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Chronic myeloid leukemia - Section 3

How to treat chronic myeloid leukemia in 2017

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Take-home messages

- The advent of tyrosine kinase inhibitors has substantially changed biology and outcome of the disease.
- With optimal management, patients achieve an almost normal life expectancy which results in an important annual increase of the prevalence of CML.
- Treatment free remission is feasible for an important minority of patients but requires stringent surveillance.

Introduction

Overall survival (OS) in patients with chronic myeloid leukemia (CML) under treatment with imatinib approaches 90% at 5 years and 83% at 10 years.[1] Since the advent of second- and third-generation tyrosine kinase inhibitors (TKIs), faster and deeper remissions have been reported, including complete cytogenetic remission (CCyR), major molecular remission (MMR), and deep molecular response (MR^4, $MR^{4.5}$).[2,3] To date, none of the clinical trials involving new therapies have shown a survival advantage, although the ENESTnd trial[2] did demonstrate a favorable progression-free survival in CML patients treated with nilotinib.

A number of different TKIs are now available, giving many treatment options for CML. Evidence-based care requires an understanding of the optimal use of these drugs, their specific early and late toxicities, the prognostic significance of achieving treatment milestones, and the critical importance of molecular monitoring. Efficacy is important, but treatment choice does not depend on efficacy only. Choosing among various treatment options is informed by understanding the distinct benefits and risks of each agent, along with careful consideration of patient-specific factors, such as risk status, age, and comorbidities. After failure of first-line TKI, a switch to a second- or third-line therapy is recommended. As a result, the influence of a certain TKI therapy on OS has become more difficult to assess.[4,5]

Treatment aims

With a newly diagnosed patient, aims of therapy should be discussed since choosing the optimal first line therapy depends on the knowledge of the options and aims. Individual aims (according to age and social situation of the patient) consist of (i) the chance to maintain normal survival probabilities, (ii) reduction of the risk of accelerated phase and blast crisis, (iii) good tolerability of the therapy avoiding severe side effects, (iv) rapid cytogenetic and molecular response with (v) the chance of deep molecular remission allowing eventual treatment discontinuation, and (vi) preservation of fertility.

First line therapy

Proof of CML diagnosis depends on the detection of the t(9;22) translocation by cytogenetic analysis, the juxtaposition of BCR and ABL by fluorescent in situ hybridization (FISH) or (in most cases preferred and fastest) by multiplex RT-PCR. Immediate start of therapy may be required in case of very high leukocyte counts with the risk of leukostasis. In such cases, transient therapy with hydroxyurea (40 mg/kg body weight) may be required, until the BCR-ABL test result is available. Treatment should be accompanied by urine alkalization (pH 6.4-6.8) with sodium hydrogen carbonate. Allopurinol should be avoided due to xanthin accumulation with risk of renal failure. After confirmation of the BCR-ABL fusion, TKI therapy should be commenced at full dose. Pretherapy with hydroxyurea dose should be tapered in parallel.

Choice of first line therapy depends on the treatment aims of the patient. Imatinib (400-800 mg/d), nilotinib (300 mg twice daily) and dasatinib (100 mg/d) are available and licenced. Chance to achieve early molecular response, major molecular response and deep molecular response is higher with nilotinib or dasatinib, but survival probability is almost identical compared to imatinib. Vascular, cardiac, pulmonary or metabolic

comorbidities and risk factors should be considered in the choice of initial therapy. Imatinib is frequently accompanied by fluid retention and muscle cramps, nilotinib by hyperglycemia and hypercholesterolemia and cardiovascular events, dasatinib by pleural effusions and thrombocytopenia.
In order to reduce treatment costs, generic imatinib might be used as first line therapy. This approach should be balanced against the risk of progression according to the individual risk profile and the chance to discontinue therapy in case of durable deep molecular response.
Early treatment phase is frequently accompanied by transient cytopenias, mostly in patients with splenomegaly. Treatment interruption is recommended in case of grade 3 or 4 neutro- or thrombocytopenia only. In case of liver toxicity, gradual dose adjustment might be considered.

Treatment after intolerance

Intolerance to first line therapy should prompt symptomatic therapy, dose adjustment and/or change of the TKI, if required. Some adverse events are transient, e.g. cytopenias, diarrhea, rash, liver function abnormalities, other should prompt immediate stop of therapy, e.g. vascular events on nilotinib therapy. Recommended dose of alternative therapy after TKI intolerance is identical to the dose of the respective drug as first line therapy.[6]

Treatment after resistance

In case of hematologic, cytogenetic, or molecular resistance or relapse according to ELN criteria, change of therapy should be considered. Check of compliance, check of pharmacokinetic interaction, cytogenetic and BCR-ABL1 mutation analysis is recommended and should guide the choice of the alternative drug. In chronic phase, nilotinib should be administered at a dose of 400 mg twice daily, dasatinib at 100 mg/d, bosutinib with 400 mg/d start dosis and dose increase to 500 mg/d if tolerated and ponatinib at 30 mg/d with dose adjustments to 15 or 45 mg/d according to tolerability and efficacy.[7-10]

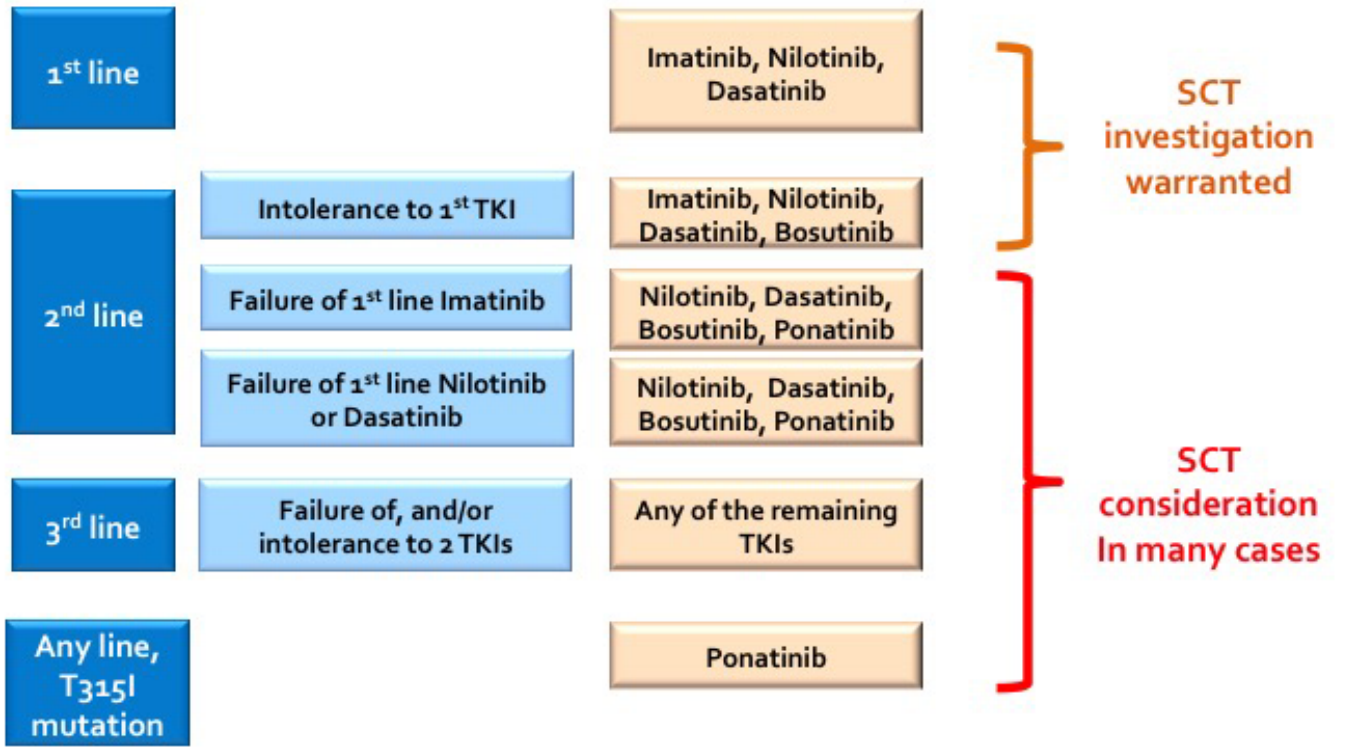

Figure 1. Recommended treatment options for CML patients in chronic phase. SCT = stem cell transplantation.

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Allogeneic stem cell transplantation

Allogeneic stem cell transplantation remains an option for cure if available first- and second line drugs fail according to ELN criteria and the likelihood of response to salvage therapies is low. Since responses to second and later lines of therapy are limited and depend on the individual mutation profile, allogeneic stem cell transplantation should be considered on an individual basis for eligible patients.[11]

Treatment free remission

The likelihood of treatment free remission after stopping TKI therapy is 40-60% for patients in deep molecular remission after long term TKI therapy. Eligibility depends on the consolidated achievement of deep molecular remission determined in a standardized laboratory after long-standing TKI therapy. The impact of stopping strategies in CML will be enormous for patients, health care systems, and society at large. Studies are underway which will guide physicians in determining when it is safe and most promising to stop TKI therapy in CML patients. This will have a large economic impact on CML treatment. With the increasing prevalence of CML patients and the high costs of TKI treatment per year, stopping treatment in CML will result in a considerable and durable reduction of treatment costs world-wide. The important question of how to increase the proportion of patients is being addressed by treatment optimization studies.[12,13]

The impact of (pegylated) interferon alpha to improve the rate of patients without disease recurrent is currently being tested in a series of clinical trials using IFN in parallel with TKI therapy or as maintenance after TKI discontinuation.[14]

New treatment options

Combination trials investigate the impact of the inhibition of BCR-ABL1 independent pathways to target residual stem cells. The allosteric ABL1 inhibitor Asciminib (ABL001) demonstrates promising results in mono- and combination therapies and targets resistant disease including all known BCR-ABL1 ATP-binding site mutations.[15]

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