How I treat CML blast crisis

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Abstract

Blast crisis (BC) is the major remaining challenge in the management of chronic myeloid leukemia (CML). It is now generally accepted that BC is the consequence of continued BCR-ABL activity leading to genetic instability, DNA damage and impaired DNA repair. Most patients with BC carry multiple mutations, and up to 80% show additional chromosomal aberrations in a non-random pattern. Treatment with tyrosine kinase inhibitors (TKI) has improved survival in BC modestly, but most long term survivors are those who have been transplanted.

Patients in BC should be treated with a TKI according to mutation profile +/- chemotherapy with the goal of achieving a second chronic phase and proceeding to allogeneic stem cell transplantation (allo-SCT) as quickly as possible. Although long term remissions are rare, allo-SCT provides the best chance of a cure in BC. Investigational agents are not likely to provide an alternative in the near future.

In view of these limited options prevention of BC by a rigorous and early elimination of BCR-ABL is recommended. Early response indicators should be used to select patients for alternative therapies and early transplantation. Every attempt should be made to reduce, or eliminate BCR-ABL consistent with good patient care as far as possible.
Introduction

Blast crisis (BC) is the major remaining challenge in the management of chronic myeloid leukemia (CML). The introduction of an inhibitor targeted at the BCR-ABL tyrosine kinase (imatinib) has fundamentally changed treatment of CML.¹ BCR-ABL expression can be reduced by imatinib to very low or non-detectable levels in the majority of patients.² Median survival in chronic phase (CP) is estimated at a median of 25 to 30 years. Progress to advanced phase CML or BC has been reduced to 1 - 1.5% per year ¹ as compared to more than 20% per year in the pre-imatinib era.³ Prevalence of CML is estimated to increase by a factor of about 10 within the next 40 years.⁴ Once BC has appeared, however, the prognosis of imatinib treated patients is not much better than that after conventional therapy.⁵ Median survival after diagnosis of BC currently ranges between 7 and 11 months as compared to 3 to 4 months in the pre-imatinib era. Very few long term survivors after diagnosis of BC have been reported. Most of these represent recipients of transplants during a second CP. The therapeutic dilemma of BC has recently been well summarized.⁶ More research is needed to fully understand the mechanisms underlying progression to BC. It is distressing that in CML BC a true malignancy evolves under our eyes. The two current burning questions in CML are: How can we best manage patients who progress to BC in spite of appropriate treatment? How can we best prevent BC?

How I define and diagnose BC

First attempts at the definition of BC date back more than forty years.⁷ The generally used definition which underlies virtually all current clinical CML trials and the European LeukemiaNet (ELN) management recommendations rests on at least 30% blasts in blood or marrow or the demonstration of extramedullary blastic infiltrates.⁸ The more recent WHO definition proposes a blast count of 20% in analogy to the definition of acute myeloid

³
leukemia (AML). Both definitions are not supported by biological evidence. A new definition would regroup approximately 10% of patients. Patients with 20 to 29% blasts have significantly better prognoses than patients with more than 30% blasts. Since most clinicians and trialists would likely use the definition based upon their own data and experience I suggest awaiting the results of clinical and biological research for a new evidence-based definition of BC.

To diagnose BC, I do complete blood and differential counts and a bone marrow analysis with cytogenetics (Table 1). Cytogenetic evolution is the most consistent predictor of blast transformation. Flow cytometry or cytochemistry are needed to determine the type of BC (myeloid or lymphoid). Molecular genetics with mutation analysis are needed to choose the appropriate tyrosine kinase inhibitor (TKI). Consensus recommendations when to perform mutation analyses have been published on behalf of the ELN. A donor search for allo-SCT should be started immediately.

What are the clinical and laboratory features observed in BC? Do they play a role in prognostic prediction?

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 WBC and blast counts, decreased hemoglobin values and platelet numbers and, in up to 80% of BC patients, additional cytogenetic aberrations (ACA) in addition to the Philadelphia (Ph)-chromosome. Most frequent are the so called “major route” ACA (trisomy 8, additional Ph-chromosome, isochromosome (17q), trisomy 19) which are non-random and considered relevant for the pathogenesis of BC. Less frequent are the so called “minor route” cytogenetic aberrations involving chromosome 3 aberrations, loss of the Y-chromosome and other rarer aberrations. Minor route ACA are less likely involved in
BC-pathogenesis and may mainly indicate genetic instability. The impact of major route ACA at diagnosis on progression and survival has been shown.\textsuperscript{15}

A variety of mutations has been associated with progression to BC. Mutations of the BCR-ABL tyrosine kinase domain have been observed in up to 80\% of patients.\textsuperscript{11,16} ABL-mutations in late CP with upfront imatinib resistance have been associated with a greater likelihood of progression to BC.\textsuperscript{17} Other mutations associated with BC include p53 mutations in about 24\% of myeloid BC, p16 mutations in about 50\% of lymphoid BC\textsuperscript{18,19} and more recently characterized mutations such as RUNX-1, IKZF1 (Ikaros), ASXL1, WT1, TET2, IDH1, NRAS, KRAS and CBL in 3 – 33\% of myeloid and/or lymphoid BC.\textsuperscript{20-22} In addition, a profoundly altered gene expression profile has been reported in CD34 positive BC cells as compared to CP cells.\textsuperscript{23,24} Genes overexpressed, down regulated or deregulated in BC include SOCS2, CD52, HLA antigens, PRAME, JunB, Fos, FosB, II8 and genes of the Wnt/ß-catenin pathway.\textsuperscript{25}

Several features have been associated with an unfavorable prognosis such as clonal evolution, more than 50\% blast cells, high platelet counts, short duration of the CP and extramedullary disease.\textsuperscript{26-28} Although non-random, chromosomal individuality of each clonal evolution is a characteristic feature of BC similar to other cancers, which has been compared with speciation in evolution.\textsuperscript{29,30} The most important predictor of a poor prognosis is an unsatisfactory response to initial therapy.

**What is the rationale for treating BC?**

Treatment of BC is guided by our understanding of BC pathogenesis. Good in depth reviews on the biology of BC have been published.\textsuperscript{31-33} According to current evidence BC is the direct consequence of continued BCR-ABL activity\textsuperscript{31}, possibly via oxidative stress and reactive oxygen species (ROS)\textsuperscript{34,35}, causing DNA damage and impaired DNA repair\textsuperscript{36} (Figure 1) and,
in a vicious circle, genomic instability by more mutations, gene doublings, translocations and chromosomal breakage.\textsuperscript{37} 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 ROS in hemopoietic cells.\textsuperscript{38}

This consideration underlies the therapeutic principle in CML to hit “hard and early” in order to reduce the BCR-ABL positive cell pool as early and as deep as possible and to thereby achieve the best possible outcome.\textsuperscript{39} The validity of this principle may be limited by quiescent CD34 positive CML cells which evade currently available pharmacotherapy\textsuperscript{40} or by a speculative preexisting genetic instability responsible for the generation of BCR-ABL.\textsuperscript{41} The clinical improvement by TKI treatment in parallel to BCR-ABL reduction and the postponement (or prevention) of BC in most patients with TK-inhibition (8-year-incidence of BC in IRIS \textsuperscript{1} less than 8\% under standard imatinib) support the conclusion that BCR-ABL is the driving force behind disease progression. The transient nature of response to TK-inhibition in BC demonstrates that most cells are still sensitive to BCR-ABL inhibition, but that BCR-ABL independence has been achieved in some cells which then 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-ABL.

This is confirmed by experience of the German CML Study Group (Fig. 2). The cumulative incidence of BC, as a consequence of more effective treatment early on, has decreased from close to 70\% after 8 years 25 years ago to currently about 5\% in CML Study IV under an optimized dose of imatinib.\textsuperscript{42}

**Management of BC - what we have learned from the pre-imatinib era**

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) whereas 70% did not.\textsuperscript{43-45} The cells of the responding BC frequently showed features of lymphoid morphology and were TdT positive.\textsuperscript{46} 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, ara-C and methotrexate ranged between 15% and 50%. Response was only of short duration. Responders survived a median of 3 to 10 months as compared to 1 to 5 months in non-responders.

In the 1980s and 1990s AML-type induction therapies were applied including various combinations of anthracyclines, ara-C, 5-azacytidine, etoposide, carboplatin, fludarabine, decitabine, etc.\textsuperscript{47} In a series of 162 patients with nonlymphoid BC, 31 patients treated with decitabine showed a trend for better survival at lower toxicity.\textsuperscript{48} In total, a return to CP was observed in about 10% opening a window for transplantation. No cures in the absence of stem cell transplantations were observed.

Overall, treatment of BC turned out to be less successful than that of AL in spite of considerable intensity (and toxicity), but the chance offered by a second CP for allo-SCT was recognized.

### What progress in the management of BC is offered by the availability of TKI

Once BC has been diagnosed and without clear targets available for inhibition, management depends on previous therapy and type of leukemia (myeloid or lymphoid). Best results are achieved for the few patients that return to CP and are successfully transplanted.

1. If the patient has been pretreated with conventional therapy (IFN or hydroxyurea, meanwhile the exception), a TKI (imatinib 600 – 800 mg/day, dasatinib 140 mg once daily or nilotinib 2 x 400 mg/day according to mutation profile) should be given and allo-SCT planned. Outcomes of trials with imatinib and other TKI in BC are summarized in
Table 2. Imatinib and dasatinib have been approved for all phases of CML including BC by the Food and Drug Administration and the European Medicine Agency.

**Imatinib:** Five studies on 484 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 one year survival of 22%-36% and a median survival of 6.5 – 10 months. 28,49-52

2. If BC evolves under imatinib, treatment with a 2nd generation TKI (dasatinib 140 mg or nilotinib 2 x 400 mg according to mutation profile) combined with chemotherapy as necessary should be given and allo-SCT planned as quickly as possible. In case of V299L, T315A, or F317L/V/I/C mutations, nilotinib is probably more effective than dasatinib. In case of Y253H, E255K/V, or F359V/C/I mutations, dasatinib is probably more effective than nilotinib. 11 In case of the T315I mutation an investigational approach e.g. with ponatinib should be tried. 53 Cytopenias may necessitate TKI-dose reduction or treatment interruption, substitution of erythrocytes and platelets or, in case of neutropenia, treatment with G-CSF.

**Dasatinib:** Three studies on 400 BC-patients pretreated with imatinib including 119 with lymphoid BC showed hematologic remission rates of 33%-61% (lymphoid BC 36%-80%), major cytogenetic remission (MCR) rates of 35%-56%, a one year survival of 42%-50%, a two year survival of 20%-30% and a median survival of 8–11 months.54-56

The largest of the studies, a randomized open label phase 3 study on 214 patients with 61 in lymphoid BC tried to optimize the dose-schedule of dasatinib, stratified for lymphoid and myeloid BC, and compared dasatinib at 140 mg once daily with 70 mg twice daily. The study yielded similar efficacy and improved tolerability for the once daily regimen. 56 Pleural effusion which is observed in up to one third of dasatinib treated BC patients may necessitate dose reduction, diuretics and, in some cases, corticosteroids.
Dasatinib crosses the blood-brain barrier and shows long lasting responses in Ph- positive central nervous system (CNS) disease.\textsuperscript{57} It is speculated that these effects which are different from imatinib are due to the dual specific SRC/BCR-ABL TK-inhibitory property of dasatinib. Dasatinib maintenance is recommended in responders not suitable for allo-SCT.

\textbf{Nilotinib:} Two studies have been published on 169 patients including 40 with lymphoid BC \textsuperscript{58,59} reporting hematologic response rates of 60\% (lymphoid BC 59\%), major cytogenetic response rates of 38\% (myeloid BC) and 52\% (lymphoid BC), a one year survival of 42\%, a two year survival of 27\% and a median survival of 10 months (7.9 months for lymphoid BC). Hyperglycemia which is observed in up to 40\% of nilotinib treated patients requires monitoring and may necessitate dose adaptation. Nilotinib has been approved for treating CP- and accelerated phase (AP)-CML, but not yet BC.

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

\textbf{Bosutinib}, a third 2\textsuperscript{nd} generation TKI shows in preliminary analyses similar activity in advanced phase CML as dasatinib and nilotinib.\textsuperscript{60} Bosutinib has not yet been approved for CML.

3. If TKI fail, conventional approaches remain an option, such as AML induction protocols with anthracyclines and araC etc. in myeloid BC or a trial with vincristine and prednisone (combined with dasatinib) in lymphoid BC, or 3\textsuperscript{rd} generation TKI within a clinical trial.

In summary, survival after BC is better after treatment with TKI than after conventional therapies, but with a median survival of less than one year, outcome is still unsatisfactory.

The modest survival progress that is achieved by TKI after BC is illustrated by the experience of the German CML Study Group in Fig. 3. Median survival has increased from 4 months in the pre-imatinib era (n=699) to 9 months under imatinib (n=65).
When I recommend allogeneic stem cell transplantation (allo-SCT)

If a return to CP or a complete remission has been achieved, I proceed to allo-SCT as quickly as possible, if the patient can tolerate the procedure and has a donor. The search for a donor should be instituted as early as possible. The best outcome continues to be observed in patients after transplantation, although allo-SCT is successful in only a minority of BC patients mostly after prior return to a second CP. In an overview of the European Group for Blood and Marrow Transplantation from 1980 - 2003 two year survival rates are 16%–22%. Most patients were transplanted in the pre-imatinib era. In a recent report from the German CML Study Group, 3 year survival of 28 imatinib pretreated patients transplanted in advanced phases (25 in BC) was 59%. The data show convincingly that allo-SCT represents the best chance of long term remission or cure in BC. 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 needed to achieve a second CP. In lymphoid BC, dasatinib should be combined with vincristine and prednisone.

In BC after imatinib failure a 2nd generation TKI (according to mutation profile) has to be weighed against other options such as AL-type therapy (also in combination with TKI) to give the best chance of a return to CP or cyto reduction. If patients carry the T315I mutation, this has to be considered in choosing the appropriate regimen (investigational agents such as ponatinib, AL-type therapy) followed by allo-SCT. Transplantation should be performed with a HLA identical related or matched unrelated donor and an EBMT-score 0-4. Standard conditioning with busulfan and cyclophosphamide (BuCy) or total body irradiation (TBI) should be used. Reduced intensity conditioning is not recommended in this situation outside studies. Sudden onset BC under imatinib is a rare event, but full disease eradication by allo-SCT may be successful and is warranted. Post-transplantation maintenance with TKI
appears reasonable. Maintenance with dasatinib is recommended in lymphoid BC for neuroprophylaxis as it is known to cross 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 recommendations more CML patients are now transplanted in second chronic or advanced phases than in first CP. Most long term survivors shown in Fig. 3 represent transplant recipients (72%).

What is the promise of new investigational approaches?

A number of investigational approaches are under exploration. A selection is shown in Table 3. Some agents are in clinical trial and can be tried after conventional treatments (TKI and AL-type therapy) have failed. Some approaches may be suitable for BC prevention.

**Imatinib in combination**: Several small studies have focused on the combination of imatinib at 600 mg – 800 mg with chemotherapy or other agents. In a phase 1/2 trial on 16 BC-patients imatinib 600mg daily was combined with mitoxantrone/etoposide. Hematologic response rate was 81% with a one year survival of about 50% including 6 patients after allo-SCT. Another study combined imatinib 600 mg with decitabine in 10 patients and reported a median survival of 15 weeks. The combination of imatinib 600 mg with low dose ara-C and idarubicin in 19 patients with myeloid BC showed hematologic remissions in 47%. Median survival was 5 months. In a phase 1 study with the combination of the farnesyltransferase inhibitor lonafarnib with imatinib 2 out of 3 BC patients showed hematologic improvement. A study on 12 patients combining imatinib and homoharringtonine after priming with G-CSF reported hematologic or cytogenetic response in all patients. None of these studies has provided convincing evidence that the combinations are superior to imatinib alone.
3rd generation TKI: New 3rd generation TKI such as the pan-BCR-ABL inhibitor ponatinib show promise, since in addition to recognizing the T315I mutation, ponatinib also shows efficacy in BC and Ph+ ALL. A phase 2 study on 449 ponatinib treated patients, 94 in BC or Ph+ ALL, showed after a median follow-up of about 5 months, complete cytogenetic remission (CCR) and major molecular remission (MMR) rates in BC of 27% and 22%, respectively. No data on survival were reported yet. Similarly, the ABL switch pocket inhibitor DCC-2036 showed efficacy against T315I and in BC in a phase 1 study. These TKI may be the best choice of investigational agents in clinical trials.

PP2A activation: A new target of interest is the tumor suppressor protein phosphatase 2A (PP2A) which shows decreased activity in BC through upregulation of its inhibitors suppressor of variegation, enhancer of zeste and trithorax (SET) and cancerous inhibitor of PP2A (CIP2A). The PP2A activator fingolimod (FTY720) induces apoptosis in CML-BC and Ph+ALL progenitors and may be a candidate for BC-treatment and prevention. Likewise, a novel SET antagonist (OP449) is selectively cytotoxic to CML cells and restores PP2A’s tumor suppressive function. Also CIP2A inhibition increases PP2A activity.

Self-renewal of leukemia stem cells: Another target potentially relevant for BC management or prevention is the self-renewal of leukemia stem cells (LSC) in vivo or leukemia initiating cells (LIC) in vitro. BCL6 has been identified as a critical effector of the BCR-ABL downstream target FoxO in self-renewal signaling of CML initiating cells. Pharmacologic inhibition of BCL6 in combination with BCR-ABL inhibition is proposed for eradication of LIC in CML. Dual inhibition of BCL6 and BCR-ABL is an interesting approach that merits exploration for application to BC, but BCL6 inhibitors are not yet available for clinical use. A similar role for survival maintenance of CML stem cells has been reported for the hypoxia-inducible factor 1α (HIF1α), a master transcriptional regulator of the cellular and systemic...
hypoxia response.\textsuperscript{80} Inhibition of the HIF1$\alpha$-pathway may provide another strategy for eradicating LSC in CML.

Clinical studies are ongoing to explore antagonists of the transmembrane protein smoothened (SMO) which plays a role in the hedgehog pathway and is essential for the maintenance of LSC\textsuperscript{81,82} such as cyclopamine, GDC-0449 (Genentech), LDE225 (Novartis), BMS833923 or PF0444913 (Pfizer) in combination with 2\textsuperscript{nd} generation TKI for activity against BC-LSC and self renewal.\textsuperscript{83} GDC-0449 has shown activity in basal cell carcinoma (18 of 33 patients responded)\textsuperscript{84} and in medulloblastoma. Similarly, the Jak2-inhibitor SAR503 in combination with dasatinib significantly reduced LSC suggesting abolishment of LSC self renewal capacity.\textsuperscript{85}

A new cell surface biomarker, IL1 receptor accessory protein (IL1 RAP), has been specifically identified on CML stem cells and might offer a new therapeutic target in the future.\textsuperscript{86}

\textit{Induction of apoptosis}: Preclinical studies are investigating activation of apoptosis in BC-cells by various drugs and combinations. The BCL2 inhibitor ABT-737 combined with imatinib or with the diterpenoid triptolide reduces anti-apoptotic proteins thereby inducing apoptosis and cell death in K562 cells and in cells from BC-patients.\textsuperscript{87,88} The MEK inhibitor PD184352 combined with the farnesyltransferase inhibitor BMS-214662 similarly induces apoptosis in K562 cells and CD34+ CML stem cells.\textsuperscript{89} Also p53 stabilization with the novel compound MI-219 which inhibits human homolog double minute 2 induces apoptosis in cell-line and primary BC-cells.\textsuperscript{90} And recently, the dual Jak2/Abl kinase inhibitor ON044580 was shown to induce apoptosis in cells from BC patients and in imatinib resistant cells including T315I.\textsuperscript{91}

\textit{More drugs} are in clinical and in preclinical evaluation. These drugs include omacetaxine (a semisynthetic derivative of homoharringtonine),\textsuperscript{92} arsenic trioxide which showed synergy
with imatinib, histone deacetylase (HDAC) inhibitors, aurora kinase inhibitors alone or in combination e.g. with TK- or HDAC-inhibitors, HSP90 inhibitors, mTOR inhibitors (rapamycin), and other substances (for review see Giles et al. 93, 2008, Quintas-Cardama 2008 94 and 2009 95 and Hehlmann et al., 2011 4).

None of these approaches is likely to provide a breakthrough in the near future, since due to the numerous blastic genotypes and their instability no single therapeutic approach can soon be expected to be successful in all patients.

Can BC be prevented? Is early prediction possible?

The low progression rates of CML under TKI indicate that BC can be prevented (see Fig. 2). Also, it is well known that very low or undetectable BCR-ABL transcripts after allo-SCT correlate with low relapse rates.96,97 Imatinib treated patients who have achieved MMR enjoy durable responses with virtually no progression to AP or BC up to now.42,98 Patients who have achieved stable complete molecular remission experience, in about 40% of cases, continued remissions even in the absence of treatment.99 The challenge is how to identify early those patients who are at risk to proceed to BC in order to be able to offer alternative treatment to this patients group.

At diagnosis, risk scores provide information on the likelihood of progression.100,101 The EUTOS score which was developed from imatinib treated patients has a predictive value of not reaching a CCR by 18 months of 34% and recognizes a small group of high risk patients (ca. 12%) with a significantly higher progression rate.102 *In addition, distinct markers such as major route ACA 15, p190 BCR-ABL 103 and signs of acceleration may be suitable for early

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* The EUTOS score uses two variables at diagnosis (spleen size in centimeters below costal margin and percentage basophils) and separates two risk groups. It is calculated by the formula: EUTOS score = (7x basophils) + (4 x spleen size). A score of >87 indicates high risk.
prediction of progression (table 4). Also BMI1 and CIP2A levels at diagnosis have been reported predictive of BC. 74,104

Another indicator of progression risk is clonal evolution i.e. the acquisition of ACA in the course of the disease. 105-108 The relevance of clonal evolution has not changed in the imatinib era. 109-112 Mutations may be associated with clonal evolution. 113 The pattern of chromosome abnormalities is not altered by TKI treatment. 114 The prognostic impact of ACA may depend on the type of ACA. 112 Some ACA types (major route, complex karyotypes) appear to imply poorer prognosis than others that may only indicate genetic instability. 115 Acquired ACA are high risk features by ELN definition and indicate treatment failure if they appear under therapy. 8 The prognostic relevance of rare clonal evolution in Ph-negative cells (observed in less than 5% of cases) remains uncertain. 116-119 The evolution of gene expression profiles may also allow to diagnose disease progression. 120

Early response indicators are the probably best predictors of progression. 8,121 These include cytogenetic and molecular responses determined by monitoring all patients. Failure to achieve defined landmarks will detect high risk patients as early as 3 months after diagnosis. 122-124 Table 4 summarizes the response levels and time points for response categorization 42,98,122-124 Patients who do not respond satisfactorily and are classified as high risk need alternative approaches, such as early 2nd generation TKI, treatment intensification or an early allo-SCT. 8,125 If the patients have a donor and have no medical contraindications, the risk of progression to BC has to be weighed against the risk of early transplantation and of chronic graft-versus-host-disease. With the current progress in donor selection and post-transplantation management the risk of transplantation seems acceptable if compared to the risk of BC. If the patients are too old or have other medical contraindications that preclude allo-SCT or have no donor, investigational agents should be tried (Table 3).
Conclusion - how I manage CML-BC

The algorithm in Fig. 4 gives an overview on how I approach management of a patient with BC. Treatment goal is the return to CP or the induction of a remission. Mainstays are TKI taking into account the type of mutation (see above), and allo-SCT as quickly as possible. If TKI alone are not sufficient, AL-type induction therapy should be tried, araC and anthracyclines for myeloid BC, vincristine and prednisone in lymphoid BC, or TKI in combination with AL-type induction therapy. Management of primary BC follows the same principle except that imatinib should be tried first in myeloid BC. Treatment decisions have to be adapted to the individual patients' situations and needs as required. Hematologic, cytogenetic and molecular monitoring are mandatory (Table 1). Cytopenias may necessitate dose adaptation, substitution therapy and treatment with G-CSF. In lymphoid BC, intrathecal neuroprophylaxis may be indicated. Investigational approaches are recommended only after all other options have failed. Allo-SCT without prior return to CP or at least cytoreduction is a high risk procedure and discouraged. An option is transplantation in aplasia without waiting for marrow recovery.

In view of the limited therapeutic options once BC has been diagnosed the best management of BC is probably its prevention by a rigorous and early reduction to low levels, or elimination of BCR-ABL. Regular molecular monitoring is required (Table 4). The current understanding of pathogenesis of CML-BC as a consequence of continued BCR-ABL activity provides the rational for this approach. Patients with high risk features at diagnosis 100-102, unsatisfactory response to therapy (e.g. no major cytogenetic response or less than 90% BCR-ABL reduction by 3-months) 122-124 or signs of progression under therapy such as clonal evolution should receive more intensive therapies to prevent progression and BC. With the availability of optimized imatinib protocols 42,126,127 and 2nd generation BCR-ABL inhibitors first line 128,129 which induce deeper remissions faster I recommend every attempt to eliminate
BCR-ABL as early as possible. I expect that more efficacious therapies and early treatment intensification in patients with high risk features or unsatisfactory responses will further reduce progression and transformation to BC.
Authorship

Contribution: R.H. was the sole author of this paper

Conflict-of-interest disclosure: The author declares no competing financial interests.

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References


## Table 1

### BC-Diagnostics

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<th>Test at diagnosis of BC</th>
<th>Test rationale</th>
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<tr>
<td>CBC with differential and bone marrow</td>
<td>Proportions of blasts, promyelocytes and basophils?</td>
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<tr>
<td>Flow cytometry and/or cytochemistry</td>
<td>Myeloid or lymphoid phenotype?</td>
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<tr>
<td>Cytogenetics</td>
<td>Clonal evolution?</td>
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<td>Molecular genetics</td>
<td>Mutation profile? Choice of TKI</td>
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<td>Donor search (if applicable)</td>
<td>Allo-SCT</td>
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### Follow-up under therapy

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<th>Return to CP?</th>
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<tr>
<td>Bone marrow and cytogenetics</td>
<td>Ascertainment of 2\textsuperscript{nd} CP</td>
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<td>Molecular genetics</td>
<td>Monitoring of BCR-ABL transcript levels under TKI and after allo-SCT</td>
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<tr>
<td>In lymphoid BC: spinal fluid cytology</td>
<td>Intrathecal instillation for neuroprophylaxis</td>
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BC = blast crisis, CBC = complete blood count; CP = chronic phase, TKI = tyrosine kinase inhibitor, allo-SCT = allogeneic stem cell transplantation
## Treatment of BC by BCR-ABL TKI

<table>
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<tr>
<th>Drug</th>
<th>Patients</th>
<th>CR</th>
<th>Survival</th>
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<td></td>
<td></td>
<td>MBC / LBC</td>
<td>12 months</td>
<td>Median, months</td>
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<td>Imatinib</td>
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<td>300 – 600 mg</td>
<td>58 (20 LBC)</td>
<td>12%</td>
<td>NA</td>
<td>NA</td>
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<td>400 – 600 mg</td>
<td>229 (MBC only)</td>
<td>16%</td>
<td>30%</td>
<td>6.9</td>
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<td>300 – 1000 mg</td>
<td>75 (10 LBC)</td>
<td>16%</td>
<td>22%</td>
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<tr>
<td>600 mg</td>
<td>30</td>
<td>13%</td>
<td>36%</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>600 mg</td>
<td>92 (20 LBC)</td>
<td>17%</td>
<td>29%</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Dasatinib</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>50 – 100 mg</td>
<td>33 (10 LBC)</td>
<td>52% / 90%</td>
<td>~22% a</td>
<td>~ 6</td>
<td></td>
</tr>
<tr>
<td>bid</td>
<td>157 (48 LBC)</td>
<td>35% / 56% b</td>
<td>49% / 30%</td>
<td>11.8 (5.3)</td>
<td></td>
</tr>
<tr>
<td>70 bid vs. 140 mg qd</td>
<td>210 (61 LBC)</td>
<td>25 – 28% / 40 – 50%</td>
<td>34 – 39% / 39 – 46%</td>
<td>8 (10)</td>
<td></td>
</tr>
<tr>
<td>Nilotinib</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>up to 1200 mg</td>
<td>33 (9 LBC)</td>
<td>18%</td>
<td>NA</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>400 – 600 mg</td>
<td>136 (31 LBC)</td>
<td>40%</td>
<td>42%</td>
<td>10</td>
<td></td>
</tr>
</tbody>
</table>

LBC: lymphoid blast crisis; MBC: myeloid blast crisis; HR: hematologic remission, includes complete HR, return to CP and no evidence of leukemia; CR: cytogenetic response, includes complete, partial, minimal and minor response when available; NA: not available; TKI: tyrosine kinase inhibitors

a at 18 months; b only complete and major cytogenetic response listed. Updated from 5.
Table 3

Investigational approaches
(Selection)

<table>
<thead>
<tr>
<th>Mode of action</th>
<th>Agent(s)</th>
<th>Phase</th>
<th>Target(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3rd generation TKI</td>
<td>Ponatinib&lt;sup&gt;53&lt;/sup&gt;</td>
<td>II</td>
<td>Pan-BCR-ABL including T315I</td>
</tr>
<tr>
<td></td>
<td>DCC-2036&lt;sup&gt;72&lt;/sup&gt;</td>
<td>I</td>
<td>Abl-switch pocket</td>
</tr>
<tr>
<td>PP2A activation</td>
<td>Fingolimod (FTY720)&lt;sup&gt;75&lt;/sup&gt;</td>
<td>preclinical</td>
<td>PP2A</td>
</tr>
<tr>
<td></td>
<td>SET antagonist OP449&lt;sup&gt;76&lt;/sup&gt;</td>
<td>preclinical</td>
<td>SET</td>
</tr>
<tr>
<td></td>
<td>CIP2A inhibitor&lt;sup&gt;74&lt;/sup&gt;</td>
<td>preclinical</td>
<td>CIP2A</td>
</tr>
<tr>
<td>Survival of LSC</td>
<td>BCL6 + TK inhibitors&lt;sup&gt;78&lt;/sup&gt;</td>
<td>preclinical</td>
<td>BCL6 + BCR-ABL</td>
</tr>
<tr>
<td></td>
<td>HIF1α inhibitor&lt;sup&gt;80&lt;/sup&gt;</td>
<td>preclinical</td>
<td>HIF1α</td>
</tr>
<tr>
<td></td>
<td>IL1 RAP antibodies&lt;sup&gt;86&lt;/sup&gt;</td>
<td>preclinical</td>
<td>IL1 RAP</td>
</tr>
<tr>
<td></td>
<td>Smoothened inhibitors in combination with TKI&lt;sup&gt;83&lt;/sup&gt; (dasatinib, nilotinib)</td>
<td>preclinical</td>
<td>Smoothened (hedgehog pathway) + BCR-ABL</td>
</tr>
<tr>
<td></td>
<td>Jak2 inhibitor + dasatinib&lt;sup&gt;85&lt;/sup&gt;</td>
<td>preclinical</td>
<td>Jak2 + BCR-ABL, LSC</td>
</tr>
<tr>
<td>Activation of apoptosis</td>
<td>BCL2-inhibitor ABT-737&lt;sup&gt;88&lt;/sup&gt;</td>
<td>preclinical</td>
<td>Anti-apoptotic proteins</td>
</tr>
<tr>
<td></td>
<td>Triptolide&lt;sup&gt;87,88&lt;/sup&gt;</td>
<td>preclinical</td>
<td>Anti-apoptotic proteins</td>
</tr>
<tr>
<td></td>
<td>Dual-kinase inhibitor ON044580&lt;sup&gt;91&lt;/sup&gt;</td>
<td>preclinical</td>
<td>BC, T315I</td>
</tr>
<tr>
<td></td>
<td>MEK inhibitor PD184352 + farnesyltransferase inhibitor BMS-214662&lt;sup&gt;89&lt;/sup&gt;</td>
<td>preclinical</td>
<td>MEK1, MEK2, RAS</td>
</tr>
<tr>
<td>Others</td>
<td>Omacetaxine&lt;sup&gt;92&lt;/sup&gt;</td>
<td>II / III</td>
<td>BCR-ABL, T315I, BC</td>
</tr>
</tbody>
</table>

TKI: tyrosine kinase inhibitor; PP2A: protein phosphatase 2A; LSC: leukemia stem cells, MEK: mitogen-activated protein kinase kinase
## Early response prediction

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>Baseline</th>
<th>3 months</th>
<th>6 months</th>
<th>12 months</th>
<th>Endpoint</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Historical</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mahon et al. 1998 (IFN)</td>
<td>116</td>
<td>CHR</td>
<td></td>
<td></td>
<td></td>
<td>MCR</td>
</tr>
<tr>
<td>Baccarani et al. 2009 (imatinib, review)</td>
<td>NA*</td>
<td>CHR</td>
<td>CCR</td>
<td></td>
<td></td>
<td>OS</td>
</tr>
<tr>
<td><strong>Baseline</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hasford et al. 2011 (EUTOS)</td>
<td>2060</td>
<td>high risk</td>
<td></td>
<td></td>
<td></td>
<td>CCR**</td>
</tr>
<tr>
<td>Fabarius et al. 2011</td>
<td>1151</td>
<td>major route ACA*</td>
<td></td>
<td></td>
<td></td>
<td>OS</td>
</tr>
<tr>
<td>Verma et al. 2009</td>
<td>1292</td>
<td>P190 (R-A)</td>
<td></td>
<td></td>
<td></td>
<td>PFS</td>
</tr>
<tr>
<td><strong>Clonal evolution</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baccarani et al. 2009 (review)</td>
<td>NA</td>
<td>any time</td>
<td></td>
<td></td>
<td></td>
<td>OS</td>
</tr>
<tr>
<td><strong>Response</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hanfstein et al. 2012</td>
<td>692</td>
<td>MR 10%, MCR</td>
<td>MR 1%, CCR</td>
<td></td>
<td></td>
<td>OS</td>
</tr>
<tr>
<td>Hehlmann et al. 2011</td>
<td>1014</td>
<td></td>
<td></td>
<td></td>
<td>M MR (=MR 0.1%)</td>
<td>OS</td>
</tr>
<tr>
<td>Marin et al. 2012</td>
<td>282</td>
<td>MR 9.84%</td>
<td>MR 1.67%</td>
<td>MR 0.53%</td>
<td></td>
<td>OS</td>
</tr>
<tr>
<td>Jabbour et al. 2011</td>
<td>435</td>
<td>M CR</td>
<td>CCR</td>
<td></td>
<td></td>
<td>OS</td>
</tr>
</tbody>
</table>

*NA: not applicable, ACA: additional cytogenetic aberrations, CHR: complete hematologic remission; CCR: complete cytogenetic remission; MR: molecular response; MMR: major molecular remission, MCR: major cytogenetic remission; OS: overall survival, PFS: progression free survival; EFS: event free survival, ** CCR at 18 months

Percentages are according to international Scale (IS)^130
Legends

Fig. 1 Mechanisms of BCR-ABL activity in CML and blast crisis, leading to stimulation of proliferation and to induction of genetic instability, DNA damage and impaired DNA-repair. Reactive oxygen species (ROS) induced by BCR-ABL are thought to mediate DNA damage and genetic instability. Data are from Skorski 2002 34, Melo and Barnes 2007 31, Radich 2007 32 and Perrotti et al. 2010 33.

Fig. 2 Prevention of BC by more effective treatment in early CP as shown by the German CML Study Group experience 1983 – 2011. CML study I compared busulfan vs. hydroxyurea (HU) vs. interferon α (IFN) monotherapy, CML study II IFN in combination with HU vs. HU alone, CML study III and IIIA IFN in combination with intensive chemotherapy vs. allo-SCT and CML study IV imatinib 400 mg vs. imatinib in combination with low dose araC vs. imatinib in combination with IFN vs. imatinib after IFN-failure vs. imatinib at 800 mg. For references see 42

Fig. 3 Survival with BC in the preimatinib and imatinib eras. Most long term survivors (72%) are transplant recipients. German CML Study Group experience. Data are from the German CML-studies I – IV. For references see 42

Fig. 4 Management algorithm of CML-BC. Mainstays are TKI and rapid allo-SCT.
Role of BCR-ABL in CML and blast crisis

**Fig. 1**

BCR-ABL

Stimulation of signaling and proliferation and decreased apoptosis leading to expansion of the myeloid compartment

CP-CML

DNA damage and impairment of DNA repair leading to genetic instability and clonal evolution with ACA in up to 80% of cases and multiple mutations within and outside the BCR-ABL kinase domain

Progression to BC
Cumulative Incidence of blast crises
1983 – 2011

--- BU (n = 188, 115 events, recruitment 1983 – 1990)
--- HU (n = 308, 182 events, recruitment 1983 – 1990)
--- IFN mono (n = 134, 67 events, recruitment 1986 – 1990)
--- IFN + HU (n = 226, 92 events, recruitment 1991 – 1995)
--- IFN + HU, study III (n = 621, 145 events, recruitment 1995 – 2001)
--- IFN + HU, study IIIA (n = 669, 82 events, recruitment 1997 – 2002)
--- Imatinib (n = 1340, 48 events, recruitment since 2002)
Survival after blast crisis 1983 – 2011

- CML IV (imatinib; n = 65, 47 died, median survival: 9 months)
  18 alive, 13 patients transplanted
  imatinib era
- CML I – IIIA (n = 699, 678 died, median survival: 4 months)
  21 alive, 15 patients transplanted
  pre-imatinib era

n = 764 patients
Management of CML in blast crisis

Fig. 4

Blast crisis after conventional $T_x$

- Imatinib
  - Failure
    - RtoCP / Cytoreduction
      - SCT
        - Relapse
      - AL-induction $T_x$
        - Failure
        - Failure
          - Investigational agents

Blast crisis under imatinib

- Failure
  - $2^{nd}$ generation TKI
    - *
      - Imatinib
      - $2^{nd}$ generation TKI

SCT: Stem cell transplantation; RtoCP: Return to chronic phase; AL: Acute leukemia; $T_x$: Treatment
* $2^{nd}$ generation TKI and AL-induction therapy may be combined.
How I treat CML blast crisis

Rüdiger Hehlmann