abnormalities) applied to patients ≤55 years, and that these factors retained their independent impact in this subgroup of patients individually stratified according to age, gender and Rai stage. In the study by Parikh *et al.*, the authors found that patients in Rai 0 stage with mutated *IGHV* genes or patients in Rai stage 0 with either 13q deletion or normal FISH had an overall survival comparable to that of the sex- and age-matched population. Indeed, the overall survival was significantly longer in young patients with no adverse factors (median overall survival not reached), one adverse factor (13 years), or two adverse factors (7.7 years). Bearing in mind that most young CLL patients die of their disease[7,17] and that their relative survival is definitely shortened, there is clear room for improvement in the therapeutic options for these patients.

In summary, Parikh *et al.*[16] reported the clinical and biological characteristics of the largest series of CLL patients ≤55 years old at diagnosis published so far and included for the first time the analysis of the biomarkers identified in the last 15 years. They showed that patients ≤55 years with CLL frequently had high-risk disease resulting in a shorter time to first treatment and a significantly reduced overall survival compared to that of a sex- and age-matched population. A comparison with historical series did not show a significant improvement in overall survival through the decades for this subgroup of patients. The authors, nevertheless, identified a subgroup of patients ≤55 years with good risk CLL who had an overall survival comparable to that of a sex- and age-matched population in the 10 years following diagnosis. A longer follow-up is required to confirm this comparable overall survival in the long-term because of the long life expectancy of individuals of this age. Furthermore, the retrospective nature of the study resulting in variable availability of biomarker data, heterogeneity in the treatment given to patients, and lack of information on recently described recurrent mutations in CLL necessitates additional studies that could improve the management of patients diagnosed with CLL at a young age.

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Bortezomib just for induction or also for maintenance in myeloma patients with renal impairment?

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In this issue of Haematologica Scheid *et al.* report on a prospective multicenter clinical trial conducted by the GMMG and Hovon groups which evaluated the prognostic role of renal impairment in patients with multiple myeloma treated with bortezomib before and after autologous stem cell transplantation.[1]

Patients were randomized to receive induction (3 cycles) with either VAD (vincristine, adriamycin, dexamethasone) or PAD (bortezomid, adriamycin, dexamethasone) followed by autologous transplantation and maintenance therapy with either thalidomide (VAD-arm) or bortezomib (1.3 mg/m^2 every 2 weeks) (PAD arm). Eighty-one of the 827 patients (10%) included in the trial had a creatinine level ≥2 mg/dL and represent the focus of the study. In this subset of patients those treated with bortezomib (PAD arm) had a significantly higher progression-free survival rate than those in the VAD arm (3-year progression-free survival 48% *versus* 16%, respectively). The same held true for overall survival (3-year overall survival 74% *versus* 34%, respectively). Moreover, in bortezomib-treated patients the outcome was similar for those with creatinine ≥2 mg/dL or <2 mg/dL. These results indicate that this bortezomib-based approach not only improves outcome but also overcomes the adverse prognostic influence of renal impairment.

Approximately 20% of patients with multiple myeloma present with a creatinine concentration ≥2 mg/dL, a factor associated with poorer survival as demonstrated in the Durie and Salmon classification (stage B) and in the International Staging System (high β2 microglobulin levels are partially associated with abnormal renal function).[2,3] However, these classifications systems were derived from patients treated with conventional chemotherapy, and it has been suggested that renal impairment may no longer be a negative prognostic factor with the use of novel agents, such as bortezomib, thalidomide and lenalidomide.[4,5] Nevertheless, it should be noted that renal impairment is a frequent exclusion criterion in large randomized trials and information about these patients, particularly those with severe impairment (creatinine clearance <30 mL/min) is, therefore, scanty.

The activity of novel agents in patients with renal impairment has been extensively reviewed in several recent papers.[4,5] Bortezomib can be administered at the full approved dose because its pharmacokinetics is not affected by the degree of renal impairment. Similarly, no dose reductions are required for thalidomide (although clinical data are limited), while the pharmacokinetics of lenalidomide is affected by its renal route of excretion and dose adjustments are recommended for moderate/severe renal impairment.[4,5]

Bortezomib has produced similar response rates and progression-free survival in relapsing patients with and without renal impairment (glomerular filtration rate > or ≤50 mL/min), but with a trend to a shorter overall survival in those with severe/moderate renal impairment.[6] A similar picture was observed in newly diagnosed patients (VISTA trial).[7] As far as lenalidomide is concerned, in the combined analysis of the multiple myeloma 009/010 phase III studies[8] no significant differences in response rates were observed among patients with no/mild renal impairment *versus* moderate *versus* severe renal impairment, but progression-free survival and overall survival were shorter in the cohorts with moderate/severe renal impairment.

The present study by Scheid *et al.*[1] focused on a subset of patients who were candidates for autologous stem cell transplantation (ASCT), all of whom had a creatinine clearance <50 mL/min (median 26 mL/min), and clearly illustrated that the presence of baseline renal impairment had a detrimental effect in the VAD followed by ASCT and thalidomide maintenance arm, with a 50% reduction in overall survival compared to that in patients with normal renal function. By contrast the PAD regimen used in this trial appeared to abrogate the negative prognostic influence of renal impairment. One relevant question is whether the benefit in both progression-free and overall survival observed in the PAD arm is just due to the effect of induction treatment or if the maintenance phase with bortezomib also plays a relevant role in this subset of patients with renal impairment. Interestingly, although there was a trend to a higher renal response rate in the PAD arm than in the VAD arm after induction, the difference was not statistically significant. This suggests that not only induction but also maintenance with bortezomib after ASCT may be important in this high-risk population defined by renal impairment.

Overall, this prospective study shows that in transplant candidates with moderate/severe renal impairment a bortezomib-based regimen may be a standard of care.

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