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Treatment of chronic myeloid leukemia in blast crisis

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Blast crisis (BC) is the sword of Damocles hanging over every patient with chronic myeloid leukemia (CML). In the past, CML virtually always progressed to BC. Conventional treatment of BC has been notoriously unsatisfactory resulting in only transient response and prolonging survival only marginally once BC has been diagnosed. In chronic phase (CP) CML, BCR-ABL tyrosine kinase inhibition (TKI) is highly efficacious and prolongs survival significantly. Progression to BC is slowed down in most patients and possibly prevented in some. The current challenge is how well (or how poorly) TKI improves prognosis after diagnosis of BC, and how we can make best use of the limited options that are available.

In this issue of the journal, Palandri and the GIMEMA CML group report on 92 patients with CML BC under imatinib treatment over a period of six years.[1] This is the longest currently available observation of imatinib in BC. Median survival is, at 7.5 months after diagnosis of BC, about twice as long as with historical controls. After a median observation time of 66 months, 7 patients (8%) are alive, 3 after allogenous stem cell transplantation (allo-SCT). In comparison, 605 BC patients of the German CML Study group treated with conventional chemotherapy or with interferon α (IFN) show a median survival after diagnosis of BC of four months (Figure 1).[2] Only 21 patients (3.5%) are alive after a median observation time of 6.4 years, 15 after allo-SCT. The progress with survival Palandri *et al.* report is modest, but probably real.

Definition of blast crisis

Comparisons like this largely depend on the definition of BC and thereby on the time of its diagnosis. First attempts at the definition of BC date back about 40 years.[3] The generally used definition which underlies virtually all current clinical CML trials (including the ELN management recommendations)[4] rests on at least 30% of blasts in blood or marrow and the demonstration of extramedullary blastic infiltrates. This definition is not supported by biological evidence and is therefore arbitrary. The more recent WHO definition proposes a blast count of 20% in analogy to the definition of AML. This is, however, also arbitrary without any biological evidence. It has been shown that a change of definition, e.g. to a blast count of 20%, would regroup up to 10% of patients. Patients with 20-29% blasts, currently classified as accelerated phase, had a significantly better prognosis than patients with more than 30% blasts.[5] Most clinicians and trialists, therefore, will likely stick with the definition for which they have the most data, observe ongoing research closely, and wait for additional evidence on the biology of BC for a new evidence based definition.

Role of BCR-ABL in evolution to blast crisis

In contrast to the CP in which with BCR-ABL a pathogenetically relevant target is available for intervention, no such structure is known for BC. Since the elucidation of pathogenesis of CP-CML 20 years ago, a considerable body of information has been assembled on the evolution from CP to BC and on the role BCR-ABL may play in it.[6-9] According to this work, BCR-ABL tyrosine kinase (TK) has two key effects in CML: i) the stimulation of signaling pathways and of proliferation; and ii) the modulation of response to DNA damage and mutagenesis via reactive oxygen species (ROS) causing, in a vicious circle, genomic instability by more mutations, gene doublings, translocations and chromosomal breakage.[9] The latter effect of BCR-ABL would explain what is observed during progression of CML to BC leading to the conclusion that the therapeutic goal in CML should be the elimination of BCR-ABL.

This consideration underlies the therapeutic principle in CML to hit *hard and early* in order to reduce the BCR-ABL positive cell pool as much as possible and thereby achieve the best possible outcome. The validity of this principle may be limited by quiescent CD34 positive CML cells which evade currently available pharmacotherapy. The success with TK-inhibition and the postponement of BC in most patients with TK-inhibition confirms 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 CML 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 best approach to the management of blast crisis is its prevention. Figure 2 summarizes the roles of BCR-ABL in CML and in progression to BC.

Treatment of blast crisis

Once BC has been diagnosed and without clear targets available for inhibition, several approaches can be chosen which depend on previous therapy and type of blast cells (myeloid or lymphoid). Best results are achieved for the few patients that return to CP and are successfully transplanted. Response to treatment is the single most important prognostic factor for survival with BC.[10,11] Figure 3 provides a flow diagram for treatment decisions in BC.

If the patient has been pre-treated with conventional therapy (IFN or hydroxyurea, now the exception), a TK-inhibitor (imatinib 600–800 mg) should be tried.[12-15] Outcomes of trials with imatinib and other TK-inhibitors in BC are summarized in Table 1. Hematologic and cytogenetic responses are achieved with imatinib in about 50% and 15% respectively, and 12-month survival ranges around 25-30%, also confirmed by Palandri *et al.*[1]

If BC evolves under imatinib treatment, a second generation TK-inhibitor (dasatinib or nilotinib) should be tried.[16-20] The longest follow-up with second generation TK-inhibitors is available for 157 dasatinib treated patients (70 mg bid) with hematologic and cytogenetic response rates of 33% and 35% respectively for

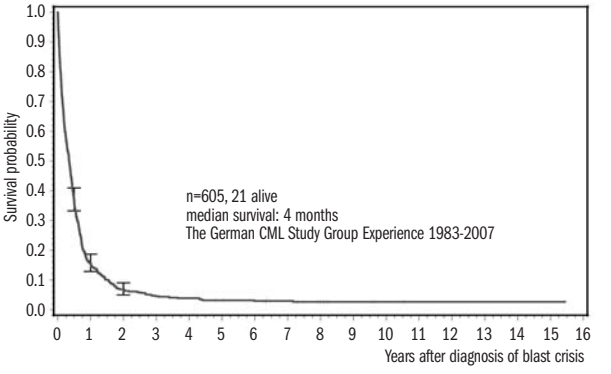

Figure 1. Survival after diagnosis of blast crisis in 605 patients treated within the German CML studies I-III A (for references see Hehlmann *et al.*, 2007).[2] Treatment of chronic myeloid leukemia was with busulfan, hydroxyurea (HU), interferon α (IFN) or a combination of HU and IFN. Treatment of blast crisis included acute leukemia induction-type treatment and various single agents (ara-C, thioguanine, vincristine/prednisone etc.) as appropriate.

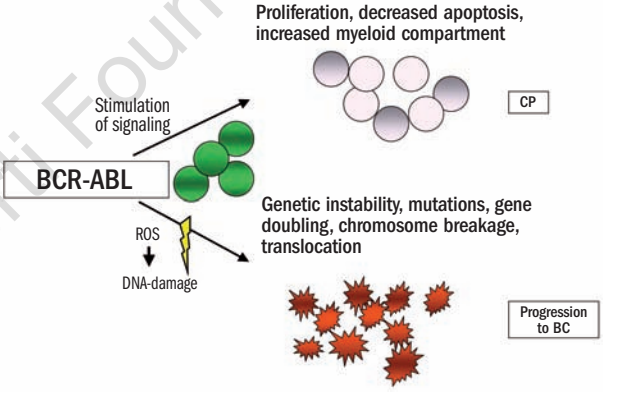

Figure 2. Role of BCR-ABL in CP-CML by stimulation of proliferation and in progression to blast crisis by promotion of genetic instability.

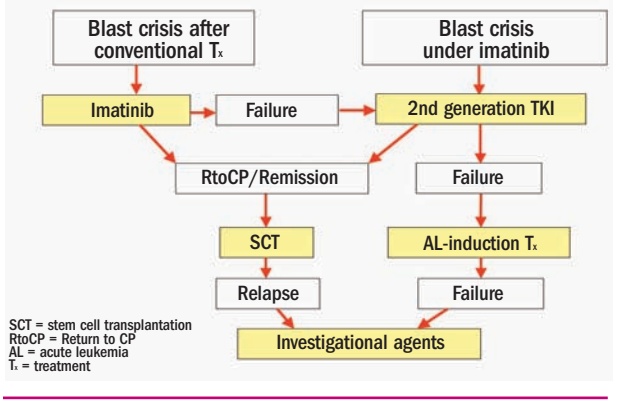

Figure 3. Algorithm for the treatment of blast crisis. This algorithm can only give a general overview. Treatment decisions have to be adapted to the individual patients' situations and needs as appropriate.

myeloid BC, and 36% and 56% respectively for lymphoid BC. The 24-month overall survival reported at ASH 2007 was 38% for myeloid BC and 26% for lymphoid BC with a median survival of 11.8 and 5.3 months respectively.[17,18] A single daily dose of dasatinib 140 mg seems to be equally efficacious and more tolerable. Dasatinib crosses the blood-brain barrier and shows long lasting responses in Philadelphia positive central nervous system disease.[21] 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. Giles *et al*. reported on 136 BC patients treated with nilotinib (400-600 mg bid), the largest study with this agent.[20] Hematologic and cytogenetic response rates were 21% and 40% respectively, and overall survival at 12 months was 42%. For dosage, response and survival details of other studies see Table 1.

If a return to CP or a complete remission has been achieved, transplantation is recommended. In the EBMT report by Gratwohl *et al.*,[22] 2-year survival after allo-SCT is only 16-22%, but in the German series mentioned above most long-term BC survivors had been transplanted. Deininger *et al*. report a median survival of 8.85 months after transplantation in 68 patients with advanced phases including 37 patients with BC.[23]

Phase II studies with other TKIs like bosutinib and INNO-406 are ongoing. Preliminary data with bosutinib showed hematologic responses in 78% and major cytogenetic responses in 60% of CML patients with advanced-stage disease.[24] In a Phase I study on 46 CML and ALL patients including 7 with BC, INNO-406 was well tolerated and showed responses in a heavily pretreated patient cohort.[25]

If also second generation TK inhibitors fail, conventional approaches remain an option, such as AML induction protocols with anthracyclines and AraC, etc. in myeloid BC, or a trial with vincristin and prednisone in lymphoid BC. Results with conventional treatment have been reviewed by Morris and Dutcher in 2005 who report a median survival of 3.5-15 months in responders and 2-6 months in non-responders.[26]

More recent studies focus on the combination of chemotherapy with imatinib. In a Phase I/II trial on 16 patients, Frühauf *et al*. combined imatinib 600mg daily with mitoxantrone/etoposide.[27] 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 with BC and reported a median survival of 15 weeks.[28] The combination of imatinib 600 mg with low dose cytarabine and idarubicin in 19 patients with myeloid BC showed hematologic remissions in 47%. Median survival was five months.[29] In a Phase I study with the combination of the farnesyltransferase inhibitor lonafarnib with imatinib, 2 out of 3 BC patients showed hematologic improvement.[30]

More drugs are under clinical and in pre-clinical evaluation. These drugs include arsenic trioxide which showed synergy with imatinib, histone deacetylase (HIDAC) inhibitors, aurora kinase inhibitors alone or in combination, e.g. with small molecule TK- or HIDAC-inhibitors, HSP90 inhibitors, mTOR inhibitors (rapamycin), the tumor suppressor PP2A and other substances (for review see Giles *et al.*, 2008).[24] In summary, in spite of great efforts in treatment optimization and drug development, treatment of BC remains unsatisfactory.

Prospects

Alternative approaches aim at a better understanding of the pathophysiology of BC and at the recognition of features with prognostic impact.

Good in depth reviews on the biology of BC are available.[6-8] The key feature of CML progression is the genetic instability with additional chromosomal changes and mutations providing proliferative advantage and leading to BCR-ABL independence (*point of no return*). It has been observed that the higher the BCR-ABL level in advancing CML is, the shorter the time to

Table 1. Treatment of chronic myeloid leukemia blast crisis in the era of BCR-ABL tyrosine kinase inhibition.

Responses and overall survival in blast crisis

Study	Drug	Patients	HR[3]	CR[4]	Survival (overall)			
			MBC[2]/LBC[1]	MBC[2]/LBC[1]	at 12 months	at 24 months	at 36 months	median
Palandri *et al.*, 2008[1]	Imatinib 600 mg	92 (20 LBC[1])	50%	17%	29%	18%	11%	7 mo
Druker *et al.*, 2001[12]	Imatinib 300-600 mg	58 (20 LBC[1])	55%/70%	12%	NA[5]	NA[5]	NA[5]	NA[5]
Sawyers *et al.*, 2002[13]	Imatinib 400-600 mg	229 (MBC[2] only)	52%	16%[7]	30%	< 20%	NA[5]	6.9 mo
Kantarjian *et al.*, 2002[14]	Imatinib 300-1000 mg	75 (10 LBC[1])	52%	16%	22%	NA[5]	NA[5]	6.5 mo
Sureda *et al.*, 2003[15]	Imatinib 600 mg	30	60%	13%	36%	< 20%	NA[5]	10 mo
Talpaz *et al.*, 2006[16]	Dasatinib 50-100 mg bid	33 (10 LBC[1])	61%/80%	52%/90%	~22%[6]	NA[5]	NA[5]	~6 mo
Cortes *et al.*, 2008[17] and Gambacorti *et al.*, 2007[18]	Dasatinib 70-100 mg bid	157 (48 LBC[1])	33%/36%	35%/56%[7]	49%/30%	38%/26%	NA[5]	11.8 mo (5.3 mo)
Kantarjian *et al.*, 2006[19]	Nilotinib up to 1200 mg	33 (9 LBC[1])	39%	18%	NA[5]	NA[5]	NA[5]	NA[5]
Giles *et al.*, 2008[20]	Nilotinib 400-600 mg bid	136 (31 LBC[1])	21%	40%[7]	42%	31%[6]	NA[5]	~10 mo

[1]LBC: lymphoid blast crisis; [2]MBC: myeloid blast crisis; [3]HR: hematologic remission, includes complete HR, return to CP and no evidence of leukemia; [4]CR: cytogenetic response, includes complete, partial, minimal and minor responses when available; [5]NA: Not available; [6]at 18 months; [7] only complete and major cytogenetic response listed.

mutations which render patients resistant to therapy. Resistance mutations in late CP are associated with greater likelihood of progression to BC, confirming the significance of BCR-ABL for the development of mutations and of genetic instability for disease progression.[31] The most frequently observed genetic aberrations are a second Philadelphia chromosome, trisomy 8, isochromosome 17, trisomy 19, alone or in various combinations, and complex aberrations. Up to 80% of BC patients show some forms of chromosomal changes. Cytogenetic evolution appears to be the most consistent predictor of blastic transformation.

The most frequently observed mutations involve p53 (in 25% of myeloid BC) and p16/AKT (in about 50% of lymphoid BC). A more recent observation is the activation of nuclear beta-catenin in granulocyte-macrophage progenitors which appears to enhance self-renewal activity and leukemic potential.[32]

To study genetic changes in BC more comprehensively, gene expression microassays are being used to identify genes which are up- or down-regulated in BC in comparison to normal or CP cells. Comparing CD34 positive CML blast cells with normal or chronic phase CD34 positive cells two studies found 103 and 114 differentially expressed genes respectively.[33,34] Among the top up- or down-regulated genes associated with progression, genes of transcriptional regulation, signal transduction and apoptosis were identified. These data provide new insights into the molecular phenotype of blasts and the mechanism of transition from CP to BC. The identified genes might serve as prognostic markers to recognize patients at diagnosis with an increased probability for development of BC. A BC-signature might qualify patients for an early allo-SCT and might provide targets for new interventions in the future.

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Treatment of older adults with acute myeloid leukemia: state of the art and current perspectives

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Acute myeloid leukemia (AML) is a disease of older adults, with a median age at diagnosis of 67 years in the United States. Decisions regarding the aggressiveness and timeliness of therapy are challenging in older adults, as the disease biology predicts for chemotherapy resistance, and intensive therapy is accompanied by high treatment-related mortality. In older patients, complete remission rates to standard remission induction therapy range from 40-60%, with limited long-term survival. Newer treatments are less-aggressive, with the promise of near-comparable response rates to standard cytotoxic therapy. Clinical trials should be considered at every stage of treatment in this group of patients.

Why focus on older adults with acute myeloid leukemia?

Epidemiology

AML is the most common leukemia subtype, with an estimated 13,000 new diagnoses yearly in the USA.[1] It is also a disease of older adults, commonly defined as people > 60 years of age, with a median age at diagnosis of 67 years.[2] This translates to a yearly incidence of new AML diagnoses in the USA of 17.6/100,000 for people 65 years of age or older, compared to 1.8/100,000 for people <65 years. Worldwide, the incidence of AML in older adults is increasing, likely due to the effects of environmental exposures during an industrial age, the late effects of chemotherapy and radiation therapy used to treat solid tumors, and the aging population as a whole, a respectable percentage of whom harbor known or as yet undiagnosed antecedent hematologic disorders. Case finding within this undiagnosed population will result in continued upward incidence trends.

Distinguishing biological characteristics

Compared to younger adults, older AML patients are more likely to have AML with poor-risk cytogenetics (such as abnormalities of chromosomes 5, 7, 8, or complex cytogenetics) and less likely to have good-risk cytogenetic findings, such as the balanced, core binding factor abnormalities, including the t(8;21) in which the *AML1-ETO* genes are juxtaposed, inv (16) and t(16;16) involving the CBFB-MYH11 chimeric product, and the PML-RARα mutation (t(15;17)).[3-7] Despite the overriding dismal prognostic implications of advanced age, cytogenetics still have relevance in predicting outcome, with fortunate older adults with leukemias typified by a CBF abnormality experiencing five-year overall survival rates of 20%, compared to 0% for those with poor-risk features.[8] Whether newly identified molecular lesions, such as FMS-like tyrosine kinases 3 (*flt3*) internal tandem duplications (ITDs) and mutations of nucleophosmin (NPM) play a role in older AML patients has yet to be determined.

Secondary AML, which is less responsive to chemotherapy, is also common in this age group, comprising between a quarter and half the cases, compared to < 10% in younger adults.[7,9] As a result, AML in older adults is more likely to arise from a more proximal stem cell disorder, and with abnormalities in more than one hematopoietic cell lineage.[1] Further chemotherapy responsiveness is mediated by greater expression of genes that confer drug resistance, such as MDR1, the P-glycoprotein (gp170) chemotherapy