PERSPECTIVE ARTICLE

Optimal management of elderly/old Ph+ acute lymphoblastic leukemia patients

Robin Foà,[1] Sabina Chiaretti,[1] Felicetto Ferrara[2] and Giovanni Pizzolo[3]

[1]Hematology, Department of Transitional and Precision Medicine, Sapienza University of Rome, Rome; [2]Hematology, Hospital "Antonio Cardarelli", Naples and [3]Department of Medicine, Azienda Ospedaliera Universitaria Integrata di Verona, Verona, Italy

Correspondence: R. Foà
rfoa@bce.uniroma1.it

Received: October 15, 2025.
Accepted: December 19, 2025.
Early view: January 22, 2026.

https://doi.org/10.3324/haematol.2025.300060

Abstract

Today, Philadelphia-positive acute lymphoblastic leukemia (Ph+ ALL) is a curable disease. In real life, too many adult ALL patients are not adequately worked up at diagnosis and treated, and this occurs, in particular, in elderly/old individuals. Here, we present representative case descriptions to discuss how Ph+ ALL patients diagnosed in their seventh, eight and ninth decade of life can, through a timely, accurate and personalized administration of tyrosine kinase inhibitor (TKI), without systemic chemotherapy, experience long-lived responses, minimal residual disease negativity, and a good quality of life. In this scenario, stopping TKI administration can also be considered. This perspective article represents a proof of concept that, nowadays, even in elderly/old Ph+ ALL, the disease can be cured or kept under prolonged control if adequately managed.

Introduction

Philadelphia-positive acute lymphoblastic leukemia (Ph+ ALL) is the most frequent genetic subgroup of adult ALL, with an incidence that progressively increases with age. In patients over the age of 50, at least 50% of B-lineage ALL are Ph+.[1] Ph+ ALL is defined by the *BCR::ABL1* rearrangement with a subsequent dysregulation of the *ABL1* tyrosine kinase activity.[1] Since the early 2000s, the introduction of tyrosine kinase inhibitors (TKI) in the management of Ph+ ALL has dramatically improved the outcome of what used to be the ALL subgroup with the most unfavorable prognosis.[1] Prior to the advent of TKI, the only likelihood of long-term survival was associated with the infrequent possibility of undergoing an allogeneic stem cell transplant, particularly in elderly patients. Over the years, the prognosis of Ph+ ALL patients of all ages has markedly improved with the front-line administration of a TKI, either associated with reduced intensity chemotherapy or alone.[1] In the last 25 years, in the GIMEMA co-operative studies, the use in induction of a TKI plus steroids without systemic chemotherapy has been pioneered.[1,2] This approach has been used in patients of all ages. More recently, a further advancement has been made by the addition of immunotherapy in consolidation, namely the bispecific monoclonal antibody blinatumomab. Our group has shown that, for Ph+ ALL patients, an induction with the second generation TKI dasatinib and steroids followed by a consolidation with 2-5 cycles of blinatumomab is associated with a complete hematologic remission (CHR) in 98% of cases, with very high rates of molecular response.[3] The long-term follow-up has shown survival rates in the range of 75-80%, with 50% of patients treated only with dasatinib and blinatumomab.[4] Very promising results have recently been reported with the third generation TKI ponatinib plus blinatumomab, also in elderly patients.[5,6] The superiority of a front-line targeted-immunotherapeutic strategy compared to a classic TKI-chemotherapy approach has been conclusively documented for the first time in a phase III randomized trial.[7]

In the review recently published in the New England Journal of Medicine by one of our authors (RF),[2] the dichotomy between an optimal strategy for the management of adult Ph+ ALL patients of all ages and the real-life scenario was underlined (see Foà, Figure 4[2]). If not all pieces of the puzzle are in place, management of many, possibly most, Ph+ ALL patients worldwide is suboptimal. This has a profound impact on treatment decisions, the clinical course of the disease, and the overall outcome. This inadequate management impacts in particular on elderly/old patients, who are frequently not tested for the presence of the *BCR::ABL1*

rearrangement at presentation. As a consequence, they do not receive potentially life-saving treatment.

In this perspective article, we describe a group of representative Ph$^+$ ALL patients diagnosed in their seventh, eight and ninth decade of life. These patients were adequately worked up, treated upfront with a TKI that was tailored to their clinical history and associated comorbidities, and did not receive systemic chemotherapy. We witnessed a prolonged life expectancy with a concomitant good quality of life. These patients represent a proof of concept on how, today, elderly/old Ph$^+$ ALL can be successfully managed even into their nineties.

Case 1

In December 2006, a 73-year-old woman was referred to the Hematology Center of the Sapienza University in Rome with mild anemia and leukocytosis (Hb 10.1 g/dL, WBC 41.3x10^9/L, platelets 161x10^9/L, lymphoid blasts 90% in the blood and marrow). The past medical history was significant for hypertension, hiatal hernia, cholecystectomy and hysterectomy for non-neoplastic reasons. Flow-cytometry analysis on bone marrow cells identified 80% B-common blasts, while the karyotype showed a t(9;22)(q32q11) translocation. The molecular profile was consistent with a *BCR::ABL1* fusion transcript accounting for the p210 isoform. The patient was diagnosed with Ph$^+$ ALL, enrolled in the GIMEMA LAL1205 trial,[8] and started treatment with dasatinib (140 mg/daily) and steroids. She achieved a complete hematologic response (CHR) with 0.05 *BCR::ABL1/ABL1* x100 copies within three months. Due to pleural effusion, the patient stopped dasatinib and started imatinib 600 mg/daily, which was further reduced to 400 mg/daily due to hematologic toxicity. At nine months, a complete molecular response (CMR) was achieved. The patient underwent minimal residual disease (MRD) monitoring every three months for two years, and then twice a year, with no major complications associated with the TKI administration. In June 2022, considering her general condition and prolonged CMR, imatinib was suspended. She died in December 2022 at the age of 89 from a non-hematologic disease, 16 years after the diagnosis of Ph$^+$ ALL (that had been managed only with TKI) and a persistent and prolonged (11 years) CMR.

Case 2

In September 2007, an 89-year-old man was admitted to the Hematology Center of Verona because of fatigue and back pain. The blood count showed Hb 12.6 g/dL, WBC 27.6x10^9/L, with 70% blasts, platelets 60x10^9/L. The diagnostic work-up documented the presence of a Ph$^+$ (p190) pre-B ALL. The patient was treated according to the GIMEMA LAL0201-B trial for elderly Ph$^+$ ALL patients (>60 years) with imatinib and prednisone.[9] Because of his age, imatinib was administered at 400 mg daily. At day +45, the patient was in CHR and in complete cytogenetic response (CCyR). At +12 months, he was in major molecular response and was enjoying a very good quality of life. At +18 months, he lost the molecular response; this was followed two months later by a hematologic relapse. At that time (May 2009), the patient was almost 91 years old. In view of his good clinical condition, he was treated with dasatinib (100 mg daily). Due to some side effects, dasatinib had to be modulated. After one month, the patient had regained a CHR and a CCyR that persisted for a further six months. A second relapse was diagnosed in February 2010. He eventually passed away in March 2010 due to cardiac complications at the age of 92, 28 months after the diagnosis of Ph$^+$ ALL.

Case 3

In April 2007, a 67-year-old woman was admitted to the Hematology Center of the “Cardarelli” Hospital in Naples. The blood count showed Hb 8.9 g/dL, WBC 7.8x10^9/L, with 80% blasts, platelets 25x10^9/L. She was diagnosed with Ph$^+$ (p210) B-common ALL. An ischemic cardiopathy was recorded in her recent medical history. The patient was treated according to the GIMEMA LAL0201-B trial[9] for elderly Ph$^+$ ALL (>60 years) with imatinib (800 mg daily) and prednisone. Imatinib was reduced to 600 mg after four weeks due to hematologic toxicity and lower limb edema. The patient obtained a CHR associated with a cytofluorimetric MRD negativity that persisted over time. During the follow-up, the dosing of imatinib was tailored according to tolerability and side effects. Treatment continued for eight years (up to 2015) and was then stopped. Thereafter, she continued to maintain a normal blood count. The patient passed away in 2022 due to cardiovascular complications while in remission at the age of 82, 15 years after the diagnosis of Ph$^+$ ALL and eight years after stopping treatment.

Case 4

In February 2016, an 85-year-old woman was diagnosed with Ph$^+$ ALL (p190) at the Hematology Center of the Sapienza University in Rome. The medical history was significant for hypertension and mild bilateral carotid stenosis. The blood count showed Hb 8.5 g/dL, WBC 2.1x10^9/L, with 8% blasts, platelets 70x10^9/L. The bone marrow aspirate showed 80% of pre-B blasts. The patient was enrolled in the GIMEMA LAL1811 trial[10] and started treatment with steroids and ponatinib (45 mg/daily). A CMR was achieved at day +28. The patient underwent a short TKI discontinuation due to an uncontrolled hypertension and edema. Ponatinib was resumed at 30 mg/daily for two years since diagnosis and then at 15 mg/daily. MRD monitoring remained persistently negative. In February 2019, the patient experienced atrial fibrillation and heart failure with a reduced ejection fraction, and TKI treatment was stopped. After regression of the symptoms, an attempt was made to restart ponatinib but the patient experienced hyperkalemia and syncope, and ponatinib was no longer resumed. MRD remained negative after TKI discontinuation. The patient died of old age at the age of 92, 4.2 years after stopping ponatinib.

Discussion

The clinical history of these 4 cases provides representative examples of how elderly/old Ph+ ALL patients can be successfully managed in the TKI era if adequately worked up and treated. All were diagnosed in their seventh, eighth or ninth decade of life. In all patients, the gene fusion that characterizes Ph+ ALL was defined at presentation, and they were all treated upfront with a TKI plus steroids (without systemic chemotherapy) according to a national clinical protocol or by entering a trial open at the given time in Italy. Case 1 was enrolled in the GIMEMA LAL1205 protocol,[8] that considered the front-line use of dasatinib and steroids for all adult patients, with no upper age limit. Cases 2 and 3 were treated according to the GIMEMA LAL0201-B trial,[9] the first protocol designed to treat front-line Ph+ ALL patients with a TKI (imatinib) and steroids in induction without systemic chemotherapy; the protocol was limited to elderly patients (>60 years). Case 4 entered the GIMEMA LAL1811 trial[10] for elderly (>60 years) patients or for patients unfit to receive chemotherapy, and was treated with ponatinib and steroids. At the time of diagnosis, the patients were 73, 89, 67, and 85 years of age, respectively. They all had a past medical history and comorbidities that prompted the treating physicians to enroll them in a TKI-based clinical protocol that omitted systemic chemotherapy or to treat them according to a completed clinical trial, and TKI doses were modulated at diagnosis and during follow-up according to the individual performance status and tolerability.

Clearly, expertise in the use of TKI in elderly patients is required. The 4 patients were diagnosed and treated at the hematology center that over the years has co-ordinated the multicenter GIMEMA protocols for adult Ph+ ALL in Italy (Sapienza University, Rome) or at centers that actively participated in the clinical trials. MRD was monitored in all patients, allowing the depth of response in each individual case to be documented. In 3 patients in long-lasting CHR and in deep response, TKI were stopped. Two patients (cases 3 and 4) stopped TKI administration after eight and three years of treatment, respectively, while in sustained MRD negativity; the disease remained under control for a further eight and 4.2 years, respectively, and these patients remained in CHR. Two patients died at the age of 92. One (case 2) passed away 28 months after the diagnosis of Ph+ ALL, which had been made at the age of 89. During this time, he had enjoyed a normal and active life and had successfully responded to two TKI. One patient (case 4) was diagnosed at the age of 85, lived for seven more years, and died of old age while off treatment in CMR. One patient (case 1) died at the age of 89 due to other causes, 11 years after the diagnosis of Ph+ ALL; death occurred while the patient was in CMR and after having stopped imatinib. The last patient (case 3) died at the age of 82 in CHR, 15 years after the diagnosis, and eight years after stopping imatinib treatment.

Clearly, the 4 patients described here benefited from this personalized approach and the ongoing efforts of the national network in Italy for adult ALL. In real life around the world,[2,11] how many elderly/old ALL patients are tested at presentation and within one week from diagnosis for the *BCR::ABL1* gene fusion? And for such patients, how often is a TKI immediately available? And how often is MRD monitored, particularly in elderly patients? Luckily, the 4 patients were either enrolled in a nationwide protocol open at the time in Italy for Ph+ ALL patients or were treated (with imatinib and steroids) according to a previous protocol. Centers participating in clinical trials benefit from a centralized management of the biologic samples for the diagnostic work-up and for a standardized MRD monitoring during the clinical follow-up. This enables: i) a uniform work-up of patients of all ages at presentation; ii) a prompt TKI administration; iii) monitoring of the depth of the response during treatment; and iv) tailoring of the TKI on the basis of the individual tolerability, which is a key aspect of treating elderly/old patients. This approach led the treating physicians to stop TKI administration in 3 patients. In 2 patients, this continued for eight and 4.2 years, and in the last patient (aged 89) for seven months. The 3 patients eventually died of old age and other non-hematology-related causes while maintaining a CHR. In the era of targeted treatment for Ph+ ALL patients of all ages, treatment-free remission (TFR) is becoming a very relevant and timely topic,[12] even in what used to be considered the hematologic malignancy with the worst prognosis. The clinical course of these 3 patients suggests that, also in elderly Ph+ ALL treated only with a TKI, TFR may be an endpoint of treatment if MRD monitoring is included in the clinical follow-up. In addition, it should be remembered that, in Ph+ ALL treated with a TKI, an *in vivo* host immune modulation, including a marked decrease in immunosuppressive T-regulatory (Treg) cells,[3,13,14] that may help control the disease has been observed, also in elderly patients.[15]

The clinical history of these 4 cases clearly illustrates how elderly/old Ph+ ALL patients can be successfully managed if correctly and rapidly diagnosed and immediately treated with a TKI and steroids, including patients in their nineties. In addition to responding to treatment, obtaining a CHR (often a CMR) and stopping treatment, all patients enjoyed a very good quality of life. What would have been the outcome of these patients if the *BCR::ABL1* rearrangement had not been identified at presentation and a TKI not immediately administered? Chemotherapy and palliative treatment would have been the only options. All efforts should, therefore, be made to enable elderly/old ALL patients in all countries, independently of the socio-economic conditions, to be correctly worked up and treated.[2] These cases represent a proof of concept that elderly/old Ph+ ALL patients can be cured of their disease,

lead a prolonged and good quality of life, stop treatment, and not die of the disease. Paradoxically, this would also represent a cost-saving strategy compared to 'standard'/ poorly effective treatment.

Disclosures

No conflicts of interest to disclose.

Contributions

RF planned this Perspective Article and wrote the manuscript; SC contributed with 2 patients; FF and GP contributed with one patient each. All authors were involved in the design and selection of content of the article, and all approved the final version of the manuscript for publication.

Funding

All studies conducted over the years on Ph⁺ acute lymphoblastic leukemia have been partly supported by Associazione Italiana per la Ricerca sul Cancro (AIRC) 5x1000, Special Program Metastases (21198), Milan, Italy (to RF).

Data-sharing statement

Data related to this Perspective Article are available on reasonable request to the Corresponding Author.

References

1. Foà R, Chiaretti S. Philadelphia chromosome-positive acute lymphoblastic leukemia. N Engl J Med. 2022;386(25):2399-2411.
2. Foà R. Ph-positive acute lymphoblastic leukemia - 25 years of progress. N Engl J Med. 2025;392(19):1941-1952.
3. Foà R, Bassan R, Vitale A, et al. Dasatinib-blinatumomab for Ph-positive acute lymphoblastic leukemia in adults. N Engl J Med. 2020;383(17):1613-1623.
4. Foà R, Bassan R, Elia L, et al. Long-term results of the dasatinib-blinatumomab protocol for adult Philadelphia-positive ALL. J Clin Oncol. 2024;42(8):881-885.
5. Kantarjan H, Short NJ, Haddad FG, et al. Results of the simultaneous combination of ponatinib and blinatumomab in Philadelphia chromosome-positive ALL. J Clin Oncol. 2024;42(36):4246-4251.
6. Chiaretti S, Leoncin M, Elia L, et al. Efficacy and toxicity of frontline ponatinib plus blinatumomab for adult Ph+ ALL patients of all ages. Intermediate analysis of the GIMEMA ALL2820. Blood. 2024;144 (Suppl 1):835.
7. Chiaretti S, Di Trani M, Skert C, et al. First results of the phase III GIMEMA ALL2820 trial comparing ponatinib plus blinatumomab to imatinib and chemotherapy for newly diagnosed adult Ph+ acute lymphoblastic leukemia patients. Blood. 2025;146(Suppl 1):439.
8. Foà R, Vitale A, Vignetti M, et al. Dasatinib as first-line treatment for adult patients with Philadelphia chromosome-positive acute lymphoblastic leukemia. Blood. 2011;118(25):6521-6528.
9. Vignetti M, Fazi P, Cimino G, et al. Imatinib plus steroids induces complete remissions and prolonged survival in elderly Philadelphia chromosome-positive patients with acute lymphoblastic leukemia without additional chemotherapy: results of the Gruppo Italiano Malattie Ematologiche dell'Adulto (GIMEMA) LAL0201-B protocol. Blood. 2007;109(9):3676-3678.
10. Martinelli G, Papayannidis C, Piciocchi A, et al. INCB84344-201: ponatinib and steroids in frontline therapy for unfit patients with Ph+ acute lymphoblastic leukemia. Blood Adv. 2022;6(6):1742-1753.
11. Chiaretti S, Foà R. How I treat adult Ph+ ALL. Blood. 2025;145(1):11-19.
12. Dragani M, Ansuinelli M, Papayannidis C, et al. Tyrosine kinase inhibitor discontinuation in nonallografted Philadelphia-positive acute lymphoblastic leukemia patients: a Campus ALL real-life study. Haematologica. 2025;110(5):1177-1181.
13. Puzzolo MC, Radice G, Peragine N, et al. Host immune system modulation in Ph+ acute lymphoblastic leukemia patients treated with dasatinib and blinatumomab. Blood. 2021;138(22):2290-3229.
14. Ansuinelli M, Peragine N, De Propris MS, et al. Immunomodulatory effect of dasatinib plus blinatumomab versus ponatinib plus blinatumomab in newly diagnosed Ph+ acute lymphoblastic leukemia patients. Blood. 2024;144(Suppl 1):838.
15. Sakaguchi S, Mikami N, Wing JB, Tanaka A, Ichiyama K, Ohkura N. Regulatory T cells and human disease. Annu Rev Immunol. 20;38:541-566.