Present results and future perspectives in optimizing chronic myeloid leukemia therapy

Angelo M. Carella,[1] Giuseppe Saglio,[2] Xavier F. Mahon[3] and Michael J. Mauro[4]

[1]Hematology and BMT Unit, Ospedale Policlinico San Martino, Genova,Italy; [2]Dipartimento di Scienze Cliniche e Biologiche Università di Torino and Ospedale Mauriziano di Torino, Italy; [3]Bergonié Cancer Institute, University of Bordeaux, France and [4]Myeloproliferative Neoplasms Program, Memorial Sloan Kettering Cancer Center, New York, NY, USA

E-mail: angelomcarella@gmail.com

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The presence of the Philadelphia chromosome and BCR/ABL1 fusion, combined with an elevated leukocyte count and other less specific clinical and hematological features, defines chronic myeloid leukemia (CML). In the last two decades, tyrosine kinase inhibitors (TKIs) have revolutionized CML treatment.[1] The challenge now is to eradicate the disease. Three main crucial questions remain: first, which TKI should be used as first-line therapy, given the 'embarrassment of riches' with regard to the choices; second, who should discontinue TKI, and when; and last, what about the future?

Which TKI should be chosen as first-line therapy?

Being the first TKI to receive approval for the treatment of CML, imatinib has definitely changed the natural history of this disease. The recently published update of the IRIS trial shows that patients assigned to receive imatinib 400 mg per day have an estimated overall survival (OS) rate of 83.3% at 10 years, almost matching that of a control population without CML.[2] However only approximately half of the originally enrolled patients (48.3%) completed study treatment with imatinib with such a long follow-up; discontinuation occurred in 15.9% of patients because of insufficient therapeutic effect and in 6.9% of cases because of adverse events; in addition, during study treatment 6.9% of the patients progressed to accelerated or blast crisis. Most of the patients who discontinued imatinib and who were not transplanted were subsequently moved to alternate treatment.

As it is well known that the final outcome in terms of OS and progression free survival (PFS) of CML patients correlates to the depth and rapidity of the cytogenetic and molecular responses achieved, the European LeukemiaNet (ELN) recommendations have established molecular and cytogenetic parameters to be achieved by patients at specific timepoints after the start of TKI therapy. If these parameters are not achieved, a switch of TKI, if possible, is recommended.[3]

The second-generation TKI dasatinib, initially approved in 2006 as second-line treatment for patients resistant or intolerant to imatinib,[4] was finally approved as a first-line therapy in 2010 following the results of the phase 3 DASISION study.[5] In this study the cumulative one-year major molecular response (MMR; 0.1% BCR-ABL) rate was 46% for dasatinib and 28% for imatinib. At five years, the cumulative MMR rate remained higher with dasatinib (76%) than with imatinib (64%). Whereas only 16% of the patients treated with dasatinib failed to achieve, at three months, early molecular response (EMR; a threshold of BCR-ABL is seen to correlate with OS and PFS) this percentage was 36% with imatinib.[6] Finally, very deep molecular responses (DMR; MR4, MR4.5), which were of greater interest due to the understandable desire of many patients to achieve treatment free remission (TFR), were definitely higher with dasatinib than with imatinib (MR4.5 42% *vs.* 32%). However, the five-year OS and PFS rates for dasatinib were 91% and 85%, respectively, and did not differ from that observed with imatinib; in addition, dasatinib therapy was associated with risk of developing pleural effusion.[6]

Nilotinib is a second-generation TKI which was accepted in 2007 for the treatment of CML resistant or intolerant to imatinib.[7] It was approved for first-line treatment of chronic phase CML in 2010, following the positive results from the phase 3 ENESTnd study.[8] In the aforementioned trial, after a minimum follow-up of five years, the rates of MMR and MR4.5 continue to be significantly higher in both nilotinib arms *versus* the imatinib arm (MMR: 77 and 77.2% *versus* 60%; MR4.5: 53.5 and 52.3% *versus* 31.4%), with more than half of the nilotinib-treated patients achieving MR4.5 by five years. Comparing nilotinib 300 mg twice daily (BID) with imatinib 400 mg daily, several differences emerge at the three month landmark on therapy: 91% of nilotinib-treated *versus* 67% of imatinib-treated patients achieved BCR-ABL transcript levels ≤10% EMR; 56% of nilotinib *versus* only 16% of imatinib patients achieved BCR-ABL transcript levels ≤1%. Although rates of freedom from progression to accelerated phase and blastic phase (AP/BC) remain statistically higher in the nilotinib-treated patients (96.3% and 97.8% for nilotinib *versus* 92.1% for imatinib), the estimated rate of OS is statistically superior only for nilotinib 400 mg BID arm patients compared to imatinib. Importantly, the occurrence of metabolic changes such as worsening glycemic control and lipid increase as well as cardiovascular events (CVEs) increasing over time with follow-up has been more frequently observed in both nilotinib arms. Although mainly observed in patients with an increased Framingham risk score, predictive of CVEs,[9] increased attention to cardiovascular risk assessment and comorbidities for all CML patients is warranted.

Frontline use of bosutinib was initially investigated in the phase 3 BELA trial, but this study failed to meet its primary endpoint of complete cytogenetic response (CCyR) at 12 months.[10] Bosutinib has been subsequently re-investigated *versus* imatinib for chronic phase CML patients at a dosage of 400mg per day in the phase 3 BFORE trial. In this study, the proportion of patients who achieved MMR at 12 months (primary endpoint) was greater with regard to statistical significance in the bosutinib group, compared with the imatinib group: 47.2 *versus* 36.9 percent, respectively.[10] Deeper molecular responses were also higher in the bosutinib group

compared to the imatinib group: MR4, 20.7% *vs.* 12.0% (*P*=0.01) and MR4.5, 8.1% *vs.* 3.3% (*P*=0.02). Such findings confirm the efficacy of second-generation TKIs and their ability to induce faster and deeper molecular responses relative to that observed with imatinib.[11]

In conclusion, imatinib has indeed changed the landscape of CML. Subsequently developed TKIs, dasatinib, nilotinib, and bosutinib, are potential alternatives to imatinib as first-line therapy, mainly due to the deeper and faster molecular responses they induce. In our opinion, initial treatment with second-generation TKIs should be offered initially to patients with higher risk of progression. Alternatively, imatinib could be the initial therapy for all patients, with the incorporation of early switch to second-generation TKIs if optimal response is not achieved at three months.

Cessation of treatment

Until now the recommendation for TKI therapy in CML was to continue treatment indefinitely. However, there are numerous justifiable reasons for stopping TKI therapy. Off-target effects of TKIs and severe adverse drug reactions have been increasingly reported. These side effects may not only impair the quality of life, but some of them, such as pulmonary arterial hypertension, pleural effusion, or vascular occlusive events may potentially modify life expectancy. In addition, it is forbidden to administer TKIs to pregnant women, and experience in pediatric CML cases reveals growth disruption resulting from TKI therapy. The patients' requests are also important; the question of whether TKI therapy is necessary lifelong is frequently asked.

Clinical trials have demonstrated the feasibility of stopping TKIs in patients with durable and deep MR beyond MMR.[12-15] The convincing results of all of these studies have validated the concept of TFR, which has increasingly become the main focus of clinical trials in CML.[16] The *sine qua non* condition for proposing TKI cessation is the achievement of a sustained DMR. A certified laboratory is necessary to perform and validate the robust molecular monitoring needed for safety during TFR studies. Great reassurance is to be found in the reproducibility of TFR studies over time, and with the adaption of more pragmatic and applicable criteria for patient consideration.[17]

Half of the patients who are eligible for TKI discontinuation remain treatment-free, while the other 50% recover optimal response upon therapy re-introduction. Most of the molecular recurrence occurs in the first six months following TKI cessation. One cannot overstate the importance of the safety observed to date in TFR trials, evidenced by preserved TKI sensitivity and prompt re-induction of molecular response in patients rechallenged after molecular recurrence. Of interest is a peculiar transitory TKI withdrawal syndrome reported in a minority of patients; the mechanism is unknown.[18] A key question emerging from the experience with TFR trials relates to the evidence of persisting leukemic cells (e.g., persistent BCR-ABL detection) without exhibiting true relapse, and how this status should be defined (functional cure?).

The number of patients who are stopping TKI treatment is increasing over time and it may be possible to re-attempt TKI cessation more than once in the same patient. Encouraging results have emerged from a multicenter study entitled RE-STI, where eligible patients, i.e., those with a second sustained DMR, remained in TFR in one third of cases.[19]

Although extensive long-term experience is limited, substantial knowledge accumulated during the last years justifies moving TFR strategies from research to clinical practice.

The future of CML

The future of CML therapy must answer those questions pending from the torrid pace of advance over the last 20 years. While treatment choices are many, selecting the safest and optimal path to cure still needs perfection. One point oft forgotten is the longitudinal cost of TKI therapy in varying health care systems; with movement from indefinite to, ideally, defined duration therapy, this debate will evolve. Continued development of more precise prognostic information derived at diagnosis, such as BCR-ABL fusion type,[20] the role of cytogenetic abnormalities aside from the Ph chromosome,[21] and the formulation of an idealized risk score best able to predict outcome, including that of survival,[22] is ongoing. It is possible that a more meticulous scrutiny of early response and a more individualized assessment of response will better aid decision making regarding any need for change in treatment. Particular attention must be paid to comorbid conditions, especially cardiovascular disease, both at diagnosis and with therapy change, given the available data on the increase in risk and impact of comorbidities on outcome.[23]

During therapy, the past had us focus on the quantitation of BCR-ABL 'burden' by conventional means (cytogenetic) whereas the present is sharply focused on the molecular assessment of disease burden. Such assessment increasingly utilizes next-generation sequencing, allowing for increased sensitivity, clarity regarding ABL kinase domain mutations, and clonal hierarchy. This technique may open the door to a broader consideration of molecular changes during the course of CML, including the impact of non-BCR-ABL clonal markers and clonal hematopoiesis on CML and other comorbid condition risks.

Therapy should continue to evolve, with advances including non-ATP site allosteric inhibitors with ABL001 (asciminib) showing great promise in single-agent phase I data,[24] bolstered by its ability to be safely combined with available TKIs for potential synergy. In addition, later generation ABL kinase inhibitors have also moved into early clinical development, including two agents with expected activity against the T315I mutation, namely PF114 (Fusion Pharma) and K0706 (Sun Pharma Advanced Research Company [SPARC]). Unmet needs continue to consist of the treatment of advanced phase disease, with novel options emerging for lymphoid transformation, and more needed for myeloid blast phase. In addition, particular focus is being concentrated on novel agents able to either deepen suboptimal molecular response to TKIs or facilitate a second TFR.

While the future is very bright for those diagnosed with CML, risks remain, and success requires informed choice, careful navigation of adverse events and response mile-

stones, prompt recognition of progressive disease, continued utilization of allografting in the proper settings, and prudent and timely selection of candidates for treatment cessation.

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