



Blast and accelerated phase CML: room for improvement

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Tyrosine kinase inhibitors (TKIs) revolutionized the treatment of chronic myeloid leukemia (CML). With TKI therapy, the percentage of patients who progress to accelerated phase (AP) or blast phase (BP) CML has decreased from more than 20% to 1% to 1.5% per year. Although AP- and BP-CML occur in a minority of patients, outcomes in these patients are significantly worse compared with chronic phase CML, with decreased response rates and duration of response to TKI. Despite this, TKIs have improved outcomes in advanced phase CML, particularly in de novo AP patients, but are often inadequate for lasting remissions. The goal of initial therapy in advanced CML is a return to a chronic phase followed by consideration for bone marrow transplantation. The addition of induction chemotherapy with TKI is often necessary for achievement of a second chronic phase. Given the small population of patients with advanced CML, development of novel treatment strategies and investigational agents is challenging, although clinical trial participation is encouraged in AP and BP patients, whenever possible. We review the overall management approach to advanced CML, including TKI selection, combination therapy, consideration of transplant, and novel agents.

LEARNING OBJECTIVES

- Understand the treatment approach to accelerated and blast phase CML in de novo disease and occurring in patients with underlying CP-CML
- Understand response rates and outcomes in patients with advanced CML treated with TKI, TKI and chemotherapy, and hematopoietic stem cell transplantation

CLINICAL CASE

NM is a 54-year-old woman diagnosed with chronic myeloid leukemia (CML) in chronic phase (CP), after presenting with a white blood cell (WBC) count of $270 \times 10^9/L$, hemoglobin of 7.5g/dL, and platelets of $100 \times 10^9/L$. She was initiated on imatinib, which she took irregularly and eventually discontinued. She established care with a new physician and resumed imatinib when she was found to have a WBC count of $68 \times 10^9/L$, hemoglobin of 10.4g/dL, and platelets of $129 \times 10^9/L$. After initial response, peripheral blood polymerase chain reaction for BCR-ABL rose to 35% after 6 months. A bone marrow biopsy specimen demonstrated CP-CML, and she was switched to dasatinib 100mg daily. After 7 months of treatment on dasatinib, BCR-ABL rose from less than 1% to 8.013%. A repeat bone marrow biopsy specimen did not show increased

blasts, but *M351T* and *T315I* mutations and *KMT2A* partial duplication were identified. She was started on ponatinib 45mg daily. Four months after ponatinib initiation, polymerase chain reaction for BCR-ABL rose to more than 50%, and bone marrow biopsy specimen showed 25% myeloblasts along with rising peripheral WBC count. She was transferred to our hospital and received cytarabine 200mg/m² intravenously daily for 7 days and idarubicin 12mg/m² for 3 days. Ponatinib was resumed at the end of induction. She went into a second CP and underwent haploidentical stem cell transplant with posttransplant cyclophosphamide. She received fludarabine, melphalan, and total body irradiation for conditioning. She remains in complete molecular remission 9 months after transplant and has discontinued tyrosine kinase inhibitor (TKI) therapy.

Introduction

Chronic myeloid leukemia is a myeloproliferative neoplasm characterized by the Philadelphia chromosome (Ph) that affects 1 to 2 per 100 000 new patients per year and comprises 15% of leukemias in adults.¹ The disease is driven by a reciprocal translocation of chromosomes 9 and 22, which results in the BCR-ABL fusion protein and dysregulated tyrosine kinase activity. Patients most commonly present in CP, but without treatment, CP-CML will progress to accelerated phase (AP-CML) and blast crisis (BP-CML) within 3 to 5 years. Tyrosine kinase inhibitors revolutionized the care of CML with the approval of imatinib, the only first-generation TKI. Three second-generation TKIs, dasatinib, nilotinib, and bosutinib, are also available for frontline use. Progression to advanced CML is due to continued BCR-ABL activity, which results in not only continued proliferation of leukemic cells but further genetic instability and DNA damage. This invariably leads to clonal evolution and mutations both inside and outside the BCR-ABL kinase domain, as well as additional chromosomal abnormalities (ACAs). This review focuses on treatment considerations for patients who have or progress to AP- and BP-CML, including TKI selection, consideration, and timing of hematopoietic stem cell transplantation (HSCT), and emerging therapies.

Definition and epidemiology of advanced phase CML

The overall incidence of AP- and BP-CML at diagnosis is 3.5% and 2.2%,² respectively, and with the introduction of TKIs, the number has decreased significantly. Long-term follow-up of the International Randomized Study of Interferon and ST1571 trial demonstrated 6.9% cumulative progression to AP- or BP-CML after 10 years.³ This number is lower in recent long-term studies, likely due to improvements in the management of patients with CP-CML with an inadequate response.⁴ A lower incidence of

transformation is associated with initial treatment with second-generation TKIs compared with imatinib.⁴

Complicating the epidemiology and treatment of advanced phase CML are the different classification systems used to define AP- and BP-CML (Table 1), which include the International Blood and Marrow Transplant Registry (IBMTR),⁵ M. D. Anderson Cancer Center (MDACC),⁶ European LeukemiaNet,⁷ and World Health Organization (WHO) criteria.⁸ One major difference between classification systems is the threshold blast percentage used to distinguish CP-, AP-, and BP-CML, with the WHO defining BP as a blast percentage of more than 20% and all other classification systems using a threshold of more than 30%. Of note, the acquisition of major-route ACAs on treatment is considered a hallmark of AP-CML, and the WHO also considers the presence of major-route ACAs at diagnosis as diagnostic for AP-CML.⁸ The WHO has also recently included provisional criteria based on initial response to TKIs (Table 1), which will require further validation in prospective trials.⁸

The varying classification systems and their definitions of advanced CML must be kept in mind when interpreting and applying trial results to individual patients. The MDACC and IBMTR criteria are more frequently used as eligibility criteria in clinical trials, and National Comprehensive Cancer Network (NCCN) guidelines disfavor use of the WHO classification system for this reason.⁹ Overall, the lack of uniformity seen in these major classification systems emphasizes a clinical spectrum within each phase of the disease. Recommendations for treatment in AP- or BP-CML are therefore rarely one-size-fits-all.

Treatment of AP-CML

The initial goal of therapy in advanced phase CML is to revert to a CP or a remission prior to HSCT. The hematologic and complete cytogenetic responses (CCyRs) to the various TKIs in advanced CML are summarized in Table 2.

Table 1. Major classification systems used in chronic myeloid leukemia

MDACC	IBMTR	European LeukemiaNet	WHO
Accelerated phase			
PB blasts 15%-29%	PB or BM blasts 10%-29%	PB or BM blasts 15%-29%	PB or BM blasts 10%-19%
PB blasts + promyelocytes \geq 30%	BP blasts + promyelocytes $>$ 20%	PB blasts + promyelocytes \geq 30%	
PB basophils \geq 20%	PB basophils \geq 20%	PB basophils \geq 20%	PB basophils \geq 20%
Platelets \leq 100 \times 10 ⁹ /L (unrelated to therapy)	Platelets \leq 100 \times 10 ⁹ /L (unrelated to therapy) or $>$ 1000 \times 10 ⁹ /L (unresponsive to therapy)	Platelets \leq 100 \times 10 ⁹ /L (unrelated to therapy)	Platelets \leq 100 \times 10 ⁹ /L (unrelated to therapy) or $>$ 1000 \times 10 ⁹ /L (unresponsive to therapy)
Splenomegaly (unresponsive to therapy)	Anemia Hb $<$ 8g/dL (unresponsive to therapy) Splenomegaly (unresponsive to therapy)		Splenomegaly (unresponsive to therapy)
Cytogenetic evolution on treatment	Cytogenetic evolution on treatment	Cytogenetic evolution on treatment	ACA/Ph+ major route, complex karyotype, or 3q26.2 abnormalities, at diagnosis Cytogenetic evolution on treatment <i>Provisional:</i> failure to achieve CHR to first TKI; any indication of resistance to 2 sequential TKIs; occurrence of $>$ 2 mutations on BCR-ABL during TKI
Blast phase			
PB or BM blasts \geq 30%			PB or BM blasts \geq 20%
Extramedullary blast proliferation			Extramedullary blast proliferation

BM, bone marrow; Hb, hemoglobin; PB, peripheral blood.

Table 2. Summary of hematologic and cytogenetic responses to TKI in advanced phase CML*

	CHR		CCyR		MMR	OS	
	AP	BP	AP	BP	AP	AP	BP
Imatinib	70% - > 90%	11%-35%	16%-60%	0%-10%	19%-63%	50%-60% at 5 years	7-10 months [†]
Nilotinib (de novo)	>90%	—	80%-90%	—	70%	90% at 3 years	
Nilotinib (progressed)	22%-46%	21%-42% [‡]	0%-21%	14%-38% [§]	10%	60%-70% at 2 years	32% at 2 years
Dasatinib (de novo)	>90%	—	80%-90%	—	70%	90% at 3 years	
Dasatinib (progressed)	45%-52%	28%-61% [‡]	18%-33%	27%-35% [§]	10%	60%-70% at 2 years	30% at 2 years
Bosutinib (progressed)	57% [‡]	28% [‡]	40% [§]	50% [§]	11%	60% at 4 years	17% at 4 years
Ponatinib (progressed)	55% [‡]	32% [‡]	24%	18% [§]	34%	84% at 1 year	29% at 1 year

*Adapted from Bonifacio et al.¹⁰[†]Median OS.[‡]Hematologic response.[§]Major cytogenetic response.

In patients presenting with de novo AP-CML, responses to TKIs are robust. Imatinib results in CCyRs of 60% to 80% and major molecular responses (MMRs) of 40% to 60%,^{11,12} and these responses are further improved in de novo AP patients whose only hallmark of AP is the presence of ACAs. Second-generation TKIs have greater potency and BCR-ABL selectivity compared with imatinib. CCyRs and MMRs were 90% and 76% with nilotinib and dasatinib, respectively, in newly diagnosed AP patients.¹¹ Most patients were diagnosed with AP based on isolated clonal evolution or basophilia, again demonstrating how heterogeneity in classification systems makes interpretation of responses with different interventions challenging. Consistent with NCCN guidelines, we approach initial management of patients with de novo AP-CML similarly to patients with CP-CML, especially if they have low-risk Sokal scores or isolated ACA/Ph+ abnormalities as their only AP feature.⁹ Of note, certain ACA abnormalities are higher risk than others, which may affect treatment decisions (Table 3). Milestones are not well defined in AP-CML, but monitoring of BCR-ABL is recommended at 3-month intervals, as in CP. Failure to achieve milestones as used in CP-CML should prompt consideration change in therapy and HSCT.

Prognosis, however, is worse in AP patients who progress from CP while on treatment. For these patients, CCyRs and complete

hematologic remission (CHR) rates are 10% to 20% and 20% to 30% for nilotinib,¹⁹ 30% and 50% for dasatinib,²⁰ and 40% and 57% for bosutinib.²¹ Ponatinib is a third-generation BCR-ABL inhibitor that overcomes many mutations that confer resistance to earlier-generation TKIs, including the gatekeeper *T315I* mutation. The Ponatinib Ph+ ALL and CML Evaluation trial enrolled 267 heavily pretreated patients with CML, including 83 patients in AP.²² Ponatinib resulted in CCyR and CHR rates of 24% and 55% in AP patients, respectively, with median duration of response lasting 12.9 months.²³ However, arterial and venous thrombosis were frequent adverse events (AEs), leading to discontinuation for severe AEs in 11% of patients. The overall cumulative incidence of AEs was 25% in the 5-year follow-up, including 21% serious AEs.²³ The Ponatinib in Participants with Resistant Chronic Phase Chronic Myeloid Leukemia to Characterize the Efficacy and Safety of a Range of Doses (OPTIC) trial evaluated lower starting doses of ponatinib and de-escalated doses once BCR-ABL levels reached 1%, and longer-term follow-up of this cohort may support alternate dosing of ponatinib to improve tolerability and efficacy.²⁴ Omecataxine is a protein synthesis inhibitor with approval by the US Food and Drug Administration (FDA) for AP-CML resistant or intolerant to TKIs, including the *T315I* mutation. In a phase 2 trial of heavily pretreated patients with CML, among the 51 AP patients, 29% achieved CHR and 4% CCyR.²⁵ These responses are less than that seen with ponatinib but can be considered in this patient population with few remaining options.

Ultimately, selection of a TKI is affected by patient comorbidity, costs, prior treatment, and BCR-ABL mutational status. Better definitions of AP-CML are needed with more refined risk stratification and treatment indications, as certain patients with de novo AP-CML behave similar to those with CP-CML. Table 3 summarizes clinical, chromosomal, and molecular risk factors that, if present in AP patients, may warrant more aggressive approaches. Patients with AP-CML with excess blasts often need treatment such as BP-CML. Given the higher response rates, later-generation TKIs are preferred over imatinib for de novo AP, and a switch in TKI is warranted for patients progressing from CP; if applicable, selection should be made based on *ABL1* kinase domain mutations. Ponatinib is the only FDA-approved TKI with activity against the *T315I* mutation, although it carries a risk of vascular occlusive events. Although our patient did not demonstrate overt signs of AP-CML, progression on imatinib and then dasatinib is concerning. Given

Table 3. Prognostic risk factors in advanced phase CML

Characteristic	Poor risk factors
Clinical ^{13,14}	Blast % (most important prognostic indicator, greater impact in AP compared with BP) Older age Anemia Thrombocytopenia Basophil % Prior TKI Myeloid immunophenotype
Chromosomal ^{13,15-17}	+8, +Ph, i(17q), +17, +19, +21, 3q26.2, 11q23, -7/7q, complex, del17p, hyperdiploidy, chromosome 15 abnormalities
Molecular ^{15,18}	<i>TP53</i> <i>ASXL1</i> Acquisition of new mutations during TKI treatment (<i>ABL1</i> kinase mutations, <i>TP53</i> , <i>KMT2D</i> , <i>TET2</i>)

the presence of the *T315I* mutation while taking dasatinib, she was switched to ponatinib for further management.

Treatment of BP-CML

Chemotherapy in addition to a TKI is generally recommended in patients with BP-CML, with the type of induction chemotherapy guided by the myeloid or lymphoid lineage of the blasts. Induction chemotherapy is recommended in conjunction with TKI as response rates associated with TKI treatments alone are inadequate. Response to single-agent imatinib is significantly lower in BP-CML, with CCyRs occurring in approximately 10% of patients and median overall survival (OS) around 7 to 10 months.²⁶ Responses are slightly improved with second generation TKIs.^{27,28} In the Ponatinib Ph+ ALL and CML Evaluation trial, ponatinib demonstrated an 18% CCyR in 62 patients with BP-CML and a median duration of response of 6 months.²² Of note, nilotinib is not FDA approved for BP-CML.

Multiple chemotherapy regimens have been explored in combination with TKIs in small, retrospective studies.¹³ Cytarabine-based regimens, including 7-day continuous infusion of cytarabine 200mg/m² and daunorubicin 60mg/m² on days 1 to 3 (7+3)²⁹ and fludarabine, cytarabine, granulocyte colony-stimulating factor, and idarubicin, are commonly used for CML in myeloid blast crisis.³⁰ Hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone in combination with dasatinib has demonstrated efficacy in lymphoid blast crisis.³¹ Cytogenetic responses of approximately 30% are seen with myeloid induction regimens in combination with imatinib.²⁹ A retrospective analysis of 477 patients with BP-CML treated with chemotherapy, TKI and chemotherapy, or non-TKI-based therapy demonstrated that patients treated with TKI in combination with chemotherapy had superior survival compared with TKI alone or non-TKI-based therapy (5-year OS, 30% vs 14% vs 9%).¹³ Although the numbers

were too small to make a definitive comparison, dasatinib led to improved outcomes compared with imatinib. Rates of CCyR and MMR were also significantly higher with TKI and chemotherapy combination.¹³ However, intense therapy may not be feasible in all patients. TKIs with hypomethylating agents have demonstrated some efficacy and OS benefit.^{32,33}

Overall, BP-CML is a rare entity, and defining unified treatment guidelines is challenging. However, patients with high blast burden almost always need treatment with standard chemotherapy in addition to TKIs. For the rare patient with de novo blast crisis, some experts consider use of TKI alone with close monitoring, although there are little data to guide this approach.¹⁰ Patients who are unfit for chemotherapy and with lower blast burden may also be candidates for TKI alone with close monitoring. In the case of our patient, she was treated with standard 7+3 induction chemotherapy and ponatinib given the *T315I* mutation. We also use higher doses of TKI for BP-CML compared with CP-CML, consistent with FDA labeling indications.

HSCT in advanced CML

HSCT is an important management tool in advanced CML given poorer responses and inadequate response durability to initial therapy.³⁴ For BP-CML especially, most long-term survivors are transplant recipients. Recent analysis demonstrates 5-year OS rates of more than 90% for patients undergoing transplantation in CP.³⁵ This decreases to 60% in patients who undergo transplantation in AP/BP.³⁵ Patients who have transplantation after achievement of a second CP do significantly worse compared with patients who undergo transplantation in their first CP. The choice of myeloablative vs reduced-intensity conditioning is unclear, although the latter may be a reasonable alternative as it offers similar survival rates at the cost of earlier posttransplant

Table 4. Novel therapies in advanced CML under investigation

Drug class	Clinical trials	N	Response
Asciminib (BCR-ABL TKI)	Hughes et al ⁴¹ (phase 1—asciminib in CP/AP CML after TKI failure) NCT02081378 (phase 1—asciminib±TKI in CP/AP/BP CML after TKI failure) NCT03595917 (phase 1—asciminib + dasatinib + prednisone in Ph+ ALL/CML lymphoid BP)	N=9 (AP)	CHR 8/9 (AP) MMR 1/9 (AP)
HQP1351(BCR-ABL TKI)	Jiang et al ⁴³ (phase 2—HQP1351 in <i>T315I</i> -mutated CP/AP CML)	N=23 (AP)	MHR 78% (AP) MCyR 52% (AP)
K0706 (BCR-ABL TKI)	NCT02629692 (phase 1/2—K0706 in AP/CP/BP CML after TKI failure)		
PF-114 (BCR-ABL TKI)	Turkina et al ⁴⁴ (phase 1—PF-114 CP/AP CML after TKI failure or <i>T315I</i>)	N=51 (CP/AP)	MHR 42% (CP/AP) MCyR 29% (CP/AP)
PHA-739358 (aurora kinase inhibitor)	Borthakur et al ⁴⁵ (phase 1—PHA-739358 in AP/BP CML)	N=29 (AP/BP)	HR 14% (AP/BP)
SCH 6636 (farnesyl transferase inhibitor)	Cortes et al ⁴⁶ (phase 1—SCH 6636 CP/AP/BP CML after imatinib failure)	N=15 (AP/BP)	CHR 14% (AP/BP)
Venetoclax (BCL2 inhibitor)	Maiti et al ⁴² (retrospective—venetoclax + TKI)	N=9 (BP)	ORR 75% (BP)
BP1001 (liposomal Grb-2 antisense oligonucleotide)	Ohanian et al ⁴⁷ (phase 1/1b—BP1001±low-dose cytarabine in advanced myeloid malignancies)	N=5 (BP)	ORR 1/5 (BP)
Nivolumab (anti-PD-1)	NCT02011945 (phase 1b—nivolumab + dasatinib in CP/AP CML)		
Inotuzumab (anti-CD22)	Jain et al ⁴⁸ (phase 1/2—inotuzumab+bosutinib in Ph+ ALL/CML lymphoid BP)	N=2 (BP)	ORR 1/2 (BP)

BCL2, B-cell lymphoma 2; HR, hematologic response; MCyR, major cytogenetic response; MHR, major hematologic response; ORR, overall response rate.

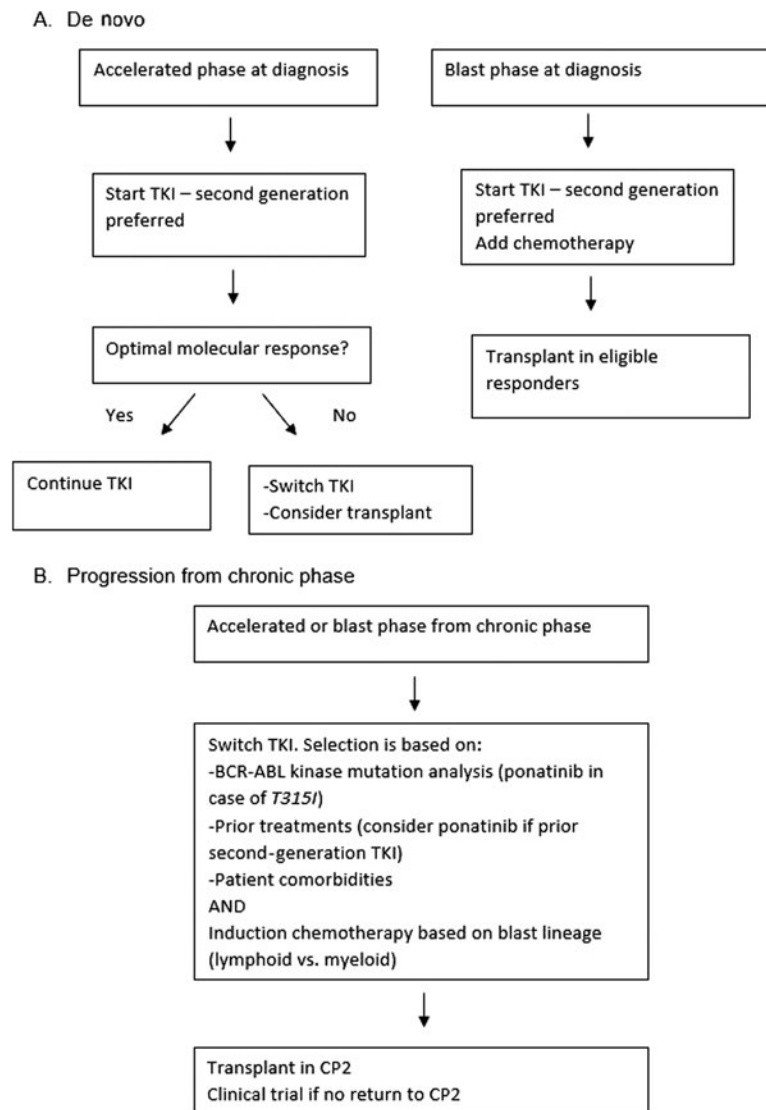


Figure 1. Algorithm for treatment of (A) de novo or (B) progressed advanced phase CML.

relapse.³⁶ Overall 5-year OS rates were 53% in both myeloablative and reduced-intensity conditioning groups.

For AP patients, however, timing of transplant can be difficult. Certain de novo AP patients have outcomes similar to CP-CML, with 1 study suggesting that transplant can be deferred in AP patients who lack high-risk characteristics, including total CML disease duration more than 12 months, hemoglobin less than 10g/dL, and peripheral blood blasts more than 5%.³⁷ For most de novo AP patients, treatment with TKI alone is likely sufficient, with subsequent transplantation decisions based on the patients' response to therapy. However, HSCT is recommended in all eligible patients who have progressed to AP from CP and all BP patients, including those presenting with de novo disease.⁹

Once a patient has undergone HSCT, the use and duration of TKI maintenance after transplantation are unknown. In Ph+ acute lymphoblastic leukemia, maintenance TKI improves leukemia-free survival, relapse, and OS.³⁸ Smaller prospective studies have demonstrated safety of maintenance TKI with lower rates of

relapse in CML.³⁹ However, a recent IBMTR analysis of maintenance TKI after transplant for CML showed no benefit at 100 days in terms of OS, leukemia-free survival, relapse rates, transplant-related mortality, and chronic graft-versus-host disease.⁴⁰ NCCN guidelines recommend 12 months of maintenance TKI, although data guiding this recommendation are unclear.⁹ Minimal residual disease monitoring is an essential tool to determine duration and need for TKI maintenance, although firm guidelines in this area are needed. Our patient was offered transplant after reverting to CP with ponatinib and induction chemotherapy. She discontinued ponatinib at 6 months given its side effect profile and lack of residual disease on follow-up.

Novel therapeutics for advanced CML

Despite dramatic improvements in outcomes for patients with CP-CML, patients with AP- and BP-CML have significantly worse prognosis, and thus new therapeutic approaches are needed. Table 4 summarizes novel therapeutics currently under investiga-

tion. Asciminib, an allosteric inhibitor that binds to the myristoyl site of the BCR-ABL tyrosine kinase, has demonstrated efficacy in heavily pretreated patients with CML.⁴¹ In 9 patients with AP-CML, 8 had a CHR, and 1 of 9 had an MMR. As asciminib targets a distinct binding site compared with other TKIs, its development and recent approval open the possibility for future TKI-TKI drug combinations, which are being evaluated in phase 1 and 2 trials (NCT03595917; NCT03578367). Other novel small-molecule inhibitors, including newer-generation TKI inhibitors, are also under evaluation (Table 4). Venetoclax, a selective B-cell lymphoma 2 inhibitor, has shown synergism with TKIs in eliminating leukemic stem cells in advanced CML, with encouraging response rates for venetoclax and TKI combinations in retrospective studies for CML in myeloid BP.⁴² Given dysfunction in immune surveillance within CML, immune therapies could potentially be leveraged in advanced phase CML, particularly in TKI-resistant patients. Overall, treatment of advanced phase CML remains a challenge, and prevention of disease progression is the most paramount strategy. Clinical trial participation is encouraged for all patients who develop or have advanced phase CML.

Conclusions

TKI therapy revolutionized the care of patients with CML. Although the incidence of AP- and BP-CML has declined, prognosis is significantly worse, and TKI therapy is not as effective. In addition to small numbers and limited evidence to guide treatment, it is important to recognize that there is heterogeneity in the definitions of AP and BP, complicating treatment decisions. Our general approach to patients with advanced CML is summarized in Figure 1. Given limited options in advanced CML, prevention of progression with strict adherence to evidence-based treatment guidelines for CP-CML remains the best strategy; however, novel therapeutics and treatment strategies are being explored for the small group of patients who do transform.

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Off-label drug use

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