eJHaem

British Society for Haematology

Ruxolitinib is effective in the treatment of a patient with refractory T-ALL

1 | CASE PRESENTATION

In 2014, a 56-year-old female with a history of lobular breast carcinoma with invasive ductal component, hormone-receptor–positive, and human epidermal growth factor receptor 2 (HER2) positive, presented with cutaneous lesions of the upper front body. Skin biopsy revealed infiltration of immature blastoid cells, positive for CD7, CD5, CD10, TdT, CD38, cytoplasmatic CD3 but negative for surface CD3, CD34, MPO, CD8, with a proliferation index of 80-90%. Subsequent bone marrow (BM) examination identified a cell population with the same phenotype. Fluorescence in situ hybridization identified a *KMT2A* rearrangement, other than AFF1. According to the WHO 2016 Classification, the case was categorized as precursor T-cell acute lymphoblastic leukemia (T-ALL). Specific treatment following the German Multicenter Study Group on Adult Acute Lymphoblastic Leukemia (GMALL) 07/03 protocol was initiated [1]. The patient reached complete hematological remission (hCR) but remained positive for measurable residual disease (MRD) (real-time quantitative polymerase chain reaction (qRT-PCR), detection limit of 1×10^{-5} for both markers). According to protocol, after first consolidation, the patient proceeded to human leukocyte antigen matched related donor allogeneic hematopoietic stem cell transplantation, achieved molecular complete remission and complete resolution of the skin lesions.

In the following years, the patient suffered a series of cutaneous relapses while maintaining complete donor chimerism and MRD negativity until May 2018. After that, the MRD results turned positive at the above-mentioned detection level while maintaining hCR. Cutaneous relapses were treated as shown in Table 1. The last cutaneous relapse occurred on the right leg (Figure 1A) in March 2020, as confirmed by histology and immunohistochemistry (Figures 1B and 1C). The patient was enrolled in the Molecularly Aided Stratification for Tumor Eradication Research (MASTER) program [2], where a whole genome and transcriptome sequencing performed on the skin biopsy identified several molecular alterations among which there were two heterozygous Janus kinase 3 (*JAK3*) mutations: A573V (variant allele frequency (VAF) 53%) and M511I (VAF, 56%). For both mutations, expression was confirmed by RNA sequencing. In addition, the *KMT2A* rearrangement was identified as a *KMT2A-ELL* gene fusion by RNA sequencing, and other T-ALL recurrent mutations (*U2AF1* R35L,

NOTCH1 L1678P, and *CCND3* R190fs) were detected. Given the recent clinical evidence regarding the sensitivity of T-cell prolymphocytic leukemia to *JAK2* inhibition and the preclinical data in transformed lymphocyte cells regarding the inhibition of JAK1/JAK3 using the *JAK* inhibitors ruxolitinib or tofacitinib [3,4], the decision was made to pursue therapy with ruxolitinib in combination with tofacitinib. Due to major contraindications to tofacitinib in our patient (deep vein thrombosis of the jugular and subclavian vein and heart failure NYHA III), the salvage therapy with ruxolitinib 10 mg twice daily was initiated. An interim examination on day 15 revealed moderate anemia (Hb 10.5 g/L) with otherwise no relevant side effects from the therapy. The cutaneous lesions completely dissolved (Figure 1D), donor chimerism was 100%, but MRD remained positive at the detection limit (1×10^{-5}). At the second staging on day 50, we could confirm a complete remission of the skin lesions. No further treatment related toxicities were encountered. Ruxolitinib was discontinued after 5 months due to a cutaneous relapse and increasing MRD in peripheral blood and BM. A therapy with decitabine and venetoclax was started and soon after, due to lack of response, multiple infectious complications and relevant clinical deterioration, treatment deescalation was discussed with the patient and a best supportive care therapy was pursued.

2 | DISCUSSION

T-ALL is a rare, aggressive T-cell malignancy. Chemotherapy alone cures only 25-45% of the cases, and despite improvements in the understanding of the origin of the disease, survival remains dismal, with only 50% alive at 5 years [5]. Thus, novel treatment agents and strategies are urgently needed.

Comprehensive molecular analyses have already identified a large number of T-ALL-specific oncogenes [6]. Still, the genetic defects underlying the malignant proliferation and survival of the leukemic cells remain clinically unexploited. Recent studies showed that most cases of T-ALL present with recurrent chromosomal aberrations or mutations [7]. Thus, molecular screening in diagnostic and relapse setting may open-up additional treatment options. The most frequent genomic alterations in T-ALL affect PI3K/AKT/mTOR, JAK/STAT, RAF/MEK/ERK, or *NOTCH1* signaling pathways [7].

TABLE 1 Description of therapies used since diagnosis, best response, and main side effects

Timeline/event	Therapy	Result
January-April 2015 Initial diagnosis	Prephase, induction, and consolidation therapy based on GMALL 07/03-Protocol including prophylactic cranial irradiation. [1]	Complete regression of cutaneous lesions, bone marrow puncture: hematological CR, MRD positive
June 2015	Related donor-allogenic, HLA-matched blood stem cell transplantation (conditioning: TBI 8 Gy/fludarabine, immunosuppression with CsA/MMF)	Hematological CR, MRD negative (<5 × 10^{-4}), bone marrow chimerism: 98-100% donor
May 2016 and September 2016: 1st and 2nd cutaneous relapse (Hematological CR, MRD positive[a], bone marrow chimerism: 100% donor)	Radiotherapy (8 × 3 Gy right lower leg, 15 × 2 Gy distal right lower leg), DLIs	Hematological CR, MRD negative, bone marrow chimerism: 100% donor Complete dissolution of skin lesions, postradiogenic alterations
April 2017, November 2017, May 2018: 3rd, 4th, 5th cutaneous relapse (hematological CR, MRD negative[a], bone marrow chimerism: 100% donor)	Radiotherapy (15 × 2 Gy right upper leg, 8 × 3 Gy right lower leg, 15 × 2 Gy abdomen)	Hematological CR, MRD negative, bone marrow chimerism: 100% donor Complete dissolution of skin lesions
November 2018: 6th cutaneous relapse (hematological CR, MRD borderline positive[a], bone marrow chimerism: 100% donor)	Radiotherapy (15 × 2 Gy abdomen)	Hematological CR, MRD borderline, bone marrow chimerism: 100% donor Complete dissolution of skin lesions
March 2019: 7th cutaneous relapse (PB: MRD borderline positive[a])	3 cycles of nelarabine	MRD PB: borderline complete dissolution of skin lesions
December 2019: 8th cutaneous relapse (PB: MRD borderline positive[a])	3 cycles of nelarabine/cyclosphosphamide	MRD PB: negative, regressive cutaneous lesions
March 2020: 9th cutaneous relapse (PB: MRD borderline positive[a])	Ruxolitinib10 mg twice daily	MRD PB: borderline Complete dissolution of skin lesions, moderate anemia (Hb: 10.5 g/dL)

Abbreviations: CR: complete remission; CsA: cyclosporine; DLI: donor lymphocyte infusion.; Gy: gray; HLA: human leukocyte antigen; JAK: Janus kinase; MMF: mycophenolate mofetil; MRD: measurable residual disease; PB: peripheral blood; T-ALL: T-cell acute lymphoblastic leukemia; TBI: total body irradiation.
[a]Detection limit 1 × 10^{-5}.

The JAK/STAT signaling pathway plays an essential role in normal hematopoiesis. *JAK2* helps in the maintenance of hematopoietic stem cells and various stages of myelopoiesis [8], whereas *JAK1* cooperates with *JAK3* for lymphopoiesis. *JAK3* mutations have been reported in 10-16% of T-ALL patients, with *JAK3* M511I being the most frequently identified mutation [9]. *JAK3* mutations have been reported to be dependent on binding to the common γ chain of cytokine receptor complexes [10].

Targeted therapy with tofacitinib, a pan-JAK inhibitor, in combination with ruxolitinib was suggested based on the sequencing results. This was supported by previous preclinical data regarding its effectiveness of targeting *JAK3* mutations as well as a successful therapy with tofacitinib described in a single-patient case report with T-ALL and a *JAK3* mutation [11,12]. Accordingly, tofacitinib, combined with ruxolitinib, has an enhanced potency in vitro in other disease models aiming to inhibit the IL2RG-JAK1-JAK3-STAT5B signaling pathway [13]. As *JAK3* mutants are dependent on *JAK1* signaling for their cellular transformation, it is possible to use both JAK1/JAK2 and JAK3-selective inhibitors in *JAK3* mutation–positive leukemia [11]. However, as previously mentioned, due to existing contraindications to tofacitinib, single-agent ruxolitinib was initiated.

As seen in previous publications in T-ALL murine xenograft models, the patient showed a remarkable response of the skin lesions with ruxolitinib, independently of the presence of *JAK1* or *JAK2* mutations.[14]

Inline, JAK3 M511I was found to obtain an increased JAK/STAT signaling by acquiring an additional mutation in the pseudokinase domain, which was also present in our patient.[15]

Since our patient had complete donor chimerism, we assumed that the graft versus leukemia effect was sufficient to maintain an hCR in the BM but not to prevent the skin relapse. Leukemic cells were able to evade immune surveillance and migrate into peripheral tissues; however, single-agent ruxolitinib was able to induce complete remission of the extramedullary relapse in our case.

Our results illustrate the potential benefit of the JAK inhibitor ruxolitinib in *JAK3*-mutated refractory T-ALL and emphasize the importance of integrating molecular markers in current treatment decision making for patients with T-ALL. Further exploration of this targeted therapeutic strategy in molecularly stratified patient cohorts is warranted.
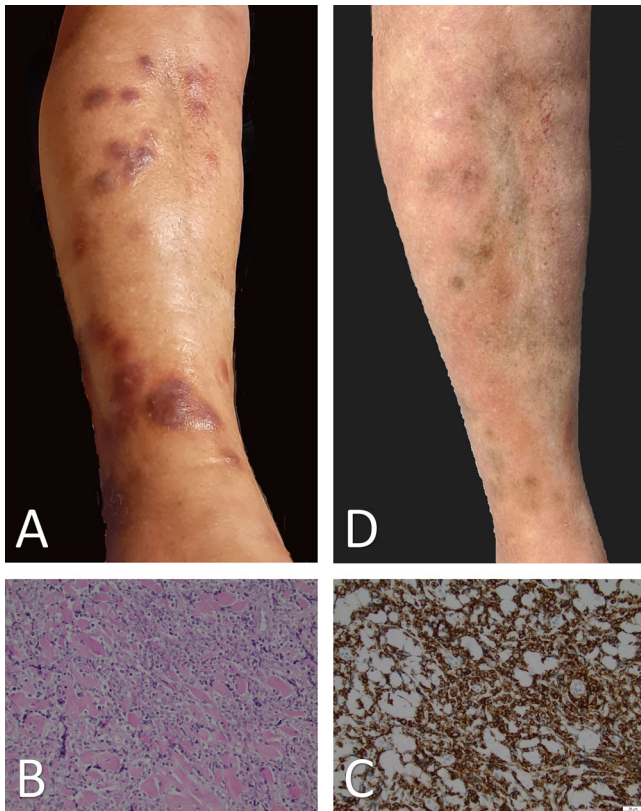
AUTHOR CONTRIBUTIONS

FIGURE 1 (A) Cutaneous lesions right leg before treatment largest nodule 2 cm × 2 cm in diameter and (B) skin biopsy showing diffuse dermal infiltrates of small, monotonous blastoid cells, sparing the epidermis; HE, original magnification: 200×. (C) Immunohistochemistry of cutaneous lesions showing CD5 positivity of neoplastic infiltrates; original magnification: 200×. (D) Clinical control after 15 days of treatment

the data, and all authors read and contributed to the final version of the manuscript.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

Sonia Jaramillo[1]

Hannah Hennemann[1]

Peter Horak[2]

Veronica Teleanu[2]

Christoph E. Heilig[2]

Barbara Hutter[3,4]

Albrecht Stenzinger[5,6]

Hanno Glimm[7,8,9]

Benjamin Goeppert[5]

Carsten Müller-Tidow[1]

Stefan Fröhling[2,6]

Stefan Schönland[1]

Richard F. Schlenk[1,10]

[1] Department of Hematology, Oncology, and Rheumatology, Heidelberg University Hospital, University of Heidelberg, Heidelberg, Germany

[2] Division of Translational Medical Oncology, National Center for Tumor Diseases (NCT) Heidelberg, and German Cancer Research Center (DKFZ), Heidelberg, Germany

[3] Computational Oncology, Molecular Diagnostics Program, NCT and DKFZ, Heidelberg, Germany

[4] Division of Applied Bioinformatics, DKFZ, Heidelberg, Germany

[5] Institute of Pathology, University of Heidelberg, Heidelberg, Germany

[6] German Cancer Consortium (DKTK), Heidelberg, Germany

[7] Department of Translational Medical Oncology, NCT Dresden, Dresden, and DKFZ, Heidelberg, Germany

[8] Center for Personalized Oncology, NCT Dresden and University Hospital Carl Gustav Carus Dresden, Technical University of Dresden, Dresden, Germany

[9] Translational Functional Cancer Genomics, NCT and DKFZ, Heidelberg, Germany

[10] NCT-Trial Center, NCT Heidelberg, DKFZ and Heidelberg University Hospital, Heidelberg, Germany

Correspondence

Richard F. Schlenk, MD, NCT Trial Center, National Center for Tumor Diseases, German Cancer Research Center and Heidelberg University Hospital, Im Neuenheimer Feld 130.3, 69120 Heidelberg, Germany.

Email: richard.schlenk@nct-heidelberg.de

ORCID

Sonia Jaramillo https://orcid.org/0000-0002-2397-3070

Richard F. Schlenk https://orcid.org/0000-0003-2215-2059

REFERENCES

1. Raff T, Gökbuget N, Lüschen S, et al. Molecular relapse in adult standard-risk ALL patients detected by prospective MRD monitoring during and after maintenance treatment: data from the GMALL 06/99 and 07/03 trials. Blood. 2007;109:910-915.

2. Horak P, Klink B, Heining C, et al. Precision oncology based on omics data: the NCT Heidelberg experience. Int J Cancer. 2017;141(5):877-886.

3. Gomez-Arteaga A, Margolskee E, Wei MT, et al. Combined use of tofacitinib (pan-JAK inhibitor) and ruxolitinib (a JAK1/2 inhibitor) for refractory T-cell prolymphocytic leukemia (T-PLL) with a JAK3 mutation. Leuk Lymphoma. 2019;60(7):1626-1631.

4. Govaerts I, Jacobs K, Vandepoel R, et al. JAK/STAT pathway mutations in T-ALL, including the STAT5B N642H mutation, are sensitive to JAK1/JAK3 inhibitors. Hemasphere. 2019;3(6):e313.

5. Boucheix C, David B, Sebban C, et al. Immunophenotype of adult acute lymphoblastic leukemia, clinical parameters, and outcome: an analysis of a prospective trial including 562 tested patients (LALA87). French Group on Therapy for Adult Acute Lymphoblastic Leukemia. Blood. 1994;84:1603.

6. Mullighan CG, Goorha S, Radtke I, et al. Genome-wide analysis of genetic alterations in acute lymphoblastic leukaemia. Nature. 2007;446:758-764

7. Girardi T, Vicente C, Cools J, et al. The genetics and molecular biology of T-ALL. Blood. 2017;129(9):1113-1123.

8. Akada H, Akada S, Hutchison RE, et al. Critical role of Jak2 in the maintenance and function of adult hematopoietic stem cells. Stem Cells. 2014;32:1878-1889.

9. Zhang J, Ding L, Holmfeldt L, et al. The genetic basis of early T-cell precursor acute lymphoblastic leukaemia. Nature. 2012;481(7380):157-163.

10. Haan C, Rolvering C, Raulf F, et al. Jak1 has a dominant role over Jak3 in signal transduction through gammac-containing cytokine receptors. Chem Biol. 2011;18:314-323.

11. Degryse S, de Bock CE, Cox L, et al. JAK3 mutants transform hematopoietic cells through JAK1 activation, causing T-cell acute lymphoblastic leukemia in a mouse model. Blood. 2014;124:3092-3100.

12. Bilori B, Thota S, Clemente MJ, et al. Tofacitinib as a novel salvage therapy for refractory T-cell large granular lymphocytic leukemia. Leukemia. 2015;(12):2427-2429.

13. Maude SL, Dolai S, Delgado-Martin C, et al. Efficacy of JAK/STAT pathway inhibition in murine xenograft models of early T-cell precursor (ETP) acute lymphoblastic leukemia. Blood. 2015;125:1759-1767.

14. Losdyck E, Hornakova T, Springuel L, et al. Distinct acute lymphoblastic leukemia (ALL)-associated Janus kinase 3 (JAK3) mutants exhibit different cytokine-receptor requirements and JAK inhibitor specificities. J Biol Chem. 2015;290(48):29022-29034.

15. Degryse S, Bornschein S, de Bock CE, et al. Mutant JAK3 signaling is increased by loss of wild-type JAK3 or by acquisition of secondary JAK3 mutations in T-ALL. Blood. 2018;131(4):421-425.