and Marrow Transplantation (EBMT) Transplantation Complications Working Party and the National Institute of Health (NIH) (Bethesda, USA). This e-tool is a free, open-source web application, distributed as a normal website or a mobile application (accessible at: *www.uzleuven.be/egvhd)*. The App allows the diagnosis of classic and late acute, as well as classic and overlap

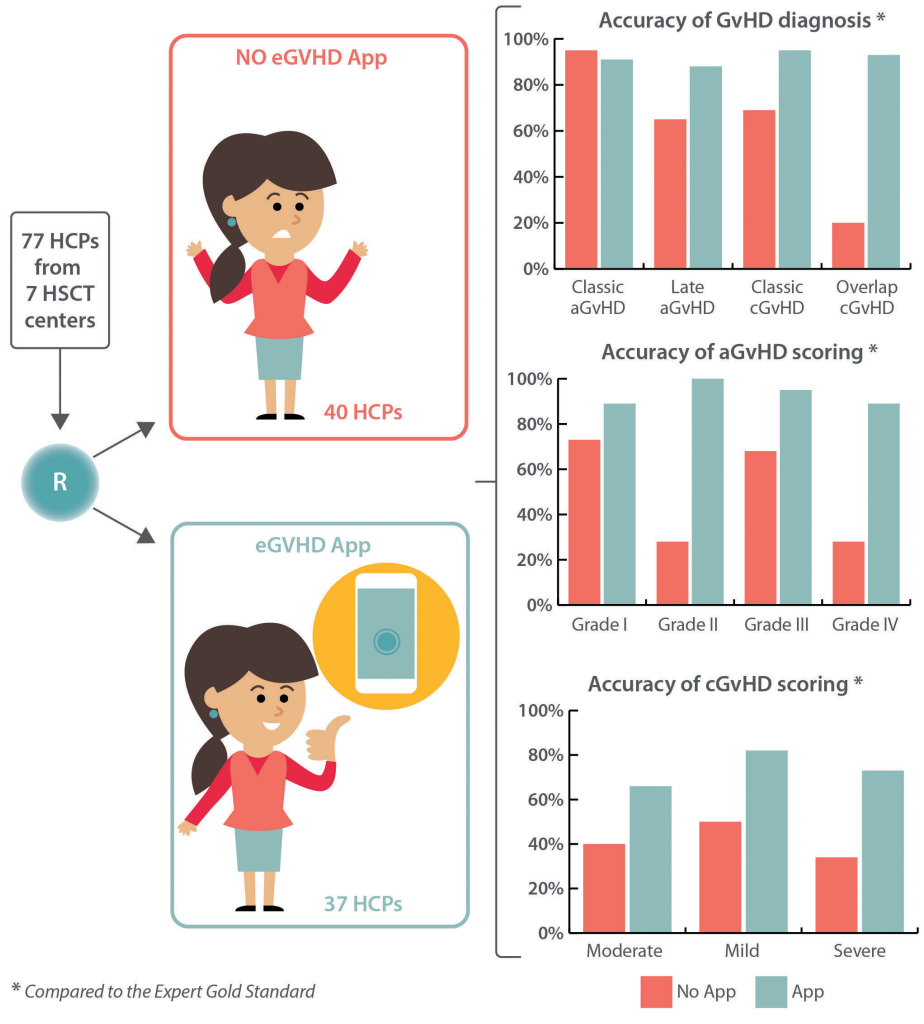

Figure 1. Graft-*versus*-host disease (GvHD) assessment tools used in the study. Healthcare professionals (HCPs) in hematopoietic stem cell transplantation (HSCT) centers were randomized to evaluate GvHD with or without a new electronic tool: the eGVHD application (eGVHD App). No App group, n=40; eGVHD App group, n=37. aGvHD: acute GvHD; cGvHD: chronic GvHD.

chronic GvHD, using the most up-to date guidelines [Mount Sinai Acute GvHD International Consortium (MAGIC) for acute and NIH 2014 for chronic GvHD].

The study presented in this issue of the Journal[4] was performed in 7 Belgian centers practising allogeneic hematopoietic stem cell transplantation (HSCT) and included 77 health care practitioners (HPCs), among whom 58 were physicians (75%), 15 were data managers (19%), and 4 held another position. They were invited to evaluate the diagnosis and severity score of 10 clinical vignettes (4 acute and 6 chronic GvHD) validated by a group of 10 separate GvHD experts (Expert Gold Standard) who implemented the latest guidelines. For their evaluation, the 77 HCPs were randomized to either use their usual GvHD assessment tools without the eGVHD App (No App group, n=40) or to use the eGVHD App (App group, n=37) (Figure 1).

The most frequently reported GvHD guidelines referenced by HPCs in the No App group were the Glucksberg[5] and the NIH 2014[6] criteria. They assessed GvHD of the 10 case vignettes mostly by their own knowledge (62%) or by using the 2014 GvHD evaluation sheet (23%), the 2005 NIH evaluation sheet (15%), or a self-designed scoring document (15%). The use of the App compared to the No App group improved the number of vignettes with a correct diagnosis [10/10 *vs*. 6.5/10, respectively; OR=6.14 (95%CI: 2.83-13.34; $P<0.001$)] as well as the number of vignettes with correct GvHD scoring [9/10 *vs*. 4.5/10, respectively; OR=6.29 (95%CI: 4.32-9.15; $P<0.001$)]. Assessment of GvHD was significantly better in the App group for both acute (aGvHD) (OR=17.89; 95%CI: 8.47-37.79; $P<0.001$) and chronic (cGvHD) (OR=4.34; 95%CI: 2.79-6.74; $P<0.001$) GvHD. As shown in Figure 1, agreement between the HPCs' results and the Expert Gold Standard evaluations also showed the superiority of the use of the eGVHD App. For GvHD diagnosis, the No App group more often misdiagnosed late acute and overlap chronic GvHD by considering them as classic cGvHD. Scoring of aGvHD was frequently false in the No App group, in particular for grades II and IV, confused with cGvHD and grade III aGvHD, respectively. Scoring for cGvHD tended to be over-estimated (15%) or under-estimated (9%) by the App group without misclassification, while both diagnosis and scoring were frequently erroneous in the No App group.

Agreement between HPCs was superior in the App group (0.73 *vs*. 0.56 in the No App group) independently

of the center, the degree of experience, and professional background. The use of the App was, however, time consuming for the HCPs who had not used it before the study. Despite this limiting factor, they found it useful and reported that they would be willing to use it in their daily practice.

Thus, this well-performed randomized study demonstrates that the eGVHD App provides superior accuracy and reliability for GvHD assessment compared to usual care, even for experienced physicians.[4] The improvement can mainly be explained by the use of the most up-to-date guidelines, the limitation of physician's subjectivity during the evaluation, and the fact that the e-tool provides pictures and definitions of GvHD features that help physicians to better categorize GvHD symptoms.

The need for harmonization in the diagnosis and scoring of GvHD has been recognized for many years and several other attempts have been made to improve this by the use of electronic tools[7,8] but generally without success. The eGVHD App is available everywhere (*www.uzleuven.be/egvhd*) and could be used by any practitioner. The App could be of particular interest to HPCs with limited GvHD experience and can also be used for training. It remains to be seen whether the use of the eGVHD App, by improving the grading of GvHD in daily practice, could have an impact on clinical decisions and transplant outcomes.

In the era of fast developing electronic devices and of 'big-data' analyses, the eGVHD App represents the first e-tool to be made widely available with the potential to improve the quality of GvHD data in clinical research. Such an App should be implemented in clinical trials aiming to evaluate and treat GvHD after allogeneic HSCT, as well as in large-scale transplant data bases.

References

1. Atkinson K, Horowitz MM, Biggs JC, Gale RP, Rimm AA, Bortin MM. The clinical diagnosis of acute graft-versus-host disease: a diversity of views amongst marrow transplant centers. Bone Marrow Transplant. 1988;3(1):5-10.
2. Weisdorf DJ, Hurd D, Carter S, et al. Prospective grading of graft-versus-host disease after unrelated donor marrow transplantation: a grading algorithm versus blinded expert panel review. Biol Blood Marrow Transplant. 2003;9(8):512-518.
3. Schoemans H, Goris K, Durm RV, et al. Development, preliminary usability and accuracy testing of the EBMT 'eGVHD App' to support GvHD assessment according to NIH criteria-a proof of concept. Bone Marrow Transplant. 2016;51(8):1062-1065.
4. Schoemans HM, Goris K, Van Durm R, Fieuws S, et al. The eGVHD App has the potential to improve the accuracy of graft-versus-host disease assessment: a multicenter randomized controlled trial. Haematologica 2018; 103(10):1698-1707.
5. Glucksberg H, Storb R, Fefer A, et al. Clinical manifestations of graft-versus-host disease in human recipients of marrow from HL-A-matched sibling donors. Transplantation. 1974;18(4):295-304.
6. Jagasia MH, Greinix HT, Arora M, et al. National Institutes of Health Consensus Development Project on Criteria for Clinical Trials in Chronic Graft-versus-Host Disease: I. The 2014 Diagnosis and Staging Working Group report. Biol Blood Marrow Transplant. 2015;21(3):389-401.
7. Levine JE, Hogan WJ, Harris AC, et al. Improved accuracy of acute graft-versus-host disease staging among multiple centers. Best Pract Res Clin Haematol. 2014;27(3-4):283-287.
8. Dierov D, Ciolino C, Fatmi S, et al. Establishing a standardized system to capture chronic graft-versus-host disease (GVHD) data in accordance to the national institutes (NIH) consensus criteria. Bone Marrow Transplant. 2017;52(Suppl 1):S102.