REVIEW ARTICLE

Dan L. Longo, M.D., *Editor*

Philadelphia Chromosome–Positive Acute Lymphoblastic Leukemia

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The Philadelphia chromosome (Ph) was the first cytogenetic abnormality associated with a human cancer, chronic myeloid leukemia (CML).[1] The rearrangement between chromosome 9 and chromosome 22, a hallmark of the disease, contains the *BCR-ABL1* fusion gene, which encodes for a constitutively activated tyrosine kinase signaling protein that sustains the leukemia.[2-7] In the late 1990s, the first tyrosine kinase inhibitor (TKI), imatinib, was developed, which changed the natural history of CML.[8] Before TKIs were available, patients with CML had a median overall survival of about 3.5 years. With TKIs, patients have a life expectancy similar to that of the general population, without chemotherapy and allogeneic stem-cell transplantation.[9,10] The unique story of the Ph chromosome and the clinical implications are shown in Figure 1.

The Ph chromosome can also be found in patients with acute lymphoblastic leukemia (ALL). Although rare in children (incidence, 2 to 5%), this entity (Ph-positive ALL) represents the most common genetic subgroup in ALL in adults, with an overall incidence of 20 to 25%.[11,12] The incidence increases with age and accounts for more than 50% of cases of ALL in patients who are older than 50 years of age (Fig. 2).[13]

For decades, Ph-positive ALL was considered the leukemia with the worst outcome, in both children and adults, because of the poor response to conventional multiagent chemotherapy.[14-16] Allogeneic stem-cell transplantation was the only chance for a cure, which was achievable in only a minority of patients because of older age and a poor response to conventional treatment. The scenario changed when the use of TKIs was extended from CML to Ph-positive ALL.

In this review, we discuss how TKIs have improved the outcome of Ph-positive ALL and how we foresee management of the disease in adults in the near future. In particular, we consider the current role of conventional chemotherapy and allogeneic transplantation, with a focus on the close interaction between clinic and laboratory that is necessary for good management of Ph-positive ALL in adults, including the elderly.

TKIs in the Frontline Management of Ph-Positive ALL

Before the introduction of TKIs, the response to systemic chemotherapy was limited, and the long-term survival rate for adults with Ph-positive ALL was low, in the range of 10 to 20%,[11,14-16] particularly for the many patients who could not undergo allogeneic transplantation. When TKIs were first used, they were added to chemotherapy regimens. The rates of hematologic remission and survival increased (Table 1),[17-47] but the combination was associated with notable toxic effects and deaths during induction.[17-26,28,30,33-35,39-42] The experience was similar in the

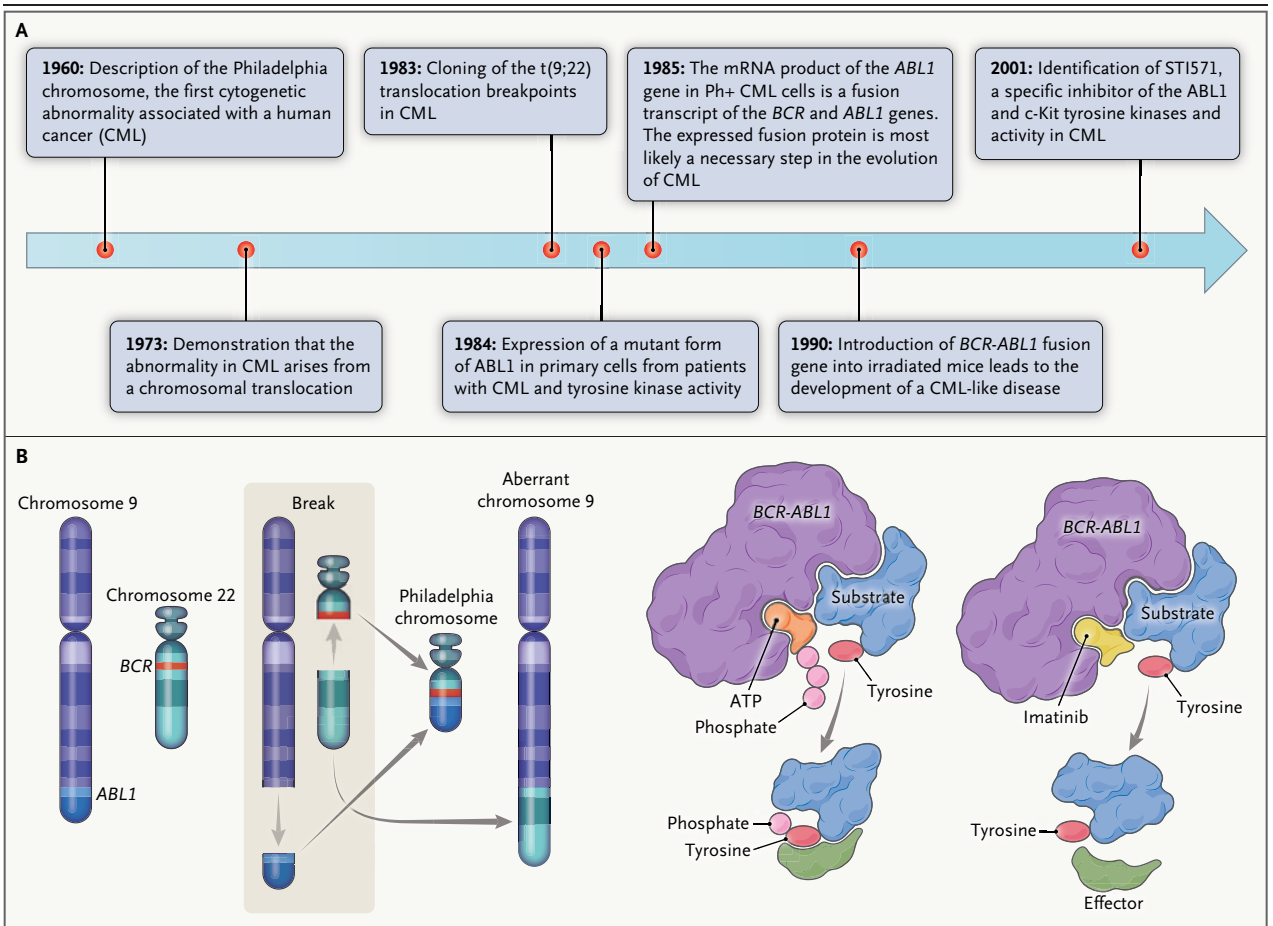

Figure 1. History and Genetic Features of the Philadelphia Chromosome and Mechanism of Action of Imatinib.

Panel A shows the timeline[1-8] from the discovery of the t(9;22) translocation to the development of imatinib (previously called STI571), the first tyrosine kinase inhibitor. Panel B shows the breakpoint and various isoforms, as well as the mechanism of action of imatinib. CML denotes chronic myeloid leukemia, mRNA messenger RNA, and Ph+ Philadelphia chromosome–positive.

LAL0904 study conducted by GIMEMA (Gruppo Italiano Malattie Ematologiche dell'Adulto), in which imatinib was initially added to the chemotherapy backbone, and a switch was made to a sequential protocol, with imatinib followed by chemotherapy.[31]

These findings prompted the design of clinical trials in which TKIs were administered with reduced-intensity chemotherapy, an approach that led to equally satisfactory clinical results with fewer side effects. Since 2004, in all GIMEMA multicenter frontline trials in Italy, a TKI (first, second, or third generation) has been used in induction (plus glucocorticoids and central nervous system prophylaxis), without the addition of systemic chemotherapy.[30,31,35-37,44] This change in practice has required identification of *BCR-ABL1* within 1 week after diagnosis, which is feasible in clinical trials with centralized biologic testing. Postinduction treatment varied among the protocols.[31,36,37] These studies showed that induction therapy with a TKI alone, plus glucocorticoids and central nervous system prophylaxis, was associated with a complete hematologic remission in 94 to 100% of all adults with Ph-positive ALL, with virtually no deaths during induction. Moreover, many of these studies did not impose an upper age limit for eligibility. The open question was how best to manage the postinduction phase. Most patients received systemic chemotherapy, with or without allogeneic transplantation.

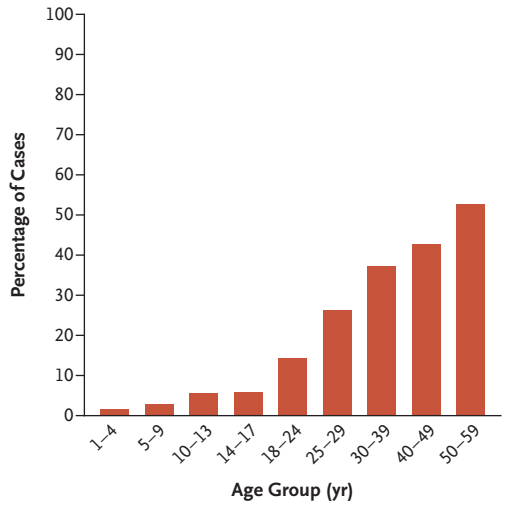

Figure 2. Incidence of the *BCR-ABL1* Rearrangement in Philadelphia Chromosome–Positive Acute Lymphoblastic Leukemia, According to Age Group.
The data are from Chiaretti et al.[13]

Over the years, monitoring of measurable residual disease (MRD; previously known as minimal residual disease) has emerged as a key element in the management of ALL, including Ph-positive ALL, for a more precise definition of the depth of the response to treatment. It is well recognized that to eradicate the disease and to cure patients with ALL, a sustained MRD-negative status for bone marrow must be the primary end point of treatment.[48] MRD can be monitored by means of flow cytometry, but most multicenter groups use a real-time quantitative polymerase-chain-reaction (RQ-PCR) assay because of the specific *BCR-ABL1* fusion marker in Ph-positive ALL. These tests are often carried out in central laboratories (see below). Patients with no MRD fare better[48-54]; a negative status before transplantation has a good effect on the outcome.[55,56]

IMPROVING THE RESULTS OBTAINED WITH INDUCTION WITH TKIS

TKIs have greatly improved induction treatment, and more potent TKIs than imatinib — dasatinib and ponatinib — are currently being tested in the randomized phase 3 study, PhALLCON (ClinicalTrials.gov number, NCT03589326). In using TKIs, a number of considerations should be taken into account. First, most patients with Ph-positive ALL are elderly, and many are unfit for multiagent chemotherapy and transplantation. Second, the depth of response to frontline therapy needs to be increased further to reduce the risk of relapse. Third, MRD can be monitored more precisely with molecular techniques. Fourth, immunotherapy is witnessing a new era in the management of cancer, including hematologic cancers,[57] and different monoclonal antibodies are active in B-lineage ALL.[58-60] Fifth, *BCR-ABL1* activity is critical for the immunogenicity of CML cells.[61] Finally, in patients with CML, the host immune system can be boosted through interferon alfa and TKI treatment,[62] an approach that may also extend to Ph-positive ALL.

In this context, the bispecific monoclonal antibody blinatumomab has gained attention.[58] Refinement of the techniques used to produce monoclonal antibodies has led to the development of antibodies that target two antigens (Fig. 3). Blinatumomab targets CD19, an antigen present in virtually all B-lineage ALL cases, and CD3, which is present on all T lymphocytes. As shown in Figure 3, blinatumomab binds to B-lineage ALL cells, and the antileukemic effect is exerted through the immune system by activating host T cells.[63] This is important because many effector T cells are present, particularly in the context of persistent or recurrent MRD, making blinatumomab a very attractive prospect for improving the response to TKIs in Ph-positive ALL, with or without chemotherapy.

This was the rationale behind the design of GIMEMA LAL2116 D-ALBA, a phase 2 study that evaluated frontline treatment of Ph-positive ALL in adults, with no upper age limit.[37] It was a trial of chemotherapy-free induction and consolidation treatment based on the use of the second-generation TKI dasatinib plus glucocorticoids, followed by at least two cycles of blinatumomab and additional dasatinib. At the end of the induction phase, 98% of patients had a hematologic remission, and 29% had a molecular response (a complete molecular response or a response with nonquantifiable disease [i.e., disease below the threshold of quantification defined in the EuroMRD Consortium guidelines[64,65]]). The rate of molecular response, the primary end point of the study, increased to 60% after two

Table 1. Trials of Tyrosine Kinase Inhibitors (TKIs) for Frontline Treatment of Philadelphia Chromosome–Positive Acute Lymphoblastic Leukemia.*

Study Group and Regimen	No. of Patients	Age	CHR	Molecular Response†	Disease-free Survival	Overall Survival	Allo-SCT Allocation
		median (range)			*percent*		
First-generation TKI							
GMALL[17]	92		96				
Imatinib + CHT, alternating regimen	47	46 yr (21–65)		26 after cycle 2 of induction	52 at 2 yr (EPR)	36 at 2 yr	77
Imatinib + CHT, concurrent regimen	45	41 yr (19–63)		27 after cycle 2 of induction	61 at 2 yr (EPR)	43 at 2 yr	77
GMALL[18]: imatinib vs. CHT (induction)	55						
Imatinib	28	66 yr (54–79)	96	5.6×10^{-5} at wk 4†	29.5 at 18 mo	57 at 18 mo	NA
CHT	27	68 yr (58–78)	50	3.2×10^{-4} at wk 4†	35 at 18 mo	41 at 18 mo	
GRAALL[19]: imatinib + CHT	30	65.8 yr (58–78)	72	NA	58 at 1 yr (RFS)	66 at 1 yr	NA
GRAALL[20]: imatinib + CHT	45	45 yr (16–59)	96	29 after induction	51 at 18 mo	65 at 18 mo	48
GRAALL[21] (updated): imatinib + CHT	45	45 yr (16–59)	96	29 after induction	44 at 4 yr	52 at 4 yr	53
GRAALL[22]: group 1, imatinib + low-dose CHT; group 2, imatinib + CHT	268	47 yr (18–59)	Group 1: 98 Group 2: 91	Group 1: 28.6 Group 2: 22.6 After cycle 2 of induction	54 at 5 yr	45 at 5 yr	63
JALSG[23]: imatinib + CHT	80	45 yr (15–64)	96	NA	60 at 1 yr (EFS)	76 at 1 yr	61
JALSG[24] (updated): imatinib + CHT	99	45 yr (15–64)	97	NA	50 at 5 yr	43 at 5 yr	61
PETHEMA[25]: imatinib + CHT	30	44 yr (8–62)	90	21 after induction	30 at 4 yr	30 at 4 yr	53
PETHEMA[26]: imatinib + low-dose CHT	29	38 yr (NA)	100	39 after induction	63 at 2 yr (EFS)	NA	90
NILG[27]: imatinib + CHT	59	45 yr (20.4–66)	92	25 at wk 10	39 at 5 yr	38 at 5 yr	57
Canada[28]: imatinib + CHT	32	46 yr (18–60)	94	10 after induction	50 at 3 yr (EFS)	53 at 3 yr	50
UKALL[29]: imatinib + CHT	175	42 yr (16–64)	92	NA	50 at 4 yr (RFS)	38 at 4 yr	46
GIMEMA[30]: imatinib only	29	69 yr (61–83)	100	4 after induction	48 at 1 yr	74 at 1 yr	NA
GIMEMA[31]: imatinib followed by CHT	49	45.9 yr (16.9–59.7)	100	NA	50 at 3 yr	69 at 3 yr	
MDACC[32] (updated): imatinib + CHT	45	51 yr (17–84)	93	20 after induction	43 at 5 yr	43 at 5 yr	18

Second-generation TKI							
MDACC[33]: dasatinib + CHT	35	52 yr (21–77)	94	18 after induction	60 at 2 yr	64 at 2 yr	12
MDACC[34] (updated): dasatinib + CHT	72	55 yr (21–80)	96	65 at any time point	44 at 5 yr	46 at 5 yr	17
GIMEMA[35]: dasatinib	53	53.6 yr (23.8–76.5)	100	15 after induction	51 at 20 mo	69 at 20 mo	NA
GIMEMA[36]: dasatinib followed by CHT	60	41.9 yr (18.7–59.1)	97	18 after induction	47 at 5 yr	56 at 2 yr	37
GIMEMA[37]: dasatinib followed by blinatumomab	63	54 yr (24–82)	98	29 at induction, 60 after blinatumomab	88 at 18 mo	95 at 18 mo	38
EWALL[38]: dasatinib + low-dose CHT	71	69 yr (59–83)	96	11 at first time point	28 at 5 yr (RFS)	36 at 5 yr	20
U.S. intergroup[39]: dasatinib + CHT	60	44 yr (20–60)	90	NA	62 at 3 yr	69 at 3 yr	43
KAALLWP[40]: nilotinib + CHT	90	47 yr (17–71)	91	86 at any time point	72 at 2 yr (HRFS)	72 at 2 yr	63
EWALL[41]: nilotinib + low-dose CHT	36	66 yr (55–85)	97	NA	NA	NA	NA
Third-generation TKI							
MDACC[42]: ponatinib + CHT	37	51 yr (27–75)	100	26 at CHR	81 at 2 yr (EFS)	80 at 2 yr	24
MDACC[43] (updated): ponatinib + CHT	65	47 yr (39–61)	100	83 at any time point	67 at 5 yr	71 at 5 yr	20
INCB84344–201 (formerly GIMEMA 1811)[44]: ponatinib	44	66 yr (26–85)	86 at wk 24	40 at wk 24	Median duration of CHR not reached	Median OS not reached	NA
MDACC[45]: ponatinib + blinatumomab	24	60 yr (34–83)	100	64 at cycle 1	NA	95 at 14 mo	0
PETHEMA[46]: ponatinib + CHT	30	49 yr (19–59)	100	47	97 at 2 yr	97 at 2 yr	87
DFCI[47]: dasatinib + asciminib	12	66 yr (53–86)	100	NA	NA	NA	NA

* Allo-SCT denotes allogeneic stem-cell transplantation, CHR complete hematologic remission, CHT chemotherapy, EFS event-free survival, EPR estimated probability of remission, HRFS hematologic relapse–free survival, NA not available, OS overall survival, and RFS relapse-free survival.

† The molecular responses are shown as percentages except for GMALL[18] (imatinib vs. CHT [induction]), for which molecular response is shown as the BCR-ABL transcript level (represented as the ratio of *BCR-ABL1* to *GAPDH* [the glyceraldehyde-3-phosphate dehydrogenase gene]).

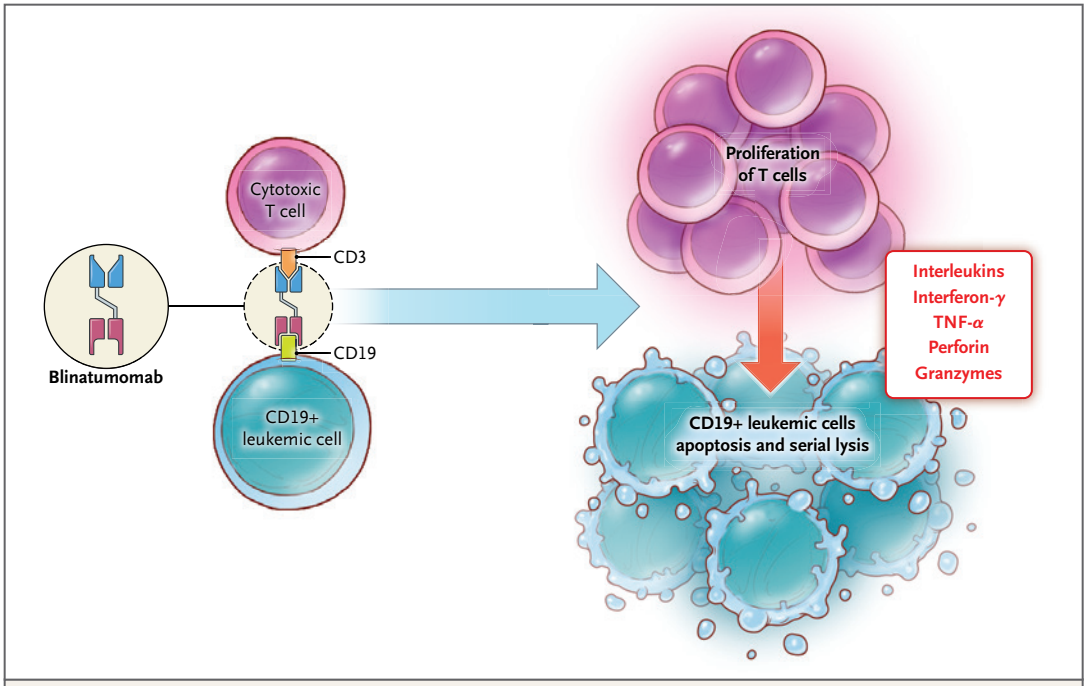

Figure 3. Mechanism of Action of the Bispecific Monoclonal Antibody Blinatumomab.
TNF-α denotes tumor necrosis factor α.

cycles of blinatumomab. The rate increased further after additional cycles of blinatumomab. The overall and disease-free survival rates were 95% and 88%, respectively, at 18 months. The presence of additional genetic abnormalities at diagnosis (*IKZF1*^{plus} [i.e., *IKZF1* deletion plus additional genetic aberrations]) was a negative prognostic factor,[37] as previously reported.[66,67] Postconsolidation treatment, including transplantation, was left open; most patients who received allografts had MRD. The positive outcome of the protocol has been confirmed with estimated disease-free and overall survival rates of 71% and 80%, respectively, at 3 years.[68] Patients with no evidence of MRD still remain free from events. In patients who underwent allogeneic transplantation (29 patients [50%]; median age, 52 years), transplant-related mortality was low (10%), possibly because of the chemotherapy-free induction–consolidation strategy.[68] The host immune status was investigated after different cycles of blinatumomab: a progressive increase in CD3 and CD8 T cells, natural killer cells, and natural killer T cells was documented, pointing to the possible role of an activated immune compartment in controlling the disease in the absence of chemotherapy.[36,69]

These results are the basis for the current GIMEMA LAL2820 protocol (NCT04722848), a phase 2 randomized study of total therapy for Ph-positive ALL in adults. The experimental treatment consists of ponatinib followed by blinatumomab. Ponatinib is a third-generation TKI that is effective against the T315I *ABL1* mutation, which confers resistance to first- and second-generation TKIs. The control treatment is the combination of imatinib (the only TKI approved worldwide for the frontline treatment of Ph-positive ALL) and chemotherapy. Randomized assignments to the experimental and control groups are made in a 2:1 ratio, and a crossover is planned for patients in the control group who have a poor treatment response. This study will assess whether systemic multiagent chemotherapy can be omitted from induction–consolidation treatment and whether a proportion of cases can be managed without systemic chemotherapy and allogeneic transplantation. Among patients without additional unfavorable genetic abnormalities (e.g., *IKZF1*^{plus}) at diagnosis, those

Table 2. Ongoing and Completed Trials of Treatment for Relapsed or Refractory Disease.*

Study Group or Trial Name and Drug	No. of Patients	Age	Hematologic Response	Molecular Response	Overall Survival	Allo-SCT
		median (range)	%	%		%
ALCANTARA[70]: blinatumomab	45	55 yr (23–78)	36	86	7.1 mo	44
INOVATE[71]: inotuzumab vs. SOC						
Inotuzumab	38	NA	66	84	8.7 mo	41
SOC	27	NA	55	33	8.4 mo	19
MDACC[72]: inotuzumab + bosutinib	16	62 yr (19–74)	87	56	13.5 mo	33
French groups[73]: ponatinib with or without CHT	29	55 yr (21–78)	79	13	9.9 mo	35
French groups[74]: ponatinib + blinatumomab	26	58 yr (18–81)	96	88	41%	31
MDACC[45]: ponatinib + blinatumomab	14	38 yr (24–61)	91	82 at cycle 1	39%	29
MDACC[75]: ponatinib + venetoclax + dexamethasone	9	37 yr (26–73)	55	44	72% at 6 mo	None
China[76]: ponatinib + venetoclax + dexamethasone†	19	42 yr (22–74)	68	47	NA	35

* SOC denotes standard of care.
† The regimen was administered only in patients with T315I mutations.

who have a deep and sustained molecular response and no evidence of *ABL1* mutations on MRD-positive cells during induction–consolidation therapy will not undergo chemotherapy and transplantation but will undergo only close monitoring for MRD.

The M.D. Anderson Cancer Center is investigating the combination of ponatinib and blinatumomab administered simultaneously as frontline therapy. At a median follow-up of 9 months, the results are promising, with overall and event-free survival rates of 95%.[45] A long-term comparison between the two trials may provide insights into the advantage of the simultaneous treatment strategy over the sequential strategy.

MANAGEMENT OF RELAPSE

Despite the improvements discussed above, a proportion of patients still have a relapse, and the management of relapse is challenging (Table 2).[70-76] Evaluations for MRD are increasingly common, particularly for patients enrolled in multicenter clinical trials. Patients should be closely monitored for MRD in order to identify an early disease recurrence and prevent a full-blown relapse. The therapeutic options for relapse have improved now that TKIs play a primary role in the frontline treatment and less (or no) chemotherapy is used in induction therapy. On the basis of phase 2 and 3 studies, two monoclonal antibodies — blinatumomab and inotuzumab ozogamicin — have been approved for the management of relapse. Blinatumomab is approved for the treatment of adults and children with relapsed or refractory B-cell ALL and for patients in a first or second complete remission with MRD of 0.1% or more. Since most patients will not have received blinatumomab as part of their frontline treatment, this is probably the best option for managing a recurrence of disease,[70] particularly at the level of MRD,[77] possibly in combination with ponatinib.[45,74] Inotuzumab, a CD22-directed antibody–drug conjugate approved for the treatment of relapsed or refractory adult B-lineage ALL (with ≥5% marrow blasts), has also shown efficacy in relapsed Ph-positive ALL.[71,72]

The third targeted strategy for treating recurrent disease is tisagenlecleucel, the first chimeric antigen receptor (CAR) T-cell immunotherapy approved for children and young adults with advanced ALL.[78] Promising results are emerging from other CAR T-cell products.[79-81] Very often, these treatments are used as a bridge to trans-

plantation, which remains the primary option for both patients with a full-blown relapse and those with persistent or recurrent MRD. As noted above, many patients are not eligible for an allogeneic transplant because of age, coexisting conditions, or both. This is an even greater issue with relapsed disease. An approach under investigation is to combine a TKI with venetoclax, a BCL2 inhibitor.[75,76]

Finally, central nervous system relapse is an emerging clinical issue. The following three factors account, in part, for this problem: the more frequent use of chemotherapy-free approaches, the broader use of flow cytometry to identify leukemic cells in the cerebrospinal fluid,[82] and the prolonged life expectancy for patients, leading to the identification of extramedullary relapses. In view of these factors, central nervous system prophylaxis should be provided continuously and appropriately during treatment.

ROLE OF ALLOGENEIC TRANSPLANTATION

Although allogeneic transplantation has been, and possibly still is, the standard approach to curative therapy for patients with Ph-positive ALL, its role is debated. Chalandon et al.[22] and Sasaki et al.[83] reported that transplantation did not improve survival for patients with no MRD. Since the depth of the treatment response is continually increasing, owing to the more potent TKIs and immunotherapy, it is likely that fewer patients will undergo transplantation as part of the frontline treatment program. However, patients in hematologic remission who have persistent MRD, with *IKZF1*^{plus} mutations, deleterious *ABL1* mutations, or both, should be considered for allogeneic hematopoietic stem-cell transplantation at the earliest convenience. The situation is different for patients with a relapse after a second hematologic (and possibly molecular) remission, who should undergo allogeneic transplantation as soon as possible. After transplantation, preemptive or prophylactic TKI maintenance therapy should be considered, particularly for patients with MRD. The duration of maintenance therapy has not yet been established and varies widely.[84,85]

Finally, autologous stem-cell transplantation might also have a role in the treatment of Ph-positive ALL, as long as the collected stem cells are molecularly negative for residual leukemic cells.[22,86] After transplantation, TKI maintenance therapy is strongly recommended.

ROLE OF LABORATORY TESTING IN MANAGEMENT

The improvements in the outcome of Ph-positive ALL originate from an understanding of the biology of the disease, including the role of *BCR-ABL1* mutations. Testing for such mutations should be performed within a few days after diagnosis in patients of all ages in order to implement TKI treatment as soon as possible. In most protocols for childhood and adult ALL, a 1-week period of glucocorticoid pretreatment is implemented, during which the genetic testing can be completed. Since a complex genetic profile at presentation is associated with an unfavorable prognosis,[37,66,67] these aberrations should be investigated.

MRD, which plays a key role in prognosis and treatment decisions, should be monitored in all patients at various time points. Although MRD can be assessed by means of flow cytometry, most groups rely on an RQ-PCR assay of *BCR-ABL1* because of its greater specificity and sensitivity. Efforts are under way to determine whether MRD assessment on the basis of immunoglobulin–T-cell receptor gene rearrangement may refine conventional *BCR-ABL1* monitoring, since in a proportion of cases, discordant results between the methods have been reported.[53,87] The ongoing GIMEMA LAL2820 trial is testing MRD with the use of both markers to determine their reliability. In some cases, MRD is detected but is not quantifiable by RQ-PCR. More sensitive technologies (e.g., droplet digital PCR) have been shown to be useful in refining MRD quantification in such cases, in both Ph-negative ALL[88] and Ph-positive ALL.[89] The presence of *BCR-ABL1* mutations, particularly the T315I mutation, confers resistance to first- and second-generation TKIs (imatinib, nilotinib, and dasatinib) but not to the third-generation TKI ponatinib. A search for *BCR-ABL1* mutations should therefore be performed if the leukemic clone is not cleared by ongoing treatment and at relapse. In the GIMEMA protocols, the search for mutations is carried out on MRD-positive samples, and it has been shown that blinatumomab clears the T315I mutation.[37]

An effort should be made to ensure that the

resources for this laboratory workup are in place and that it is performed in a timely manner to guide treatment decisions. In some parts of the world, cooperative study groups run multicenter national or international protocols that provide the best treatment options and the necessary laboratory tests at diagnosis and during clinical follow-up. In many multicenter networks, tests are carried out centrally in certified laboratories using standardized technologies. This approach allows a rapid turnaround time and a uniform characterization of diagnostic material and samples obtained for assessment of MRD, as well as central banking of biologic material.

Accessibility and Sustainability

A key question is whether an integrated clinical and laboratory evaluation, which is essential for good management of Ph-positive ALL, is feasible. In the real-world setting, several aspects are not guaranteed. First, if the Ph chromosome is not detected within a few days after the diagnosis of ALL, implementation of the best therapeutic approach will be delayed. Second, TKIs are not always available, at least not all of them, and lack of availability makes rapid use of a TKI and a switch of agents, when necessary, unfeasible. Third, *ABL1* mutations are often not properly investigated, and the methods used vary widely. Fourth, monitoring for MRD is too often not available or not adequately carried out. Fifth, the interval between a request for testing and the reported results is often too long to allow a timely therapeutic intervention. Finally, the availability of blinatumomab and inotuzumab is limited worldwide, and the availability of CAR T cells is even more limited.

The related question is cost coverage. In many countries, all or most of the components of a closely integrated clinical and laboratory evaluation, listed above, require out-of-pocket payments, thus limiting the evaluation to a minority of patients. This reality is difficult to accept, since Ph-positive ALL is an illuminating example of how a laboratory-driven approach coupled with treatment with effective drugs has completely changed the management and outcome of the disease. Survival rates have improved from about 10 to 20% before the introduction of TKIs to current rates of 50 to 60%. The improvement in survival is even more impressive for elderly patients, who respond as well as younger patients to TKIs and can be treated with oral TKIs alone. Paradoxically, if molecular information were used in a timely way to identify patients of all ages who had Ph-positive ALL, with TKI treatment administered immediately, the costs of treatment would be reduced in the long run. The oral treatment for such patients, which can largely be administered at home, would greatly limit the hospitalization time usually required for non–Ph-positive ALL cases and for unidentified Ph-positive cases. Finally, we are probably approaching a new era in which, like patients with CML,[90] patients with Ph-positive ALL who are in complete and prolonged remission may be able to stop taking TKIs,[91] which could ultimately lead to cost savings for health care systems by reducing the costs of drugs and the costs associated with long-term side effects.

Concluding Remarks and Future Prospects

The management of Ph-positive ALL changed greatly after the introduction of TKIs and keeps changing through an always more biologically driven approach to evaluation and treatment. Once it has been recognized that a patient carries *BCR-ABL1*, the immediate initiation of induction treatment with a TKI (plus glucocorticoids), with or without deintensified chemotherapy, results in a hematologic remission in virtually all patients, with a proportion of patients also having no MRD. Induction needs to be consolidated to increase the rates of negativity for MRD. This can be done with multiagent chemotherapy, transplantation, or both. Recent data indicate that very high rates of molecular response can be obtained with a TKI and the bispecific monoclonal antibody blinatumomab, without the need for systemic chemotherapy and allogeneic transplantation.[37,45] These results clearly throw into question the role of intensive chemotherapy and transplantation in the overall frontline management of Ph-positive ALL. We hope that the current studies will conclusively clarify whether many or most cases of Ph-positive ALL can be managed, and the patients cured, without systemic chemotherapy and transplantation. This would mean that with an improved understanding of the biology of Ph-positive ALL, the tools to stratify and precisely monitor the disease over

time, and the availability of targeted treatment and immunotherapy, the disease that for decades was the most lethal hematologic cancer might be controlled without systemic chemotherapy and transplantation. We already have the illuminating example of acute promyelocytic leukemia, which in many cases can be managed, and patients cured, with targeted treatment and without chemotherapy and transplantation, if it is identified at presentation through molecular testing.[92]

A final word on coronavirus disease 2019 (Covid-19), which has had an effect worldwide in the past 2 years. In Italy, which was heavily hit as of February 2020, particularly in the northern regions, few patients with Ph-positive ALL have been affected by Covid-19 and, more important, most cases of Ph-positive ALL continued to be managed, even during the peaks of the pandemic.[93,94] This is largely due to the national multicenter protocols in place and the fact that induction treatment in Italy is based on a TKI (plus glucocorticoids), without systemic chemotherapy. During the first peak of the pandemic (in the spring of 2020), the dasatinib–blinatumomab induction and consolidation protocol was open, meaning that for about 6 months, patients were receiving a combination of targeted and immune-based treatment. Thus, patients received no systemic chemotherapy and had very limited hospitalization time. Virtually all patients could continue their treatment during the pandemic, and no Covid-19–related deaths were recorded.

In 2010, the Philadelphia Chromosome Symposium: Past, Present, and Future commemorated the 50th anniversary of the discovery of the Ph chromosome and the extraordinary story of how it led to the successful treatment of CML with imatinib, the first TKI.[95] The symposium participants in 2010 could not have known what the future would bring. Only a few years later, most patients with CML would have a life expectancy similar to that of the normal population,[9,10] and now, we may succeed in managing many cases of Ph-positive ALL without systemic chemotherapy or allogeneic transplantation.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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