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An Update on the Management of Advanced Phase Chronic Myeloid Leukemia

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Abstract

Purpose of Review While most patients with chronic myeloid leukemia (CML) present in a chronic phase and are expected to have a normal life expectancy, some patients present with or progress to a more aggressive accelerated phase (AP) or blast phase (BP) of CML. Herein, we discuss the diagnostic considerations of advanced phase CML and review its contemporary management.

Recent Findings Later-generation, more potent BCR::ABL1 tyrosine kinase inhibitors (TKIs) such as ponatinib may result in superior outcomes in patients with advanced phase CML. For CML-BP, combination approaches directed against the blast immunophenotype appear superior to TKI monotherapy. The role of allogeneic stem cell transplantation is controversial in CML-AP but has consistently been shown to improve outcomes for patients with CML-BP.

Summary Advanced phase CML, particularly CML-BP, remains a poor risk subtype of CML. However, novel combination approaches using later-generation TKIs are being explored in clinical trials and may lead to improved outcomes.

Keywords Philadelphia chromosome · BCR::ABL1 · Chronic myeloid leukemia · Ponatinib · Accelerated phase CML · Blast phase CML

Abbreviations

CML	Chronic myeloid leukemia
ELN	European LeukemiaNet
WHO	World Health Organization
BM	Bone marrow
WBC	White blood cells
ACA	Additional cytogenetic abnormality
PB	Peripheral blood
CNS	Central nervous system

Introduction

The outcomes of patients with chronic myeloid leukemia (CML) dramatically improved with the development of tyrosine kinase inhibitors (TKIs) targeting the BCR::ABL1 oncoprotein. Over 95% of patients with CML present with chronic phase disease (CML-CP), and in the current TKI era, most of these patients experience a normal life expectancy [1–3]. However, a minority of patients present with or eventually progress to more advanced phase disease (i.e., accelerated or blast phases) despite TKI therapy [4–7]. The outcomes of these patients with advanced phase CML are significantly worse than their counterparts with chronic phase CML, with survival outcomes that are akin to acute leukemias for patients with blast phase CML [8•]. However, the outcomes of patients with accelerated phase CML are more heterogeneous, and some patients may have relatively good outcomes with TKI monotherapy. Given the aggressive nature of advanced phase CML, more intensive, combination strategies are recommended for many of these patients, including strong consideration of allogeneic hematopoietic stem cell transplantation (HSCT), although the optimal therapy remains uncertain [9]. In this article, we will review the current classifications of advanced phase CML, risk factors for transformation, and contemporary management of both accelerated and blast phase CML, including the role of combination therapies, allogeneic HSCT, and novel treatment strategies that are being explored in ongoing clinical trials.

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Diagnostic Considerations

There are three commonly used consensus guidelines that provide definitions for advanced phase CML, including the MD Anderson Cancer Center (MDACC), European LeukemiaNet (ELN), and World Health Organization (WHO) criteria [10, 11••, 12••]. Historically, all 3 of these groups divided advanced phase CML into either accelerated phase CML (CML-AP) or blast phase CML (CML-BP); however, in a 2022 update, the WHO replaced CML-AP with the concept of "high-risk" CML, reflecting that some patients not meeting formal criteria for CML-AP using the previous definition can still have high-risk disease that may have poor prognosis and require more aggressive therapy.

Table 1 shows the definitions of CML-AP and CML-BP in these 3 consensus guidelines. Both MDACC and ELN define CML-CP as blasts ≥ 30%, while the WHO uses a cutoff of ≥ 20% [10, 11••]. Notably, all groups consider extramedullary leukemic involvement to be diagnostic of CML-BP. MDACC and ELN are unified in several criteria for CML-AP, including blasts 15–29%, clonal evolution occurring while on therapy, thrombocytopenia $< 100 \times 10^9$/L unrelated to therapy, and/or basophils > 20%; in addition, the MDACC model considers splenomegaly unresponsive to therapy to be a criterion for CML-AP. While most patients considered to have "high-risk" CML by the WHO would fall within the above definitions, this updated terminology accounts for patients with other high-risk features, for example, a patient with a low blast percentage but a 3q26.2 rearrangement [12••]. It should be noted that the optimal definitions of advanced phase CML are in flux. While we acknowledge that the term "high-risk" CML may eventually supplant that of "CML-AP," we refer to the historical definitions of CML-AP when discussing this entity in the present manuscript, as these definitions are most consistent with prior literature.

It is important to note that criteria for CML-AP (or "high-risk" CML) vary in their prognostic importance. Some additional chromosomal abnormalities (ACAs) such as alterations of 3q26.2, monosomy 7, and/or a complex karyotype are associated with particularly poor outcomes. This is in contrast with non-high-risk ACAs such as isolated trisomy 8 or -Y which have limited prognostic value [13–15]. Importantly, patients with these high-risk ACAs (particularly when they develop while on TKI therapy) may have significantly worse outcomes than patients with elevated blast percentage but without one of these high-risk ACAs [16].

Prevalence and Risk Factors for Advanced Phase CML

Presentation with advanced phase CML is relatively uncommon, observed in < 5% of patients at the time of CML diagnosis [6]. While some patients do progress to advanced phase CML despite adequate TKI therapy, the rate of transformation is less than was observed historically in the pre-TKI era, where transformation rates > 20% were reported [6]. For example, in the IRIS study that compared interferon alfa plus cytarabine to imatinib in patients with newly diagnosed CML-CP, patients in the non-TKI arm had a 12.8%

Table 1 Consensus Definitions of Advanced Phase CML

CML phase	Parameters	ELN 2020	MDACC	WHO 2016[a]	WHO 2022
Accelerated Phase	BM Blasts	15–29%	15–29%	10–19%	N/A[b]
	Platelets (x 10^9/L)	---	---	> 1000[c]	
		< 100[d]	< 100[d]	< 100[d]	
	WBC (x 10^9/L)	---	---	> 10[c]	
	Basophils	≥ 20%	≥ 20%	≥ 20%	
	Splenomegaly	---	Persistent or increasing[c]		
	Cytogenetics	Evolution of ACAs on therapy			
		---	---	Baseline ACA	
Blast Phase	PB/BM Blasts	≥ 30%	≥ 30%	≥ 20%	≥ 20%
	Disease location	CNS or extramedullary disease			

[a]The WHO 2016 criteria for CML-AP also included provision criteria for CML-AP which included failure to achieve complete response to TKI therapy or hematological resistance, occurrence of ≥ 2 ABL1 kinase domain mutations during TKI therapy, and/or any hematological, cytogenetic, or molecular indication suggesting resistance to TKI

[b]The WHO 2022 guidelines removed CML-AP as a diagnostic category and replaced it with the concept of "high-risk" CML

[c]Despite TKI therapy

[d]Not related to therapy

rate of transformation to advanced phase CML, compared with 6.9% in the imatinib arm [17]. Notably, this study allowed crossover between the 2 arms, and thus, the transformation rate in the absence of access to BCR::ABL1 TKI therapy is expected to have been even higher. With the development of even more potent later-generation TKIs and better guidance for monitoring of adequate molecular response and criteria to switch to alternative TKIs, the transformation rate in the modern era is < 5% by most estimates [9, 18].

There are several variables that may impact a patient's risk for developing advanced phase CML. These include both disease-related factors, such as baseline high-risk additional chromosomal abnormalities (e.g., – 7/7p, 3q26.2 rearrangements, and/or complex karyotype) [16, 19–21], high-risk mutations (e.g., *ASXL1*, *RUNX1*, *IKZF1*, *TP53*, or resistant *ABL1* kinase domain (KD) mutations) [22–30], or the rare *BCR::ABL1* e1a2 transcript (coding for the p190 BCR::ABL1 protein product) [31, 32], and patient-related factors, particularly adherence to daily TKI therapy [33]. Issues with proper gastrointestinal absorption of TKIs may also lead to subtherapeutic drug levels, increasing the chance for treatment failure and risk for transformation to advanced phase CML [34, 35]. Independent of the above factors, failure to achieve the recommended molecular response milestones during TKI therapy is predictive for a higher risk of transformation.

Treatment of CML-AP or High-Risk CML

De Novo CML-AP

TKI monotherapy is appropriate for many patients with de novo CML-AP as long as the expected response milestones are achieved, and most of these patients with de novo CML-AP have similar outcomes to their counterparts with CML-CP [36, 37]. In one report of imatinib therapy in 42 patients with newly diagnosed CML-AP, the 2-year progression-free survival (PFS) was 100% for patients with CML-AP by hematologic criteria alone, 93% for those with CML-AP due to the presence of ACAs alone (formally a criterion for CML-AP by the WHO), and 58% for those meeting both hematologic and ACA criteria for CML-AP, suggesting that imatinib monotherapy may be adequate for the former 2 groups but not for the latter group [36]. Notably, these differences in outcomes provide support for the newer WHO definition of "high-risk" CML rather than CML-AP. In another retrospective analysis of 51 patients with de novo CML-AP, second-generation TKIs resulted in a slightly higher but not statistically significant improvement in 3-year overall survival (OS) compared with imatinib (95% versus 87%, respectively), with survival in patients receiving a second-generation TKI that was similar to CML-CP [37]. Second-generation TKIs generally result in more rapid and deeper responses in CML and may be associated with lower rates of transformation from CML-CP to advanced phase disease, although a convincing OS benefit has not been observed in most studies [4, 5, 38, 39]. For these reasons, National Comprehensive Cancer Network (NCCN) guidelines generally recommend a second-generation TKI as first-line therapy for patients with de novo CML-AP, with the caveat that some patients may be safely treated with imatinib as long as appropriate response milestones are achieved [40].

Transformed CML-AP

Patients who progress to CML-AP while on TKI therapy have significantly worse outcomes than those who present with de novo CML-AP at the time of diagnosis [9]. In patients previously treated with imatinib, all the second-generation TKIs (i.e., dasatinib, nilotinib, and bosutinib) appear to result in similar rates of major cytogenetic response (MCyR) (30–50%) and complete cytogenetic response (CCyR) (20–40%), with better response rates observed in patients who were intolerant rather than resistant to imatinib [41–44]. Across studies, this has translated to OS rates of > 90% [45••].

For patients with CML-AP after failure of one or more second-generation TKIs, the outcomes are relatively poor with use of other second-generation TKIs. Ponatinib is a third-generation TKI that has broader activity against *ABL1* KD mutations, including T315I, which is a common mechanism of resistance to first- and second-generation TKIs [46]. In the PACE study, 83 patients with CML-AP with resistance or intolerance to dasatinib or nilotinib and/or harboring a T315I mutation received ponatinib monotherapy at a dose of 45 mg daily [47, 48]. Ponatinib resulted in a MCyR rate of 49%, a CCyR rate of 31%, and a major molecular response (MMR) rate of 22%, which translated to an estimated 5-year PFS of 22% and OS of 59% [48]. For patients with CML-AP experiencing treatment failure with a second-generation TKI, our practice is to generally use ponatinib-based therapy (or an appropriate clinical trial of a novel BCR::ABL1 TKI), as rotating through other second-generation TKIs results in suboptimal outcomes. However, several factors should be considered when selecting the appropriate TKI therapy in this scenario, including comorbidities, specific prior TKI therapies, and *ABL1* KD mutations. Given the relatively poor outcomes of patients with transformed CML-AP, TKI-based combination therapies can be considered (e.g., with a hypomethylating agent and/or venetoclax), although presently there are only scant data to support this approach in CML-AP.

Treatment of CML-BP

The outcomes of CML-BP are particularly poor, with a median survival generally less than 12 months.[9] Several factors may also influence the prognosis of patients with CML-BP. As with CML-AP, patients presenting with de novo CML-BP have superior outcomes to those who transformed while on TKI therapy.[8] The presence of high-risk cytomolecular features also impacts the clinical outcomes. Immunophenotype of the blast compartment is both prognostic and therapeutically important. CML in myeloid blast phase (CML-MBP) is approximately twice as common as CML in lymphoid blast phase (CML-LBP), and some patients can present with a biphenotypic blast phase or other rarer subtypes. Of note, CML-LBP generally has superior outcomes to CML-MBP. Immunophenotypic classification of the blast phase disease is crucial when selecting appropriate combination therapies for patients with CML-BP (i.e., an acute myeloid leukemia (AML)–like backbone for patients with CML-MBP and an acute lymphoblastic leukemia (ALL)–like backbone for patients with CML-LBP)[9].

TKI Monotherapy

Several studies have evaluated TKI monotherapy in patients with CML-BP, regardless of the immunophenotype. Outcomes with first- or second-generation TKI monotherapy are poor with relatively low rates of transient responses and median OS of 10 months or less across studies of imatinib, nilotinib, and dasatinib [49–51, 52•]. In the PACE study, ponatinib at a dose of 45 mg daily was evaluated in 62 patients with CML-BP (38 of whom were intolerant/resistant to imatinib, 24 with a T315I mutation) [47, 48]. The CCyR rate was only 18%, and the median PFS and OS were 3 months and 7 months, respectively, suggesting that outcomes are poor with ponatinib monotherapy for CML-BP, despite the relative potency of ponatinib compared with other commercially available TKIs. It should also be noted that while the OPTIC study showed that lower doses of ponatinib may offer the optimal risk–benefit profile for patients with CML-CP without a T315I mutation, there are no data to support lower doses of ponatinib monotherapy in CML-BP, regardless of T315I status [53•]. Newer TKIs are being studied in CML across different stages of disease, including asciminib and olverembatinib, although there are limited efficacy data in CML-BP. Overall, results are suboptimal with TKI monotherapy in CML-BP, and therefore, combination approaches should be strongly considered for most patients.

Combination Approaches for CML-MBP

Some studies suggest that the outcomes of patients with CML-MBP can be improved with combination therapies. In a retrospective analysis of 104 patients with CML-MBP, patients were stratified by the initial therapy received for BP disease (intensive chemotherapy alone [$n=8$], TKI alone [$n=56$], intensive chemotherapy plus a TKI [$n=20$], and hypomethylating agent plus a TKI [$n=20$]) [54]. Combination approaches resulted in higher rates of complete remission (CR) or complete remission with incomplete hematologic recovery (CRi) (57% versus 34%, $P<0.05$) and CCyR (45% versus 11%, $P<0.001$) as compared with TKI monotherapy. Driven in part by the higher rates of response, more patients who received combination therapy were able to be bridged to allogeneic HSCT (32% versus 11%, $P<0.01$). Combination therapy using a second- or third-generation TKI also resulted in higher rates of 5-year event-free survival (28% versus 0%, $P<0.05$) and 5-year OS (34% versus 8%, $P=0.23$), as compared with second- or third-generation TKI monotherapy. This study strongly supports the use of combination TKI-based therapies for patients with CML-MBP rather than TKI monotherapy.

In the prospective phase I/II MATCHPOINT study, 17 patients with CML-BP (MBP [$n=9$], LBP [$n=4$], mixed phenotype acute leukemia [$n=4$]) received FLAG-Ida (fludarabine, cytarabine, idarubicin, and G-CSF) plus ponatinib 30 mg daily [55]. The complete hematologic response (CHR) rate was 29%, CCyR rate was 47%, and MMR rate was 29%. With a median follow-up of 36 months, the median OS was 12 months and was not reached in patients who were bridged to allogeneic HSCT. The combination of decitabine and dasatinib was also explored in a prospective study of 19 patients with CML-BP (18 of whom had MBP) [56]. Seven of 17 evaluable patients (41%) achieved CHR, 5 of whom were consolidated with allogeneic SCT.

Combination therapies using a TKI and venetoclax are potentially promising future options for patients with CML-MBP. In a retrospective analysis of 9 patients with CML-MBP (all of whom had transformed on TKI therapy), 5 (56%) achieved CR/CRi, and 3 (33%) achieved CCyR, which translated to a median OS of 10.9 months. [57] In an ongoing phase II study of decitabine, venetoclax, and ponatinib for patients with advanced phase CML, 15 patients have been treated (MBP [$n=10$], transformed AP [$n=4$], Philadelphia chromosome–positive [Ph+] AML [$n=1$]) [58]. Eleven patients (73%) responded (including CR, CRi, and morphologic leukemia-free state [MLFS]), including 6 patients (40%) with CR/CRi. Four patients were bridged to allogeneic HSCT, and the median OS was 11 months. This study continues to accrue patients (ClinicalTrials.gov

NCT04188405), and this triplet combination may represent an effective option for patients with advanced phase CML, including CML-MBP, including those who are not candidates for intensive chemotherapy.

Combination Approaches for CML-LBP

The treatment approach for patients with CML-LBP is largely modeled after clinical experience with Ph + ALL. Most studies have used a hyper-CVAD (hyper-fractioned cyclophosphamide, vincristine, doxorubicin, and dexamethasone, alternating with high-dose methotrexate and cytarabine) backbone in combination with a TKI. In a retrospective study, 42 patients with CML-LBP (38 of whom transformed on prior TKI therapy) received either hyper-CVAD plus imatinib ($n = 27$) or dasatinib ($n = 15$) [59]. The complete hematological response rate (CHR) was 85% with imatinib and 100% with dasatinib, and the CCyR rates were 41% and 87%, respectively. Outcomes were superior in those who underwent subsequent allogeneic HSCT. In a later update with 23 patients with CML-LBP who received hyper-CVAD plus dasatinib, a 5-year OS of 59% was achieved, a survival outcome substantially better than reported in CML-MBP, highlighting the superior prognosis of CML-LBP [60].

Most patients with CML-LBP have a B cell immunophenotype, raising the potential for incorporating effective antibody therapies such as the anti-CD22 antibody–drug conjugate inotuzumab ozogamicin or the CD3-CD19 bispecific T cell engaging antibody blinatumomab that have shown efficacy in B cell ALL, including in some small studies of Ph + ALL [61, 62]. In an ongoing prospective study of blinatumomab plus ponatinib, 6 patients with CML-LBP were treated, 5 of whom (83%) achieved CR/CRi, including 3 with MMR and 2 with a complete molecular response (CMR) [63]. In a study of mini-hyper-CVD (dose-attenuated hyper-fractioned cyclophosphamide, vincristine, and dexamethasone, alternating with methotrexate and cytarabine), ponatinib, and blinatumomab, all 3 patients with CML-LBP achieved CR, including 2 with CMR [64].

The Role of Allogeneic HSCT in Advanced Phase CML

In the modern era, allogeneic HSCT is rarely needed for patients with CML-CP, although it still has a role for many—but not all—patients with advanced phase CML. An algorithm for the treatment of advanced phase CML and the role of allogeneic HSCT is shown in Fig. 1. For patients with de novo CML-AP, HSCT is not recommended for patients who meet appropriate molecular response milestones, as these patients can have excellent survival outcomes with TKI therapy [36, 37]. The role of allogeneic HSCT in patients with transformed CML-AP is more controversial. Some analyses have suggested no benefit with HSCT for patients with transformed CML-AP, especially then they received a ponatinib-based regimen; however, some patients with very high-risk CML-AP or with suboptimal response to TKI therapy still have poor outcomes and should be considered for HSCT [65, 66•]. While there are limited data to support HSCT decisions for CML-AP based on specific cytomolecular abnormalities, the presence of a 3q26.2 rearrangement is associated with a particularly poor prognosis, and its presence should prompt expeditious HSCT referral [20].

Most patients with CML-BP should be recommended for allogeneic HSCT if adequate response is achieved. Ideally, patients should proceed to HSCT after reversion to CML-CP, as this pre-HSCT response has been shown to be the strongest predictor of post-HSCT outcomes in patients with CML-BP [66•, 67]. In a retrospective analysis of patients with CML-MBP, allogeneic HSCT was associated with superior 5-year OS (58% versus 22% with no HSCT) [54]. In another analysis limited specifically to patients with T315I-mutated CML-BP who received ponatinib, HSCT was also associated with superior survival (4-year OS 26% versus 2% for no HSCT, $P = 0.026$) [68]. Allogeneic HSCT is also associated with superior outcomes in patients with CML-LBP, with a 5-year OS of 88% for patients who received hyper-CVAD plus dasatinib followed by HSCT versus 57% for those who did not proceed to HSCT ($P = 0.04$) [60]. However, it is possible that universal HSCT may not be required for patients with CML-LBP if adequate molecular response is achieved and with clearance of the malignant lymphoid clone using high-sensitivity next-generation sequencing measurable residual disease assays, as are commonly used to guide treatment decisions in ALL [69–71]. For patients with advanced phase CML who do undergo HSCT, the role of TKI maintenance is controversial. There was no benefit to this practice in a CIBMTR analysis, although it is still routinely used at many centers [72].

Conclusions

While the availability of more effective TKIs and guidelines to appropriately monitor therapeutic response have fortunately decreased the incidence of advanced phase CML, some patients still present with or develop CML-AP or CML-BP. Patients with de novo CML-AP can have excellent outcomes, but transformed CML-AP and CML-BP are still significant therapeutic challenges. These are

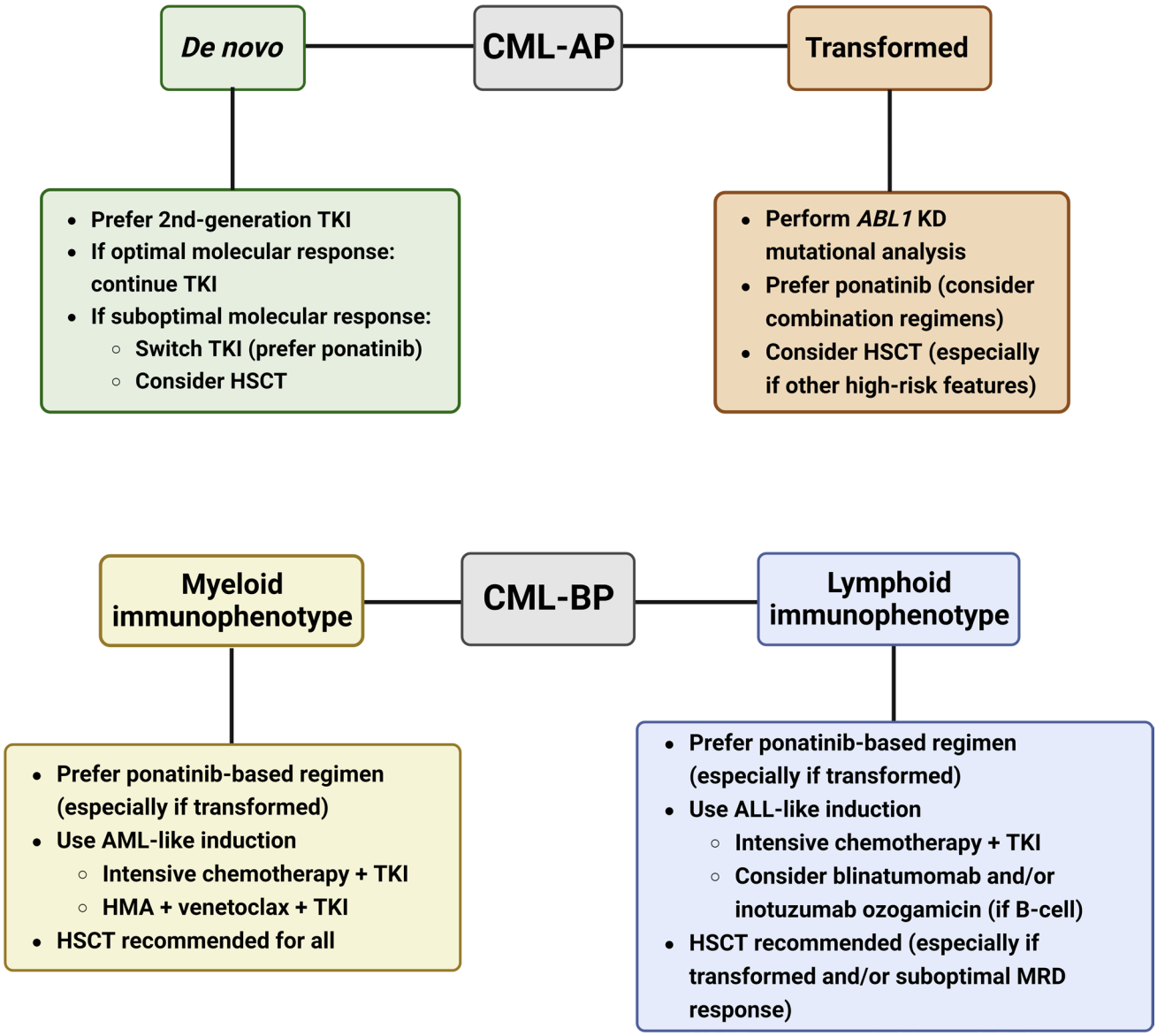

Fig. 1 Proposed treatment algorithm for patients with advanced phase CML. Abbreviations: CML, chronic myeloid leukemia; AP, accelerated phase; BP, blast phase; TKI, tyrosine kinase inhibitor; KD, kinase domain; HSCT, hematopoietic stem cell transplantation; AML, acute myeloid leukemia; HMA, hypomethylating agent; ALL, acute lymphoblastic leukemia; MRD, measurable residual disease

relatively rare diseases, and therefore, there is a paucity of robust data to guide therapeutic decisions for these entities. Given their aggressive nature, more potent TKIs such as ponatinib are generally preferred for patients without a contraindication, and combination therapies using an AML-like or ALL-like backbone have been shown to be more effective than TKI monotherapy for patients with CML-BP. Consolidation with allogeneic HSCT is recommended for most patients with CML-BP and can lead to long-term survival in a majority of patients, although the role of HSCT in patients with CML-AP is less clear. Ongoing studies with venetoclax-based combinations have shown preliminary efficacy in CML-MBP, and the use of inotuzumab ozogamicin and/or blinatumomab may also play an important role in the management of CML-LBP. Future studies understanding the pathobiology of advanced phase CML and mechanisms of resistance to BCR::ABL1 TKIs are needed to develop more effective therapies for this disease and hopefully further improve outcomes for these patients.

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Declarations

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Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- •• Of major importance

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