



New Frontiers in

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Improved Outcomes with Immunochemotherapy in Indolent and Related Lymphomas

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Orlando - A comparison of two consecutive studies in advanced follicular lymphoma showed that response rates, time to treatment failure and overall survival were significantly improved with rituximab/cyclophosphamide/doxorubicin/vincristine/prednisone (R-CHOP) vs. CHOP alone and also with R-CHOP vs. mitoxantrone/chlorambucil/prednisone (MCP). Researchers reported that the strongest contributor to improved outcomes was the addition of rituximab. Its addition to chemotherapy produces durable, long-term responses. A meta-analysis of seven randomized trials in follicular lymphoma, mantle cell lymphoma and other indolent lymphomas confirmed that the addition of rituximab to chemotherapy consistently improved remission rates, progression-free survival and overall survival. These findings suggest that the combination should become the standard of care for these patient populations. Rituximab appears to be equally efficacious for both first-line patients and for those in the relapsed/refractory setting. A cost analysis of rituximab maintenance therapy in patients with relapsed/refractory follicular lymphoma demonstrated that this treatment strategy is highly cost-effective.

Results presented here from a 10-year analysis of two consecutive studies by the German Low Grade Lymphoma Study Group (GLSG) demonstrated that the recombinant monoclonal antibody (Mab) rituximab prolongs survival in patients with advanced-stage follicular lymphoma. "In the last few decades, there has been a significant improvement in overall survival [OS] in patients with advanced-stage follicular lymphoma," stated Dr. Wolfgang Hiddemann, Director, Medical Clinic III, University of Munich, Germany.

But whether that difference was due to chemotherapy alone or to the addition of rituximab to chemotherapy was not clear. To that end, investigators compared results from the GLSG 1996 study in which

patients were treated with cyclophosphamide/doxorubicin/vincristine/prednisone (CHOP) or mitoxantrone/chlorambucil/prednisone (MCP) to those from the GLSG 2000 study in which patients were treated with either CHOP or CHOP with added rituximab (R-CHOP). The entry criteria and the distribution of risk factors were identical in both study generations and included previously untreated stage III or IV follicular lymphoma that required intervention because of the presence of B symptoms (unexplained fever, night sweats or weight loss), bulky disease, rapid progression or impairment of the hematopoietic system.

There were 381 patients in the GLSG 1996 CHOP arm vs. 148 in the MCP arm. In the GLSG 2000 study,

436 patients were randomized to the R-CHOP arm vs. 279 in the CHOP-alone arm. The total patient count was close to 1250 in the two German trials. As Dr. Hiddemann reported, the type of chemotherapy used in the two sequential studies had a limited impact on response rate (RR), although RRs were higher with CHOP (86%) than with MCP (77%).

The time to treatment failure (TTF) between the chemotherapy arms in the two studies were essentially “overlapping,” Dr. Hiddemann indicated, whereas the arm which included rituximab was “clearly superior” to all other arms. Indeed, the comparison between the earlier and the later trials showed the RR at 94% vs. 88%, TTF at median 48 months vs. 32 months, and overall survival at 89% vs. 78% at four years. Findings were all significantly better in the GLSG 2000 trial than in the GLSG 1996 trial. When investigators performed a multiple Cox regression analysis on the data, they found that the MAb was the dominant determinant behind these major differences in end points, improving the RR by 55% (OR: 0.45, $P<0.0001$), TTF by 71% (OR: 0.39, $P<0.0001$) and OS by 43% (OR: 0.57, $P=0.0064$).

“Improvement in OS was likely due to the use of rituximab, not only in first-line therapy but most probably due as well to its use in the salvage setting,” Dr. Hiddemann concluded. “From this analysis, we can see significant improvement in RR, TTF and OS, and this improvement is really due to the addition of rituximab. As such, [these data] provide a good argument for further trials using the combination of rituximab plus chemotherapy.”

Determining Survival Benefit

Investigators affiliated with another German trial sought to determine if the addition of rituximab prolonged survival in previously untreated patients with advanced, indolent or mantle cell lymphoma (MCL) treated with first-line MCP.

At a median follow-up of 47 months for the entire cohort (49 months for those who received additional rituximab and 42 for the MCP-alone group), the spokesperson for the East German Study Group, Dr. Michael Herold, Head, Hematology/Oncology, *HELIOS Klinikum Erfurt*, Germany, noted that there was an increase in adverse event (AE) rates of all grades in nearly all patients and this rate was slightly higher in the group that received additional rituximab. “However, there was practically

no difference in severe AEs between the two groups,” Dr. Herold reported, although 72% of follicular lymphoma patients who received additional MAb therapy had grade 3 to 4 toxicity in white blood counts vs. 58% of those who did not.

Rates of severe infections were similar between the two arms at 7% vs. 8% for R-MCP vs. MCP alone. Overall RRs for follicular lymphoma patients only—the majority of patients in this study—were both “clinically and statistically” more robust in the additional rituximab arm than in the chemotherapy-alone arm. At a median follow-up of 47 months, RRs were 92.4% in the R-MCP arm vs. 75% in the MCP arm, while complete response (CR) rates approached 50% vs. 25% for the R-MCP arm vs. MCP arm, respectively. These promising RRs during induction also led to improved OS rates. After approximately four years, the progression-free survival (PFS) rate was 71% for those receiving additional rituximab vs. 40% in the chemotherapy-alone arm, “an advantage of more than 30%,” Dr. Herold observed. Median OS has not yet been reached but at four years, 87% of patients receiving rituximab were still alive while 74% of those patients in the chemotherapy arm were alive. In high-risk Follicular Lymphoma International Prognostic Index patients, OS rates at four years were 81% for those who received rituximab vs. 63% for chemotherapy patients.

“I conclude that R-MCP may become the standard of treatment for advanced follicular lymphoma, especially since this was a group of elderly patients, which makes these results particularly useful,” Dr. Herold stated. In this particular study, it did not appear that patients with MCL benefited from the addition of rituximab to MCP chemotherapy.

Meta-analysis Results

Despite this finding, an updated meta-analysis presented by lead author Dr. Holger Schulz, University of Cologne, Germany, suggested that MCL patients do benefit from additional rituximab compared with chemotherapy alone. Dr. Schulz and colleagues undertook a comprehensive review of seven randomized clinical trials involving a total of 1943 patients with either follicular lymphoma ($n=1480$), MCL ($n=260$) or other indolent lymphomas ($n=203$). Across the seven randomized trials, results showed that there was a 35% statistically significant improvement in OS when rituximab was added to

chemotherapy compared with chemotherapy alone (HR: 0.65). Disease control was significantly superior by some 38% (HR: 0.62) when it was used in conjunction with chemotherapy compared with chemotherapy alone.

The risk of patients developing leukocytopenia and fever was significantly higher when rituximab was added to chemotherapy according to this meta-analysis, but this was not accompanied by an increased risk of infection, as investigators pointed out.

The authors conceded that there was “some heterogeneity” in results within the trials for the MCL subgroup. However, in patients with follicular lymphoma, combination therapy consistently improved remission rates, PFS and OS compared with chemotherapy alone—findings that prompted investigators to suggest that “the concomitant use of rituximab plus chemotherapy should become standard therapy in these patient populations.”

Salvage Therapy

Questions were raised as to whether first-line treatment with rituximab compromises its use as salvage therapy in patients with relapsed indolent lymphoma. This question appears to have been answered by a GLSG subgroup analysis of relapsed patients treated with combined immunochemotherapy (R-fludarabine/cyclophosphamide/mitoxantrone [FCM]) followed by maintenance rituximab, and whose response was compared to that in rituximab-naïve control patients. Following induction with four courses of FCM plus rituximab, patients who achieved either a CR or partial response (PR) were randomized for observation alone or to rituximab maintenance, four applications at months 3 and 9. Only 18 patients out of 268 patients with relapsed lymphoma had received previous treatment with a rituximab-containing regimen; the remaining 250 patients were MAb-naïve. But as Dr. Martin Dreyling, Assistant Coordinator, GLSG, University of Munich, and colleagues reported, results between experienced and naïve patients during induction were virtually overlapping. Specifically, in the 18 patients who had received rituximab in prior lines of therapy, the overall RR was 83% compared with 84% in naïve patients who also received R-FCM (n=183).

The CR rate was also significantly higher at 40% vs. 27% in experienced vs. naïve patients, respectively. PR rates for rituximab-naïve patients were 56% vs. 44% for R-FCM patients who had received previous

rituximab, while median PFS rates were 27 months for experienced patients vs. 17 months for naïve patients, with no difference in OS between the two groups.

As Dr. Dreyling observed, if patients prove initially refractory to rituximab, he would not use the agent as a salvage therapy. However, since most patients with indolent lymphoma respond to initial treatment with rituximab, “pre-treatment with rituximab does not compromise salvage therapy with [the same agent],” he told listeners. He added that approximately 40% of MCL patients who are pretreated with rituximab will respond to a rituximab-based salvage regimen as well.

As previously reported, the RR to rituximab given in four weekly doses of 375 mg/m² was 73% at day 50, with 10 out of 49 patients achieving a CR, three an unconfirmed CR and 23 achieving a PR (Colombat et al. *Blood* 2001;97(1):101-6). In this study, patients had stage II to IV follicular lymphoma, but had a low tumour burden on receiving treatment. They had also been recently diagnosed with their disease (within four months or less). Forty-nine evaluable patients were included in the initial cohort and 46 of these patients were available for the extended follow-up (median of 83.8 months). As reported here by the original author of the earlier study, Prof. Philippe Colombat, Head, *Hématologie et thérapie cellulaire, Hôpital Bretonneau, France*, the best overall response was 74% at day 78.

Twenty-eight percent of the study group also achieved either a CR or an unconfirmed CR and 46% achieved a PR. The median PFS for the overall study group was 23.5 months but for those who achieved a CR or an unconfirmed CR, the median PFS was 51.8 months. Those who achieved a molecular response to monotherapy rituximab also achieved a longer median PFS at 42 months compared with 14 months for those who remained Bcl₂-positive.

The median duration of response was 28.7 months. At seven years, 91% of the group was still alive and seven patients out of the original cohort were still free of disease. “Long-term tolerance was good, with only 13 serious AEs observed in 13 patients during the additional four years of follow-up,” Dr. Colombat observed. “In this long-term patient population, we have confirmed the efficacy of rituximab as monotherapy [in that] seven years after only one [course] of treatment, we have only observed four deaths out of 46 patients and seven patients are long-term progression-free survivors and appear to be cured.”

Cost Effectiveness

A Canadian cost analysis based on a model using results from the main randomized trial of rituximab maintenance therapy in patients with relapsed/refractory follicular lymphoma showed that the strategy is highly cost-effective. As presented by Dr. Joseph Mikhael, Division of Hematology, UHN-Princess Margaret Hospital, and Assistant Professor of Medicine, University of Toronto, Ontario, the model simulates the movement of patients from progression-free health state to a progressed health state or death based on data from this pivotal study. "In the base case model, the PFS and OS benefits of rituximab maintenance therapy were conservatively assumed to last only five years," he reported. Direct annual medical costs, including drug acquisition and administration costs, were based on 2005 Canadian dollars. Results from the model indicated that rituximab maintenance resulted in a gain of 0.8 quality-adjusted life years (QALY), at an incremental cost of \$17,136. The estimated cost for each QALY gained was \$20,428, well below the benchmark of \$50,000 per QALY that has been established as the cut-off point for cost-effectiveness for most interventions. "This pharmacoeconomic model demonstrates that maintenance therapy with rituximab is a cost-effective approach for the management of patients with follicular lymphoma," Dr. Mikhael concluded.

Questions and Answers

The following section is based on discussions with Dr. Wolfgang Hiddemann, Director, Medical Clinic III, University of Munich, Germany, and Dr. Michael Herold, Head, Hematology/Oncology, *HELIOS Klinikum Erfurt*, East German Study Group, Germany, during the scientific sessions.

Q: *Do you have any data suggesting that patients who received rituximab prior to relapse do not respond as well to rituximab-chemotherapy after relapse?*

Dr. Hiddemann: The trial we did in the salvage situation where we used FCM vs. R-FCM was closed very early on because the R-FCM arm was clearly better. But we had a small number of patients who had received R-CHOP first and then who received R-FCM for salvage treatment; we had about the same proportion of patients who had been treated with CHOP and then who received R-FCM, and RR and overall outcomes were not different. It is our impression from about 50 patients in the salvage setting that patients will respond to another round of rituximab/chemotherapy [on relapse].

Q: *Have you examined the rate of transformation in various chemotherapy arms based on initial response?*

Dr. Hiddemann: Yes, and we did not see a difference. And if I may answer a question about secondary leukemias that nobody has raised, we can say that the rates of secondary acute myeloid leukemia were highest in the MCP trial at 5.6% compared with 1.2% in the CHOP arm. There were no differences in AML rates between CHOP and R-CHOP [in the GLSG 2000 trial, either].

Q: *Do you see an improvement in outcomes in MCL patients with the addition of rituximab?*

Dr. Herold: Only 19% of the cohort we analyzed were MCL patients but in MCL, we do not see an improvement by adding rituximab, neither with respect to remission nor concerning all survival parameters. In our study, there were no differences between the treatment arms, and the PFS rates in MCL patients in the study were only 57% at four years, so their prognosis is not good. □

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Medical Frontiers International Inc.
132 chemin de l'Anse, Suite 100, Vaudreuil, Quebec J7V 8P3

