Innovation in hematology. Perspectives: CML 2016

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With modern drug treatment [imatinib, tyrosine kinase inhibitors (TKI)] survival with chronic myeloid leukemia (CML) has almost normalized. Results of clinical trials show that survival with CML has improved significantly over the last decades[1] (Figure 1) and that life expectancy of patients with CML approaches that of the general population (Figure 2).[2] Subgroups of patients, e.g. those with complete cytogenetic remission, may reach normal survival times.[3]

Nevertheless, survival with CML in population-based registries[4,5] is still lower than normal, in a recent analysis of the Dutch CML-registry by 10%-15%.[6] Five to 7% of patients progress to advanced phases and blast crisis.[7,8] Another 5%-10% may receive suboptimal treatment such as hydroxyurea, particularly in the elderly, or as a consequence of poor adherence. Lack of adherence to prescribed medication is considered to be the main reason for suboptimal treatment and inferior outcome,[9] and may result from reduced quality of life in the face of adverse drug effects of life-long treatment. The matter has become a key topic of current research, in particular with regards to attempts to discontinue treatment when durable deep molecular responses have been reached and personalization of treatment according to individual patients' needs.

Various trials try to define conditions which allow treatment discontinuation with the highest chance of success. Duration of TKI treatment, depth of molecular remission and duration of deep remission seem to play a role. Other conditions may be patients' risk profile at diagnosis and line of therapy. The goal is to improve the proportion of patients who stay free of relapse [i.e. no loss of major molecular remission (MMR)].[10] Treatment- and relapse-free survival ranges around 40% in the discontinuation trial with the longest follow up (STIM-study, median observation 5.5 years).[11] Most relapsing patients regain the same depth of response after resumption of pre-discontinuation treatment. Some progress in optimizing treatment discontinuation can be expected from a large ongoing European discontinuation study (Euro-SKI) (Saußele and Mahon, 2016, manuscript in preparation). So far, there is no indication that type or dose of TKI results in differences in discontinuation outcome.

The other important approach to improving outcome of CML-treatment is individualization of treatment by considering patients' variables at diagnosis or response levels at defined milestones to optimize drug dosage and select the right drug for the right patient. Patients' variables may be the classical risk scores, or individual molecular markers such as transcript type or expression of genes, or gene groups, thought to be of prognostic relevance.[12,13] The b2a2 transcript type has been consistently associated with lower response rates and longer times to response. An expression signature at diagnosis of 20 genes has recently been shown to correlate with outcome.[14] Whether the early detection of low level resistance mutants with more sensitive detection methods, such as next generation sequencing provides an advantage for treatment choice and outcome, still remains a subject for discussion. Pre-existing comorbidities have guided the selection of TKI since the availability of 2nd-generation (2G-) TKI to decrease toxicity and increase efficacy. Epidemiological studies and registries are used to define better patients' characteristics at diagnosis.

Another approach to treatment personalization is optimizing individual drug doses according to blood drug levels or patient tolerability. In contrast to some 2G-TKI, a

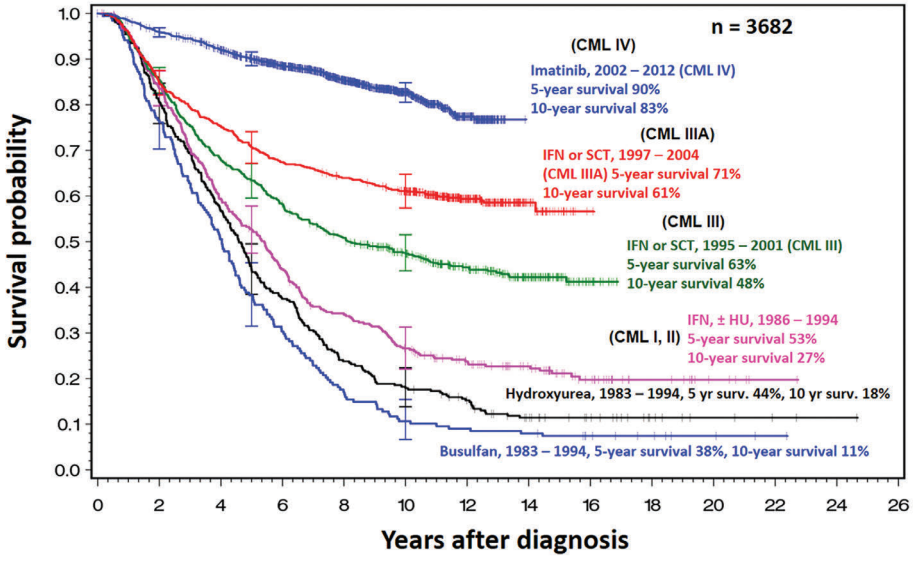

Figure 1. Survival with chronic myeloid leukemia in five consecutive randomized studies of the German CML Study Group since 1983; update 2016.

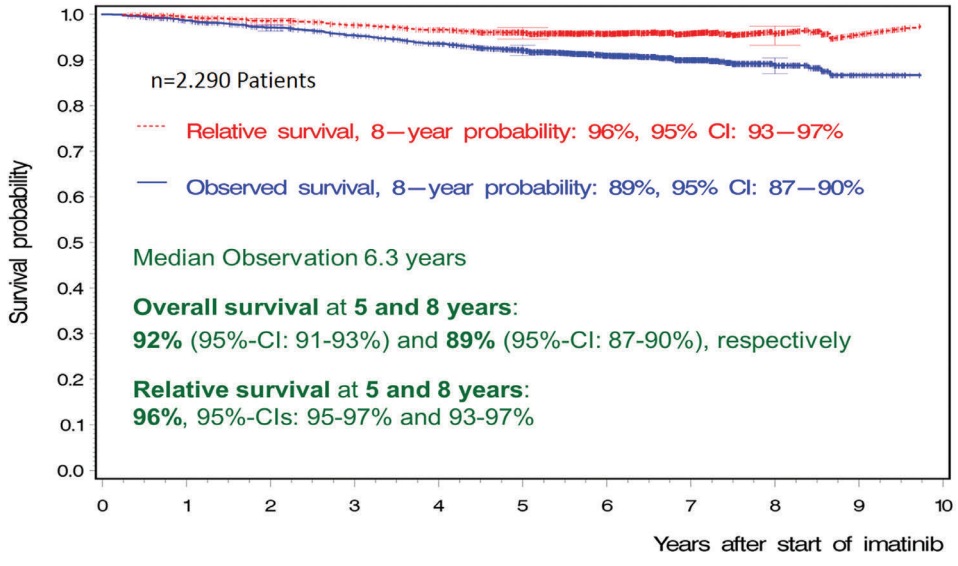

Figure 2. Relative and overall survival of 2290 chronic myeloid leukemia (CML) patients from the European Treatment and Outcome Study (EUTOS) for CML treated with imatinib in six clinical trials and prospectively enrolled between 2002 and 2006 from Dutch, French, German, Italian, Nordic and Spanish Study Groups[2] (courtesy of Dr. M. Pfirrmann).

systematic optimization of imatinib dosage has never been done. A recent study[15] has shown that molecular response such as measured by major molecular response (MMR) after 12 months can be improved in up to 80% of patients if the imatinib dose was increased in patients with suboptimal drug levels. Likewise in the German CML-Study, IV imatinib dosage in the 800 mg arm was tailored according to tolerability providing superior responses.[8] This agrees with a recent systematic review of 5 randomized trials comparing imatinib 400 mg and 800 mg (or 600 mg), which finds a 30% higher MMR rate at 12 months with imatinib 800 mg similar to that with 2G-TKI.[16] In no instance do we have convincing evidence that any TKI provides an overall survival advantage over another, at the high survival rate we never might achieve. Patients' factors such as risk profile and TKI resistance seem to overrule choice of TKI, TKI dose or TKI in various combinations with regard to survival. In addition, more patients die in the meantime from comorbidities than from CML.[17] Differences in overall survival may thus become too small in relation to the limited power of the trials. Attempts are being made to improve survival further by TKI in combination with interferon (IFN), or IFN maintenance, or by better drugs that overcome resistance and achieve deeper responses faster. Hematopoietic cell transplantation tailored according to patients' and transplantation risks may provide a good chance of cure with minimal transplantation-related mortality.[18]

A challenges is that a substantial minority of patients still progresses to blast crisis which is only poorly treatable - maybe some new markers, or cytogenetics in the course of disease, provide an earlier clue for progression than rising blasts. Cost, less a problem in Europe than elsewhere, is likely to improve after the imatinib patent expires in most countries in 2016. Most CML survivors are faced with life-long treatment and suffer from reduced quality of life. Attempts at treatment discontinuation result in 60% relapses, with uncertainty as to whether the remainder can be considered cured in the presence of residual disease in most cases. Suboptimal patient education probably contributes to a lack of adherence and to suboptimal outcomes in a considerable portion of patients.

Although progress with CML has fundamentally changed the outcome of CML, overall survival is still reduced, quality of life is hampered by potentially life-long treatment, and a minority of patients still die of CML. For most patients with CML, cure, or at least a normal life, has not yet been achieved.

Innovation in education and training to improve knowledge on CML

The European Investigators on CML (EI-CML) and the European LeukemiaNet (ELN) have long standing programs on mutual information and training. Examples are the annual EI-CML meetings that have taken place across Europe since 1993, the annual ELN-Symposia in Mannheim (with regular meetings of the CML-working group since 2004), educational meetings on CML and other myeloid neoplasias (ELN-Frontiers Meetings) all over Europe 2006-2014, and educational meetings for young hematologists in Naples (2009-2014). The CML-meetings organized by the European School of Hematology (now the John Goldman conferences) attract young scientists to present their research data to the CML-community. In recent years, the ELN-breakfast meetings at the ASH meeting have been popular, and more weight is put on ELN-workpackage meetings in the context of the EHA-conferences. The sessions of the ELN-EHA scientific working group on CML are the latest addition to the European CML community's efforts to improve education on CML, primarily for physicians, but also for patients. Since 2006, the CML group of ELN publishes international management recommendations for CML,[19] with a new edition planned for 2016.

Innovation in technology

Disease monitoring and attempts at treatment discontinuation require specific and sensitive monitoring techniques. To this end, molecular analyses of BCR-ABL 1 have been standardized by an international co-operation within ELN and EUTOS for CML, and an international

scale has been introduced for standardized BCR-ABL 1 monitoring.[20] To achieve a higher sensitivity, allowing more reliable detection of deep responses at the $MR^{4.5}$ and MR^{5} levels, digitalized PCR (dPCR) was established. This new modification of PCR-technology reproducibly achieves sensitivities of 10^{-5} (MR^{5}) in routine analysis.

Further topics currently being addressed are the initiating event(s) of CML pathogenesis, the role of CML-stem cells in the maintenance of residual disease, the relevance of genomic changes, gene expression and epigenetics for treatment and outcome, and the optimization of drug treatment with new drugs or combinations, e.g. with IFN. It is hoped that by systematically addressing these questions progress will be made in our understanding of CML, which will enable us to improve management and prognosis.

The current goal of the ELN-EHA SWG for CML is the further improvement of survival, achievement of definite cures, and a normal quality of life for all patients with CML. This will be accomplished by continued research programs, clinical trials and educational programs. The ELN-EHA SWG for CML-session in Copenhagen will illustrate and promote this goal.

References

1. Hehlmann R. CML--Where do we stand in 2015? Ann Hematol. 2015;94 Suppl 2:S103-105.
2. Pfirrmann M, Baccarani M, Saussele S, et al. Prognosis of long-term survival considering disease-specific death in patients with chronic myeloid leukemia. Leukemia. 2016;30(1):48-56.
3. Gambacorti-Passerini C, Antolini L, Mahon FX, et al. Multicenter Independent Assessment of Outcomes in Chronic Myeloid Leukemia Patients Treated With Imatinib. J Natl Cancer Inst. 2011;103(7):553-561.
4. Höglund M, Sandin F, Hellstrom K, et al. Tyrosine kinase inhibitor usage, treatment outcome, and prognostic scores in CML: report from the population-based Swedish CML registry. Blood. 2013;122(7):1284-1292.
5. Hoffmann VS, Baccarani M, Hasford J, et al. The EUTOS population-based registry: incidence and clinical characteristics of 2904 CML patients in 20 European Countries. Leukemia. 2015;29(6):1336-1343.
6. Thielen N, Visser O, Ossenkoppele G, Janssen J. Chronic myeloid leukemia in the Netherlands: a population-based study on incidence, treatment, and survival in 3585 patients from 1989 to 2012. Eur J Haematol. 2015 Oct 31. [Epub ahead of print]
7. Deininger M, O'Brien SG, Guilhot F, et al. International Randomized Study of Interferon Vs STI571 (IRIS) 8-Year Follow up: Sustained Survival and Low Risk for Progression or Events in Patients with Newly Diagnosed Chronic Myeloid Leukemia in Chronic Phase (CML-CP) Treated with Imatinib. Blood. 2009;114(22):1126.
8. Hehlmann R, Muller MC, Lauseker M, et al. Deep molecular response is reached by the majority of patients treated with imatinib, predicts survival, and is achieved more quickly by optimized high-dose imatinib: results from the randomized CML-study IV. J Clin Oncol. 2014;32(5):415-423.
9. Noens L, Hensen M, Kucmin-Bemelmans I, Lofgren C, Gilloteau I, Vrijens B. Measurement of adherence to BCR-ABL inhibitor therapy in chronic myeloid leukemia: current situation and future challenges. Haematologica. 2014;99(3):437-447.
10. Rousselot P, Charbonnier A, Cony-Makhoul P, et al. Loss of Major Molecular Response As a Trigger for Restarting Tyrosine Kinase Inhibitor Therapy in Patients With Chronic-Phase Chronic Myelogenous Leukemia Who Have Stopped Imatinib After Durable Undetectable Disease. J Clin Oncol. 2014;32(5):424-430.
11. Etienne G, Rea D, Guilhot J, et al. Long-Term Follow-up of the French 1 Stop Imatinib Study (STIM1) in Chronic Myeloid Leukemia Patients. ASH Annual Meeting Abstracts. 2015. (Abstract 345).
12. Hanfstein B, Lauseker M, Hehlmann R, et al. Distinct characteristics of e13a2 versus e14a2 BCR-ABL1 driven chronic myeloid leukemia under first-line therapy with imatinib. Haematologica. 2014;99(9):1441-1447.
13. Jain P, Kantarjian HM, Luthra R, et al. Impact of the Type of BCR-ABL Fusion Transcripts on Response and Survival in Patients with Chronic Phase CML Treated with Four Frontline TKI Modalities. Blood 2016;126(23):598.
14. Kok CH, Leclercq TM, Watkins D, et al. A 20 Gene Expression Signature That Predicts Early Molecular Response Failure in Chronic Phase CML Patients Treated with Frontline Imatinib. Blood. 2015;126:(23):596.
15. Rousselot P, Johnson-Ansah H, Huguet F, et al. Personalized Daily Doses of Imatinib By Therapeutic Drug Monitoring Increase the Rates of Molecular Responses in Patients with Chronic Myeloid Leukemia. Final Results of the Randomized OPTIM Imatinib Study. Blood. 2015;126(23):133.
16. Hoffmann VS, Hasford J, Hehlmann R. Systematic Review and Meta-Analysis of Randomized Trials Comparing Imatinib 400 Mg/d Vs. Imatinib 800 Mg/d, and Imatinib 400 Mg/d Vs. Second Generation TKIs in Chronic Phase CML-Patients. Blood. 2015;126(23):2787.
17. Saussele S, Krauss MP, Hehlmann R, et al. Impact of comorbidities on overall survival in patients with chronic myeloid leukemia: results of the randomized CML Study IV. Blood. 2015;126(1):42-49.
18. Gratwohl A, Pfirrmann M, Zander A, et al. Long-term outcome of patients with newly diagnosed chronic myeloid leukemia: a randomized comparison of stem cell transplantation with drug treatment. Leukemia. 2016; 30:562-569.
19. Baccarani M, Deininger MW, Rosti G, et al. European LeukemiaNet recommendations for the management of chronic myeloid leukemia: 2013. Blood. 2013;122(6):872-884.
20. Cross NCP, White HE, Colomer D, et al. Laboratory recommendations for scoring deep molecular responses following treatment for chronic myeloid leukemia. Leukemia. 2015;29(5):999-1003.