disease in NPM1-mutated acute myeloid leukemia: a study from the German-Austrian Acute Myeloid Leukemia Study Group. J Clin Oncol. 2011;29(19):2709-2716.
20. Terwijn M, van Putten WL, Kelder A, et al. High prognostic impact of flow cytometric minimal residual disease detection in acute myeloid leukemia: data from the HOVON/SAKK AML 42A study. J Clin Oncol. 2013;31(31):3889-3897.
21. Freeman SD, Virgo P, Couzens S, et al. Prognostic relevance of treatment response measured by flow cytometric residual disease detection in older patients with acute myeloid leukemia. J Clin Oncol. 2013; 31(32):4123-4131.
22. Jongen-Lavrencic M, Grob T, Hanekamp D, et al. Molecular minimal residual disease in acute myeloid leukemia. N Engl J Med. 2018;378(13):1189-1199.

Therapy-related acute lymphoblastic leukemia

Josep-Maria Ribera

Clinical Hematology Department. ICO-Hospital Germans Trias i Pujol, Josep Carreras Research Institute, Badalona, Universitat Autònoma de Barcelona, Spain

E-mail: jribera@iconcologia.net

doi:10.3324/haematol.2018.200311

Therapy-related acute lymphoblastic leukemia (t-ALL) refers to ALL developed in patients who have received prior cytotoxic therapies, including chemotherapy and/or radiotherapy for solid or hematologic cancers. In this issue of *Haematologica*, Aldoss *et al.*[1] report the largest retrospective study of patients from a single institution with analysis focused only on cases with prior exposure to cytotoxic therapies. The frequency of t-ALL was 10%, an important subset of patients showed cytogenetic abnormalities similar to those found in therapy-related acute myeloid leukemias (t-AML) or therapy-related myelodysplastic syndromes (t-MDS), and the outcome of t-ALL patients was poorer than that of the *de novo* ALL patients, especially for those who did not undergo allogeneic hematopoietic stem cell transplantation (alloHSCT).

Similar to t-AML or t-MDS, the pathogenesis of t-ALL is attributed to the genotoxic effect of cytotoxic therapies on hematopoietic progenitor cells, but the precise mechanisms are less understood than those of therapy-related myeloid neoplasias. An underlying constitutional predisposition shared by the malignancies and ALL cannot be ruled out, especially for cases with s-ALL. In this sense, some studies have observed a higher prevalence of malignant neoplasms among first-degree relatives of patients with t-ALL or s-ALL. Ten to15% of therapy-related leukemias are t-ALL,[2] and it is frequently confounded with the so-called secondary ALL (s-ALL), that refers to the patients with ALL with antecedent neoplasia but without exposure to cytotoxic therapy. Both t-ALL and s-ALL are infrequent (less than 2%-10% of all ALL cases)[1,3-14] (Table 1), and are unfortunately often considered together in most case series or registry studies. The precise distinction of both types of ALL is important, especially for t-ALL, because prior exposure to cytotoxic therapies could have an impact on both treatment-related morbidity and mortality and on response to chemotherapy and the subsequent use of alloHSCT.[15]

Clinically, t-ALL arises in older patients than *de novo* ALL, and there is a female and white ethnicity preponderance in some series, different to what occurs in newly diagnosed ALL patients. Pediatric cases of t-ALL have also been described.[14] An important question is to know whether t-ALL is biologically different from *de novo* ALL. No significant differences have been reported in the white blood cell (WBC) count, the frequency of central nervous system or other extramedullary infiltration, or in the frequency of the different leukemia phenotypes (T-ALL or B-cell precursor ALL), although some studies have described a lower WBC count in t-ALL patients.[1] However, important differences have been observed regarding genetic background, showing a predominance of high-risk genetic subtypes in t-ALL compared with *de novo* ALL. The most consistent genetic abnormality found across studies is the 11q23 (*KMT2A*) rearrangement, followed by monosomies of chromosomes 5, 7 and/or 17, hypodiploidy, and in some studies, by the Philadelphia (Ph) chromosome (Table 1).[1,2-14,16] Except for the latter rearrangement, these genetic abnormalities are similar to those found in t-AML or in t-MDS and support the etiologic role of prior chemotherapy in the pathogenesis of t-ALL. Alterations of tumor suppressor genes at the 11q23 chromosomal regions may also predispose the cells to both solid and hematological cancers. The 11q23 rearrangements are frequently observed in patients who have received topoisomerase II inhibitors. As occurs in *de novo* Ph-positive ALL, the p190 BCR-ABL subtype is predominant, but the frequency of associated chromosomal abnormalities (ACA, especially monosomies), is higher in cases with Ph-positive t-ALL.[16] Large molecular studies are lacking in t-ALL and, consequently, the frequency of specific subgroups such as the BCR-ABL-*like* is unknown.

Large epidemiological studies have shown that any previous malignancy can lead to an increased incidence of s-ALL or t-ALL, which establishes this ALL as a separate entity.[9,11,12] Among all cancer survivors, those with prior cancer treatment have a higher probability to develop ALL than those with no prior treatment, with this increased risk being observed at any age.[11,12] Regarding the type of previous solid cancer, breast cancer constitutes the most common prior solid malignancy across the series, probably related to its high frequency, the elevated utilization of alkylator and topoisomerase II inhibitors as well as radiotherapy, and the excellent long-term survival for this disease. Lymphomas and other lymphoproliferative disorders encompass the most frequent antecedent of

Table 1. Main studies on therapy-related acute lymphoblastic leukemia (t-ALL) and secondary acute lymphoblastic leukemia (s-ALL).

Author (year)	N t-ALL/ s-ALL	Frequency	Age (median, [range]), years	Most frequent antecedent solid tumor	Most frequent antecedent hematologic cancer	Interval prior malignancy-ALL (median [range]), months	Main cytogenetic findings[1]	CR	HSCT in CR1	OS/EFS
Pagano (1999)	21	2.3%	58 (33-78)	Breast	Hodgkin's lymphoma	27 (4-170)	t(9;22) 11q23	12 (57%)	NR	OS: median 5 months
Shivakumar (2008)	10[12]	NR		Breast	Lymphoma	<18 yr: 36 (3-240) 18-59 yr: 26 (6-192) ≥60 yr: 22 (4-168)	11q23 t(9;22) Complex karyotype	40/72 (56%)	14/40	OS: median 6-7 months
Tang (2012)	44 30/14	9.6%	65 (30-86)	Breast	Lymphoma	t-ALL: 36 (6-216) s-ALL: 144 (7-420)	11q23, t(9;22) -5, -7 -17, -17p Hypodiploid	t-ALL: 18/30 (60%) s-ALL: 10/14 (71%)	NR	EFS: 13% (3-yr)
Abdulwahab (2012)	23 (all t-ALL)	6.9%	51 (17-75)	Breast	Lymphoma	48 (5-360)	11q23 t(9;22)	17/21 (81%)	5/18	OS: 37% (3-yr)
Ganzel (2015)	32 23/9	4%	55 (3.3-87) t-ALL: 52 (3.3-76) s-ALL: 75 (23-87)	Breast	Lymphoma	64 (2-336) t-ALL: 72 (9-336) s-ALL: 48 (2-336)	t(9,22) Hypodiploid -7/7p- 11q23	25 (86%)	6/25	OS: 25% (2-yr)
Giri[3] (2015)	79	1.9%	62 (21-90)	Breast	Lymphoma	60 (12-198)	NR	NR	NR	OS: 6.8% (5-yr)
Kelleher (2016)	24 16/8	5.3%	t-ALL: 55 (20-78) s-ALL: 65 (25-72)	Breast	Lymphoma	t-ALL: 37 (7-333) s-ALL: 84 (29-219)	t(9;22) Hypodiploidy 11q23	t-ALL: 15/16 (94%) s-ALL: 6/8 (75%)	3/21	OS: t-ALL: 71% (3-yr) s-ALL: 38% (3-yr)
Rosenberg[3] (2017)	371 184/187	3%	NR	Breast	Lymphoma	67 (2.6-277)	NR	NR	NR	NR4
Swaika3 (2018)	772	6.6%	NR	Breast Prostate	Lymphoproliferative neoplasms Myeloid neoplasms	60 (2-473)	NR	NR	NR	OS: 10% (5-yr)
Aldoss (2018)	93 (all t-ALL)	9.1%	55 (23-85)	Breast	Lymphoproliferative neoplasms	82 (10-608)	t(9;22) 11q23 -5/5q-/-7/7q- Complex karyotype	79/93 (85%)	49/79	OS: 46% (2-yr)

[1]In order of frequency; [2]Seven own patients and 94 collected from the literature. [3]Epidemiologic study. [4]Patients with t-ALL were at significantly increased risk of death compared to *de novo* ALL patients. NR: not reported; CR: complete remission; HSCT: hematopoietic stem cell transplantation; CR1: first complete remission; OS: overall survival; EFS: event-free survival.

hematologic cancer, and the same reasons for breast cancer could be applied to explain this high frequency of t-ALL. In studies including large series, patients with a previous primary hematological malignancy had a higher risk for s-ALL or t-ALL as compared to solid organ neoplasms.[12] The latency from prior diagnosis of cancer to t-ALL varies among the case series, but in general it tends to be shorter than in s-ALL and slightly longer than in t-AML or in t-MDS. Among t-ALL cases, those with *KMT2A* rearrangements show a shorter time interval and those with a Ph-positive rearrangement show a longer interval between the previous cancer and the development of leukemia.[1,2-14,16]

Regarding the therapy of t-ALL patients, there is concern about the possible impact of previous exposure to chemotherapy and/or to radiotherapy on the toxicity of the chemotherapeutic agents given in induction and consolidation. However, the tolerability and the treatment-related mortality were similar to that observed in *de novo* ALL in most studies.[1] In some studies, the CR rate was similar, but in others it was lower than in newly diagnosed ALL cases (Table 1). Considering the retrospective nature of most of the studies and the long period of patient recruitment, data regarding the measurable (minimal) residual disease (MRD) clearance are very limited. As the selection to proceed to alloHSCT was not based on MRD levels, the perception of their poor prognosis (similar to what occurs in t-AML and t-MDS) explains the higher use of transplantation in these patients in some series.[1,15] Given the advanced age of most t-ALL patients, reduced-intensity regimens are more frequently used for conditioning. The transplant-related mortality and the rate of relapse after transplantation have shown to be similar to those of *de novo* ALL in some studies.[1] However, when considering the transplanted and non-transplanted cases together, the survival of t-ALL patients is poorer than that observed in *de novo* ALL (Table 1), this difference being especially evident in the group of non-transplanted cases.[1] Population-based studies also have shown a poorer outcome for ALL patients with antecedent neopla-

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

Marie Therese Rubio

Service d'Hématologie, CHRU Nancy, Hôpital Brabois, and CNRS UMR 7365, Equipe 6, Biopole de l'Université de Lorraine, Vandoeuvre les Nancy, France

E-mail: mt_rubio@hotmail.com

doi:10.3324/haematol.2018.200303

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