15 Management of Philadelphia Chromosome-Positive Acute Lymphoblastic Leukemia

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15.1 Introduction

Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph-positive ALL) comprises approximately 30% of ALL cases in adults, with a progressively increasing incidence with age. The Philadelphia chromosome is derived from a translocation between *ABL1* on chromosome 9 and a breakpoint cluster region (BCR) on chromosome 22, resulting in a BCR-ABL1 fusion gene [1]. The two most prominent BCR-ABL1 transcripts in ALL are the p190 and p210 transcripts, which are seen in approximately 75% and 25% of cases, respectively [2]. Ph-positive ALL is an aggressive disease with increased risk for central nervous system (CNS) involvement. [2] Prior to the advent of tyrosine kinase inhibitors (TKIs), treatment with standard chemotherapy resulted in complete remission (CR) rates of 50–60%, with long-term survival rate of less than 20% [2, 3]. Allogeneic hematopoietic stem cell transplant (HSCT) was the only potentially curative modality. Despite a potential for cure with HSCT, non-relapse mortality and relapse rates after transplant remain high, ranging from 30% to 50% [4]. Furthermore, a large proportion of patients with Ph-positive ALL are older and have significant comorbidities that further limit their ability to tolerate an intensive approach.

In recent years, the development and incorporation of TKIs through all stages of therapy have significantly improved survival outcomes in patients with Ph-positive ALL, resulting in 5-year survival rates as high as 70–80%. As TKIs have revolutionized the treatment of Ph-positive ALL by producing deep molecular remissions, the role of allogeneic HSCT has become less clear [5]. Novel treatment modalities including more potent TKIs, bispecific T-cell engagers (e.g., blinatumomab), drug conjugate monoclonal antibodies (e.g., inotuzumab ozogamicin), and chimeric antigen receptor T-cell (CAR-T) therapies have provided more options for patients with Ph-positive ALL. In this chapter, we will provide an overview of the current and future paradigms in the treatment of patients with Ph-positive ALL and discuss ongoing challenges that need to be addressed in order to further optimize clinical outcomes.

15.2 Prognostic Significance of Genomic and Chromosomal Aberrations

Genomic alterations are frequently seen in patients with Ph-positive ALL. The most common genomic aberration is deletion of *IKZF1*,

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S. H. Faderl et al. (eds.), *Acute Leukemias*, Hematologic Malignancies,
https://doi.org/10.1007/978-3-030-53633-6_15

which is seen in up to 84% of patients [6]. The *IKZF1* gene is located on chromosome 7q12 and encodes for the Ikaros transcription factor [6]. Deletion of exons 4–7 is the most frequent deletion that occurs along the *IKZF1* gene. Loss of exons 4–7 leads to the expression of dominant-negative Ikaros isoform, resulting in reduced tumor suppression function, and confers poor outcomes [7–9]. *CDKN2A/B* is located on chromosome 9p21, and deletions of these genes are present in approximately 40% of Ph-positive ALL cases [8]. Approximately 50% of patients with *IKZF1* deletion will have co-occurrence of *CDKN2A/B* and/or *PAX5 gene deletions.* Together, this genotype is often referred to as "IKZF1-plus" and *has* been associated with worse disease-free survival (DFS) and overall survival (OS) [9]. Another genomic aberration observed in approximately 10–20% of patients is the *BTG1* deletion*,* which has been associated with inferior DFS and remission duration [10]. *BTG1* is located on chromosome 12q21 and plays a role in apoptosis and glucocorticoid response [11]. Additionally, poor prognosis has been observed in patients with two or more deletions, irrespective of the gene involved [10]. Other less common aberrations, including *MEF2C* and *KRAS*, have been associated with a favorable prognosis [9]. It is important to note that most genotypic prognostic studies have been performed in patients who received first- or second-generation TKIs. It remains to be determined whether more potent later-generation TKIs such as ponatinib may be able to overcome the prognostic impact of some of these alterations.

Approximately 60–80% of patients with Ph-positive ALL will harbor additional chromosomal abnormalities (ACAs), most frequently with alterations chromosomes 7, 9, and 14. The presence of −9/9p and/or +der(22)t(9;22) has both been associated with poorer outcomes [12, 13]. In one analysis, patients with one or more these poor-risk ACAs in the absence of hyperdiploidy had significantly shorter 5-year relapse-free survival (RFS; 33% vs. 59%, $P = 0.01$) and OS (24% vs. 63%, $P = 0.003$). Interestingly, adverse outcomes were seen in patients treated with imatinib or dasatinib but not in those treated with ponatinib, suggesting that ponatinib may overcome the negative prognostic impact of poor risk ACAs.

15.3 Tyrosine Kinase Inhibitors

The *BCR-ABL1* fusion gene affects multiple tyrosine kinase signaling pathways leading to leukemic cell proliferation, differentiation arrest, and resistance to apoptosis [6]. BCR-ABL TKIs prevent adenosine triphosphate (ATP) from binding to the BCR-ABL1 oncoprotein, thereby inhibiting hyperactive downstream signaling [6]. The introduction of BCR-ABL TKIs in the treatment of Ph-positive ALL has improved survival outcomes. Imatinib was the first TKI to be discovered with high specificity for BCR-ABL1 oncoprotein. However, high rates of resistance to imatinib have been reported. This is thought to be secondary to point mutations within the *ABL1* domain. Point mutations that can occur within the *ABL1* kinase domain may be at the contact site (e.g., T315I, F317L), SH2 binding site (e.g., M351T), the ATP binding loop (e.g., Y253 and E255), or activating loop [1, 14]. Another mechanism of resistance is the overexpression of SRC family kinases (e.g., LYN, HCK), which leads to stabilization of activated conformation of BCR-ABL1, resulting in decreased drug binding and increased leukemic cell proliferation [15].

The established mechanisms of resistance to imatinib therapy subsequently led to the development of the second-generation TKIs (e.g., dasatinib, nilotinib, and bosutinib), which were designed to potentially overcome these resistance mechanisms. Second-generation TKIs have shown activity against most known imatinib-resistant *ABL1* mutations, with the notable exception of T315I. T315I is commonly known as a "gatekeeper mutation" and is extremely resistant to all first- and second-generation TKIs [2, 12, 16]. Approximately 75% of the patients treated with a first- or second-generation TKI will develop T315I mutation at relapse, leading to treatment failure [17, 18]. As a result, a third-generation TKI known as ponatinib was developed, with potent activity against both wild-type

and mutant BCR-ABL1, including T315I. Because of its broader spectrum of activity and promising clinical data, ponatinib is currently the preferred TKI inhibitor for the treatment of Ph-positive ALL at our institution.

While TKIs are an integral component to the treatment of Ph-positive ALL, the depth and duration of response with single-agent TKIs is suboptimal. Survival outcomes are significantly improved when combined with multi-agent chemotherapy regimens. A summary of TKI-based regimens in the frontline and relapsed and refractory (R/R) settings are shown in Tables 15.1 and 15.2, respectively.

15.3.1 Imatinib

Improvement in outcomes was seen when imatinib was combined with intensive chemotherapy in the frontline setting, demonstrating high CR rates greater than 90%, with OS ranging from 30% to 50%. [19–27, 37, 51] In a 13-year follow-up of a phase II study from MD Anderson Cancer Center, 54 patients with newly diagnosed Ph-positive ALL were treated with imatinib in combination with hyper-CVAD (hyperfractionated cyclophosphamide, vincristine, and doxorubicin dexamethasone alternating with high-dose cytarabine and methotrexate) chemotherapy [25].

Table 15.1 Treatment of Ph-positive ALL with TKI-based regimens in the frontline setting

	Reference	*N*	Median age, years (range)	CR, %	Overall CMR, %	OS, %	HSCT, %
Intensive chemotherapy							
Imatinib	Lee et al. [19]	20	41 (16–71)	95	45	33 (5 years)	85
	Yanada et al. [20]	80	48 (15–63)	96	38	76 (1 year)	61
	de Labarthe et al. [21]	45	45 (16–59)	96	29	65 (1.5 years)	51
	Bassan et al. [22]	59	45 (30–66)	92	–	38 (5 years)	72
	Tanguy-Schmidt et al. [23]	45	45 (16–59)	96	61	52 (4 years)	76
	Fielding et al. [24]	169	42 (16–64)	92	–	38 (4 years)	72
	Daver et al. [25]	54	51 (17–84)	93	45	43 (5 years)	30
	Chalandon et al. [26]	133	45(21–59)	91	23	46 (5 years)	65
	Lim et al. [27]	87	41 (16–71)	94	89	33 (5 years)	64
Dasatinib	Ravandi et al. [28]	72	55 (21–80)	96	60	46 (5 years)	17
	Ravandi et al. [17]	97	44 (20–60)	88	–	69 (3 years)	42
Nilotinib	Kim et al. [29]	90	47 (17–71)	91	86	72 (2 years)	70
	Liu et al. [30]	30	40 (21–59)	100	83	45 (4 years)	53
Ponatinib	Jabbour et al. [31, 32]	76	46 (21–80)	100	86	78 (3 years)	24
Low-intensity chemotherapy							
Imatinib	Chalandon et al. [26]	135	49 (18–59)	98	28	46 (5 years)	62
Dasatinib	Rousselot et al. [18]	71	69 (59–83)	96	24	36 (5 years)	19
	Chiaretti et al. [33]	60	42 (19–60)	97	19	58 (3 years)	42
Nilotinib	Ottmann et al. [34, 35]	79	65 (55–85)	94	42	47 (4 years)	16
	Chalandon et al. [36]	60	47 (18–59)	98	–	96 (1 year)	52
Chemotherapy-free							
Imatinib	Vignetti et al. [37][a]	29	69 (61–83)	100	4	74 (1 year)	–
Dasatinib	Foà et al. [38][a]	53	54 (24–77)	100	15	69 (2 years)	34
	Fedullo et al. [9][a]	63	55 (24–82)	97	36	94 (1 years)	19
Ponatinib	Martinelli et al. [39][a]	42	69 (27–85)	93	46	83 (3 years)	–

Abbreviations: *CMR* complete molecular response, *CR* complete remission, *N* number of patients, *HSCT* hematopoietic stem cell transplantation, *OS* overall survival, *TKI* tyrosine kinase inhibitors

[a]TKI plus corticosteroids

[b]Dasatinib plus corticosteroids followed by blinatumomab consolidation for at least two cycles

Table 15.2 Treatment of Ph-positive ALL with TKI-based regimens in the relapsed and refractory setting

	Reference	*N*	Median age, years (range)	CCyR, %	MCyR, %	Median OS, months
Monotherapy						
Imatinib	Ottmann et al. [40]	56[a]	50 (22–78)	–	–	4.9
Dasatinib	Porkka et al. [41]	46	48	54	57	8.0
	Ottmann et al. [42]	36	46 (15–85)	58	42	–
	Lilly et al. [43]	84	52 (21–77)	–	70 vs. 52[b]	9.1 vs. 6.5[b]
Nilotonib	Ottmann et al. [44]	41	46 (18–75)	32	50	5.2
Ponatinib	Cortes et al. [45, 46]	449[c]	62 (20–80)	38	47	–
Combination therapy						
Dasatinib + hyper-CVAD	Benjamini et al. [47]	34[d]	52 (21–77)	42	35	–
Dasatinib + hyper-CVAD	Ravandi et al. [48]	23[e]	49 (21–69)	43	65	–
Bosutinib + INO	Jain et al. [49]	14[f]	62 (19–74)	73	–	–
TKI + blinatumomab	Assi et al. [50]	20	65 (30–77)	71	75	Not reached

Abbreviations: *BP-CML* blast phase chronic myeloid leukemia, *CCyR* complete cytogenetic response, *INO* inotuzumab-ozogamicin, *MCyR* major cytogenetic response, *N* number of patients, *OS* overall survival, *TKI* tyrosine kinase inhibitors, Hyper-CVAD (hyperfractionated cyclophosphamide, vincristine, doxorubicin dexamethasone alternating with cytarabine and methotrexate)

[a]48 patients with Ph-positive ALL and 8 patients with BP-CML

[b]Dasatinib 140 mg daily was associated with higher MCyR and median OS than patients receiving dasatinib 70 mg twice daily

[c]32 patients with Ph-positive ALL and 417 patients with CML. The results provided are only in patient with ALL

[d]19 patients with Ph-positive ALL and 15 patients with BP-CML

[e]14 patients with Ph-positive ALL and 9 patients with BP-CML

[f]12 patients with Ph-positive ALL and 2 patients with BP-CML

CR was achieved in 93%, and among those who achieved CR, 87% achieved complete cytogenetic response (CCyR), 45% achieved complete molecular response (CMR), 38% achieved major molecular response (MMR, defined as BCR-ABL/ABL <0.1%). The 5-year OS and DFS rates were both 43%. Sixteen patients (30%) underwent allogeneic HSCT in first remission. No difference in DFS were observed in transplanted and non-transplanted patients (43% vs. 63%, $p = 0.52$). However, a trend toward improved outcomes (5-year DFS 82% vs. 33%, $p = 0.16$), although not statistically significant was seen in young patients <40 years, treated with imatinib plus hyper-CVAD followed by HSCT. The insignificant finding is most likely due to limited sample size in this subset of patients.

In a large prospective study, the outcome of newly diagnosed Ph-positive ALL patients treated with imatinib-based therapy ($n = 175$) was compared with the outcome of patients treated with chemotherapy alone ($n = 266$) [24]. Patients in the imatinib cohort were stratified to receive either imatinib in conjunction with the second cycle of induction therapy ($n = 89$, referred as "early imatinib") or imatinib as monotherapy after completing two cycles of induction therapy ($n = 86$, referred to as "late imatinib"). The CR and 4-year OS rates were significantly higher with imatinib plus chemotherapy compared to chemotherapy alone (CR: 92% vs. 82%, $p = 0.004$; OS: 38% vs. 22%, $p = 0.003$). When comparing the outcomes of early and late imatinib cohorts, a trend toward improved survival was seen with earlier exposure of imatinib ($p = 0.1$). By multivariate analysis, imatinib benefitted both transplanted and non-transplanted patients.

Despite improved outcomes with imatinib, several limitations exist, including poor CNS penetration and high incidences of secondary resistance and relapse, mainly driven by development of the T315I mutation. The suboptimal outcomes with imatinib-based therapy have subsequently led to the development of more potent second- and third-generation TKIs.

15.3.2 Dasatinib

Dasatinib is a multi-targeted kinase inhibitor of BCR-ABL1 and SRC-family kinases. Dasatinib inhibits BCR-ABL1 with binding affinity approximately 325 times more compared to imatinib [52]. Furthermore, the fact that dasatinib inhibits SRC-family kinases is important, as it is a known mechanism of resistance in downstream pathways that has been observed in imatinib-treated patients [15]. Another potential advantage of dasatinib is its enhanced penetration of the CNS compared to imatinib [1, 15]. Dasatinib has shown promising results both as a single agent and when combined with chemotherapy in the R/R setting, providing a rationale for utilizing dasatinib in the frontline setting. In a phase II study, the combination of dasatinib plus hyper-CVAD was studied in 72 patients (median age of 55 years) with untreated Ph-positive ALL [28]. The CR rate was 96%, and among those who achieved CR, 57 (83%) achieved CCyR after one cycle and 64 (93%) achieved MMR. Twenty-two patients (31%) relapsed, including 8 (36%) with CNS relapse despite receiving 8 prophylactic doses of intrathecal (IT) chemotherapy. Thirteen relapsed patients underwent a mutational analysis, and 7 patients (54%) developed *ABL* mutations: 4 with T315I, 2 with V299L, and 1 with F359V [28]. The 5-year OS rate was 46%. A subsequent multicenter trial that evaluated the same regimen in 97 younger patients (median age 44 years) with newly diagnosed Ph-positive ALL, similarly demonstrated a high combined CR and complete remission with incomplete hematologic recovery (CRi) rate of 88%. The 3-year OS and RFS rates were 69% and 62%, respectively [17]. A landmark analysis showed a statistically significant improvement in the 3-year RFS and OS (p = 0.038 and 0.037, respectively) in patients who underwent HSCT in first remission [17]. However, data are not available regarding the molecular response of patients who did or did not receive transplant. We therefore do not know whether the HSCT benefit was seen in all subgroups or whether HSCT selectively benefited those with suboptimal early molecular response.

Recent studies have shown that dasatinib plus low-intensity or chemotherapy-free regimens appear to be an effective option, particularly in untreated older or unfit Ph-positive ALL patients [18, 33, 38]. One study evaluated 71 older patients (median age 69 years) with untreated Ph-positive ALL who were treated with dasatinib, dexamethasone, and vincristine. In this study, CR was achieved in 96% of patients, and CMR was achieved in 24%. The 5-year OS and EFS rates were 28% and 36%, respectively. A mutation analysis was conducted in 21 relapsed patients and 18 (75%) acquired T315I mutation and one acquired F317L [18]. Risk-adapted lower-intensity regimens have also been studied in younger populations. In the GIMEMA LAL 1509 study, 60 younger patients (median age 42 years) were treated with dasatinib plus corticosteroids [33]. Patients who did not achieve CMR by the end of induction therapy (day 85) subsequently received chemotherapy and/or allogeneic HSCT. Fifty-eight patients (97%) achieved CR and 11 (19%) achieved CMR at day 85. Importantly, the CMR rate was significantly lower in this study than CMR rates seen with dasatinib and intensive chemotherapy, suggesting that chemotherapy may contribute to deeper responses. Patients harboring both *IKZF1 deletion* plus *CDKN2A/B* and *PAX5* deletions had inferior DFS and higher incidence of relapse of 40% vs. 65% and 40% vs. 14% at 18 months, respectively. For the entire population, the 3-year OS rate was 58%. Interestingly, superior DFS was observed in patients who achieved CMR compared to those who did not, despite these patients receiving only dasatinib and corticosteroids (day 85 DFS rates: 75% vs. 44%, p = 0.06) [33]. These results suggest that early, deep response to therapy may identify patients who may have good options with minimal therapy. With this, chemotherapy-free treatment has become an attractive option that has opened new avenues, with investigators exploring other combinations including dasatinib plus blinatumomab.

15.3.3 Nilotinib

Ongoing studies have demonstrated promising results when combining nilotinib with intensive chemotherapy in patients with newly diagnosed Ph-positive ALL. A phase II study evaluating nilotinib plus chemotherapy has found an overall CR of 91%, CMR of 86%, and a 2-year OS of 72%. Notably, patients who achieved deep molecular remissions had favorable survival outcomes, regardless of whether or not they underwent allogenic HSCT in first remission [29]. Another study showed similar results with CR achieved in 100% of patients, and CMR achieved in 83.3% [30]. Nilotinib was also studied in combination with low-intensity chemotherapy in older patients, resulting in CR and 2-year OS rates of 87% and 67%, respectively [34, 44]. Although the published data on nilotinib combinations are encouraging, the follow-up is generally short. Additionally, like imatinib and dasatinib, nilotinib does not have activity against the T315I mutation, likely limiting its potential to lead to durable remissions and cure in the absence of HSCT.

15.3.4 Ponatinib

Ponatinib has shown substantial anti-leukemic activity as monotherapy in a pivotal phase II (PACE) trial, demonstrating major cytogenetic response (MCyR) and CCyR rates of 47% and 38%, respectively. Despite this, the long-term survival outcomes remain low, with 3-year OS of 18% [45, 46]. In a single-center phase II study, 76 patients (median age 47 years) with newly diagnosed Ph-positive ALL received ponatinib (45 mg daily for 14 days during the first cycle, then continuously in subsequent cycles) plus hyper-CVAD [31, 53]. Two deaths from myocardial infarction potentially related to ponatinib treatment were noted in an initial report. Therefore, the protocol was amended to reduce the dose of ponatinib to 30 mg daily starting the second cycle, with further reduction to 15 mg daily once CMR was achieved. Thirty-five patients (46%) had at least one underlying CV risk factor including hypertension, hyperlipidemia, diabetes, coronary artery disease, and peripheral artery disease. All patients achieved CR, with 83% achieving CMR and 97% achieving MMR. No early mortality during induction therapy was noted. The 5-year continuous CR, EFS, and OS rates were 83%, 67%, and 71%, respectively. A landmark analysis at 6 months demonstrated a favorable trend toward improved OS in patients who did not undergo HSCT compared with those who did (87% vs. 70%, $p = 0.32$). In addition, no CNS relapses were observed in patients who received 12 prophylactic doses of IT chemotherapy. The most common grade 3–4 adverse events were transaminase (32%), increased bilirubin (17%), pancreatitis (17%), hypertension (16%), bleeding (13%), and skin rash (12%). After protocol amendment using lower ponatinib doses and better control of cardiovascular risk factors, no further significant vascular toxicities were encountered.

Ponatinib at a daily dose of 45 mg in combination with corticosteroids was evaluated in a phase II (GIMEMA) study in 42 older or unfit patients (median age 68 years) with newly diagnosed Ph-positive ALL [39]. The CR and CMR rates were 75% and 46% at 24 weeks, respectively; the estimated 2-year OS was 66%. The incidence of CMR with ponatinib was 20–25% higher than that of the combination of dasatinib and corticosteroids. Dose reductions were frequent, as only 15 patients (36%) were able to tolerate the initial dose of 45 mg daily at 24 weeks. During the study, 13 serious adverse events were reported including two deaths suspected to be related to ponatinib. It is possible that lower doses of ponatinib in elderly patients may improve tolerability without compromising efficacy. Given the lower rate of CMR with corticosteroids compared to intensive chemotherapy (46% vs. 83%), there is interest in evaluating the use of ponatinib with inotuzumab ozogamicin and/or blinatumomab, in hopes of reducing treatment-related mortality, achieving deeper responses and further improving outcomes.

With the positive outcomes seen with newer TKIs, the selection of the best TKI in the front-

line setting has been increasingly questioned. There are no randomized head-to-head trials comparing the different TKIs. However, one multicenter meta-analysis and a propensity analysis have demonstrated improved response rates with ponatinib [54, 55]. When compared to hyper-CVAD plus dasatinib, a propensity score analysis showed improved OS with hyper-CVAD plus ponatinib (2-year: 83% vs. 61%; $p = 0.03$), which was likely driven by deeper remissions obtained with ponatinib (82% CMR rate) compared with dasatinib (65% CMR rate) and lower resistance rate driven by the acquisition of T315I mutation [55]. Some authors have considered whether baseline sequencing could identify patients who are most likely to benefit from later-generation TKIs, perhaps due to the presence of a pre-existing *ABL1* resistance mutation. In the study by Rousselot and colleagues of dasatinib plus low-intensity chemotherapy, 36 patients were tested for *ABL1* mutations by polymerase chain reaction (PCR) at the time of relapse, and 75% of patients were positive for the T315I mutation. The detection of this mutation was associated with early relapses compared to patients without it (median of 7 months vs. not reached, $p < 0.001$) [18]. While these findings suggested that perhaps baseline sequencing could help to select the optimal TKI, another study from MD Anderson Cancer Center using highly sensitive and specific Duplex Sequencing in 63 patients with untreated Ph-positive ALL prior to TKI initiation and during treatment showed that the very low-level *ABL1* mutations present at baseline do not contribute to relapse [53]. Of note, using this highly accurate sequencing method, a pre-treatment T315I mutation was only identified in 1 of 63 tested patients. Additional studies confirmed the superior accuracy of Duplex Sequencing compared to PCR for detection of *ABL1* mutations. Thus, the practice at our institution is not to use baseline sequencing to select TKI therapy; rather, we use ponatinib as the frontline TKI for all patients without an absolute contraindication (e.g., active, severe cardiovascular disease).

15.4 CNS Prophylaxis

CNS relapse remains a significant therapeutic challenge in patients with Ph-positive ALL. The incidence of CNS relapse ranges from 8% to 17%, despite the use of TKI combination therapies and prophylactic IT chemotherapy [56]. This has led to the investigation of identifying the adequate number of IT chemotherapy needed to prevent CNS relapses. A retrospective review conducted at our institution compared the rate of CNS relapse in patients with newly diagnosed Ph-positive ALL treated with ≤8 or >8 prophylactic ITs plus hyper-CVAD and a TKI (mainly dasatinib) [57]. Higher incidence of CNS relapse was observed in those treated with ≤8 prophylactic ITs compared to those treated with >8 prophylactic ITs (10% vs. 0%, $p = 0.23$). The 3- and 6-year CNS RFS was 89% and 88%, respectively, in patients receiving ≤8 prophylactic ITs and 100% in patients receiving >8 ITs, respectively ($p = 0.041$). In a multivariate analysis, use of more prophylactic ITs (median of 12 treatments) was associated with decrease rate of CNS relapses ($p = 0.03$) [57]. As a result, the protocols at our institution were amended to increase the number of IT chemotherapy administrations to 12 for the treatment of newly diagnosed Ph-positive ALL. The optimal number of prophylactic IT chemotherapy needed in patients with R/R Ph-positive ALL is currently unknown, although we routinely repeat 6–8 doses of IT chemotherapy at the time of relapse.

15.5 Monoclonal Antibodies and Immunotherapy

15.5.1 CD19 Targeted Antibody

Blinatumomab is a bispecific T-cell engager (BiTE) that binds to CD3-positive cytotoxic T cells and CD19-positive B cells, resulting in apoptosis [58]. A small retrospective study showed that the combination of blinatumomab with a TKI, mainly ponatinib, was efficacious in 20 patients, with R/R Ph-positive ALL. Of the 20 patients included, 6 patients had posi-

tive MRD prior to the initiation of therapy. Overall, 50% achieved CR, 71% achieved CCyR, 75% achieved MMR, and all MRD-positive patients achieved MRD negativity [50]. In another small retrospective study, evaluating the combination of TKIs and blinatumomab found that 8 out of 9 patients with R/R Ph-positive ALL achieved MRD negativity after a median of one cycle, suggesting that this combination is an effective consolidation method for Ph-positive ALL patients to achieve or maintain CMR [59].

The GIMEMA LAL2116 D-Abla trial is the first trial that evaluated the sequential use of dasatinib plus corticosteroids as induction followed by consolidation with blinatumomab for at least two cycles in 63 patients with a median age of 54 years (range, 24–82 years) [60]. After the second cycle of blinatumomab, 32 patients (60%) achieved a molecular response, with 22 patients (41%) achieving CMR and 10 patients (19%) with positive non-quantifiable *BCR-ABL1* transcripts. The rates of molecular responses further increased after subsequent cycles of blinatumomab, with rates of 69.2% after the third cycle and 79.4% after the fourth cycle. At the 12-month follow-up, the OS and DFS rates were 94.2% and 87.8%, respectively. In a mutation analysis conducted in 15 patients with positive MRD before the administration of blinatumomab, 6 patients acquired T315I mutation and 1 acquired E255K; however, these mutations cleared after initiation of blinatumomab [60]. Ongoing studies are evaluating the benefit of ponatinib plus blinatumomab, and the sequential use of ponatinib plus low-intensity chemotherapy as induction followed by blinatumomab (ClinicalTrials.gov Identifier: NCT03263572, NCT03147612). These combination therapies may provide safer and effective treatment modalities in the older population that is unsuitable for intensive chemotherapy or allogeneic HSCT. Early data suggest that both treatment options appear to be beneficial in preventing the emergence of T315Im, decreasing treatment-related mortality, deepening molecular responses, and, in turn, leading to more durable remissions.

15.5.2 CD22 Targeted Antibody

Inotuzumab ozogamicin (INO) is a CD22-directed antibody that is bound to calicheamicin, a potent alkylating agent [61]. The outcomes of INO in patients with R/R Ph-positive ALL were evaluated in a phase I/II (INO-1010) and a phase III (INO-1022) study [61, 62]. A total of 38 patients (16 from INO-1010 and 22 from INO-1022) with Ph-positive ALL were treated with INO compared to 27 patients treated with standard chemotherapy. Of note, 19 patients (86%) in the INO group and 26 patients (96%) in the standard chemotherapy group had prior treatment with one or more TKIs. Higher rates of CR/CRi and MRD negativity were achieved in patients receiving INO compared to standard chemotherapy; the CR/CRi rates were 56–73% and 56%, respectively, and the MRD negativity rates were 63% and 19%, respectively. However, no difference in OS and progression-free survival (PFS) were observed [61].

In a phase I/II study, 12 patients with R/R Ph-positive ALL and 2 patients with blast phase chronic myeloid leukemia were treated with bosutinib (300–500 mg/day) plus INO at a weekly dose of 0.8 mg/m^2 on day 1 and 0.5 mg/m^2 on day 8 and 15 followed by 1 mg/m^2 once every 4 weeks for patients who achieved a response. All but one patient (92%) achieved CR/CRi. Of the 11 patients (79%) who achieved CR/CRi, 91% (10/11) achieved CCyR, 79% (8/11) achieved MRD negativity, and 55% (6/11) achieved CMR. The median OS and EFS were 8.2 and 8.1 months, respectively [49]. The most common adverse event was elevated alanine transaminase, and no cases of veno-occlusive disease reported. Given the promising activity of INO, continued studies are underway to fully assess the safety and efficacy in patients with Ph-positive ALL (ClinicalTrials.gov Identifier: NCT01363297, NCT02311998).

15.5.3 Chimeric Antigen Receptor T-Cell Therapy

CAR-T-cell immunotherapy involves T cells that have been modified genetically to effec-

tively target cell surface and exert cytotoxic effects, in this case, against CD19-positive B cells [63]. Currently, tisagenlecleucel (KYMRIAH®, Novartis), a CD19-directed autologous CAR-T-cell therapy, has been approved for the treatment of relapsed B-cell ALL in patients younger than 26 years. A paucity of literature suggests that the utilization of anti-CD19 CAR-T therapy for the treatment of relapsed Ph-positive ALL after standard chemotherapy or allogeneic HSCT may be a viable option [63]. Well-designed studies are warranted to fully assess the clinical outcomes of CAR-T patients with Ph-positive ALL and to determine who is most suitable for this approach.

15.6 Venetoclax

Venetoclax is a BCL2 inhibitor that has activity in hematological malignancies that express high levels of BCL-2, including Ph-positive ALL. However, in preclinical models, when venetoclax is given as monotherapy, resistance due to upregulation of MCL1, an antiapoptotic BCL2 family member, has been observed [64]. The combination of TKIs and venetoclax have shown to have synergistic activity in preclinical studies. Evidence has suggested that venetoclax plus a BCR-ABL1 TKI may potentially overcome MCL1-mediated resistance seen with venetoclax therapy. The highest degree of synergy was observed with dasatinib and ponatinib. This is due to the inhibition of LYN kinase, known to play a major role in cell proliferation and apoptosis. Inhibiting LYN activity leads to reduced STAT5 phosphorylation, thereby preventing MCL1 upregulation [65]. Preclinical studies evaluating dasatinib plus venetoclax demonstrated superior cytotoxic effects when compared to either agents alone [66]. Given the promising results in preclinical trials, the combination of venetoclax plus ponatinib in R/R Ph-positive ALL is presently being studied at our institution (ClinicalTrials.gov Identifier: NCT03576547).

15.7 Role of Allogeneic Hematopoietic Stem Cell Transplant

Historically, the standard of care in adults with Ph-positive ALL was combination chemotherapy followed by allogeneic HSCT in all eligible patients. Allogeneic HSCT has improved survival outcomes; however, high incidences of relapse and non-relapse mortality are limiting factors. As TKIs have revolutionized the treatment of Ph-positive ALL, the role of allogeneic HSCT has become less clear. Evidence has shown a trend toward improved outcomes with earlier generation TKIs (e.g., imatinib) followed by HSCT compared to chemotherapy alone. However, this benefit was generally not seen in patients who achieved deep molecular responses with TKI and intensive chemotherapy [24–26, 28]. However, among patients who do undergo HSCT, outcomes are better for patients with deeper pre-HSCT molecular response. For example, in one large study, including 441 patients treated with TKI followed by HSCT, OS was significantly better in patients who achieved CMR at the time of HSCT [67]. Deeper molecular responses may also identify patients who do not need to undergo HSCT in the first remission. One study evaluated the impact of CMR in 85 patients with Ph-positive ALL who received TKI plus hyper-CVAD without subsequent allogenic HSCT [68]. The 4-year OS and RFS rates in patients who achieved CMR at 3 months were 66% and 61%, respectively. Overall, these excellent long-term survival results for patients who did not undergo HSCT suggest that HSCT may be safely deferred in first remission for patients who achieve CMR by 3 months of therapy. Thus, our preference is to use the TKI and regimen associated with the highest rate of early CMR.

For patients who remain MRD-positive at 3 months after induction therapy, the historical standard of care has been allogeneic HSCT. However, in the blinatumomab era, it has becomes less clear whether allogenic HSCT is needed to further improve survival outcomes in patients who achieved negative MRD after blina-

tumomab initiation. In the BLAST trial, patients with MRD-positive B-cell ALL (mainly Ph-negative) received blinatumomab (15 μg/m^2 per day by continuous IV infusion) for up to four cycles [69]. After the first cycle, complete MRD response was achieved in 80% of patients (75% in patients with Ph-positive ALL). A post hoc analysis found no significant difference in OS in patients who underwent allogenic HSCT compared with those who continued to receive chemotherapy after MRD negativity was achieved (p = 0.24). As a result, data from this trial was extrapolated to guide treatment decision in patients with Ph-positive disease at our institution. Our preference is to enroll patients in a clinical trial with blinatumomab or INO, with the goal of achieving MRD clearance, which may translate to durable remissions. Given the high risk of transplant-related morbidity and mortality, the decision for HSCT should be individualized, accounting for underlying comorbidities and risk factors [69].

Several studies have been conducted evaluating the clinical outcomes of maintenance therapy after allogeneic HSCT. In the largest retrospective study including 473 transplanted patients, 157 patients received a TKI (mainly imatinib) for primary prophylaxis against relapse. Primary prophylaxis with TKIs was associated with an improved OS (p = 0.002), as well as reduced risk of relapsed (p = 0.01) and non-relapse mortality (p = 0.01) [70]. In another study, imatinib (400 mg daily) was administered to patients with MRD positivity after allogeneic (n = 25) or autologous HSCT (n = 2). MRD negativity was achieved in 14 patients (52%) after a median duration of 1.5 months. A high relapse rate of 92% was observed in patients who failed to achieve MRD negativity. Additionally, a study reported by Pfeifer and colleagues showed that the use of imatinib both prophylactically and pre-emptively was associated with lower relapse rate and durable remissions in Ph-positive ALL [71]. Published studies thus far have demonstrated the rationale of utilizing TKIs as maintenance therapy post allogenic HSCT [72]. To date, there is no consensus on which TKI is best for maintenance therapy, and future studies are needed to evaluate ponatinib in this setting. Our approach is to give post-HSCT TKIs for at least 2–3 years, usually with ponatinib, given its broader range of activity.

15.8 Conclusion

The incorporation of TKIs into induction, consolidation, and maintenance therapy has greatly improved clinical outcomes and is considered the standard of care for adults with Ph-positive ALL. Despite the significant progress in generating deep molecular remission, frequent relapses remain to be a challenge. There has been significant advancement in understanding the biology of the disease and prognostic impact of genomic and chromosomal abnormalities. This led to the development of novel treatment modalities, including more potent TKIs (e.g., ponatinib), bispecific T-cell engager (e.g., blinatumomab), drug conjugate monoclonal antibodies (e.g., inotuzumab ozogamicin), and CAR-T therapies all propagating the hope to further improve clinical outcomes. Figure 15.1 illustrates the proposed treatment algorithm for patients with Ph-positive ALL. Further studies are needed to shed light on the role of reduced or chemotherapy-free induction therapy, the benefit of allogenic HSCT in first remission, and the effect of prophylactic TKI post-HSCT.

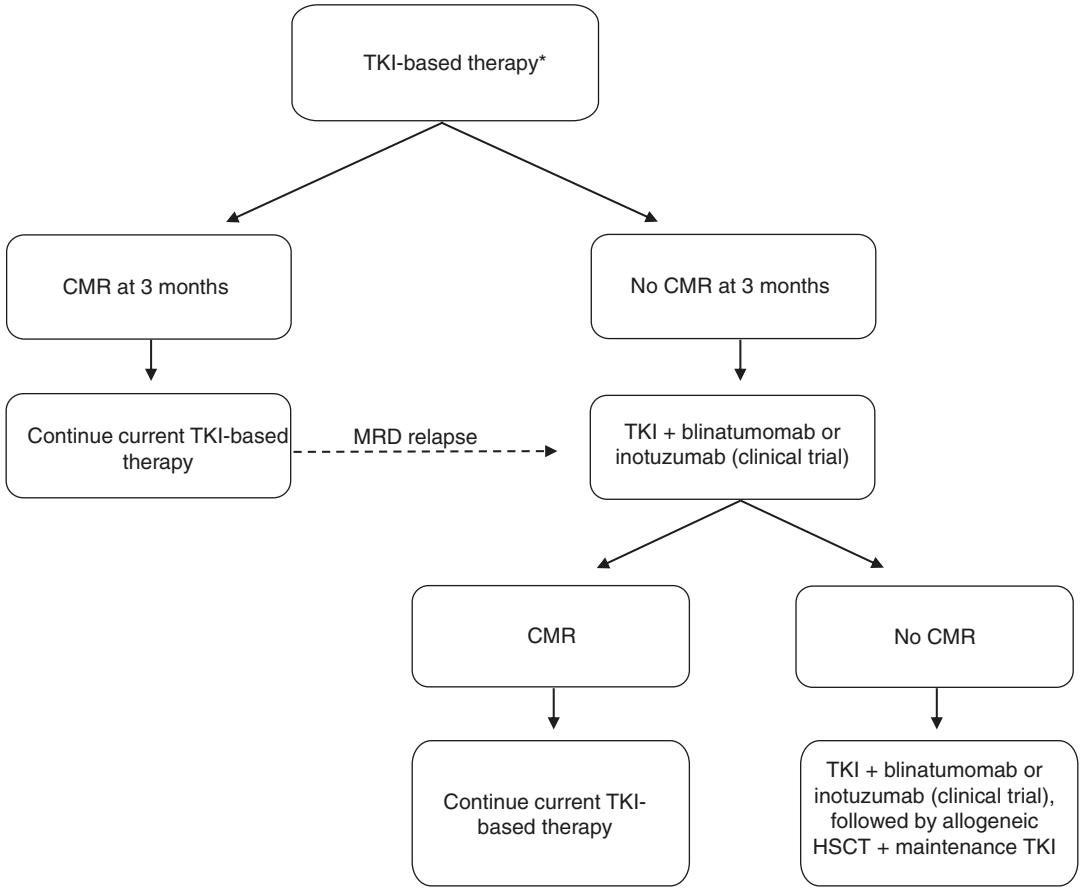

Fig. 15.1 Treatment algorithm of newly diagnosed Ph-positive ALL at MD Anderson Cancer Center. Abbreviations: *CMR* complete molecular response, *HSCT* hematopoietic stem cell transplant, *MRD* minimal residual disease, *TKI* tyrosine kinase inhibitor

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