CHAPTER 8

Summary and future perspectives

SUMMARY AND FUTURE PERSPECTIVES

It was not even 2 decades ago that there was no effective therapy for CML and most patients died from progression to advanced disease within a few years after diagnosis. Only young and fit patients were found eligible for myeloablative allogeneic stem cell transplantation, which often resulted in high morbidity and mortality rates. Nowadays, while the outcome of CML patients has dramatically improved due to the advent of TKI therapy, focus has shifted from prolonging survival in all to the minority of patients resistant to TKI therapy and to further improvement of already achieved good cytogenetic and molecular response rates.

The impact of TKI therapy on overall survival is impressive (**chapter 2**). Five-year overall survival for all ages increased impressively from 36% in the pre-TKI period to 79% after the advent of TKIs, with most benefit for young- and middle aged patients, while the elderly benefit least. This is probably due to the fact that a substantial part of older patients are not being treated with any TKI. This is remarkable in an era where all TKIs are reimbursed by the insurance companies and financial hurdles should not be an issue. Possible explanations for this TKI deprival are therapeutic nihilism in case of elderly patients and overly and inappropriate cautiousness to prescribe a TKI in case of comorbidities. This is a suboptimal situation, as, in the majority of these patients, a TKI can be found which suits the patient's profile. To improve outcome of CML patients across all age groups, we therefore recommend to centralize treatment of CML to centers with sufficient numbers of patients in order to achieve the best care for all CML patients.

As no reliable epidemiological data are available on incidence and other demographic data of CML across Europe, the EUTOS study which is described in **chapter 3**, was performed. Through this study, reliable data on incidences of CML and baseline characteristics of CML patients in 23 different countries were retrieved. We found a uniform incidence with no typical regional patterns. The results obtained in this study and in the above mentioned NCR database in **chapter 2** underline the importance of performing population-based studies. They not only provide real-life data outside investigator- and company sponsored clinical trials, but they also mirror the healthcare system in means of treatment, response and survival, they help to plan healthcare and provide insight in cost-efficacy. Imatinib, nilotinib and dasatinib are expensive drugs (estimated costs: €30.546, €40.322 and €49.539 per year per CML patient respectively) and as CML prevalence is increasing every year due to survival gains, treatment of this disease has increasing macro-economic consequences. Our data are important for health care authoritites and insurance companies.

Although CML therapy has improved so much since 2001, there is still need for further improvement, especially for those not achieving a desired molecular response. A strategy to improve molecular response rates was expected to be the addition of conventional

chemotherapeutic agents to TKIs. In the HOVON 78 trial (**chapter 4**), newly diagnosed patients were randomized between high dose imatinib alone or high dose imatinib in combination with two successive cycles of intermediate-dose cytarabine, a pyrimidine nucleoside analogue, which showed synergistic effects to imatinib in *in-vitro* studies. Unfortunately, no significant improvement of major molecular response was observed after 12 months in patients randomized to receive the combination of cytarabine with imatinib. However, this study did not reach the prespecified power due to declining inclusion after the introduction of the second generation TKIs nilotinib and dasatinib and therefore no definite conclusions on the addition of chemotherapy could be drawn. Other combinations of TKIs with chemotherapeutic agents or targeted therapies may be effective in deepening response.

Persistent low level residual disease is probably caused by TKI resistant leukemic stem cells (LSCs). In several in-vitro studies, resistance of LSCs against all TKIs available was demonstrated. Still, successful stopping of treatment with TKIs was shown in a French study. We also investigated whether patients in long-standing deep molecular response could safely discontinue imatinib (**chapter 5**). Our study showed that 61% of patients who discontinued imatinib had relapsed 2 years after discontinuation and all regained $MR^{4.5}$ after reinitiation of imatinib. This means that 39% of patients is still free of relapse despite LSCs persistence. The mechanisms underlying sustained molecular responses or relapse are speculative and must be unraveled. Presumably, control of the leukemic clone by immunological mechanisms plays an important role in persistent freedom from relapse after discontinuation. The concern that cessation of imatinib might lead to genomic instability due to re-exposure of LSCs to BCR-ABL kinase activity, and thus to a higher chance of transformation after a stopping trial did not materialize. We therefore feel it is safe to discontinue imatinib in patients in long-standing deep molecular response. A large European trial on discontinuation of imatinib but also dasatinib or nilotinib is currently ongoing. Results of this trial in combination with previous stop trials might guide future treatment guidelines wherein patients in deep molecular response may discontinue TKI therapy. These developments emphasis the major financial consequences when a substantial part of CML patients is able to discontinue TKI therapy.

Thus, LSCs are responsible for CML relapse after discontinuation and as they are resistant to the different TKIs, other pharmacological therapies to eliminate them must be explored. BCR-ABL drives several important downstream signaling pathways (**chapter 6**), necessitating a cooperative interplay to cause leukemogenic potential. These pathways are important research items, as they may function as therapeutic targets in future studies. Of importance, the activation or inhibition of these pathways must be restricted to the leukemic cells and not affect normal hematopoiesis as non-leukemia specific pharmacologic manipulation will induce unintentional hematological toxicities.

That LSCs are important in CML is also reflected in the translational study described in **chapter 7**. The LSC burden at diagnosis not only correlates with clinical parameters but also predicts early and late molecular response and the occurrence of hematological adverse event in nilotinib treated patients. Moreover, this study validates two highly sensitive methods (multiparameter flow cytometry (MPFC) and sorting plus FISH) to discriminate LSCs from normal hematopoietic stem cells (nHSCs). In addition, they enable identification of LSC specific targets. In fact, we are currently in the process of validating potential CML stem cell specific targets as a result of this work.