Ofatumumab in diffuse large B cell lymphoma?

Christian Gisselbrecht
Hôpital Saint Louis, Paris

In this issue of Blood, Matasar and colleagues report the results of salvage treatments with anti-CD20 ofatumumab in combination with ifosfamide, carboplatinum, etoposine (ICE) or dexamethasone, high-dose cytarabine, cisplatin (DHAP) in relapsed refractory diffuse large B-cell lymphoma (DLBCL) before transplantation. They conclude that replacing rituximab with ofatumumab in second-line therapy is a promising approach.1

The development of rituximab, a chimeric anti-CD20 antibody, represented a revolutionary advance in the therapy of lymphomas. Despite these major advances, salvage treatments remain a challenge as we are now observing patients more refractory to any available treatment. Salvage therapy using autologous stem transplantation (ASCT) is still the standard of care, and requires efficient re-induction treatment. In 2 prospective randomized studies, CORAL2 or the Canadian Study LY12,3 only half of the patients underwent ASCT due to an insufficient response rate to R-ICE (rituximab and ICE), R-DHAP (rituximab and DHAP), or R-GDP (rituximab and gemcitabine, dexamethasone, platinum). Moreover, it did not seem that 1 regimen was clearly superior to the other.

In the CORAL study, the factors that significantly affected the response (P < .0001) after 3 cycles of R-ICE or R-DHAP were: refractory/relapse <12 months after initial treatment, second-line adjusted International Prognostic Index (saaIPI) >1, and prior exposure to rituximab. For patients experiencing an early relapse and having received chemoinmunotherapy, the overall response rate (ORR) was 46% with only 22% complete remission (CR). These parameters comprise a poor-prognosis group of patients where any progress in salvage therapy should be readily detected.

Large phase 3 studies with the introduction of new drug combinations require a major investment and will be problematic given the lack of progress in ORR reported in novel phase 2 study.

Ofatumumab, a human anti-CD20 monoclonal antibody that targets a different epitope than rituximab, demonstrated activity in rituximab-refractory indolent lymphomas.4 In this issue, Matasar et al report on a prospective phase 2 study of ofatumumab combined with salvage regimens ICE (O-ICE; 35 patients) or DHAP (O-DHAP; 26 patients). The 61 relapsed DLBCL or transformed follicular lymphoma patients treated with rituximab chemotherapy in the study had poor-prognosis features: 48% had a saaIPI index of 2 or 3, 48% had primary refractory disease, and 33% had duration of response <12 months.

The 61% ORR achieved was similar to the 63% ORR of the CORAL study. However, because all patients have been previously exposed to rituximab, the achieved ORR is more impressive. They achieved their experimental goal (ORR of 60% or greater), and for the 29 patients with 2 or more adverse prognostic factors, the ORR was 59% with 31% in CR. There was no unexpected new toxicity, but nephrotoxicity was still a concern with DHAP and suggests that the substitution of cisplatin to an alternative platinum such as oxaliplatin may be of benefit.5 The number of transplants performed was 34 (55%), a borderline increase from CORAL. The evaluation of response was the main end point. However, in DLBCL, determining response is often difficult due to the presence of residual masses6 with analysis of survival the only confirmatory demonstration of efficacy. A significant difference in overall survival has been reported in another recent lymphoma study between 2 regimens despite an apparent similar response rate.7 In the current study, it is hard to predict survival. With a short follow-up, for patients with an saaIPI of 2 or 3, the median progression-free survival of 177 days was still low compared with the 189 days in the CORAL study. For patients with CR <12 months, the median PFS was 261 days, compared with 164 days for CORAL. With the many limitations inherent in such studies, only randomized studies will determine if the approach reported indeed represents an advance in treatment.

Several other anti-CD20 are in development (especially obinutuzumab, which also has activity in rituximab-resistant lymphoma)8 and may also be candidates for future study. Multiple new agents targeting various pathways have also shown clinical activity in lymphoma. The ORR in relapsed DLBCL was in the order of 30%, with a few complete remissions of short duration. Their true benefit may be only detectable when they are combined with standard regimens.9

Matasar et al report the first phase 2 study combining a novel anti-CD20 to salvage chemotherapy. The investigators claimed that, because of the selection of a higher percentage of poor-prognosis patients, these results are superior to those obtained with R-ICE or R-DHAP. The data are encouraging and give the basis for the ongoing randomized study with rituximab vs ofatumumab DHAP regimens.

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REFERENCES
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TWIST it but don’t spin it

Jane F. Apperley

In this issue of Blood, Ross et al report the TWISTER study in which imatinib was stopped in chronic myeloid leukemia patients with undetectable minimal residual disease (UMRD) and show that >40% remained off treatment without recurrence at 2 years.1

This is the first prospective study to confirm the observations of the Stop Imatinib (STIM) study, in which 40% of patients who had achieved deep molecular responses (MRs) on imatinib could discontinue the drug without experiencing relapse,2 which led to speculation that “cure” could be achieved by using oral tyrosine kinase inhibitors (TKIs) alone. Subsequently, randomized phase 3 studies comparing the more potent second generation TKI (2GTKI) with imatinib as first-line therapy showed that these very deep responses were obtained more rapidly and probably in a higher proportion of patients than with imatinib3,4 and resulted in the dilemma currently besetting chronic myeloid leukemia patients and their physicians, namely the choice of the first-line agent.

In STIM, patients were carefully selected and had undetectable disease for a minimum of 2 years, as measured by quantitative reverse-transcription polymerase chain reaction (qRT–PCR) assays at their local laboratory. Furthermore, this negative result was confirmed before study entry by the central laboratory where the qRT–PCR assay was capable of detecting 5-log reductions in BCR-ABL1 transcript levels. Many patients had been negative by qRT–PCR for considerable periods of time (median, 36 months; range, 24 to 85 months). Since then, successful discontinuation of TKIs has been reported retrospectively, but now, Ross et al have reproduced the STIM results in a prospective study of 40 patients with UMRD by using a qRT–PCR assay with a sensitivity of 4.5 log.

Eligibility criteria were similar to those in STIM, with a minimum of 3 years of imatinib and a minimum of 2 years of UMRD. The primary end point of treatment-free remission (TFR) at 2 years was met by 47% of the patients. Fifteen of the 22 patients who relapsed did so within 6 months, and all relapsing patients responded promptly with similarly deep MRs on reintroduction of imatinib (see figure), a reassuring fact for any patient contemplating treatment cessation. qRT-PCR for bone marrow offered no advantage over qRT–PCR for peripheral blood with respect to predicting or identifying early relapse, another welcome finding. This group previously investigated the role of patient-specific BCR-ABL1 DNA PCR5 in identifying residual disease in patients with transcripts undetectable by qRT–PCR. BCR-ABL1 DNA was identified in all the evaluable patients in TFR, suggesting that this test is not predictive for the ability to remain off treatment and that mechanisms other than direct inhibition of Bcr-Abl1 are responsible for continuing remission.

Patients who had previously received interferon were more likely to remain in TFR.


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