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

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ABSTRACT

Philadelphia-positive acute lymphoblastic leukemia (Ph+ ALL) is today a curable disease. In the 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. We hereby discuss, through representative case descriptions, how Ph+ ALL patients diagnosed in their seventh, eight and nineth decade of life through a timely, accurate and personalized tyrosine kinase inhibitor (TKI) administration, in the absence of systemic chemotherapy, can experience long-lived responses, minimal residual disease negativity, and a good quality of life. To an extent that 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] In the early 2000's, 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 TKIs, the only long-term survival likelihood was associated to 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 frontline administration of TKIs associated with reduced intensity chemotherapy or alone.[1] In the last 25 years, in the GIMEMA cooperative studies the use in induction of a TKI plus steroids without systemic chemotherapy was pioneered.[1,2]. This approach has been used in patients of all ages. More recently, a further advancement has come from the addition of immunotherapy, namely the bispecific monoclonal antibody blinatumomab, in consolidation. 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 responses.[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 frontline targeted-immunotherapeutic strategy compared to a classic TKI-chemotherapy approach has been for the first time conclusively documented in a phase III randomized trial.[7]

In the review recently published in the New England Journal of Medicine by one of the authors (RF), the dichotomy between an optimal strategy for the management of adult Ph+ ALL patients of all ages and the real-life scenario was underlined and illustrated in Figure 4[2]. If not all pieces of the puzzle are in place many/most Ph+ ALL patients worldwide are suboptimally managed. This has a profound impact in treatment decisions, clinical course of the disease and overall outcome. This non-optimal management scenario impacts in particular on elderly/old patients, who frequently are not tested for the presence of the *BCR::ABL1* rearrangement at presentation and, as a consequence, are not treated with a potentially life-saving approach.

In this perspective article we describe representative Ph+ ALL patients diagnosed in their seventh, eight and nineth decade of life who were adequately worked up, treated upfront with a TKI, tailored

according to the clinical history and associated comorbidities, did not receive systemic chemotherapy and 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 41.3 $x10^{9}$/L, platelets 161 $x10^{9}$/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 CHR with 0.05 *BCR::ABL1*/*ABL1* x100 copies within 3 months. Due to pleural effusion, the patient stopped dasatinib and started imatinib 600 mg/daily, further reduced to 400 mg/daily due to hematologic toxicity. At 9 month 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 conditions and prolonged CMR, imatinib was suspended. She died in December 2022 at the age of 89 because of a non-hematologic disease, 16 years after the diagnosis of Ph+ ALL managed only with TKIs and a persistent and prolonged (11 years) CMR.

Case 2

In September 2007, an 89-year-old gentleman was admitted at the Hematology Center of Verona because of fatigue and back pain. The blood count showed Hb 12.6 g/dL, WBC 27.6 $x10^{9}$/L, with 70% blasts, platelets 60 $x10^{9}$/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 leading a very good quality of life. At +18 month he lost the molecular response, that preceded by 2 month a hematologic relapse. At the time (May 2009), the patient was almost 91. In view of the good

clinical conditions, he was treated with dasatinib (100 mg daily). Due to some side effects, dasatinib had to be modulated. After 1 month, the patient had regained a CHR and a CCyR that persisted for 6 further 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 lady was admitted at the Hematology Center of the Cardarelli hospital in Naples. The blood count showed Hb 8.9 g/dL, WBC 7.8 $x10^9$/L, with 80% blasts, platelets 25 $x10^9$/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 4 weeks due to hematologic toxicity and lower limb oedema. 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 8 years (up to 2015) and was then stopped. Thereafter, she always maintained 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 8 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 2.1 $x10^9$/L, with 8% blasts, platelets 70 $x10^9$/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 2 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, ponatinib restart was attempted but the patient experienced hyperkalemia and syncope, and ponatinib was no longer resumed. MRD remained negative after TKI discontinuation. The patient died of senectus at the age of 92, 4.2 years after stopping ponatinib.

DISCUSSION

The clinical history of these 4 cases represents paradigmatic examples on 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 the GIMEMA LAL1205 protocol[8], that contemplated the use frontline 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 frontline 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 had 73, 89, 67 and 85 years of age, respectively, with 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 to modulate the TKI doses at diagnosis and during the follow-up according to the individual performance status and tolerability. Clearly, expertise in the use of TKIs in elderly patients is required. The 4 patients were diagnosed and treated at the hematology center that over the years has coordinated 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 and this allowed to document the depth of the response in each individual case. In 3 patients in long-lasting CHR and in deep response, TKIs were stopped. Two patients (cases 3 & 4) stopped TKI administration after 8 and 3 years of treatment while in sustained MRD negativity and the disease remained under control for 8 and 4.2 further years remaining in CHR. Two patients died at the age of 92. One (case 2) passed away after 28 months of a normal and active life after the diagnosis of Ph+ ALL was made at the age of 89 having successfully responded to two TKIs. One patient (case 4) was diagnosed at the age of 85, lived for 7 years and died of old age in CMR and off treatment. One patient (case 1) died at the age of 89 due to other causes, 11 years after the diagnosis of Ph+ ALL while in CMR and having stopped imatinib. The last patient (case 3) died at the age of 82 in CHR, 15 years after the diagnosis and 8 years after stopping imatinib treatment.

Clearly, the 4 patients hereby described benefitted from this personalized approach and the national network ongoing in Italy for adult ALL. In the worldwide real life[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 of all ages or were treated (with imatinib and steroids) according to a previous protocol. Centers participating in clinical trials benefit from a central handling of the biologic samples for the diagnostic work-up and during the clinical follow-up for a standardized MRD monitoring. This enables *i)* a uniform work-up of patients of all ages at presentation, *ii)* a prompt TKI administration, *iii)* a monitoring of the depth of the response during treatment, *iv)* a tailoring of TKI on the basis of the individual tolerability, a key aspect in elderly patients. This approach led the treating physicians to stop the TKI administration in 3 patients. In 2 patients this continued for 8 and 4.2 year, and in the last patient aged 89 for 7 months. The 3 patients eventually died in persistent CHR of old age and other non-hematology related causes. 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 the worst hematologic malignancy. 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. It should also be recalled 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 if correctly and rapidly diagnosed and immediately treated with a TKI and steroids can be successfully managed, 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 options. All efforts should therefore be made to enable elderly/old ALL patients in all countries, and 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 eventually pass away due to other causes. Paradoxically, this would also represent a cost-saving strategy compared to ‘standard’/poorly effective treatment.

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