CML End Phase and Blast Crisis: Implications and Management

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Rüdiger Hehlmann, Susanne Saußele, Astghik Voskanyan, and Richard T. Silver

12.1 Introduction

Blast crisis (BC) is among the remaining challenges in the management of CML. Although an acute or terminal phase of CML has been mentioned in the beginning of the twentieth century [1], it was only in the 1960s that a definition of the terminal phase of CML was attempted. Morrow Jr. et al. [2] defined the terminal phase as the interim extending from the first clinical change heralding the onset of the final phase of disease to the time of death. Defining signs and symptoms were mainly fever, abdominal discomfort in the left upper quadrant, weakness, and dyspnea (without cardiac failure). Karanas and Silver [3] included laboratory values and determined that 30% myeloblasts and promyelocytes or more in the peripheral blood predicted death within 6 months more accurately than 20- < 30% myeloblasts and promyelocytes, hemoglobin <9 g%, <100.000/ml platelets, an increase of WBC after treatment of 2 weeks, or otherwise unexplained fever. In 1971 Canellos et al. [4] reported a subset of patients with blastic transformation that responded to vincristine and prednisone which was followed by the detection of terminal deoxynucleotidyl transferase (TdT) [5, 6] defining lymphoid as opposed to myeloid subtypes of BC.

BC is a malignancy that, as a rule, develops under the eyes of the treating physician. Indicators are clonal evolution with additional chromosomal abnormalities (ACA) reaching levels of up to 90% [7] and mutation levels including resistance mutations to tyrosine kinase inhibitor (TKI) treatment in up to 80% [8]. CML end phase comprises early progression with emerging high-risk ACA and late progression with failing hematopoiesis and blast cell proliferation (Fig. 12.1). BC is the end stage of this evolution. The incidence of BC has been greatly reduced by the introduction of TKI which demonstrates that BC can be prevented by effective therapy. Once BC has occurred, no effective therapy exists to date, except for the occasional return to a second chronic phase (CP2) after chemotherapy followed by transplantation [9]. Without transplantation, survival is generally less than 1 year with death due to infection or bleeding. Prevention of BC by careful monitoring treatment response and intensification of treatment, if response milestones are not reached, remain the mainstay of the treatment strategy.

R. Hehlmann (✉)
ELN Foundation, Weinheim, Germany

Medizinische Fakultät Mannheim, Universität Heidelberg, III.Medizinische Klink, Mannheim, Germany

S. Saußele · A. Voskanyan
Medizinische Fakultät Mannheim, Universität Heidelberg, III.Medizinische Klink, Mannheim, Germany

R. T. Silver
Division of Hematology/Medical Oncology, Weill Cornell Medical College, New York, NY, USA

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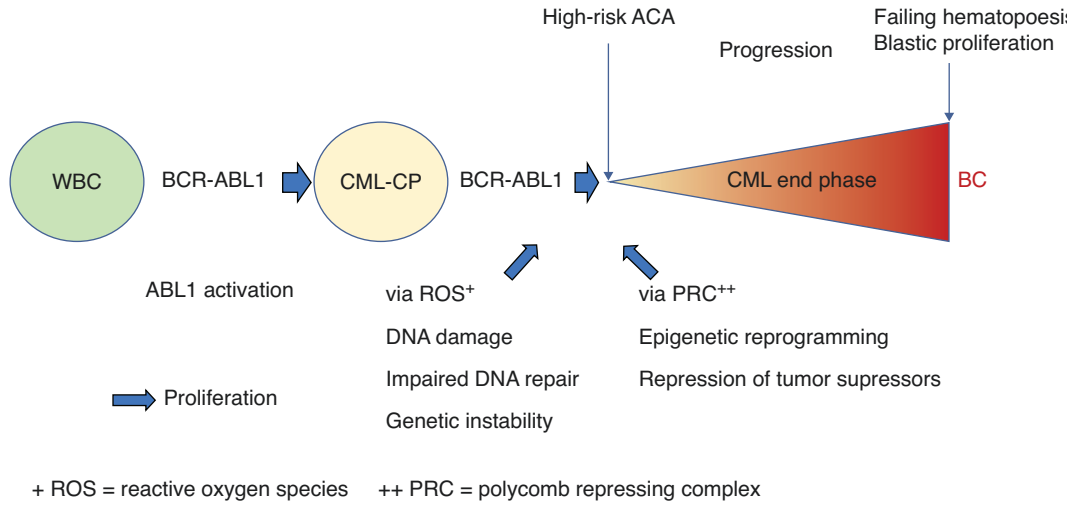

Fig. 12.1 Role of BCR-ABL1 in CML and progression to BC

For the advancement of prevention and treatment, several open questions need to be addressed:

1. Can we prevent progression to BC better by early treatment intensification according to response milestones and genetic markers (ACA, mutations)? Answer: carefully designed clinical trials with early treatment intensification could provide the answer (second generation TKI in ENESTnd, Dasision?).
2. Can we define a point in the course of the disease after which drug treatment cannot reverse clonal evolution (point of no return)? Possible answer: by systematic aligning genetic with hematologic and clinical findings.
3. What indicators precede an increase of blasts? Possible answer: careful dissection of the course of disease after the appearance of prognostically relevant genetic markers and as a proof of principle, following with targeted intervention.
4. Is genetic instability by BCR-ABL the single causative factor for clonal evolution or disease progression, or are there other predisposing factors? Answer: comparative analysis of clinical course and appearance of genetic markers with whole genome sequencing may be helpful.

This review gives a broad overview of diagnosis of BC, therapy, clonal evolution and early prediction of progression, and prevention of BC, as well as our opinion regarding the open questions.

12.2 Diagnosis

To diagnose BC, complete blood and differential counts, marrow cytology, and cytogenetics are required. Cytogenetic evolution is the most consistent predictor of blast transformation. Flow cytometry or cytochemistry is needed to determine the type of BC (myeloid or lymphoid). Molecular genetics with mutation analysis are needed to choose the appropriate TKI. Consensus recommendations for performing mutation analyses have been published by the European LeukemiaNet [8]. Tests at diagnosis and during follow-up are shown in Table 12.1.

Currently, diagnosis of BC rests on the percentage of blasts (20% or 30%) in blood or marrow [10–12], but not all patients dying of CML reach the BC-defining blast levels [13]. Earlier recognition of CML end phase might enable earlier intervention to improve prospects for BC.

Clinically, BC may present with night sweats, weight loss, fever, bone pain, or symptoms of anemia. An increased risk of infections and of bleeding is also observed. The common laboratory features include high white blood and blast cell counts, features of hematopoietic failure,

Table 12.1 Tests for BC diagnosis and monitoring of treatment

Test	Test rational
At diagnosis	
CBC with differential and marrow cytology	Proportions of blasts, promyelocytes, and basophils
Flow cytometry and/or cytochemistry	Myeloid or lymphoid phenotype
Cytogenetics	Baseline for follow-up and prognosis High-risk ACA
Molecular genetics	KD-mutation profile for choice of TKI Somatic mutations
Donor search (if applicable)	Preparation for Allo-SCT
For monitoring	
CBC with differential	Return to CP (CP2)
Marrow cytology with cytogenetics	Ascertainment of second CP or remission
Molecular genetics	Monitoring of BCR-ABL transcript levels under TKI treatment and after Allo-SCT
In lymphoid BC: CSF cytology	Intrathecal neuroprophylaxis

BC blast crisis, *CP* chronic phase, *CSF* cerebrospinal fluid, *CBC* complete blood count, *TKI* tyrosine kinase inhibitor, *SCT* stem cell transplantation, *ACA* additional cytogenetic aberrations, *PCR* polymerase chain reaction

additional cytogenetic aberrations (ACA) in addition to the Philadelphia (Ph) chromosome [14–22], and somatic mutations [23, 24].

Up to 90% of BC patients show chromosomal aberrations (termed major or minor route by Mitelman dependent on their frequency in BC) in addition to the Ph chromosome [7, 25] and up to 80% BCR-ABL1 KD mutations [8]. Various somatic mutations have been detected in BC or associated with poor risk disease when detected at diagnosis [23, 24]. Blast increase in blood or marrow represents the end stage of progression.

12.3 Genetically Based Risk Assessment

Genetically based risk assessment by ACA and somatic mutations has been proposed for a better recognition of patients at risk for progression to end phase CML and BC [26–29]. Analyzing single chromosome changes, Wang et al. [29] stratified the six most common ACA into two prognostic groups: a good risk group comprising +8, +Ph, and -Y and a poor risk group comprising i17(q10), −7/7q-, and 3q26.2 rearrangements. Based on BC-risk associated with each ACA, Gong et al. analyzed the time intervals from diagnosis to emergence of ACA, from emergence of ACA to onset of BC and survival with BC, and stratified ACA into three risk groups (high risk: 3q26.2; −7/7q-; i17(q10); complex karyotypes with high-risk ACA; intermediate 1: +8; +Ph; other single ACA; intermediate 2: other complex ACA). Hehlmann et al. suggested two groups: high-risk ACA with unfavorable impact on survival and low-risk ACA with no or little impact on survival. High-risk ACA are defined as the major route ACA +8, +Ph, i(7q), +19, +21 and + 17 (the ACA most frequently observed in BC) [7]; the minor route ACA −7/7q-, 3q26.2, and 11q23 rearrangements (less frequently observed, but negative impact on prognosis) [27, 29]; and complex aberrant karyotypes (Table 12.2). If present at low-blast counts, high-risk ACA herald death by CML [28].

Somatic mutations observed in BC and in poor-risk patients include mutations of genes associated with poor outcome also in other malignancies [30]. Also, they might enable early identification of patients at risk of progression. Frequently mutated genes include RUNX1, ASXL1, and IKZF1 [23, 24] (Table 12.2).

Mutations of the BCR-ABL tyrosine kinase domain have been observed in as many 80% of patients [8]. ABL mutations in late CP with initial imatinib resistance have been associated with a greater likelihood of progression to BC [31]. Other mutations associated with BC include p53 mutations in approximately 24% of myeloid BC, p16 mutations in approximately 50% of lymphoid BC [32, 33], and somatic mutations, such as RUNX-1, IKZF1 (Ikaros), ASXL1, WT1, TET2, IDH1, NRAS, KRAS, and CBL in 3–33% of myeloid and/or lymphoid BC [23, 24, 34, 35]. In addition, a profoundly altered gene expression profile has been reported in CD34+ BC cells compared with CP cells [36, 37]. Genes overexpressed, downregulated, or deregulated in BC

Table 12.2 Genetically based risk assessment

Chromosomal abnormalities	Somatic mutations		
High-risk ACA [29] [27] [28]	Mutated genes, selection	Frequency of mutation in BC (%) [24] $n = 39$	[23] $n = 46$
+8	RUNX 1	33,3	28
+Ph	ASXL 1	20,5	23
i(17q)	IKZF 1	17,9	33
+19	WT 1	15,4	NA
+21	TET 2	7,7	NA
+17	IDH 1/2	7,7	8
–7/7q-	CBFB/MYH11	NA	6
3q26.2	TP 53	2,6	3
11q23	ABL1-KD	33,3	58
Complex aberrant			

include SOCS2, CD52, HLA antigens, PRAME, JunB, Fos, FosB, Il8, and genes of the Wnt/β--catenin pathway [38]. Also, the evolution of gene expression profiles may allow diagnosis of disease progression [39, 40].

12.4 Pathogenetic Basis of Therapy

Treatment of BC is guided by our understanding of BC pathogenesis. Good in-depth reviews on the biology of BC have been published [41–43]. According to current evidence, BC is the direct consequence of continued BCR-ABL activity [41, 42], possibly via oxidative stress and reactive oxygen species [44, 45], causing DNA damage and impaired DNA repair [46] and, in a vicious circle, genomic instability by more mutations, gene doublings, translocations, and chromosomal breakages [47]. The latter effect of BCR-ABL would explain what is observed during clonal evolution and progression to BC. BCR-ABL has been shown to produce reactive oxygen species in hematopoietic cells [48].

An alternative model [49, 50] makes use of the observation that the polycomb repressive complex (PRC) gene BMI1 is a marker for predicting prognosis of CML [51]. Based on an integrated multiomics analysis, this model proposes pathway convergence in genetically heterogeneous BC by PRC-driven epigenetic reprogramming of BC progenitors. A PRC2-related gene set including EZH2 directs BC DNA hypermethylation silencing myeloid differentiation, whereas PRC1 including BMI1 represses tumor suppressors and maintains the BC transcriptome. Since BMI1 inhibitors (e.g., PTC596) de-repress genes involved in apoptosis, proliferation, and differentiation and since hypomethylating agents (decitabine) revert EZH2-directed hypermethylation, the model predicts that a combination of PTC596 and decitabine might prove effective for treating BC.

Figure 12.1 summarizes our current understanding of CP and BC pathogenesis.

12.5 Intensive Chemotherapy

Once BC has been diagnosed, management depends on prior therapy and type of leukemia (myeloid or lymphoid). In the late 1960s/early 1970s, attempts were made to treat BC with treatment protocols designed for acute leukemia (AL). It was observed that 30% of the patients responded to a combination of vincristine and prednisone as used for acute lymphoblastic leukemia (ALL) [4, 52]. The cells of the responding BC frequently showed features of lymphoid morphology and were TdT+ [5]. These observations have led to the distinction of lymphoid and myeloid variants of BC. The response rates to vincristine and prednisone and other drugs used for ALL, such as 6-thioguanine, 6-mercaptopurine, cytosine arabinoside, and methotrexate, ranged between 15 and 50%. Response was only of short duration. Responders survived a median of 3–10 months compared with 1–5 months in nonresponders.

Between 1980 and 1990, AML-type induction therapies were applied, including various combinations of anthracyclines, cytosine arabinoside, 5-azacytidine, etoposide, carboplatin, fludarabine, and decitabine [53]. A return to CP (CP2) was observed in approximately 10% of patients, opening a window for transplantation. No cures

in the absence of stem cell transplantation were observed. Overall, treatment of BC was less successful than that of de novo acute leukemias despite considerable intensity (and toxicity), but the advantage offered by a second CP prior to allo-SCT was recognized. Best results are probably achieved for patients who return to CP and are then successfully transplanted.

12.6 TKI Therapy

The clinical improvement with more effective treatment (10-year BC incidence 5.8–6.9% in CML study IV [54] and in the IRIS trial [55] compares to 70% BC incidence 25 years ago) is shown in Fig. 12.2. This decrease in BC incidence occurs in parallel with a reduction of BCR-ABL1 indicating that BC can be prevented by effective therapy. Treatment outcome supports the conclusion that BCR-ABL1 is the driving force behind disease progression (Fig. 12.1). Currently, most BC cases occur early after start of therapy (Fig. 12.3) indicating the disease had progressed to an advanced phase even though it appeared phenotypically early. A minority of patients progress to BC later during the course of the disease suggesting continued disease activity in some patients. Population-based progression rates are similar to those in clinical trials [56].

The transient nature of response to TKI in BC shows that most cells are still sensitive to BCR-ABL1 inhibition but that BCR-ABL1 independence has been achieved in some cells which have a growth advantage. It follows that the most effective management of BC would be its prevention by early reduction of tumor burden and elimination of BCR-ABL1.

12.7 Imatinib

1. Treatment of de novo BC should be started with imatinib, 600–800 mg/day. If the response is unsatisfactory, dasatinib 140 mg once daily or nilotinib 400 mg twice daily according to mutation profile (Table 12.3) should be tried A sensitive detection of BCR-ABL1 mutations is now possible by NGS [57]. If the profile indicates the T315I mutation, ponatinib should be

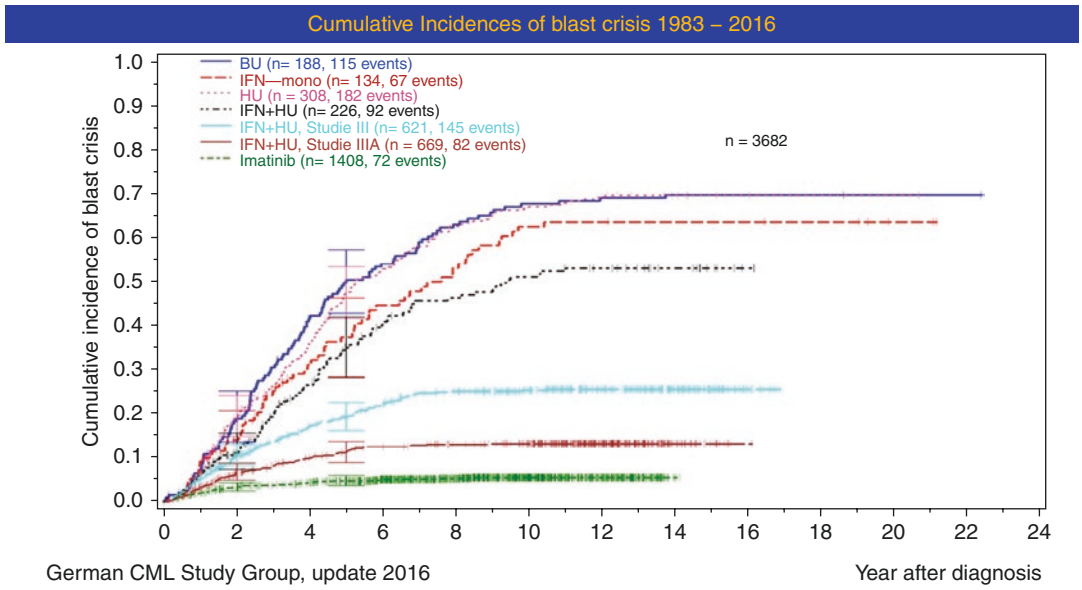

Fig. 12.2 Prevention of BC by more effective therapy. Update to [58]. *Bu* busulfan, *HU* hydroxyurea, *IFN* interferon alpha

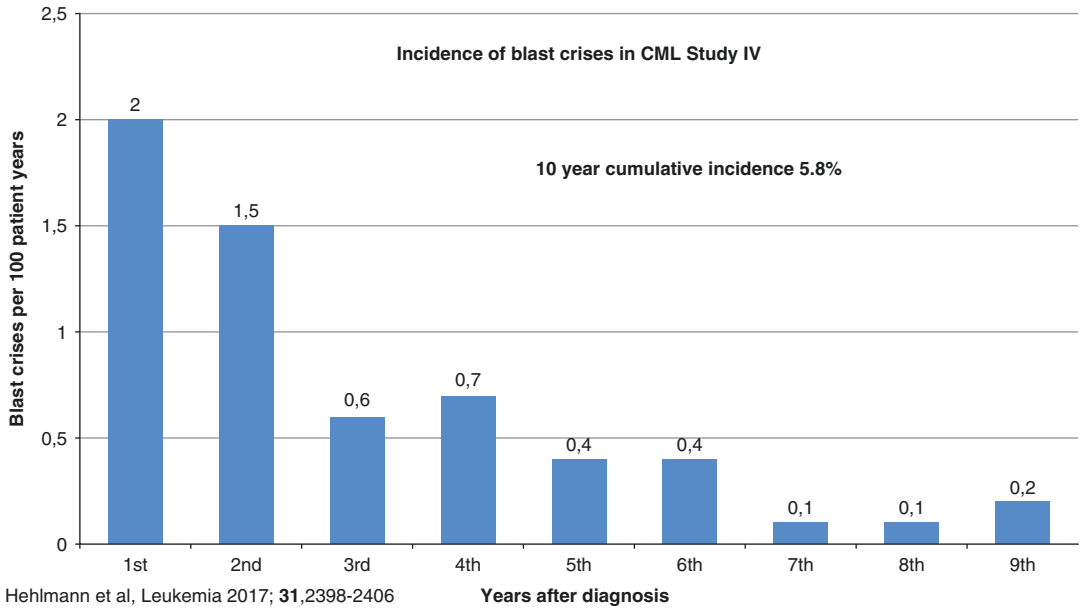

Fig. 12.3 Incidence of BC over time. Ten-year cumulative incidence of BC is 5.8% (Hehlmann et al. 2017)

Table 12.3 TKI indications based on KD mutation profile

F317L/V/I/C, T315A	Nilotinib or ponatinib
V299L	Nilotinib or ponatinib
Y253H, E255V/K, F359V/I/C	Dasatinib, bosutinib[a] or ponatinib
T315I	Ponatinib

[a]In vitro data suggest that E255K and, to a lesser extent, E255V might be poorly sensitive to bosutinib

given at a dose of 45 mg daily. Allo-SCT should be planned as early as possible [9]. Imatinib, dasatinib, bosutinib, and ponatinib have been approved for all phases of CML, including BC, by the Food and Drug Administration and the European Medicine Agency.

Five studies of 484 BC patients, 50 with lymphoid BC, showed hematologic remission rates of 50–70% (70% in patients with lymphoid BC), cytogenetic response rates of 12–17% (all responses), a 1-year survival of 22–36%, and a median survival of 6.5–10 months [59–63].

2. If BC evolves during imatinib therapy, treatment with a second- or third-generation TKI (dasatinib 140 mg, nilotinib 400 mg twice daily, bosutinib 500 mg, or ponatinib 45 mg each daily, respectively, according to mutation profile) combined with intensive chemotherapy as necessary should be given such as combinations of dasatinib or ponatinib + FLAG-IDA [64, 65], or with high-dose cytarabine and daunorubicin ("7 plus 3," [66]), for myeloid BC, or combinations of imatinib or dasatinib + hyperfractionated CVAD for lymphoid BC [67] and allo-SCT planned as quickly as possible. Cytopenias may necessitate TKI dose reduction or treatment interruption, transfusion of erythrocytes and platelets, or, in case of neutropenia, treatment with G-CSF.

12.8 Dasatinib

Three studies of 400 BC patients who had been previously treated with imatinib, including 119 with lymphoid BC, showed hematologic remission rates of 33–61% (lymphoid BC, 36–80%), major (MCR) cytogenetic remission rates of 35–56%, a 1-year survival of 42–50%, a 2-year survival of 20–30%, and a median survival of 8–11 months [68–70].

The largest of the studies, a randomized open-label phase 3 study of 214 BC patients stratified for myeloid or lymphoid (61) type, attempted to

optimize the dose schedule of dasatinib, comparing dasatinib at 140 mg once daily with 70 mg twice daily. The study yielded similar efficacy for both doses and had improved tolerability for the once-daily regimen [69]. Pleural effusion, which was observed in as many as one-third of the patients, necessitated dose reduction, diuretics, and, in some cases, corticosteroids.

Dasatinib crosses the blood-brain barrier and shows long-lasting responses in Ph + CNS disease [71]. It is speculated that these effects, which differ from imatinib, are the result of the dual specific SRC/BCR-ABL TK-inhibitory property of dasatinib. Dasatinib maintenance is recommended in responders not suitable for allo-SCT.

12.9 Nilotinib

Two studies of 169 patients including 40 with lymphoid BC [72, 73] reported a hematologic response rate of 60% in all patients (59% in lymphoid BC), major cytogenetic response rates of 38% in myeloid BC and 52% in lymphoid BC, a 1-year survival of 42%, a 2-year survival of 27%, and a median survival of 10 months (7.9 months for lymphoid BC). Hyperglycemia, which is observed in as many as 40% of nilotinib-treated patients, required monitoring and may necessitate dose adjustment. Nilotinib has been approved for treating CP and accelerated phase (AP) CML, but not BC.

The outcomes with dasatinib and nilotinib are similar to those with imatinib.

12.10 Imatinib in Combination

Several small studies have focused on the combination of imatinib at 600–800 mg with chemotherapy or other agents. In a phase 1/2 trial of 16 BC patients, imatinib 600 mg daily was combined with mitoxantrone/etoposide [74]. Hematologic response rate was 81% with a 1-year survival of approximately 50%, including six patients who had an allo-SCT. Another study combined imatinib 600 mg with decitabine in ten patients and reported a median survival of 15 weeks [75]. The combination of imatinib 600 mg with low-dose cytosine arabinoside and idarubicin in 19 patients with myeloid BC showed hematologic remissions in 47%. Median survival was 5 months [76]. In a phase 1 study with the combination of the farnesyltransferase inhibitor lonafarnib with imatinib, two of three BC patients showed hematologic improvement [77]. A study of 12 patients combining imatinib and homoharringtonine after priming with G-CSF reported hematologic or cytogenetic response in all patients [78]. Rea et al. [79] reported results of 31 patients with Ph-positive ALL or lymphoid BC treated with imatinib 800 mg/day, vincristine, and dexamethasone. Twenty-eight of 30 evaluable patients achieved complete cytogenetic remissions at a major molecular response level or better. Of 19 patients under 55 years, nine were transplanted and eight were alive 7–23 months afterward. Deau et al. [80] evaluated 36 patients with myeloid BC treated with imatinib 600 mg/day, cytosine arabinoside over 7 days, and daunorubicin up to 45 mg/m^2/day over 3 days. A complete hematologic response of 55.5% was achieved, median survival of all patients was 16 months, for responders 35.4 months, and for transplanted patients the median survival has not been reached.

None of these studies has provided convincing evidence that any of the combinations are superior to imatinib alone.

12.11 Dasatinib or Nilotinib in Combination

Milojkovic et al. [65] reported four patients who progressed to BC while on imatinib and were successfully treated with dasatinib 100 mg daily combined with fludarabine 30 mg/m^2 IV, days 1–5; cytosine arabinoside 2 g/m^2 IV, days 1–5; idarubicin 12 mg/m^2 IV, days 1–3; and G-CSF 300 mg/day sc, days 0–6 (FLAG-IDA). All patients were alive, three after and one prior to SCT. Strati et al. treated 42 BC patients with hyperfractionated cyclophosphamide, vincristine, adriamycin, dexamethasone (HCVAD) plus imatinib, or dasatinib. CCR was achieved in

58%, complete molecular remission in 25% of patients. Eighteen patients received allo-SCT in hematological remission. Median survival was 17 months and was longer in SCT recipients [67]. Ghez et al. reported on five BC patients treated with a combination of 5-azacytidine and dasatinib or nilotinib. Two patients were transplanted; one died of relapse. All other patients are alive and in hematologic remission after 11–33 months [81].

12.12 Bosutinib and Ponatinib

Bosutinib, a third second-generation TKI, shows in preliminary analyses of 48 BC patients similar activity (CCR, 29%; MMR, 28%; PFS, 7.8 months) as dasatinib and nilotinib [58, 82].

The pan-BCR-ABL third generation TKI ponatinib has, in addition to recognizing the T315I mutation, efficacy in BC and Ph + ALL. A phase 2 study of 449 ponatinib-treated patients included 62 patients in BC. After a 6 months median follow-up of the BC patients, a major cytogenetic remission rate of 18% was observed [83]. OS at 12 months was 20%.

In a recent UK study of 17 BC patients, ponatinib was given at 30 mg/day in combination with FLAG-IDA followed by allo-SCT and ponatinib maintenance [64]. One-year OS was 45.8% as estimated by the Kaplan-Meier method.

A drawback of ponatinib is its toxicity profile which requires a thorough risk-benefit assessment [84, 85]. Vascular events at a dose of 45 mg/d may be reduced by smaller doses (15, 30 mg/d).

12.13 Prognostic Factors

A cohort study of 477 BC patients [86] treated with any TKI approved for CML (imatinib, dasatinib, nilotinib, bosutinib, ponatinib) and in part combined with chemotherapy (46%) and allo-SCT (22%) showed a median OS of 12 months. By multivariate analysis, prognostic factors were analyzed for risk of death. Myeloid BC, prior TKI, age ≥ 58 years, high LDH, low platelets, no history of SCT, secondary BC, and chromosome 15 abnormalities were found to predict for an increased risk of death. The findings await confirmation.

12.14 Overall Treatment Strategy

If TKIs fail, conventional approaches remain an option, such as AL induction protocols with cytosine arabinoside and anthracyclines in myeloid BC or with vincristine and prednisone (combined with dasatinib) in lymphoid BC.

Patients with suboptimal responses by ELN criteria [87] and with less than DMR after 2–3 years (less than MR^4) should have a genetic evaluation. In patients with high-risk ACA, more intensive treatment, e.g., by allo-SCT, may be indicated. Current treatment approaches to end phase CML are summarized in Fig. 12.4.

Treatment depends on disease stage: Elimination of BCR-ABL1 by effective TKI treatment is expected to prevent progression. When high-risk ACA emerge, intensification of treatment should be considered. Also, there is evidence that earlier allo-SCT is more successful in patients with high-risk ACA. An appropriate time for changing treatment may occur when high-risk ACA emerge rather than waiting for the appearance of or an increase in blasts. Cytogenetic monitoring is indicated when response to therapy is unsatisfactory. AP should be treated as high-risk CML. Allo-SCT is recommended if response to drug treatment is not optimal. Treatment of BC consists of intensive combination chemotherapy based on AML regimens for myeloid, and ALL regimens for lymphoid, BC with or without a TKI in preparation for a prompt allo-SCT if possible. Lymphoid BC has more treatment options and a better outcome than myeloid BC.

In patients who cannot tolerate intensive chemotherapy regimens, a more palliative approach using less intensive therapy according to immunophenotype should be considered such as vincristine and prednisone in lymphoid BC.

There is emerging evidence that high-risk ACA is an indication for a timelier change of treatment which may result in a better outcome [28]. Comparing allo-SCT outcome in early with late end phase, a clinically relevant,

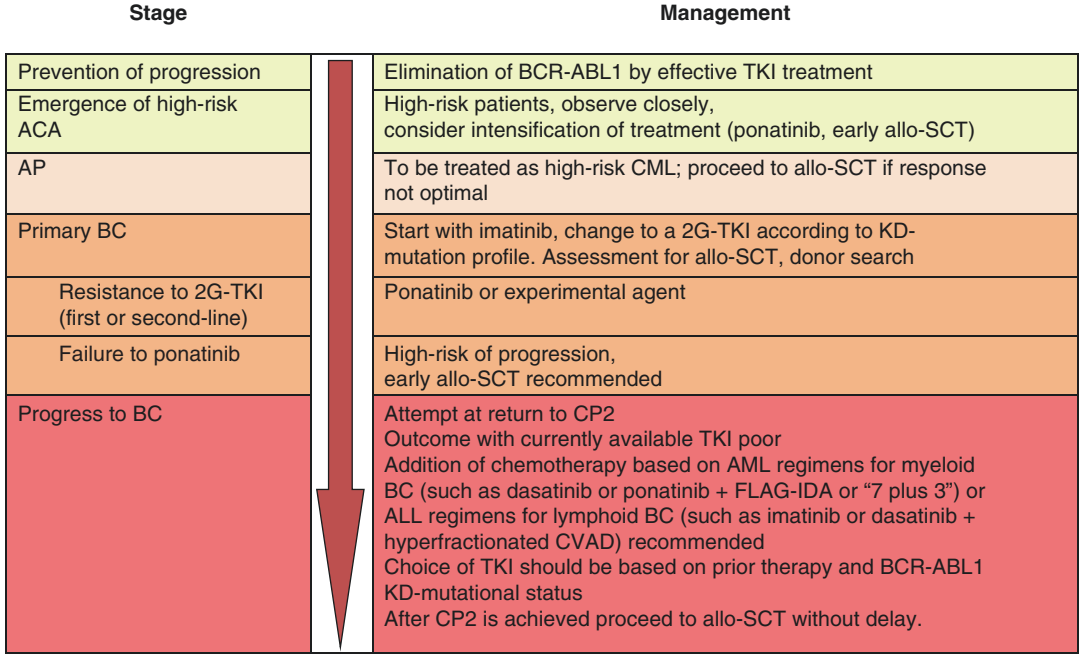

Fig. 12.4 Management strategy for end phase CML. The arrow indicates worse progression. *CP2* second chronic phase

though not statistically significant difference of 30% in 2-year survival suggests that outcome of transplanted patients with high-risk ACA depends on disease stage similar to patients without ACA [88].

In summary, survival after BC is better after treatment with TKI than after conventional therapies, but with a median survival of less than 1 year, outcome is still unsatisfactory. A 10-year survival of 19% after TKI versus 3% after conventional treatment is promising. This is illustrated in Fig. 12.5 which depicts the German CML Study Group experience. The majority of BC survivors have received a transplant.

12.15 Allo-SCT

Allo-SCT is successful in only a minority of BC patients after achieving a chemotherapy-induced remission. Nevertheless, it probably has the best outcome in BC, if the patient can tolerate the procedure and if a donor is available (Fig. 12.5). The search for a donor should be started as early as possible. In an overview of the European Group for Blood and Marrow Transplantation from 1980 to 2003, 2-year survival rates were 16–22% [89]. Most patients were transplanted in the pre-imatinib era. In a report from the German CML Study Group which was updated in 2014, the 6-year survival of 28 imatinib-pretreated patients transplanted in advanced phases (25 in BC) was 49% [9, 90]. Similar data were reported in a retrospective analysis of 83 BC patients by a Chinese group [91]. 38 BC patients were treated with allo-SCT after TKI and 45 received TKI only. After a follow-up of 30–126 months, 4-year OS was significantly better for the allo-SCT group compared to the group with only a TKI (47% vs. 10%). Another German group analyzed 40 advanced-phase patients and reported a 43% OS after 3–5 years [92].

Data suggest that allo-SCT represents the best chance of long-term survival after BC, if a second CP has been achieved.

Current experience recommends allo-SCT in primary BC after an attempt has been made with a suitable TKI selected according to mutation profile in combination with chemotherapy as

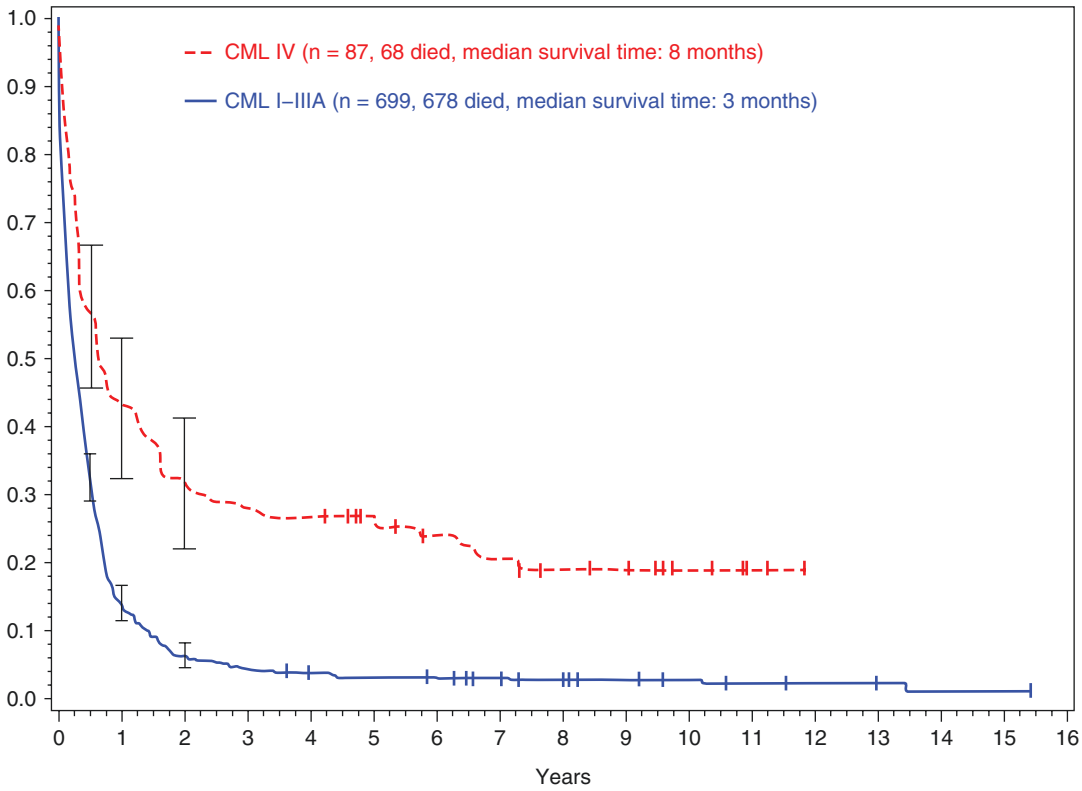

Fig. 12.5 Survival of BC patients under conventional therapy and TKI. German CML Study Group experience, updated (M. Lauseker, 2020 unpublished). Ten year survival after TKI is 19%, after conventional therapy 3%. Fifteen of 20 living patients (75%) have been transplanted

needed to achieve a second CP. In lymphoid BC, dasatinib should be combined with vincristine, prednisone, and HCVAD.

Transplantation should be performed with an HLA-identical related or matched unrelated or, if unavailable, haploidentical donor and an EBMT score of 0–4 [93]. Standard conditioning with busulfan and cyclophosphamide or total body irradiation should be used. Reduced intensity conditioning is not recommended in this situation unless it is a clinical study. Sudden-onset BC during imatinib treatment is a rare event, but full disease eradication by allo-SCT may be successful [94] and is warranted. Posttransplantation maintenance with TKI appears reasonable. Maintenance with dasatinib is recommended in lymphoid BC for neuroprophylaxis, since as mentioned, it crosses the blood-brain barrier. Monitoring of BCR-ABL transcript levels should be done at regular intervals: 3 months initially, 6 months later on, if transcripts are not detectable or stable.

As a consequence of these observations and recommendations, more CML patients are now transplanted in second chronic or advanced phases than in first CP [95].

12.16 Investigational Agents

A number of new approaches are under investigation. A selection is presented in Table 12.4. The approaches include activation of the tumor suppressor protein phosphatase 2A (PP2A), which has decreased activity in BC [111] through upregulation of its inhibitor suppressor of variegation, enhancer of zeste and trithorax (SET), and cancerous inhibitor of PP2A (CIP2A) [98, 99], or in combination with TKI [100]; inhibition of self-renewal of leukemia stem cells (LSCs) by

Table 12.4 Investigational approaches (selection)

Principle/mode of action	Agent (s)	Target (s)
PP2A activation	Fingolimod (FTY720) [96]	PP2A
	SET antagonist OP449 [97]	SET
	CIP2A inhibitor [98, 99]	CIP2A
PP2A inhibition	Sensitization of LSC to TKI [100]	Drug-insensitive LSC
Survival of LSC	BCL6 + TK inhibitors [101]	BCL6 + BCR-ABL
	HIF1α inhibitor [102]	HIF1α
	Smoothened inhibitors in combination with TKI (dasatinib, nilotinib) [103]	Smoothened (hedgehog pathway) + BCR-ABL
	Jak2 inhibitor SAR 302503+ dasatinib [104]	Jak2 + BCR-ABL, LSC
	Jak2/STAT 5 inhibition by nilotinib + ruxolitinib [105]	CML CD34+ cells
Activation of apoptosis	BCL2 inhibitor ABT-737 [106]	Anti-apoptotic proteins
	Triptolide [106] Venetoclax [118]	Anti-apoptotic proteins
	MEK inhibitor PD184352 + farnesyltransferase inhibitor BMS-214662 [107]	MEK1, MEK2, RAS
Repurposing	Axitinib (approved for renal cell cancer) [108]	BCR-ABL, T315I, BC
High-throughput sensitivity and resistance testing (DSRT)	295 anticancer agents screened: VEGFR, NAMPT inhibitors identified [109]	CML-BC
Induction of differentiation	Nilotinib + arsenic trioxide [110]	CML-BC
Epigenetic reprogramming and repression of tumor suppressors	BMI1 inhibitor PTC596 + Hypomethylating agent decitabine [50]	BMI1 EZH2

TKI tyrosine kinase inhibitor, *PP2A* protein phosphatase 2A, *LSC* leukemia stem cells, *MEK* mitogen-activated protein kinase, *VEGFR* vascular endothelial growth factor receptor, *NAMPT* nicotinamide phosphoribosyltransferase

pharmacologic inhibition of BCL6 in combination with BCR-ABL inhibition [101], of hypoxia-inducible factor 1α [102], or of smoothened which plays a role in the hedgehog pathway and is essential for the maintenance of LSC [112]; and induction of apoptosis [106, 107]. Targeting the phosphatidylinositol-3 kinase/AKT/mammalian target of rapamycin (mTOR) activation, Xie et al. reported successful treatment of a patient with myeloid BC by the combination of rapamycin and imatinib [113]. Another approach is repurposing of already approved drugs as has been proposed for axitinib, an antiangiogenic agent for treating renal cell carcinoma which also inhibits T315I mutant BCR-ABL [108]. A novel concept is the search for drug candidates effective in BC by high-throughput testing. Candidate drugs include vascular endothelial growth factor receptor (VEGFR) and nicotinamide phosphoribosyltransferase (NAMPT) inhibitors [109]. Immune checkpoint inhibitors which have been shown to improve prognosis in a variety of cancers [114, 115] are thought to offer promise also for myeloid antigens [116] and high-risk CML. After failure of at least two previous TKIs, the allosteric BCR-ABL1 inhibitor asciminib has shown efficacy in some patients with the T315I mutation or in AP [117]. Venetoclax, in combination with BCR-ABL1 TKI, has been studied in 16 Ph + heavily pretreated patients with AML (7) and myeloid BC (9). The median OS of 10.9 months for BC patients indicates some efficacy of the combination in view of the heavy pretreatment [118]. Because of the numerous blastic genotypes and their instability, no single therapeutic approach can soon be expected to be successful in all patients.

12.17 Prevention

The reduction of BC incidence with more effective therapy indicates that BC can be prevented (Fig. 12.2). Also, it is well known that very low or undetectable BCR-ABL transcripts after allo-SCT correlate with low relapse rates [119].

Further, imatinib-treated patients who have achieved DMR enjoy durable responses with virtually no current progression to AP or BC [120]. Patients who have achieved stable complete molecular remission may experience continued remission in the absence of maintenance treatment in approximately 40% of cases [121]. The challenge therefore is to identify those patients who are at early risk to develop to BC and to be able to offer more effective treatment to this special patient group.

12.18 Early Predictors of Progression

At diagnosis, risk scores provide information on the likelihood of progression [122–125]. The EUTOS score [123], developed from imatinib-treated patients, has a predictive value of 34% of not reaching a CCR by 18 months. It also recognizes a small group of high-risk patients (~12%) with a significantly higher progression rate. Distinct markers such as high-risk ACA [28], $p190^{BCR\text{-}ABL}$ [126], and signs of acceleration may also be suitable for early prediction of progression. CIP2A levels at diagnosis have been reported predictive of BC [98, 99].

The relevance of clonal evolution has not changed in the imatinib era [14, 15]. The types of chromosome abnormalities associated with progression are not altered by TKI treatment [16]. Patients with high-risk ACA are defined as high-risk patients by the ELN 2020 recommendations [87] and indicate treatment failure if they appear under therapy [127].

Failure to achieve defined response landmarks may detect high-risk patients as early as 3–12 months after diagnosis [128–131]. These include cytogenetic and molecular responses determined by monitoring all patients. Measurement of the velocity or halving time of the early decline of BCR-ABL transcripts may increase sensitivity and specificity of response measurement [132, 133]. Patients who do not respond satisfactorily and are classified as high risk may need alternative approaches, such as early second-generation TKI, treatment intensification, or an early allo-SCT [127]. If the patients have a donor and have no medical contraindications, the risk of progression to BC has to be weighed against the risks of early transplantation and of chronic GVHD. With the current progress in donor selection and posttransplantation management, the risk of transplantation seems acceptable if compared with the risk of BC. If the patient is too old or has other medical contraindications that preclude allo-SCT or has no donor, investigational agents may be tried.

12.19 Conclusion

The strategy outlined in Fig. 12.4 offers an overview of the management of a patient with BC. The treatment goal is to induce a second chronic phase (CP2) characterized by a cytogenetic or molecular remission. The main form of treatment should be a TKI followed promptly by allo-SCT if possible. If TKIs are not sufficient, for myeloid BC, cytosine arabinoside and anthracyclines in combination with dasatinib or ponatinib should be considered; for lymphoid BC, hyperfractionated CVAD plus imatinib or dasatinib (or prednisone and vincristine) may be used. Management of de novo BC follows the same principles, except that imatinib should be tried first. Treatment decisions are adapted to the need and situation of each patient. Hematologic, cytogenetic, and molecular monitoring are mandatory (Table 12.1). Cytopenias may necessitate dose adaptive substitution therapy and treatment with G-CSF. In lymphoid BC, intrathecal neuroprophylaxis is indicated. Investigational approaches are recommended only after all other options have failed.

In view of the limited therapeutic options once BC has developed, the best management is prevention by rigorous and early reduction or elimination of BCR-ABL1. Regular molecular monitoring is required. Patients with high-risk features at diagnosis, unsatisfactory response to therapy (e.g., no major cytogenetic response or less than 90% BCR-ABL reduction by 3 months), or signs of progression under therapy,

such as clonal evolution and high-risk ACA, should receive more intensive therapies. With the availability of second- and third-generation BCR-ABL inhibitors and allo-SCT as needed, every attempt should be made to eliminate BCR-ABL1 as early as possible. More efficacious therapies and early treatment intensification in patients with high-risk features or unsatisfactory responses will likely further reduce progression to BC.

12.20 Summary

TKIs have moderately prolonged survival after BC. The best prognosis is observed in patients who achieve a second CP (CP2). Allo-SCT probably further improves prognosis of patients in CP2. The choice of TKI should be directed by the mutation profile of the patient. If ponatinib is given, risk and benefit should be carefully weighed in view of its vascular risks. Likely, BC may be prevented. A careful analysis of risk factors for progression is therefore needed. Treatment intensification in patients at risk of progression may improve prognosis, but controlled studies are not available. Much is known of genetic instability and clonal evolution as causes of BC, but confirmation of our understanding by successful intervention as proof of principle is lacking.

12.21 Practice Points

- Initial diagnostics of BC should include immunophenotyping and mutation profile to direct choice of therapies.
- Cytogenetics is of prognostic value (high-risk ACA) with a more intensive approach encouraged for high-risk karyotypes.
- Treatment options include intensive chemotherapy, TKI, and allo-SCT. Treatment may improve survival but, overall, outcome remains unsatisfactory.
- Prevention of BC seems possible. The risk of progression requires careful assessment and treatment intensification in patients at risk, although prospective trials supporting this concept are still lacking.
- A better pathophysiologic understanding of clonal evolution and progression to BC is expected to result in improved outcome.

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