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.

Eva Hoster, Martin Dreyling, and Michael Unterhalt, for the German Low-Grade Lymphoma Study Group (GLSG) and the European MCL Network

Conflict-of-interest disclosure: The authors declare no competing financial interests.

Correspondence: Eva Hoster, University of Munich, Marchioninistr 15, Muenchen, Germany 81377; e-mail: eva.hoster@med.uni-muenchen.de.

References

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 antoglobulin 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 agents3 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 (10³ cells, 30% of millimeter size tumors (10⁶ cells), or 20% of clinically apparent disease (10⁸ 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 10³ to 10⁵ 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 ¹³¹I 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
detectable tumors (10⁹ cells). The ability to deliver multiple fractions of TRT now exists with the advent of fully human mAb’s. It is time to apply the principles of dose-dense chemotherapy delivery to TRT and investigate the feasibility and efficacy of multiple fractions (cycles) of these very promising agents.

Tod W. Speer

Conflict-of-interest disclosure: The author declares no competing financial interests.

Correspondence: Tod W. Speer, MD, University of Wisconsin Cancer Center, Wausau Hospital, 215 North 28th Avenue, Wausau, WI 54401; e-mail: speer@humonc.wisc.edu.

References


Response

Multiple administrations of the fully human monoclonal antibody Ofatumumab

We thank Tod W. Speer, MD, for his valuable comments, which basically underline what we have stated in our paper.1 Multiple administrations of a fully human monoclonal antibody such as Ofatumumab in immunocompetent patients would not likely induce antibody formation—and thereby make the treatment ineffective—because of the lack of immunogenicity. That this might offer significant advantages above murine or chimeric antibodies, for instance, after labeling the antibody with an isotope and performing repeated radioimmunotherapy, remains to be established by the appropriate clinical studies. In that regard, Dr Speer comes forward with interesting theoretical calculations in terms of schedules inducing the most effective cell kill. Again, these hypotheses need to be proven by clinical trials.

Anton Hagenbeek

Conflict of interest disclosure: The author declares no competing financial interests.

Correspondence: Anton Hagenbeek, MD, PhD, Department of Hematology (G03.550), University Medical Center Utrecht, Heidelberglaan 100, 3584 CX Utrecht, The Netherlands; e-mail: a.hagenbeek@umcutrecht.nl.

Reference


To the editor:

Nonmyeloablative conditioning for relapsed follicular lymphoma

Khouri et al from the M. D. Anderson Cancer Center (Houston, TX) report the long-term outcome of 47 patients with chemotherapy-sensitive follicular lymphoma who received a nonmyeloablative allogeneic stem cell transplantation from predominantly (96%) sibling donors. With a median follow-up of 60 months, only 7 patients had died from complications. The 5-year overall survival was 85%.1 Median age at transplantation was 53 years, and all patients had chemotherapy-sensitive disease.

The authors state that “these results compare favorably to earlier studies using nonmyeloablative conditioning which were associated with treatment-related mortality up to 40%.” Here they refer to a registry study by the Center for International Blood and Marrow Transplant Research (CIBMTR).2 This is not an an appropriate comparison. The patients treated by Khouri et al all had chemotherapy-sensitive disease, and an excellent performance status (as shown by the average very low International Prognostic Index [IPI]). By contrast, 33 of 113 patients in the original CIBMTR study had a decreased performance status that was associated with a 2.4 increased risk of treatment-related mortality. Sixty-six of 113 had chemotherapy-resistant disease, which was also associated with a doubling of treatment-related mortality. Survival curves illustrating the effect of performance status and disease sensitivity from this early study are shown in Figure 1 (not included in the original publication). The importance of performance status and disease sensitivity for the outcome of allogeneic transplantation has been confirmed numerous times and by multiple groups.3-6

For patients with an excellent performance status and chemotherapy-sensitive disease, the outcome with allogeneic transplantation is excellent, whether reduced intensity or myeloablative conditioning is used,3-7 and the study by Khouri et al provides further evidence for this. It does not provide evidence that nonmyeloablative conditioning is superior. In the most recent update from the CIBMTR on follicular lymphoma, the overall treatment-related mortality at 1 and 3 years was 23% to 28%, with
Fully human monoclonal antibodies and targeted radionuclide therapy

Tod W. Speer