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ACUTE LYMPHOBLASTIC LEUKEMIA

How I treat adult Ph+ ALL

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The Philadelphia (Ph) chromosome is one of the few genetic aberrations in which a casualty has been proven and, as such, represents a success in the history of medicine. This is also evident in the setting of Ph+ acute lymphoblastic leukemia (ALL), the most frequent genetic subgroup in adult ALL, whose incidence increases with age and whose prognosis, before the advent of tyrosine kinase inhibitors (TKIs), was particularly poor. The outcome and management of patients with Ph+ ALL have greatly improved since the incorporation of first-, second-, and third-generation TKIs in the therapeutic backbone and is further changing with the more recent introduction of immunotherapy. This allows for long-term survival rates currently ranging between 75% and 80%. The clinical scenario of adult Ph+ ALL has thus changed profoundly, and new challenges are emerging. In this article, illustrative clinical cases are used to discuss the current role of systemic chemotherapy and allogeneic stem cell transplant, the difficulty in treating central nervous system relapses and, more in general, relapses in the current therapeutic era, and the possibility of stopping TKIs. Finally, the challenges related to an optimal management of these patients are discussed.

Introduction

Philadelphia-positive (Ph+) acute lymphoblastic leukemia (ALL) is characterized by the t(9,22) (q34; q11) translocation that gives rise to the *BCR*::*ABL1* fusion protein.[1-4] This rearrangement leads to 3 different fusion proteins (p190, p210, and, rarely, p230), with p190 usually detected in Ph+ ALL, whereas p210 is mainly associated with chronic myeloid leukemia (CML). The *BCR*::*ABL1* rearrangement is rare in childhood ALL, whereas it increases with age, being detected in >50% of patients aged >50 years.[5,6] The prognosis of Ph+ ALL was in the past dismal, with most patients being refractory to chemotherapy. Allogeneic stem cell transplantation (allo-SCT) was the only option for eligible cases.[7-10]

The management changed radically after the introduction of tyrosine kinase inhibitors (TKIs), with imatinib being the only TKI approved in most countries for frontline treatment.[11] The first studies combining imatinib with chemotherapy led to a significant improvement for adult patients with Ph+ ALL, including the older patients, with complete hematologic remission (CHR) rates >90% and an improved overall survival (OS) and disease-free survival (DFS).[12-18] These results improved further with the second-generation TKI dasatinib, because it prevents *ABL1* mutations, with the exception of the T315I mutation, and has a potential immunomodulatory effect, as well as with nilotinib, although not licensed for Ph+ ALL.[19-22] However, the association of intensive or low chemotherapy with TKIs was associated with 1% to 5% of toxic deaths.[12-25] In the studies carried out over the years by the GIMEMA (Gruppo Italiano Malattie EMatologiche dell'Adulto) and others, induction has been based exclusively on a TKI (plus steroids), followed by consolidation chemotherapy.[26-32] Regardless of the strategy used, allo-SCT was still mandatory.

The scenario further changed after the introduction of 2 additional strategies: the third-generation pan-TKI ponatinib, active not only toward *ABL1* but also toward *FLT3, FGFR, VEGFR, KIT PDGFR, RET EPH*, and the Src family,[33] and immunotherapy, particularly the bispecific monoclonal antibody blinatumomab. Our group was the first to combine blinatumomab with a TKI in the frontline setting for adults with no upper age limit. The D-ALBA (NCT02744768) protocol was based on a dasatinib plus steroids induction, followed by at least 2 cycles of blinatumomab (maximum 5). The preliminary results showed that after the second blinatumomab cycle, 60% of patients achieved a molecular response.[34] In the final report, the OS and DFS are 80.7% and 74.6% at a median follow-up 53 months, respectively.[35] For ponatinib, 3 studies were pivotal: (1) the MD Anderson Cancer Center (MDACC) reported 6-year event-free survival and OS rates of 65% and 75%, respectively, with the combination of hyper-CVAD (cyclophosphamide, vincristine, adriamycin, dexamethasone) and ponatinib at adjusted doses[36-38]; the MDACC also tested the combination of ponatinib plus blinatumomab reporting OS and DFS of 90% and 80% at 2 years, respectively[39]; (2) the PETHEMA (Programa Español de Tratamientos en Hematología) group used ponatinib with chemotherapy with the aim of allografting all patients; the 3-year event-free survival and OS are 70% and 96%, respectively[40,41]; and (3) finally, in a GIMEMA trial for older and/or unfit patients treated only with ponatinib plus steroids, a complete molecular response (CMR) was reached in 40% of cases; OS and CHR duration were not reached.[30] Results are summarized in Table 1.[12-44] New clinical scenarios are emerging.

Table 1. Main results of clinical trials contemplating the use of first-, second-, and third-generation TKIs in the frontline setting for adult Ph$^+$ ALL

Reference, year	TKI	N	Median age (range), y	CHR, %	ED, %	Allo-SCT, %	OS, %	DFS, %	CIR, %
Intensive chemotherapy and TKIs									
De Labarthe et al, 2007[12]	Imatinib	45	45 (16-59)	96	4	51	52 (4 y)	43 (4 y)	24 (4 y)
Bassan et al, 2010[13]	Imatinib	59	47 (19-66)	92	4	63	48 (5 y)	39 (5 y)	47 (5 y)
Fielding et al, 2014[14]	Imatinib	175	42 (16-64)	92	5	60	38 (4 y)	50 (4 y)	NA
Chalandon et al, 2015[15]	Imatinib	133	45 (21-59)	91	7	65	43 (5 y)	32 (5 y)*	41 (5 y)
Daver et al, 2015[16]	Imatinib	45	51 (17-84)	93	2	30	43 (5 y)	43 (5 y)	NA
Fujisawa et al, 2017[17]	Imatinib	68	49 (18-64)	96	4	63	62 (3 y)	52 (3 y)*	17 (1 y)
Hatta et al, 2018[18]	Imatinib	99	45 (15-64)	97	3	61	50 (5 y)	43 (5 y)	15 (5 y)
Ravandi et al, 2015[19]	Dasatinib	72	55 (21-80)	96	4	17	46 (5 y)	44 (5y)	32 (5 y)
Ravandi et al, 2016[20]	Dasatinib	94	44 (20-60)	88	2	43	69 (3 y)	55 (3 y)	NA
Kim et al, 2015[21]	Nilotinib	90	47 (17-71)	91	NA	63	72 (2 y)	72 (2 y)	24 (2 y)
Chalandon et al, 2024[22]	Nilotinib	76	49 (39-54)	93	3	60	79 (4 y)	76 (4 y)†	13 (4 y)
Jabbour et al, 2018[37] Short et al, 2019[38] Kantarjian et al, 2023[40]	Ponatinib	86	46 (21-80)	100	0	20 20 23	76 (5 y) 73 (5 y) 65 (6 y)	70 (3 y)* 68 (5 y)* 65 (5 y)	11 NA 17
Ribera et al, 2022[41] Ribera et al, 2024[42]	Ponatinib	30	49 (19-59)	100	0	87	70 (3 y) 66 (4 y)	96 (3 y)* 92 (4 y)*	— 10 (4 y)
Low-dose chemotherapy and TKIs									
Chalandon et al, 2015[15]	Imatinib	136	49 (18-59)	99	1	62	43 (5 y)	42 (5 y)*	3.8 (5 y)
Rousselot et al, 2016[23]	Dasatinib	71	69 (59-83)	96	4	9.8	36 (5 y)	27 (5 y)	54 (5 y)
Ottman et al, 2018[24]	Nilotinib	72	65 (55-85)	94	1	33	47 (4 y)	42 (4 y)*	34 (4 y)
Chalandon et al, 2024[22]	Nilotinib	78	47 (39-54)	95	1	60	73 (4 y)	58 (4 y)†	30 (4 y)
Jabbour et al, 2024[25]	Imatinib	81	54 (19-82)	94	NA	48	Median, nr (2 y)	Median, nr (2 y)*	NA
	Ponatinib	164	52 (19-75)	97	NA	34	Median, nr (2 y)	Median, 29 mo*	NA
Chemotherapy-free regimens									
Vignetti et al, 2007[26]	Imatinib	30	69 (61-83)	100	0	39	74 (1 y)	48 (1 y)	47 (1 y)
Foà et al, 2011[27]	Dasatinib	55	54 (24-76)	92	0	34	69 (20 mo)	51 (20 mo)	43 (20 mo)
Chiaretti et al, 2016[28]	Imatinib	51	46 (17-60)	96	0	42	49 (5 y)	46 (5 y)	34 (5 y)
Chiaretti et al, 2021[29]	Dasatinib	60	42 (19-59)	97	0	43	56 (5 y)	47 (5 y)	28 (5 y)
Martinelli et al, 2021[30]	Ponatinib	44	66 (26-85)	95	4	NA	Median, nr	Median, 14 mo*	14
Wieduwilt et al, 2021[31]	Dasatinib	65	60 (22-87)	95	0	20	48 (5 y)	37 (5 y)	39 (5 y)
Sugiura et al, 2022[32]	Dasatinib	78	44 (16-64)	94	0	73	80 (3 y)	66 (3 y)*	23 (3 y)
Luskin et al, 2023[43]	Ascimib + dastinib	23	65 (33-85)	NA	NA	35	NA	NA	NA
Tang et al, 2024[34]	Olverembatinib + venetoclax	10	41 (27-60)	100	0	10	NA	NA	NA

CIR, cumulative incidence of relapse; ED, early death; NA, not available; nr, not reached.

*Event-free survival.

†RFS.

‡Nineteen patients were in CHR at enrollment.

Table 1 (continued)

Reference, year	TKI	N	Median age (range), y	CHR, %	ED, %	Allo-SCT, %	OS, %	DFS, %	CIR, %
Chemotherapy-free regimens plus blinatumomab									
Foà et al, 2020[35] Foà et al, 2023[36]	Dasatinib	63	54 (24-82)	98	2	50	88 (2 y) 80 (5 y)	80 (2 y) 76 (5 y)	10 (2 y) 14 (5 y)
Advani et al, 2023[39]	Dasatinib	24	73 (65-87)	92	8	4	87 (3 y)	77 (3 y)	29 (3 y)
Short et al, 2023[44]	Ponatinib	54‡	56 (20-83)	94	2	2	90 (2 y)	80 (2 y)*	6 (2 y)

CIR, cumulative incidence of relapse; ED, early death; NA, not available; nr, not reached.

*Event-free survival.

†RFS.

‡Nineteen patients were in CHR at enrollment.

We hereby present 5 cases managed at our center that illustrate the challenges we are facing today in the management of adult Ph$^+$ ALL.

Clinical case 1: transplant in the era of targeted treatment

A 24-year-old man was admitted in September 2018 for asthenia and petechiae. A full blood count (FBC) revealed mild anemia, leukopenia, and thrombocytopenia: hemoglobin (Hb) 12.5 g/dL, white blood cells (WBCs) 3.1 × 10^9/L, polymorphonucleates (PMNs) 0.6 × 10^9/L, lymphocytes 2.0 × 10^9/L, and platelets 32 × 10^9/L. He was diagnosed with p190 *BCR*::*ABL1* common ALL. Multiplex ligation-dependent probe amplification showed an *IKZF1*^{plus} genotype (namely *IKZF1* deletion plus *CDKN2A*/B and/or *PAX5* deletion). The patient was enrolled in the D-ALBA study; after dasatinib induction, he received 2 blinatumomab cycles; at the end of induction and consolidation (day +85 and day +150), measurable residual disease (MRD), evaluated by *BCR*::*ABL1* quantitative polymerase chain reaction, was persistently positive. He underwent allografting from an HLA compatible sibling after a myeloablative conditioning. PMN engraftment occurred at day +22, experiencing only a grade 3 nausea; he was in CMR after 65 months from diagnosis.

Discussion of case 1

Allo-SCT is increasingly debated: in the D-ALBA trial, allograft was left at the investigators' choice. Twenty-four patients received transplantation in first CHR; it should be underlined that most patients were not early molecular responders, reflecting a high-risk population.

The MDACC reported that combining hyper-CVAD and ponatinib resulted in a CMR rate of 84% and a 6-year OS of 70% and 87% among patients who did and did not undergo an allo-SCT, respectively.[40] The replacement of chemotherapy with blinatumomab reduced the number of patients undergoing allo-SCT to a single case.[44] The US intergroup conducted a retrospective study on 83 patients treated with hyper-CVAD plus dasatinib and achieving a CHR; 41 underwent allografting and witnessed a significantly better 12-month relapse-free survival (RFS) and OS.[20] An update focused on patients achieving a CMR at day 90; 98 underwent allo-SCT, and 132 did not. The 5-year OS and RFS were not significantly different, whereas the cumulative incidence of relapse was higher in the nonallografted subset.[20,45]

In the Ponalfil trial, based on ponatinib plus chemotherapy followed by allo-SCT, 26 of the 30 enrolled patients underwent allografting, and 23 are alive, with 17 in continuous remission, with a single death due to graft-versus-host disease.[41,42] Similarly, Nishiwaki et al[46] recently reported on the outcome of 147 patients (allo-SCT, n = 101; non–allo-SCT, n = 46) in CMR within 3 months from the start of treatment (with either imatinib or dasatinib plus chemotherapy) and showed a benefit in terms of 5-year OS and RFS in the allografted cohort: 73% and 70% vs 50% and 20%, respectively.

These data indicate that a definitive algorithm is not yet possible, and allo-SCT allocation is still, among other factors, highly dependent on the policy of the centers/working groups. To conclusively determine the need for transplant, a randomized trial powered to address this issue is mandatory. Meanwhile, in the ongoing GIMEMA ALL2820 phase 3 trial (ponatinib followed by blinatumomab in the experimental arm and imatinib plus chemotherapy in the control arm), transplant allocation relies on the presence of *IKZF1*^{plus} lesions at diagnosis, failure to achieve MRD negativity, and *ABL1* mutations, particularly the T315I mutation.[47]

As a recommendation, allo-SCT allocation should depend on biological and practical aspects: MRD persistence, evaluated by *BCR*::*ABL1* and possibly also by immunoglobulin/T-cell receptor (*IG/TR*) gene rearrangement (see case 5), after 3 months of treatment or recurrence at any time, and the presence of additional genomic lesions, particularly *IKZF1*^{plus} lesions, are clear indications for an allograft. Similarly, among practical aspects, drug availability and the possibility of performing refined MRD testing and genomic characterization are important players in driving transplant decision (Figure 1).

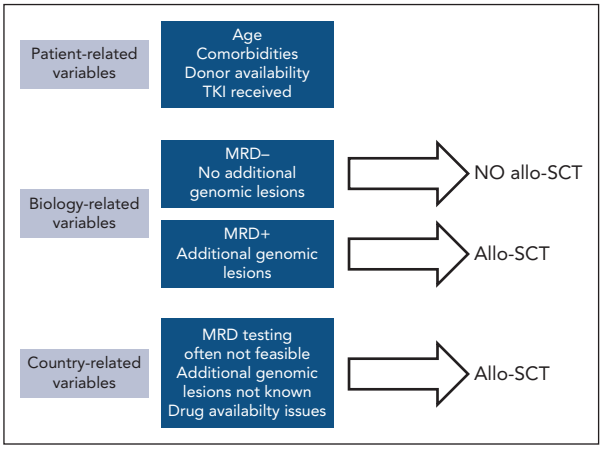

Figure 1. Schematic representation of features affecting allo-SCT allocation.

Clinical case 2: CNS relapse

A 67-year-old man was admitted in October 2019 for persistent abdominal pain and hepatosplenomegaly. An FBC showed Hb of 9.5 g/dL, WBCs of 30.1 × 10^9/L, PMNs of 9.6 × 10^9/L, lymphocytes of 20 × 10^9/L, and platelets of 65 × 10^9/L. Remote history was positive for diabetes, laminectomy, aortic valve replacement chronic gastritis, and polypectomy. The patient was diagnosed with p210 Ph^+ ALL with an *IKZF1* deletion; he started with imatinib, steroids, and medicated lumbar punctures. After 3 months, he was switched to dasatinib for molecular disease persistence (*ABL1* mutational screening was negative) and continued dasatinib for 9 months, when he developed pulmonary hypertension and was restarted on imatinib. Fifteen medicated lumbar punctures (methotrexate [MTX] and steroids) were administered. After 13 months, the patient showed a molecular increase; a diagnostic lumbar puncture documented a full-blown central nervous system (CNS) relapse. He received chemotherapy with intermediate-dose MTX and cytosine arabinoside (ARA-C), 8 additional triple-medicated lumbar punctures (triple intrechal therapy: MTX, ARA-C, and steroids), and ponatinib, achieving a CNS clearance. After 6 months, the patient experienced an atrial fibrillation, stopped ponatinib, and received inotuzumab for a further molecular increase, achieving a molecular negativity.

Discussion of case 2

CNS relapse is an emerging issue, mostly, though not exclusively, in the chemo-free era; firstly, because survival has improved, and isolated relapses are more frequent; and secondly, because CNS penetration with targeted compounds is less effective. In the D-ALBA trial, 4 of 9 relapses occurred at the CNS, and after rescue treatment, 3 patients are alive in second CHR.[34,35] Similarly, in the updated MDACC frontline trial combining ponatinib and blinatumomab, 3 isolated CNS relapses were observed.[44] The rate of CNS relapses was possibly lower in the recently published randomized phase 3 trial using nilotinib in combination with intensive vs nonintensive treatments (omission of high-dose ARA-C), in which a CNS relapse was recorded in each arm (1/11 in the intensive arm and 1/24 in nonintensive arm).[22]

How to treat CNS relapse is an open question; a minimum of 12 medicated lumbar punctures is strongly recommended. Blinatumomab and inotuzumab are not indicated because of the low CNS penetration; both compounds can, however, be administered after CNS clearance.[48,49] Chimeric antigen receptor T cells (CAR-Ts) could be a valuable option. Qi et al[50] evaluated their efficacy in 48 heavily pretreated patients with CNS involvement; 93.7% had a CNS-3 status. A CHR/CHR with incomplete recovery was achieved in 85.4% of cases, with a median OS of 16 months; neurologic events, recorded in 37.5% of cases, were manageable.

In cases with no other options available, high-dose chemotherapy and/or cranial irradiation still represent an effective strategy, which must be consolidated with transplant.

To prevent CNS, in the GIMEMA ALL2820 trial, the number of lumbar punctures was increased to 15 with triple intrechal therapy and 18 in the case of CNS involvement at diagnosis.[47] This strategy is being applied also by the MDACC. The aim is to counterbalance the omission of systemic chemotherapy.

Finally, efforts are ongoing to identify signatures predictive of CNS involvement: Sapienza et al[51] reported a molecular profiling associated with CNS involvement; 2 genes, *CENPV* and *E2F*, were downregulated, and 3, *RNF157*, *LGMN*, and *RIPOR2*, were upregulated in CNS^+ cases. Although these findings need further validations, they represent an important milestone to predict CNS localization in ALL.

Clinical case 3: Ph^+ ALL relapse in the targeted-immunotherapy era

A 49-year-old man was admitted in November 2021 after a period of asthenia. An FBC showed Hb of 9.1 g/dL, WBCs of 217 × 10^9/L, and platelets of 74 × 10^9/L. The patient was diagnosed with p190 *BCR::ABL1* B-common ALL and an $IKZF1^{plus}$ genotype. At day 28 of ponatinib,[47] he was in CHR with low MRD levels; at day 70, a 1-log increase and a *T315I* mutation were documented. The patient underwent a cycle of blinatumomab, which was followed by a hematologic relapse. He received 2 inotuzumab cycles, obtaining a CMR, and underwent allografting. On day +38, a second full-blown relapse was documented. The only remaining option was represented by CAR-T (KTE-X19). At FBC recovery after high-dose MTX and ARA-C, the patient underwent apheresis; CAR-T expansion failed, and 2 further aphereses were attempted. The third was successful, but the patient died of pneumonia the day before receiving the CAR-T product.

Discussion of case 3

Management of relapse in the era of targeted-immunotherapy treatment is challenging (Figure 2). The efficacy of blinatumomab for relapsed/refractory (R/R) Ph^+ ALL was reported in the ALCANTARA study[52]; after 2 cycles, a CHR was obtained in 36% of patients, and 88% achieved a MRD negativity. A transplant was feasible in 44% of patients. The median OS was 7.1 months, with differences among responders and nonresponders (not reached vs 3.9 months). In the final report (follow-up, 16.1 months), the median RFS and OS were 6.8 and

9.0 months, respectively, and a better OS probability was confirmed for responders.[53]

Inotuzumab ozogamicin is an anti-CD22 antibody conjugated to calicheamicin approved for R/R patients.[54] Stock et al[55] focused on Ph$^+$ ALL cases enrolled in both the 1010 and INOVATE trials. Of the 16 and 14 patients enrolled, CHR rates were 56% and 73%, respectively. Although OS and progression-free survival were not improved by inotuzumab, transplant feasibility was significantly higher in inotuzumab-treated patients (41%), ultimately prolonging progression-free survival and indicating its effectiveness as a bridge to transplant.

Asciminib, an ABL myristoyl pocket (STAMP) inhibitor, restores the negative regulator activity of ABL1.[56-58] It is the first *BCR::ABL1* TKI not targeting the adenosine triphosphate–binding site and is approved for pretreated patients with CML; resistance is induced by ABCB1 and ABCG2 overexpression and *Y139D* and *T315I* mutations.[59,60] Few data are available in Ph$^+$ ALL. Zerbit et al[61] described a heavily pretreated R/R patient who achieved and maintained a CHR and a deep molecular response with ponatinib and asciminib for 17 months. In another report, a 28-year-old man treated with inotuzumab, ponatinib, and asciminib achieved a CHR and a deep molecular response and received CAR-Ts.[62]

Furthermore, a phase 1 study tested the combination of asciminib plus dasatinib for newly diagnosed patients with Ph$^+$ ALL and CML blast crisis, establishing the recommended phase 2 dose at 80 mg/d. Molecular responses were achieved in 43% of patients with ALL.[43] As a step forward, blinatumomab is also being incorporated in this scheme (NCT03595917).

CAR-Ts represent a new frontier. In adults (aged ≥18 or 26 years in the United States and Europe, respectively), the only approved product is KTE-X19, investigated within the ZUMA-3 trial: 15 of the 55 patients who received infusion (27%) were Ph$^+$. A CHR was achieved in 71% of patients, and the Ph chromosome had no impact on response, RFS, and OS.[63]

Finally, subcutaneous (s.c.) blinatumomab was tested in a phase 1b trial using 2 different doses/schedules (250 μg/500 μg and 500 μg/1000 μg) in R/R cases[64]; 14 and 13 patients were treated with the lower and higher doses, respectively. CHR and CMR were observed in 85.7% and 92.3% and in 75% and 100% of patients with the lower and higher doses, respectively, comparing favorably with the Tower study,[65] due to the higher concentration peak obtained with the s.c. formulation. Serious adverse and adverse events were reported in 64.3% and 76.9% of patients and in 21.4% and 23.1% of patients in the 2 cohorts, respectively.

Clinical case 4: can we stop TKI in Ph$^+$ ALL?

An 85-year-old woman was admitted in March 2016 for fatigue, tachycardia, and asthenia. An FBC showed Hb of 9.5 g/dl, WBCs of 2.1 × 10^9/L, PMNs of 0.6 × 10^9/L, lymphocytes of 0.9 × 10^9/L, and platelets of 70 × 10^9/L. A diagnosis of p190 *BCR::ABL1* B-common ALL was made. Given the age, she was enrolled in the GIMEMA ponatinib protocol[30] and achieved a CMR at day +28. After 3 months, ponatinib was stopped due to a grade 3 hypertension and restarted a week later at 15 mg for a week and then at 30 mg. Treatment continued for 21 additional months at the same dose, then reduced to 15 mg for 10 months. The patient experienced 2 episodes of atrial fibrillation. Because she was in persistent CMR, treatment was discontinued. The patient died of senectus 4 years later, at the age of 92 years, in CMR.

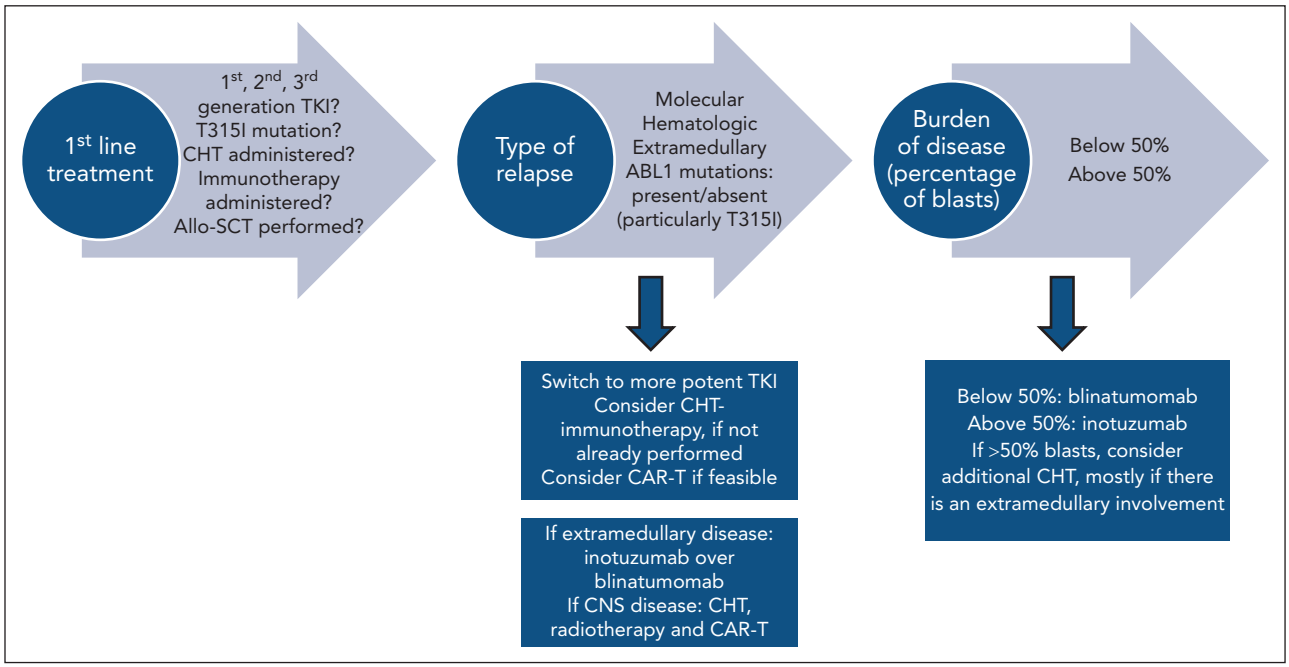

Figure 2. Algorithm of treatment decisions at relapse. CHT, chemotherapy.

Discussion of case 4

TKI discontinuation is a reality in CML, with ~50% of patients remaining in prolonged remission without treatment; TKI rechallenge is feasible and effective for patients showing molecular or clinical recurrence.[66,67] European Society of Medical Oncology, European LeukemiaNet, and National Comprehensive Cancer Network guidelines agree that a deep and persistent molecular response after TKI treatment for 3 to 5 years and no history of blast crisis are required.[68-70]

In Ph^+ ALL, TKI discontinuation is not clinical practice. Samra et al[71] reported the long-term outcomes of 9 patients who discontinued after receiving hyper-CVAD–based treatment with imatinib (n = 4), dasatinib (n = 4), and ponatinib (n = 1). The median treatment duration was 70 months, and the median deep molecular response was 47 months. After discontinuation, 3 patients experiencing a molecular relapse were successfully re-treated. We identified 14 patients who discontinued TKI (imatinib, n = 7; dasatinib and ponatinib, n = 3; nilotinib, n = 1) and received virtually no chemotherapy: all cases but 1 had achieved a molecular response. After a median treatment time of 57.5 months and a median time from discontinuation of 20.5 months, 9 patients were in remission, whereas 5, including the patient not in molecular remission, experienced a relapse (2 molecular and 3 hematologic). TKI rechallenge led to a hematologic and molecular response in 4 of 5 cases.[72]

Although both studies do not identify clinical and molecular factors associated with safe treatment discontinuation, they support the feasibility of stopping TKIs in Ph^+ ALL, presumably in those cases with an early and sustained molecular remission and after 5 years of TKI treatment. This will presumably become a reality, given the long-term results obtained at all ages with TKI plus immunotherapy and the use of refined molecular MRD monitoring techniques.

Clinical case 5: low positive *BCR::ABL1* and IG/TR negative MRD levels

A 62-year-old man was admitted in March 2018. An FBC showed Hb of 8.9 g/dL, WBCs of 24.1 × 10^9/L, PMNs of 5.4 × 10^9/L, lymphocytes of 14.4 × 10^9/L, and platelets of 140 × 10^9/L. Remote records documented a colon adenocarcinoma 14 years earlier. He was diagnosed with p190 *BCR::ABL1* common ALL with an *IKZF1* deletion. He was enrolled in the D-ALBA trial.[34] Low MRD levels were recorded at the end of induction. He received 5 blinatumomab cycles and achieved a molecular response after cycle 2. Due to pleural effusions, he was switched to imatinib. A molecular evaluation 2 months after the last blinatumomab showed a slight MRD increase. The patient was enrolled in the GIMEMA LAL2013 phase 1 trial (NCT02185781), based on the infusion of autologous in vitro expanded natural killer cells in patients with MRD^+ Ph^+ ALL.[73] After 5 infusions, a molecular response was recorded. Twenty-eight months from diagnosis, a colectomy was performed for a polypoid lesion, requiring antibiotic treatment and a colostomy. The patient is in continuous CHR 72 months later on imatinib treatment, with low *BCR::ABL1* MRD levels, whereas *IG/TR* monitoring is persistently negative.

Discussion of case 5

There is growing interest in the relapse predictivity of low MRD molecular levels. In pediatric ALL, the role of dual MRD targeting monitoring (by *BCR::ABL1* and *IG/TR*) was investigated. Cazzaniga et al[74] reported the results of dual-targeted MRD monitoring in children enrolled in the EsPhALL trial. The concordance between the 2 targets was 69%, with *BCR::ABL1* MRD levels being persistently more positive; in a few cases, a *BCR::ABL1* positivity was detected in cell-sorted non-ALL cells, suggesting a multilineage involvement. Similarly, Kim et al[75] reported 38% of discordant cases in the GRAAPH-2014 trial. Cell sorting showed a *BCR::ABL1* signal also in leukemic cells (clonal hematopoiesis). Finally, Zuna et al[76] reported a high degree of discordance between the 2 markers (*BCR::ABL1* evaluated using patient-specific genomic *BCR::ABL1* fusions) and classified patients into "typical ALL" and "CML like." Discordances were mostly detected in CML-like cases, with fluorescence in situ hybridization being helpful in ruling out the cell of origin of discordant cases[77]; no differences in outcome were observed among these 2 subsets, and MRD had an impact at TP2 in typical ALL but not in CML-like cases. Concerning multilineage involvement, Kim et al[78] reported 3 groups: C1 early-Pro, C2 inter-Pro, and C3 late-Pro, with early-Pro cases showing more immature features and enrichment for *HBSL1* and *EBF1* deletions, whereas the other subsets harbored *IKZF1*, *CKDN2A*, and *PAX5* deletions. Bastian et al[79] distinguished 2 main clusters: cluster C1, displaying multilineage features and *HBS1L* deletion enrichment; and cluster C2 being B-lymphoid oriented with *IKZF1*, *CKDN2A*, and *PAX5* deletion overrepresentation. Although genetic findings are consistent, they are not yet informative on the outcome/management of Ph^+ ALL, particularly in the immunotargeted era, with the exception of those from GRAAPH-2014 findings,[75] in which clonal hemopoiesis $(CH)^+$ patients had a lower cumulative incidence of relapse, also when censoring for allo-SCT, suggesting a greater prognostic impact of IG/TR, which is currently being investigated by next-generation sequencing methods (by ClonoSeq in the United States or within the academic setting after the Euro-MRD guidelines in Europe). Similar findings were previously reported by Short et al[80] on 44 patients evaluated at different time points and treated with various TKIs. They nonetheless pave the way to new areas of research, which will shed light on the mechanisms of resistance.

All in all, more sound data are awaited to provide more definitive conclusions. Lastly, but not less important, the MRD trajectory, rather than a single time point, might appear more informative on long-term outcome.

Conclusion

Ph^+ ALL represents the paradigm of precision medicine. The pivotal success was initially achieved with imatinib, a proof of principle of the efficacy of targeted therapy in this disease. Second- and third-generation TKIs have improved outcome, thus questioning the necessity of systemic chemotherapy in induction and also in consolidation, given the results obtained after the addition of immunotherapy, allowing for the development of the concept of a chemotherapy-free approach. New issues have arisen, such as the role of allograft in first CHR, the

possibility of stopping TKIs, and the difficulties of treating relapsed patients in the immune-targeted era. Concerning allograft, refined genetic characterization and MRD monitoring within clinical trials will definitely provide a personalized algorithm for transplant allocation. TKI discontinuation will probably become a reality, again with the support of a refined molecular workup and a strict interaction between the hematologist and the patient. It will also possibly be corroborated by immunotherapy, eliciting its effect also on the immune compartment.[81] Finally, relapse, although much less frequent, remains the most detrimental event: new compounds, for example, CAR-T cells, s.c. blinatumomab, and asciminib, open promising avenues. Efforts are ongoing to define specific treatment algorithms.

Acknowledgments

The authors thank Associazione Italiana per la Ricerca sul Cancro 5 × 1000, Special Program Metastases (21198), Milan, Italy (R.F.), Progetti di Rilevante Interesse Nazionale Italia, 2022EC7LA project (S.C.), and Finanziamento Medi Progetti Universitari 2021 (Sapienza University of Rome [S.C.]) for their support.

Authorship

Contribution: S.C. and R.F. wrote and critically revised the manuscript.

Conflict-of-interest disclosure: The authors declare no competing financial interests.

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Footnote

Submitted 29 May 2024; accepted 13 August 2024; prepublished online on *Blood* First Edition 20 August 2024. https://doi.org/10.1182/blood.2023023152.

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