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REVIEW ARTICLE

Advanced-Stage Chronic Myeloid Leukemia: Options for Difficult Treatment Situations

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Abstract

A small number of patients with chronic myeloid leukemia (CML) either present with or progress to the accelerated phase (AP) or blast phase (BP). This occurs in approximately 4–7% of patients with CML. Most patients who progress to BP-CML are of myeloid lineage, while approximately 30% are of lymphoid lineage. Due to the rarity of this condition, there are no large or randomized trials that can inform clinical decisions. Most data are from retrospective chart reviews or data from old studies when tyrosine kinase inhibitors (TKIs) were initially approved. In addition, the definition of these categories has been in continuous flux over the last 20 years, making applicability of data even more confusing. In some classifications, the cutoff is 30% blasts for the definition of BP-CML, while in others a cutoff of 20% is used. In addition, more recently the World Health Organization (WHO) classification omitted the accelerated phase and recognized only a two-phase disease, while the International Consensus Classification retained a three-phase definition and retained the accelerated phase. Therapy for patients with AP/BP-CML depends on several factors, including prior therapy, *BCR::ABL1* mutation, co-morbidities, cell lineage, and eligibility for allogeneic stem cell transplantation (alloHCT). Patients with AP-CML at presentation have a relatively favorable prognosis and may not need alloHCT if they respond appropriately to therapy. For patients with AP-CML who progressed while on TKI therapy or those with BP-CML, alloHCT is considered the only curative therapy. Our goal is to review the available data on the therapy of patients with AP-CML and BP-CML.

Key Points

Chronic myeloid leukemia (CML) in accelerated or blast phase is a rare disease.

Given its rarity, there is no clear standard of care.

We aim to review the currently available data in the treatment of patients with advanced phase CML.

1 Introduction

Chronic myeloid leukemia (CML) is caused by *BCR::ABL1*, a constitutively active tyrosine kinase generated as the result of the t(9;22)(q34;q11.2) reciprocal translocation, cytogenetically visible as the Philadelphia chromosome (Ph) [1]. In the developed world, most patients are diagnosed in the chronic phase (CP-CML), where myeloid progenitor cells are expanded, but maintain terminal differentiation capacity [2]. Without effective treatment, CP-CML inexorably progresses to the blast phase (BP-CML), an acute leukemia of myeloid or lymphoid immunophenotype. BP-CML may be preceded by a transitional state termed accelerated-phase CML (AP-CML). In developing countries, a considerable percentage of patients are diagnosed in AP/BP-CML, likely reflecting delayed diagnosis [3]. On the basis of data from the 1920s, when splenic radiation was the only treatment modality, it is estimated that the average time to blastic transformation may be 2–3 years [4]. Tyrosine kinase inhibitors (TKIs) have dramatically improved CML survival. However, translation of this progress from clinical trials into the real world is uneven. In a study based on the Swedish cancer

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registry, survival for patients with CML was close to that of age-adjusted controls [5] In contrast, in the USA, survival for patients with CML remains inferior to the general population [6]. While the precise reasons are unknown, the inferior outcomes for certain populations, such as patients with lower household income [7], suggest that access to care and adherence may play an important role. SEER data suggest there are still an estimated 1000 CML-related deaths annually in the USA.

In clinical TKI studies, progression to AP/BP-CML occurs in approximately 7% of patients, but reliable data from outside of clinical trials are unavailable. TKIs have profoundly changed the clinical course of CML. In the pre-TKI era, a large proportion of patients progressed through AP-CML, characterized by a gradual loss of differentiation capacity and increasingly challenging control of blood counts. In patients treated with TKIs, progression often manifests as resistance to successive lines of TKIs, while patients still remain in CP-CML by morphological and clinical criteria. In contrast, some patients with well-controlled disease experience sudden transformation to the blast phase. This changing clinical landscape has led to discussions about the validity of current classification systems, and the notion that CML may be a two-phased rather than a three-phased disease [8, 9]. To that point, the World Health Organization (WHO) classification in 2022 omitted AP-CML [10], while the International Consensus Classification (ICC) retained AP-CML [11]. The topic of the present review is not so much to contribute to this ongoing dispute but rather to review the mechanisms of CML progression with a focus on the therapy options for patients with advanced disease. For the purpose of this review, we will define advanced CML as the presence of morphological or cytogenetic features diagnostic of AP-CML or BP-CML.

2 Mechanisms of Progression

CP-CML is an indolent chronic disease that is dependent on *BCR::ABL1* signaling. Mortality is extremely low and typically caused by complication of excess leukocytosis such as splenic rupture or leukostasis. However, *BCR::ABL1* signaling causes genetic instability, which leads to acquisition of additional mutations. Data from the IRIS trial show that the duration of uninhibited tyrosine kinase activity is proportional to the risk of progression. Patients randomized to the interferon-α (IFN) arm were able to cross over to imatinib after 6 months. Even this relatively short delay was sufficient to increase the rate of progression [12]. Clinical experience has it that the patients who progress nowadays often have a history of low adherence or frequent dosing interruptions due to drug access issues [1, 13]. Numerous mechanisms have been implicated in the genetic instability that characterizes *BCR::ABL1*-expressing cells. Activation of phosphtitylinositol 3' kinase (PI3'K) increases reactive oxygen species, which induce DNA double strand breaks (DSB) and DNA adjuncts [14]. DSB repair is impaired by several mechanisms, including reduced expression of BRCA1 [15], increased usage of the less faithful non-homologous end joining (NHEJ) mechanism for DSB repair, and others [16]. Additionally, mismatch repair and base excision repair are compromised [17, 18]. The combination of increased DNA damage with impaired repair predictably leads accumulation of numerical and structural chromosomal abnormalities as well as point mutations. Although fully developed BP-CML is morphologically relatively uniform (aside from being of lymphoid or myeloid phenotype), no typical or even specific genetic lesion is associated with transformation (Table 1) [19]. However, the various upstream pathways seem to converge on a relatively uniform epigenetic signature whose key features are reduced activity of the polycomb repressive complex 2 (PRC2) and increased activity of PRC1 [20]. Mutations or cytogenetic abnormalities associated with the blast phase are present at diagnosis in some patients with CP-CML by morphologic criteria. Increased risk of TKI resistance and shortened survival is well documented for patients who present with major-route additional cytogenetic abnormalities [21]. Data are accumulating that patients with *ASXL1* mutations at diagnosis have inferior outcomes

Table 1 Frequency of relevant variants identified by next generation sequencing in patients with BP-CML [19, 63, 64]

Variant	Frequency (%)
IKZF1	18–33
RUNX1	25–33
ASXL1	20–23
WT-1	15.4
TET2	7.7
N-RAS	5.1
K-RAS	5.1
TP53	2.6
CBL	2.6
BCORL1	13
IDH1/IDH2	3.28
BCOR	5
GATA2	5
PHF6	5
PAX5-ZCCHC7	3
MSI2-fusion	3
U2AF1	3
UBE2A	3
KMT2D	3
SETD2	3
XPO1	3

[19]. These observations indicate that morphology alone is insufficient to locate a given patient on the path of CML progression.

3 Classification of CML Phases

CML phase definitions have been a subject of debate amongst CML experts for some time and have become even more complicated by the new International Consensus Classification (ICC) and World Health Organization (WHO) classifications [10, 11]. Most studies performed in the early TKI era were based on the MD Anderson Cancer Center (MDACC) definition of CML phases that used a cutoff of ≥ 30% blasts for BP-CML. Cytogenetic clonal evolution; peripheral blasts ≥ 15%; peripheral basophils greater ≥ 20%; peripheral blasts and promyelocytes ≥ 30%; and platelets < 100/nL (unrelated to therapy) were identified as independently associated with adverse outcomes and used to define AP-CML [4]. In 2001, the World Health Organization adopted a 20% cutoff for blast-phase CML to align with the definition of acute myeloid leukemia (AML), and defined AP-CML as a blast count 10–19% [22]. More recently, the WHO classification recommended eliminating AP-CML altogether as a separate phase but introduced a risk stratification of chronic phase [10], essentially recreating a three-phased system, except that not all suggested high-risk CP-CML variables are validated as independent prognostic factors in multivariate analysis (MVA). In contrast, the ICC retained AP-CML (Table 2). It is obvious that the resulting classification confusion is anything but helpful for patients and providers. At this point, we and others [23] prefer to retain AP-CML as a clinical useful term that denotes high risk without implying that allogeneic stem cell transplant (alloHCT) is the recommended approach for all transplant-eligible patients.

4 Management of Advanced CML

Many studies of advanced CML combined patients with AP-CML, lymphoid BP (LBP-CML), and myeloid blast phase (MBP-CML). To provide specific guidance we have separated the outcomes of AP-CML (Table 3), MBP-CML (Table 4), and LBP-CML (Table 5) whenever feasible. Therapy selection in patients with advanced CML depends on several factors including age, co-morbidities, prior therapy, eligibility for allotransplant, and *BCR::ABL1* mutation analysis [24]. The heterogeneity of treatment choice was demonstrated in the European LeukemiaNet Blast Phase Registry. Of the 240 evaluable patients identified from 11 countries, 37.1% had de novo blast phase and 30% had lymphoid LBP-CML. Overall 42.7% and 21.1% received TKI + chemotherapy and TKI alone, respectively. No specific chemotherapy regimen was used, and type of TKI also varied by country and indication [25]. With prospective data largely absent, we propose approaching the management of advanced CML from the perspective of clinical practice, using the morphological phase definitions and prior exposure to TKIs as the fundamental division lines.

Defining optimal response in advanced-phase CML is also challenging. Response definitions in CML in general is based on both depth and duration of therapy. Depth of response proceeds from hematological response to cytogenetic response to molecular response. The depth of response definitions in advanced phase CML are similar to those of

Table 2 Accelerated and blast-phase definitions

	WHO classification, 2022 [10]	ICC classification, 2022 [11]	MDACC classification [4, 37]
Accelerated phase	Omitted	BM or PB blasts 10–19% PB basophils ≥ 20% Presence of additional clonal cytogenetic abnormalities in Ph+ve cells[^]	BM or PB blasts 15–29% BM or PB blasts + promyelocytes ≥ 30% PB basophils > 20% Presence of additional clonal cytogenetic abnormalities in Ph^+ve cells Platelets < 100×10^9/L
Blast phase	≥ 20% myeloid blasts in the BM or PB or The presence of an extramedullary proliferation of blasts		≥ 30% myeloid blasts in BM or PB or extramedullary proliferation of blasts
	The presence of increased lymphoblast in BM or PB*	Presence of morphologically apparent lymphoblasts (> 5%) warrants consideration of lymphoblastic crisis	

BM, bone marrow; PB, peripheral blood; Ph^+ve, Philadelphia-chromosome-positive

*No clear cutoff for lymphoblasts

[^]Second Ph, trisomy 8, isochromosome 17q, trisomy 19, complex karyotype, or abnormalities of 3q26.2

Table 3 Select studies in patients with accelerated-phase CML-(AP-CML)

TKI	Study	*N*	CHR	CCyR	MR3	MR4.5	OS (Y)	PFS (Y)	Reference
Nilotinib, dasatinib	Retrospective multi-institutional in patients with de novo AP	69	82.6%	88.4%	79.7%	40.5%	96.8 % (5)	91.5% (5)	[32]
Dasatinib	Phase II after imatinib failure AP-CML	174	45%	32%	NR	NR	82% (1)	66% (1)	[65]
Nilotinib	Phase II after failure of imatinib and dasatinib	17	29%	0	NR	NR	80% (1)	57% (0.5)	[66]
Nilotinib	Phase II	137	31%	21%	NR	NR	70% (2)	33% (2)	[67]
Imatinib + decitabine	Phase II de novo and secondary AP/BP-CML	18	39%	NR	NR	NR	56 weeks*	NR	[42]
Dasatinib + decitabine	Phase I/II de novo and secondary AP/BP-CMLP	6	50%	50%	33%	16.6%	NR	NR	[43]
Bosutinib	Phase I/II with prior therapy to > 1 TKI	72	31%	30.5%	NR	NR	59% (4)	NR	[41]
Ponatinib	Phase II with prior therapy to ≥ 1 TKI	83	NR	24%	15.6%	4.8%	84% (1)	55% (1)	[36]

N number of patients with AP-CML, *NR* not reported, CHR complete hematological response, *CCyR* complete cytogenetic response, *MR3* BCR::ABL 1 ≤ 0.1%, *MR4.5* BCR::ABL 1 ≤ 0.0032%, *Y* year, *OS* overall survival, *PFS* progression-free survival, *AP* Accelerated phase

*Median survival

Table 4 Select studies in patients with myeloid blast phase CML (MBP-CML)

TKI	Other treatment	*N*	CHR	CCyR	MR4.5	CR/CRi	EFS/PFS (Y)	OS (Y)	Reference
Nilotinib	–	105	22.9%	30%	NR	NR	NR	32% (2)	[40]^
Imatinib	Decitabine	10	20%	NR	NR	NR	NR	15 weeks*	[42]
Dasatinib	Decitabine	18	38.9%	38.9%	16.7%		NR	NR	[43]
Imatinib, dasatinib, nilotinib, bosutinib, ponatinib	IC + TKI (20) Decitabine + TKI (20) TKI (56) IC only (8)	104		40% 50% 10.7% 0%	5.9% 0% 2.1% 0%	60% 55% 33.9% 12.5%	27% 19% 5% 0% (5)	30% 28% 13% 0% (5)	[44]

N number of patients with MPB-CML, *NR* not reported, CHR complete hematological response, *CCyR* complete cytogenetic response, *MR4.5* BCR::ABL 1 ≤ 0.0032%, *CR/Cri* complete remission/complete remission with incomplete count recovery, *Y* year, *OS*: overall survival, *EFS* event-free survival, *PFS* progression-free survival, *IC* intensive chemotherapy

*Median OS

^Included patients with *BCR::ABL1*^{T315I}

Table 5 Select studies in lymphoid blast phase CML (LBP-CML)

TKI	Treatment	*N*	CR/CRi	CCyR	uBCR::ABL1	EFS/PFS	OS (Y)	Reference
Ponatinib	–	10	NR	30%	NR	19% (1)	29% (1)	[36]
Dasatinib 70 mg bid or 140 mg daily	–	61	18%#	34%	NR	NR	21% (2)	[48]
Ponatinib 30 mg daily	Blinatumomab	6	83%	NR	33%	50% (1)	100% (1)	[53]
Imatinib 400–800, dasatinib 50–140	HyperCVAD	42	90%	58%	25%		17 months^	[50]
Bosutinib	Inotuzumab	2	50%	NR	NR	NR	NR	[54]
Nilotinib 400 bid	–	31	21%#	32%	NR	NR	10% (2)	[40]

N number of patients with LBP-CML, *NR* not reported, CCyR complete cytogenetic response, *uBCR::ABL1* undetectable BCR::ABL 1, *CR/Cri* complete remission/complete remission with incomplete count recovery, *Y* year, *OS* overall survival, *EFS* event-free survival, *PFS* progression-free survival, *NR* not reported

#Complete hematologic response

^Median survival

CP-CML: complete hematological response (CHR; normalization of blood counts and resolution of signs and symptoms of the disease and no immature cells in the in the peripheral blood), complete cytogenetic response (CCyR; no Ph-positive [Ph^+] metaphases by karyotyping), major cytogenetic response (MCyR; 0–35% Ph-positive

metaphases by karyotyping), major molecular response (MMR; BCR::ABL1 ≤ 0.1%), MR4 (BCR::ABL1 ≤ 0.01%), MR4.5 (BCR::ABL1 ≤ 0.0032%), and MR5 (BCR::ABL1 ≤ 0.001%) [26]. However, defining a time for optimal response varies and is not well defined in this patient group, as will be discussed later.

4.1 AP-CML at Presentation

One of the criteria for AP-CML is the presence of additional cytogenetic abnormalities (ACA) in Ph^+ cells. However, not all cytogenetic abnormalities are considered equal [27]. High-risk cytogenetic abnormalities associated with worse prognosis include +8, +Ph, i(17q), +17, +19, +21, 3q26.2, 11q23, −7/7q abnormalities, and complex karyotype [21, 28, 29]. Whether this is applicable to patients < 18 years old is unknown, as a small study of pediatric patients treated with imatinib found no differences in outcome between patients with and without ACA [30].

Patients who present with AP-CML based only on the presence of ACA have survival similar to patients with CP-CML, while patients presenting with morphological AP-CML have slightly worse outcomes [27]. Prospective interventional studies in the population are unavailable. In a retrospective study of 75 patients with AP-CML, 33 and 42 patients received imatinib or second-generation TKI (2G TKI). Patients who had an adequate response, defined as achieving MCyR at 3 months had excellent 3-year overall survival (OS), event-free survival (EFS) and failure-free survival (FFS) compared with those who did not: 94%, 98%, and 93% versus 75%, 42%, and 25%, respectively. A higher percentage of patients who received a 2G-TKI, namely dasatinib, bosutinib, or nilotinib, achieved BCR::ABL1 < 10% at 3 and 6 months. This study revealed that response to TKIs is the major determinant of survival, validating previous work [31]. Another retrospective study on 69 patients demonstrated that patients with AP-CML who started on 2G TKIs in the frontline setting did well, with a 2-year progression free survival (PFS) and OS of 93.7% and 96.8%, respectively [32]. In aggregate these retrospective analyses suggest that the response to TKI is the main determinant of outcome in patients with de novo AP-CML and that such individuals should be started on a 2G-TKI. A clinically important question is which criteria should be applied to define response in patients diagnosed with AP-CML. Clinically in the absence of prospective data, the field has pragmatically decided to use the same milestones of response and definitions of TKI failure in use for CP-CML [8, 26]. Although patients with AP-CML are less likely to achieve response milestones, those who do have good early response have a good prognosis [31]. Allotransplant is only recommended for patients who do not have an adequate response, and there is no role for combining TKIs with chemotherapy outside of a clinical trial.

4.2 BP-CML at Presentation

BP-CML has become rare in the Western world. Occasional patients present in BP, some of whom are initially diagnosed with *BCR:ABL1*-positive ALL or *BCR::ABL1*-positive AML [10]. Separating either of those from BP-CML can be difficult and occasionally impossible. The presence of myeloid proliferation in the background of Ph^+ ALL may point to the diagnosis of LBP-CML as opposed to *BCR:ABL1*-positive ALL. Although clinical management of de novo BP-CML and BP-CML developing on TKI therapy is similar, the outcome of patients with de novo BP-CML is better compared with BP-CML progressing from CP-CML [25, 33]. There are several important considerations for the de novo situation. For LBP-CML, it seems reasonable to extrapolate from the experience in *BCR:ABL1*-positive ALL. In practice, patients with de novo LBP-CML should be managed as in BCR:ABL1-positive ALL, including the progress that has been made in moving away from multiagent chemotherapy. Little data are available for de novo MBP-CML. While it is reasonable to treat patients with a 2G or 3G TKI plus AML-type chemotherapy, the added value of chemotherapy is not very clear due to lack of head-to-head comparisons. Some experts prefer to minimize toxicity by using TKI alone followed by alloHCT, while others recommend chemotherapy + TKI prior to alloHCT [25] to achieve a deeper response prior to transplant in the hopes of reducing relapse risk. Patients who achieve a deep molecular response pose a particular challenge, as we have no data to guide us as to whether or not to proceed with alloHCT. It is good practice to discuss potential scenarios with the patient before treatment is initiated, and then try to follow the agreed on plan.

4.3 Progression to AP-CML on TKI Therapy

In contrast to patients diagnosed with AP-CML, progression to AP-CML while on TKI therapy portends a much poorer prognosis, and alloHCT is considered standard of care for all eligible patients. Achievement of a second chronic phase prior to transplant is associated with better outcomes, both with respect to relapse-free survival and transplant-related mortality [34]. The choice of salvage TKI is dictated by prior TKI history, *BCR::ABL1* mutations and to a lesser extent co-morbidities. Extrapolating from CP-CML data, patients who progressed on imatinib are candidates in principle for a 2G TKI, which is superior to dose escalation of imatinib [35]. Overall, approximately 30% of patients may achieve CCyR. Some of the earlier studies included patients with *BCR::ABL1* mutations that are now known to be resistant to 2G TKIs, most importantly $BCR::ABL1^{T315I}$

(Table 6). Given that progression to AP-CML on any TKI is a high-risk situation, it is our practice to treat such patients with ponatinib, unless there are very strong contraindications. In the PACE study of ponatinib in patients with prior TKI failure, response of AP-CML fell between CP-CML and BP-CML, with a major hematologic response rate of 55% by 6 months, a major cytogenetic response of 39%, a complete cytogenetic response of 24%, and major molecular response rate of 16% [36]. Progression-free and OS were 55% and 84% at 12 months, respectively. Unfortunately, the AP-CML cohort of the PACE study was never updated. Data with asciminib are very limited. In the phase I study of asciminib, nine patients with AP were enrolled, including five with *BCR::ABL1*^{T315I}. Only one single patient with *BCR::ABL1*^{T315I} mutation achieved CCyR.

4.4 Progression to BP-CML on TKI Therapy

Approximately 5% of CML patients treated with TKI progress to MBP-CML (70%) or to LBP-CML (30%) [37]. As of this date, allotransplant is the only treatment modality known to cure BP-CML; therapeutic approaches bifurcate according to whether or not a patient is a transplant candidate. For allograft-eligible patients, the combination of TKI + chemotherapy/immunotherapy followed by alloHCT is the treatment of choice. As patients have progressed while on a TKI, they more likely would have developed a *BCR::ABL1*-independent resistance, hence our choice of combination therapy with a TKI. For patients who are not alloHCT candidates, palliation with single-agent TKI with or without low-dose chemotherapy may be appropriate. Treatment selection depends on several factors including prior TKI, mutation analysis, type of blast phase (MBP versus LBP), co-morbidities, and transplant eligibility. In general we recommend continuing TKI therapy, as the TKI may exhibit control on sensitive clones.

4.5 Myeloid Blast Phase

4.5.1 Single-Agent TKI

Responses with single-agent imatinib are low and non-sustained [38, 39]. Of mostly historical interest, only 20–25% of MBP-CML patients without prior TKI exposure and treated with single-agent imatinib 600 mg daily achieved CHR, with a median overall survival of approximately 7 months. Most data on 2G TKIs are based on studies of patients previously treated with imatinib. Hematological response rates are very similar with dasatinib, bosutinib, or nilotinib, with CHR ranging from 15% to 30% and median survival from 7 to 10 months [40, 41]. Single-agent ponatinib was slightly more effective. In a phase I/II study, 52 patients had MBP-CML, and 10 had LBP-CML. In patients with MBP-CML, the rates of major hematologic response (MaHR), MCyR, and CCyR were 29%, 19%, and 15%, respectively. Survival and mutations were reported for the whole group: 19 patients had no detectable mutations, 19 had mutations other than *BCR::ABL1*^{T315I}, and 21 had *BCR::ABL1*^{T315I}. There was no difference in response rate among patients who did or did not have *BCR::ABL1*^{T315I}. However, none of the three patients who harbored *BCR::ABL1*^{T315I} with an additional mutation responded to therapy. The 12 months' OS and PFS for all patients with BP-CML was 29% and 19%, respectively (Table 4).

4.5.2 TKI + Chemotherapy

TKIs have been combined with decitabine or with more intensive chemotherapy such as the fludarabine, cytarabine, G-CSF, and idarubicin (FLAG-ida) regimen for the treatment of patients with MBP-CML. A study of 28 patients (AP-CML: 18; MBP-CML: 10), 25 of whom were resistant to imatinib, evaluated the combination of decitabine with imatinib. Responses were mainly seen in patient without a *BCR::ABL1* mutation [42]. Another trial tested the combination of decitabine and dasatinib [43]. Of the 30 patients enrolled, 7, 18, and 1 had AP-CML, MBP-CML, and LBP-CML, respectively. CHR and MMR rates were 48% and 33%, respectively, and median overall survival was 13.8

Table 6 Choice of TKI based on comorbidities and *BCR::ABL1* mutations

TKI	Do not use	Avoid if possible
Imatinib	Most *BCR::ABL1* mutations	Chronic diarrhea, liver function abnormality, and congestive heart failure
Bosutinib	T315I, F317L, V299L, G250E	Chronic diarrhea and liver function abnormality
Dasatinib	T315I/A, F317L/V/I/C, V299L	Lung disorders and pulmonary hypertension
Nilotinib	T315I, Y253H, E255K/V, F359V/C/I	Cardiovascular disease, history of pancreatitis, and liver function abnormality
Ponatinib	None	Cardiovascular disease and history of pancreatitis
Asciminib	A337T, P465S, F359V/I/C	History of pancreatitis and liver function abnormality

months. FLAG-ida was combined with ponatinib in 17 patients with BP- CML. Of those, 4, 4, and 9 had mixed phenotype acute leukemia, LBP-CML, and MBP-CML, respectively. In patients with MBP-CML, the rates of CHR, CCyR, and MMR were 11.1%, 44.4%, and 11.1%, respectively. A total of 6 patients proceeded to alloHCT, and 4 were alive at last follow-up. None of the patients who did not proceed to alloHCT survived. Altogether, the combination of chemotherapy with TKI seems to yields better results than TKI alone [44]. For patients with good performance, who are a transplant candidate and able to tolerate an intensive chemotherapy regimen, the optimal choice of induction therapy may be FLAG-ida + ponatinib. Less fit patients should be offered decitabine plus TKI or TKI alone. In either case, the goal is to proceed to alloHCT if possible.

4.6 Lymphoid Blast Phase

Approximately 30% of BP-CML have a pre-B cell phenotype, while transformation to T-ALL is rare [45–47]. Patients with LBP-CML have a better prognosis when compared with patients with MBP-CML [25]. As with MBP, there is a paucity of data on the management of LBP-CML, and most data are extrapolated from *BCR:ABL1*-positive ALL studies (Table 5). The choice of TKI depends on prior TKI use, *BCR::ABL1* mutations, and co-morbidities.

4.6.1 Single-Agent TKI

Results of single-agent imatinib are poor, with a median survival of only 7 months [39]. The rates of CHR and CCyR were 21% and 32% for nilotinib, and 18% and 34% for dasatinib, respectively, in patients who progressed to LBP while on imatinib [48]. Overall survival at 24 months was 10% with nilotinib and 20% with dasatinib, highlighting the short duration of response with TKI alone in this patient population [48]. Both bosutinib [41, 49] and ponatinib were evaluated in patients who had received multiple TKIs. Of the 64 patients with BP-CML treated with bosutinib, 10 had LBP, 23 had MBP, and the rest were unclassified. The CHR rate was 17%, and CCyR rate was 28%. With ponatinib as a single agent, 62 patients with BP-CML were enrolled on the phase II trial, including 38 without and 24 with *BCR::ABL1*^{T315I}. The MaHR was 35% and 33% and CCyR 23% and 26% for those groups without and with *BCR::ABL1*^{T315I}, respectively.

4.6.2 TKI + Chemotherapy

In the largest study of TKI + chemotherapy in patients with LBP-CML, 42 patients received imatinib (27) or dasatinib (15) + hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone alternating with high dose methotrexate and cytarabine (HyperCVAD). Of those, 47% had a *BCR::ABL1* mutation, 74% had had prior TKI therapy, and 12% had had prior therapy for BP. Overall, 90%, 50%, and 25% achieved CHR, MMR, and undetectable *BCR::ABL1*, respectively. The median OS was 17 months with alloHCT. Dasatinib + HyperCVAD was associated with better OS in multivariate analysis (MVA) when compared with imatinib + HyperCVAD [50]. The combination of HyperCVAD + ponatinib is very active and probably superior to HyperCVAD + dasatinib in patients with *BCR:ABL1*-positive ALL [51]. On the basis of that data, we consider HyperCVAD + ponatinib to be optimal for all patients with LBP-CML and the only sensible choice for those who harbor *BCR::ABL1*^{T315I}. In the FLAG-ida + ponatinib trials discussed above, 4 of the 17 patients enrolled had LBP-CML. Interestingly, three patients had received imatinib for less than 5 months, indicating rapid development of LBP-CML. One patient had not received any prior TKI. Two achieved CCyR, one achieved PCyR, and one had no response. Both patients who achieved a CCyR achieved MMR [52]. All four patients proceeded to alloHCT. At the time of last follow-up, two of the four patients were alive (one non-responder and another who achieved PCyR)

4.6.3 TKI + immunotherapy

In a single-institution study of blinatumomab + ponatinib, six patients with LBP-CML were enrolled. With a median follow-up of 25 months, five (83%), three (50%) and two (33%) patients achieved CR/CRi, MMR, and undetectable *BCR::ABL1*, respectively [53]. Two of the five patients who achieved CR were alive in remission after a median follow-up of 25 months. Inotuzumab + bosutinib was also evaluated in 18 patients, including 2 with LBP-CML [54]. Overall, 83% achieved CR/Cri, and 56% achieved undetectable *BCR::ABL1*. One of the two patients with LBP-CML did not respond. CAR-T cell therapy is currently Food and Drug Administration (FDA)-approved for several hematological malignancies including *BCR:ABL1*-positive ALL. In a recent retrospective study, the outcome of 13 patients with LBP-CML who received CAR-T cell therapy was compared with 121 patients with *BCR:ABL1*-positive ALL. All outcomes were worse in LBP-CML compared with the *BCR:ABL1*-positive ALL patients. With a median follow-up of 30 months, the 2-year OS was 49.5% versus 74.5%, and the cumulative incidence of relapse was 83.9% versus 37.5% in the LBP-CML versus *BCR:ABL1*-positive ALL, respectively [55].

In summary, for patients who are eligible for intensive chemotherapy, the combination of HyperCVAD + ponatinib or blinatumomab + ponatinib should be considered. For patients not eligible for intensive chemotherapy, a TKI alone or TKI with immunotherapy would be the therapy of choice. The selection of TKI depends on *BCR::ABL1* genotype and

prior TKI exposure. Allotransplant is considered definitive consolidation until additional data are available to determine the durability of deep molecular responses on HyperCVAD/ponatinib or immunotherapy/ponatinib.

5 Allogeneic Hematopoietic Stem Cell Transplant

The outcomes of alloHCT in patients with BP-CML are inferior to those of AP-CML, and these in turn are inferior to the outcome of patients transplanted in CP-CML [56, 57]. A retrospective study from the Center for International Blood and Marrow Transplant Research (CIBMTR) and MDACC included 1361 patients with advanced-phase CML, of whom 1223 did and 138 did not receive an alloHCT. The study included patients with AP-CML both de novo and after TKI. With all the caveats of a retrospective study, there was no benefit for alloHCT over TKI continuation in patients with AP-CML. The study further confirmed that patients with de novo AP-CML may not need to proceed to alloHCT if responding appropriately. Outcome of patients with BP-CML was poor irrespective of approach; however, there was a trend for better outcome with alloHCT [58].

6 Choice of TKI

TKI selection in advanced-phase CML is dependent on prior TKI exposure, *BCR::ABL1* mutations, and co-morbidities. Approximately 50% of patients with advanced phase CML develop *BCR::ABL1* mutations. The best-known and most notorious mutation is *BCR::ABL1*^{T315I}. CML harboring *BCR::ABL1*^{T315I} is only sensitive to ponatinib or asciminib. As asciminib has very limited data in patients with AP/BP-CML, the choice in those patients is ponatinib. The sensitivity of other *BCR::ABL1* mutants to different TKIs is well studied, and the choice of TKI should be made on the basis of the available data [59, 60]. It is important to consider that the predictive value of a given *BCR::ABL1* genotype is stronger toward the negative side; i.e., no response is to be expected if a mutation is present that confers resistance. In contrast, the presence of a sensitive *BCR::ABL1* genotype does not guarantee response, as *BCR::ABL1*-independent mechanisms contribute to resistance. TKI selection needs to consider the side effect profile. For instance, one should avoid bosutinib in patients with chronic gastrointestinal (GI) problems, dasatinib in patients with a history of pulmonary disease or pleural effusions, and nilotinib/ponatinib in patients with high cardiovascular risk [61] (Table 6). All these are not absolute contraindications, but rather preferences. Generally, the more aggressive the clinical presentation, the less important tolerability is as a decision driver.

7 Experimental Therapies

Many experimental agents have been tested in BP-CML in addition to TKIs, but none of these combinations has achieved standard-of-care status. Conducting prospective clinical trials in this relatively rare and heterogeneous population is challenging and requires collaboration in large networks. For the purpose of our practical review, we will focus on approaches that are relatively close to the clinic, although they have not been evaluated in a prospective fashion. The BCL2 inhibitor venetoclax is FDA-approved for the therapy of patients with AML unfit for intensive chemotherapy. Based on its activity in AML and promising preclinical data in CML models, patients with MBP-CML were treated with venetoclax + TKI + chemotherapy. Of the nine patients reported in a retrospective study, four, three, one, and one received ponatinib, dasatinib, bosutinib, and nilotinib, respectively, which were combined with various chemotherapy backbones, including decitabine, cytarabine, clofarabine, cladribine, CPX-351, and anthracycline. Of the eight evaluable patients, six responded, with a median OS of 10.6 months [62]. The triple combination of decitabine, venetoclax, and ponatinib was evaluated in 15 patients with CML-AP (4), CML-MBP (10), or BCR:ABL1-positive AML (1). Overall, 40% achieved CR/CRi. The median OS was 11 months.

8 Conclusion

Advanced-phase CML is a rare disease with a paucity of data to guide optimal management. Decisions on therapy depend on several factors, including de novo versus secondary status, prior TKI, co-morbidities, transplant eligibility, and mutations. Further studies are needed to clarify the best therapy for those patients. Large national studies through cooperative groups or the H Jean Khoury Cure CML Consortium would be necessary to improve the outcome in this rare but important group of patients.

Declarations

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