and dexamethasone on days 1, 8, 15, and 22 of cycles 2 and 5. With this regimen of weekly bortezomib, the ORR was 85%, with a median PFS of 42 months. Grade ≥ 2 PN was observed in 24% of patients, leading to discontinuation of bortezomib in 8%. Only 10% of patients, however, reached VGPR/complete response (CR). A low rate of deep responses may possibly impact the long-term control of the disease.6

This proteasome inhibitor induces a rapid decrease in the IgM paraprotein, with a good quality of responses. Therefore, this agent appears appropriate for symptomatic WM patients with high IgM levels, risk of hyperviscosity syndrome, symptomatic cryoglobulinemia or cold agglutininaemia, amyloidosis, and renal failure due to paraprotein-related complications. Younger WM patients may also be candidates for bortezomib-based treatment because this agent is not stem cell toxic and does not show a risk of secondary malignancies. Neurotoxicity, however, remains the main limit of bortezomib-based treatments. In fact, PN is common, which is often severe and long lasting, leading to discontinuation of otherwise effective programs.

Carfilzomib, a second-generation selective proteasome inhibitor, showed a favorable toxicity profile in the myeloma setting. Notably, in a large report on the safety of single-agent carfilzomib in relapsed/refractory myeloma patients, the incidence of PN was low (13.9%), including patients with baseline neuropathy.7 Treon et al evaluated the efficacy and safety of the combination of carfilzomib, rituximab, and dexamethasone (CaRD) in 31 patients with symptomatic WM, naive to bortezomib and rituximab.1 Induction therapy consisted of intravenous carfilzomib 20 mg/m² infused over 20 minutes in cycle 1, and then 36 mg/m² in cycles 2 to 6, with intravenous dexamethasone 20 mg given on days 1, 2, 8, and 9 and rituximab 375 mg/m² on days 2 and 9 every 21 days for 6 cycles. In patients with stable disease or better, a maintenance was started 8 weeks later consisting of intravenous carfilzomib 36 mg/m² and intravenous dexamethasone 20 mg on days 1 and 2 along with rituximab 375 mg/m² on day 2 every 8 weeks for a total of 8 cycles. After therapy, median serum IgM levels decreased from 3375 to 749 mg/dL (P < .0001); bone marrow disease decreased from 60% to 5% (P < .0001); and the hematocrit increased from 32.3% to 41.3% (P < .0001). ORR was 87.1%, and 36% of patients achieved VGPR/CR. One patient attained a molecular CR (the first observation of molecular CR in WM). Responses were not impacted by the International Scoring System for WM. Treon et al also showed that the response to CaRD is independent of the presence of the CXCR4WHIM mutation (35.5% of patients in the study). This is of particular interest, given the negative impact on response carried by this mutation.8 At a median follow-up of 15.4 months, 20 patients (64.5%) remain progression free. Protocol therapy was interrupted for nonresponse or progression in 10 patients, for progressive IgA/IgG hypogammaglobulinemia with infections in 2 patients, and for cardiomyopathy in 1 patient with multiple risk factors. Grade ≥ 2 carfilzomib-related toxicities included reversible asymptomatic hyperlipasemia (41.9%). Concerning treatment-related PN, it should be underlined that only 1 patient suffered grade 2 PN, and no patient needed discontinuation of the CaRD program because of neuropathy. This is of great clinical relevance, given the high incidence of neurologic toxicity usually observed with the proteasome inhibitor bortezomib. IgG and IgA hypogammaglobulinemia, which is a common finding in advanced WM patients,9 may have been aggravated by rituximab both during induction and during maintenance.

The results reported by Treon et al indicate that the carfilzomib-based CaRD combination represents an advancement in the treatment of WM patients requiring a proteasome inhibitor-based therapy. In fact, the efficacy of the combination, associated with a very low incidence of peripheral nerve toxicity, offers a neuropathy-sparing alternative to bortezomib-based protocols. The intensity and duration of rituximab therapy, both in induction and maintenance, probably need to be reconsidered in new studies to prevent the risk of infection.

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Molecular response in CML: where is the bar?

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In this issue of Blood, Branford et al report that the prognosis of patients with chronic myeloid leukemia (CML) correlates with the rate of breakpoint cluster region–Abelson (BCR-ABL1) decline.1
For almost 10 years, the main goal of the treatment of CML with tyrosine kinase inhibitors (TKIs) has been the achievement of the so-called “major molecular response” (MMR; BCR-ABL1 ≤ 0.1% on the International Scale) (see figure). Then, the main focus shifted to the so-called “early molecular response” (EMR; BCR-ABL1 ≤ 10% at 3 months) as a predictor of a deeper response and of a better outcome. Branford et al report that a dynamic evaluation of EMR may have a greater prognostic value than the value of a single assessment at 3 months. They analyzed 507 consecutive adult patients with newly diagnosed, chronic phase CML. They confirmed that the patients (n = 97, 18%) who did not achieve the 10% level at 3 months had a poorer 4-year progression-free survival (PFS; 86% vs 99%) and overall survival (OS; 87% vs 97%) and were less likely to achieve an MMR and a deeper molecular response. However, they found that the rate of BCR-ABL1 decline from individual patient baseline over the first 3 months—assessed by estimating the number of days over which BCR-ABL1 halved—more precisely identified a subset of very poor EMRs. Of 95 patients with >10% BCR-ABL1 at 3 months, 74 (78%) had a rapid decline of transcripts level (≥50% in ≤76 days), whereas 21 (22%) had a slow or no decline. The former had a 4-year PFS (92%) and OS (95%) similar to the patients who had achieved the 10% response at 3 months, whereas only the latter had a significantly poorer outcome (PFS, 63%; OS, 58%) and a significantly lower probability of achieving an MMR (only 5% vs 54%). The conclusion is that measuring the rate of the decline is more important than a single test and better selects the poor EMRs. The study by Branford et al was presented at the last 2013 meeting of the American Society of Hematology. At the same meeting, a similar study was presented by the German CML Study Group and is now in press. This study reported on 301 patients in which the individual velocity of transcripts elimination was calculated. In the 48 patients (16% of total) with <0.35-fold decrease in 3 months, 5-year PFS and OS were inferior (77% vs 96% and 83% vs 98%, respectively). Are these 2 studies, coming from institutions that have marked the progress in CML therapy, sufficient to dismiss the prognostic value of the 3-month EMR (BCR-ABL1 ≤ 10% vs >10%) that has been introduced and confirmed by several recent studies? Logic would say yes—because any phenomenon, in this case the response, is better defined by three points and a line rather than by a single point. Moreover, a more precise identification of the truly poor responders would limit the indication to an early therapy switch, with both a clinical and a financial benefit. However, it should not be overlooked that the Australian study reported on patients treated first line with different imatinib doses (400, 600, and 800 mg), as it was also the case in the German study—where patients treated with imatinib plus interferon-α were also included.

It is unclear whether, and to what extent, the rate and amount of decline of BCR-ABL1 would prove to be significant in patients treated with a standard imatinib dose (400 mg) or with second-generation TKIs. Moreover, methodological and standardization problems are of concern, because to measure the decline of BCR-ABL1 transcripts in individual patients, the control gene cannot be ABL1 (the most commonly used worldwide), but must be BCR or β-glucuronidase (GUS). These new findings will add fuel to an already hot controversy concerning if and when to change the first-line TKI. Whatever the definition of EMR, we do not yet know whether an early switch from imatinib to a second-generation TKI would be of benefit, and if so, to what extent. A benefit can be expected, but the expectation should be supported by data that are still missing. In addition, how many patients would take advantage of a TKI change, if the dynamic evaluation of EMR selected a very poor responder subset? Would such patients require another TKI or rather allogeneic stem cell transplantation? Prospective studies will be needed. Nevertheless, one message is clear—that to further improve a treatment that is already excellent, not only new drugs, but also more careful and frequent monitoring, are required. The cost of a real-time polymerase chain reaction test is approximately the same as the cost of 1 day of TKI treatment. More frequent monitoring, as suggested by Branford et al, helps to optimize both treatment results and the use of financial resources.

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The identity of HSCs is an active area of investigation. Chitteti et al report that activated leukocyte cell adhesion molecule (CD166) regulates HSC-niche osteoblast interactions through homotypic interactions, but also identifies both human and murine long-term repopulating cells (see figure). Accumulating evidence suggests that HSCs reside in marrow in a safe harbor that protects and maintains stem cells in a quiescent or G0 state. This hematopoietic microenvironment, or niche, regulates HSC function and activation through many soluble and adhesive interactions. Defining those cell-extrinsic factors that regulate HSC fate, differentiation, and self-renewal is critical to our knowledge of normal stem cell biology and is clinically relevant in both transplantation and the treatment of liquid and solid tumors.

To determine whether CD166 identifies murine HSCs, Chitteti et al first performed transplantation assays into lethally irradiated mice with four different candidate phenotypes: Lin−cKit+Sca1−LSKCD48− cells, CD166+CD150+LSKCD48− cells, CD166−CD150−LSKCD48− cells, or CD166−CD150−LSKCD48− cells. Cells expressing the CD166+CD150+LSKCD48− phenotype engrafted significantly better than the other cell types and tended to differentiate into myeloid lineages. Limiting dilution assays (frequency of HSCs: 1/17) and serial transplantation assays (levels of chimerism: 20-fold higher than other cell types) confirmed these observations. In addition, approximately 30% of CD9−CD150−LSKCD48− cells and the side population (phenotypes with punitive stem cell activities) express CD166. Moreover, only CD166+CD9−CD150−LSKCD48− cells possessed engraftment ability, whereas CD166−CD9−CD150−LSKCD48− cells did not.

Using human cord blood, the relevance of CD166 expression on human HSCs was next determined. As in the mouse model, well-studied human HSCs (Lin−cKit+Sca1−LSKCD48− cells) were divided based on CD166 expression, and xenograft transplantation was performed into sublethally irradiated NSG mice. CD166−Lin−CD34+CD38− cells showed significantly better engraftment than CD166−Lin−CD34+CD38− cells. To further confirm the potential of CD166 as a human HSC marker, cord blood was segregated on the basis of CD166 and CD49f. Independent of CD49f expression, CD166-expressing
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