To the editor:

Mantle Cell International Prognostic Index (MIPI) not prognostic after R-hyper-CVAD

We read with interest the recent article by Hoster and colleagues from the German Low Grade Lymphoma Study Group (GLSG) and the European Mantle Cell Lymphoma Network regarding a new prognostic index (MIPI) for patients with advanced-stage mantle cell lymphoma.[1]

The MIPI was generated via a complex mathematical model. A simplified MIPI was subsequently generated with a point score system (low risk: 0-3; intermediate risk: 4-5; high risk: 6-11). Although the authors stated a high concordance between the MIPI and simplified MIPI(weighted kappa 0.79), no overall survival curves nor median time of overall survival were provided for the simplified MIPI.[1]

The MIPI score was also generated based on 455 patients from 3 randomized trials receiving heterogenous treatment regimens including an inferior regimen of CHOP (cyclophosphamide, daunorubicin, vincristine, and prednisone), MCP (mitoxantrone, chlorambucil, prednisone), Rituximab-CHOP, autologous stem cell transplant, and interferon-alpha maintenance therapy in some patients.

We have previously reported on a phase 2 trial of rituximab plus fractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone (R-hyper-CVAD) alternating every 21 days with rituximab plus high-dose methotrexate-cytarabine(MTX-AraC) and a recent update with 5 years of follow-up.[2,3] Among the 97 assessable patients (blastic variant, n = 14), the overall response rate was 97%, and a complete response (CR)/unconfirmed CR rate of 87%. We attempted to validate the simplified MIPI in these cohorts of patients treated homogenously with this regimen in the clinical trial.

Using the simplified MIPI prognostic index, the Kaplan-Meier method was used to generate the overall survival curves, and the log-rank test was used to test the difference in overall survival (OS) between patient groups. The OS curves are shown in Figure 1, and demonstrate no significant difference in OS between patients with low-risk (0-3 points), intermediate-risk (4-5 points), and high-risk (6-11 points) scores ($P = .27$). We attempted to combine patients with intermediate- and high-risk scores into a single group and compare with the low-risk group to improve the ability of the model to differentiate patients with low-risk as opposed to high-risk features. This also did not demonstrate a significant difference between the 2 cohorts ($P = .11$).

A major limitation in the generation of the simplified MIPI index by Hoster et al was the use of a heterogenous group of patients. The second major limitation was the lack of a second separate cohort to prospectively validate the index that was not described in the article. We were not able to validate the simplified MIPI in a homogenous group of patients treated with a more intensive regimen of R-Hyper-CVAD alternating with MTX-AraC, suggesting a more intensive treatment may overcome the high risk features described by Hoster and the MIPI is not applicable for the majority of patients treated with this current standard of care regimen.

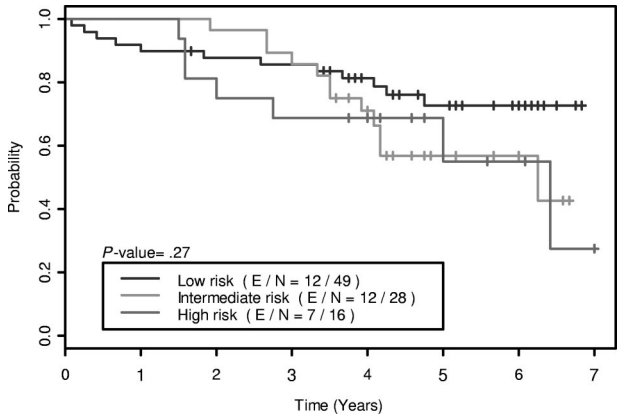

Figure 1. Overall survival between patient groups.

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Response

Statistical power and validation of the MIPI

With great interest we read the letter of Shah et al evaluating the Mantle Cell Lymphoma International Prognostic Index (MIPI) in a cohort of 93 of 97 previously untreated patients with aggressive advanced stage mantle cell lymphoma (MCL) treated with alternating cycles of rituximab plus hyperfractionated cyclophosphamide, vincristine, adriamycin, and dexamethasone (HyperCVAD) and rituximab plus high-dose methotrexate–cytarabine (MTX-AraC) within a monocentric phase 2 study.

In the published analyses, overall response rate was remarkable with 97% responding patients and no patients with either stable disease or progressive disease during induction.[1] Overall survival (OS) was also very favorable with two-thirds of patients alive

after a median follow-up of 4.8 years, presumably, and 5-year OS rates of 65%.[2]

Based on such a favorable outcome one might expect a loss of predictive power of any prognostic factor. However, external validation of a prognostic index requires careful planning, especially with regard to statistical power. Based on the observed hazard ratio of 0.5 between the low and intermediate risk groups in our original cohort, the power of the reported analysis is approximately 40% for this comparison. Accordingly, its statistical power is not sufficient to either confirm or reject the prognostic value of the MIPI.

As mentioned by Shah et al, treatment in our patient cohort (n = 455) varied in the different trials, but treatment selection was randomized and highly standardized within the study protocols. In fact, because a broad range of patient characteristics was also included in our analysis, we believe that it especially reflects the variability of standard care in advanced stage MCL patients. Within this line, the MIPI has been meanwhile also confirmed in other patient cohorts.[3]

In contrast to the statement of Shah et al, the MIPI was generated applying the commonly accepted standard procedure, the Cox regression model. In addition, the simplified prognostic index was developed to provide a simple risk assessment as bedside application. Although concordance to the quantitative MIPI was very high and median OS was almost identical according to the simplified prognostic index (not reached vs 53 months vs 27 months; not reached vs 51 months vs 29 months), we recommend the original quantitative MIPI to be used whenever possible.

In conclusion, we agree that a validation analysis is necessary for confirmation of the prognostic value of the MIPI before recommending a broad application of this tool as stated in our manuscript. However, external validation of a prognostic index requires careful planning, including selection of an adequate cohort with regard to statistical power. Currently, we and others are planning such an appropriately powered external validation applying the MIPI in recent trials of other study groups as well as the current study generation of the European MCL Network.

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To the editor:

Fully human monoclonal antibodies and targeted radionuclide therapy

I would like to applaud Dr Hagenbeek for performing the first human trial using a fully human monoclonal antibody (mAb), ofatumumab, which targets the CD20 antigen.[1] A response rate of 20% to 63% is reported and questionably one patient developed HAGA (human antiglobulin antibody). In comparison to rituximab (chimeric), the potential benefit of using a fully human mAb is a favorable toxicity profile and improved efficacy when multiple administrations are delivered. But, are these the only potential benefits?

Multiple administrations of murine or chimeric antibodies result in high rates of seroconversion to HAGA when used in targeted radionuclide therapy (TRT).[2] Considering that radionuclides are more cytotoxic than common chemotherapy agents[3] and that response rates are significantly increased when anti-CD20 antibodies are radiolabeled,[4,5] it should be compelling to initiate trials using TRT, with ofatumumab being "center stage." The linear quadratic formula can quantitate cell kill when using TRT. If a dose rate of 10 to 15 cGy/h, an effective half-life of 4 days, half-time repair of 1.5 hours, α/β equals 10, and an absorbed tumor dose of 15 to 20 Gy are delivered by a single instillation, then a 2 to 3 log cell kill should result. This scenario would sterilize 60% of clinically undetectable cell aggregates (10^3 cells), 30% of millimeter size tumors (10^6 cells), or 20% of clinically apparent disease (10^9 cells).[6] Remarkably, responses of 60% to 80% are reported after single instillations TRT when treating NHL. If the current phase 1 and 2 trials using TRT as adjuvant therapy with chemotherapy are favorable, then the prototypical lymphoma model of TRT will be that of a single administration in the adjuvant setting. This is definitely a step in the right direction and certainly may be the maximum amount of radionuclide that can be tolerated in a combined modality setting by patients heavily pretreated with chemotherapy. Recognizing that tumor growth is governed by Gompertzian kinetics, multiple cycles of dose-dense chemotherapy are used. Given subclinical tumor volumes of 10^3 to 10^5 cells, at least 3 to 4 cycles of chemotherapy are prescribed to exercise multilog cell kill. What then, would be a reasonable fractionated schedule of TRT?

The current treatment regimens of TRT for NHL use single administrations resulting in dose rates of 1 to 10 cGy/h and absorbed tumor doses in the range of 10 to 15 Gy.[7] The typical administered activity ranges from 50 to 200 mCi for Bexxar and 20 to 30 mCi for Zevalin. This results in a total body (marrow) equivalent dose of 75 cGy and 47 to 69 cGy, respectively.[8] Extrapolating from ^{131}I therapy for thyroid cancer, cumulative activities of at least 1000 mCi may be given as long as dose limiting bone marrow (BM) is monitored and 3 Gy or less for BM or 30 Gy or less for lung is not reasonably breached.[9] By all accounts, there does appear to be the potential for dose escalation and the safe delivery of multiple fractions of TRT. This is particularly sanguine when viewed in the context of our current ability to use fully human antibodies, pretargeting, and bone marrow support. Thus, it is not unreasonable to consider 3 to 6 cycles of "dose-dense" TRT, a treatment that could theoretically deliver at least 60 to 100 Gy tumor dose and eradicate clinically