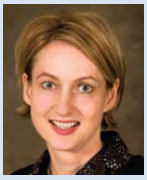
Research Review
SPEAKER SERIES

Rituximab maintenance therapy in indolent non-Hodgkin's lymphoma

October 2010



Laurie H. Sehn,

Medical Oncologist, BC Cancer Agency, Vancouver, Canada

Dr Laurie Sehn has been a Clinical Assistant Professor with the BC Cancer Agency and University of British Columbia, Canada, where she is a Medical Oncologist and Clinical Investigator with the lymphona tumour group, since 1998.

Dr Sehn graduated from McGill Medical School, Montreal, Canada, in 1991 and received her training in internal medicine at Columbia Presbyterian Medical Center, Columbia University, New York, USA. She was trained in haematology-oncology at the Dana Farber Cancer Institute and Brigham and Women's Hospital, Harvard University, Boston, and received a Masters of public health degree from Harvard School of Public Health, Harvard University in 1997. Prior to returning to Canada, she spent a year at the Dana Farber Cancer Institute as a Bone Marrow Transplant specialist.

Dr Sehn has served on the Board of Directors of the Lymphoma Foundation, Canada (LFC) since 2002, and is currently the Director of Research fellowships for the LFC. Dr Sehn's interests include all of the lymphoid cancers with particular interest in the biology and treatment of large cell lymphoma, the application of new imaging technologies such as PET scanning to lymphoma management and innovative new approaches to treatment. She is the lead investigator of a major new clinical trial focusing on the use of PET scanning in the therapy of large cell lymphoma.

This publication is a summary of a recent presentation by Dr Laurie Sehn, Clinical Assistant Professor with the British Columbia Cancer Agency and University of British Columbia, Canada. She spoke to medical oncologists, haematologists and oncology registrars in Auckland in October 2010, about rituximab maintenance therapy in indolent non-Hodgkin's lymphoma.

The last two years have witnessed a major improvement in outcome in indolent non-Hodgkin's lymphoma (NHL) with the introduction of newer agents, including the anti-CD20 monoclonal antibody rituximab. Rituximab combined with chemotherapy has become the standard of care for untreated and relapsed patients with indolent NHL. This combination improves response rates and progression-free survival (PFS) as well as overall survival (OS) in untreated patients with follicular lymphoma (FL).

The potential goals of rituximab maintenance therapy are to further improve the quality of response, extend PFS, delay time to the next chemotherapy, improve off-treatment quality of life, eradicate minimal residual disease, improve OS and allow time for new treatment options to emerge.

Potential concerns about using rituximab maintenance include the worry that prolonged depletion of B cells may increase risk of infection, the possibility of delayed secondary toxicities and the suggestion that excessive exposure to rituximab may induce resistance over time. Major phase II and III trials that have used rituximab in indolent NHL included both untreated and relapsed patients, patients with FL, small lymphocytic lymphoma (SLL) or mantle cell lymphoma (MCL), administered a variety of induction regimens.[1-7] In all trials, rituximab maintenance appeared to improve survival and PFS, regardless of how the trials were structured.

Key clinical trials

Certain clinical trials have greatly influenced NHL maintenance strategies worldwide, such as the SAKK 35/98 study, in which patients with newly diagnosed or relapsed FL received the then-standard rituximab schedule (375 mg/m^2 weekly for 4 weeks): 151 responders or patients with stable disease (SD) were then randomised to receive either 4 additional rituximab doses in the year after induction, or to observation-only.[2] Response rates to induction rituximab were 67% for untreated patients and 46% for relapsed patients. Interestingly, both treatment arms recorded very similar complete response rates and both experienced improved response over time, with no differences in toxicity. At a median follow-up of 36 months, the median event-free survival (EFS) was 12 months in the observation arm versus 23 months in the prolonged treatment arm (p=0.02); chemotherapy-naïve patients did better than those with treatment experience, as did those who responded to induction treatment. At a median follow-up of 9.5 years, median EFS values were 13 months for the observation and 24 months for the prolonged exposure arm (p<0.001).[7] Similar survival curves for those patients with SD who were then randomised suggest that the nonresponders given prolonged rituximab did not derive substantial benefit. In contrast, EFS rates were substantially improved among those patients who responded to rituximab induction (35% not progressing after 8 years). In particular, of the 20 cases of chemotherapy-naive and responding patients receiving prolonged treatment, 45% were still without event at 8 years. A persistent (although not statistically significant) difference in OS was seen between the prolonged and standard treatment arms. No long-term toxicity potentially due to rituximab was observed.

Hainsworth and colleagues compared the benefit of maintenance rituximab therapy with rituximab re-treatment at progression in patients with previously treated indolent NHL.[3] Patients with objective response (OR) or SD were randomly assigned to receive either maintenance rituximab therapy (standard 4-week courses administered at 6-month intervals) or rituximab re-treatment at the time of lymphoma progression. The duration of rituximab benefit was measured from the date of first rituximab treatment until whenever other treatment was required. Ninety (79%) of 114 patients had OR or SD after initial rituximab treatment, and were randomly assigned to treatment. PFS was prolonged in the maintenance group (31.3 vs 7.4 months; p=0.007). Final overall and complete response rates were significantly higher in the maintenance group. Duration of rituximab benefit was similar in the maintenance and re-treatment groups (31.3 vs 27.4 months, respectively). More maintenance patients remained in continuous remission and in complete remission. Both treatment approaches were well tolerated. Limitations of this trial include the relatively small number of patients and the mixed histology, with a larger number of SLL patients in the re-treatment group; it is known that SLL patients have lower response rates and shorter PFS with maintenance therapy.

The EORTC (European Organisation for Research and Treatment of Cancer) trial has had a major influence on clinical practice.[5] This trial examined the role of rituximab both in remission induction and maintenance treatment of patients with relapsed/resistant FL. 465 patients were randomised to induction with 6 cycles of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) every 3 weeks or with IV rituximab (R-CHOP) (375 mg/m^2 on day 1). A total of 334 patients who achieved complete remission (CR) or partial remission (PR) were randomised to maintenance with rituximab (375 mg/m^2 intravenously every 3 months for a maximum of 2 years or until relapse) or observation. Notably, the patients were not heavily treatment-experienced; in both groups, about 80% had received only one prior treatment, almost equally consisting of single-agent therapy or polychemotherapy. Identical

proportions of patients in the CHOP and R-CHOP groups had FLIP Index (Follicular Lymphoma International Prognostic Index; FLIPI) scores of 2 or ≥3; 33% and 37%, respectively. R-CHOP induction yielded an increased overall response rate (CHOP, 72.3%; R-CHOP, 85.1%; p<0.001) and CR rate (CHOP, 15.6%; R-CHOP, 29.5%; p<0.001). Median PFS from first randomisation was 20.2 months after CHOP versus 33.1 months after R-CHOP (HR, 0.65; p<0.001). Rituximab maintenance yielded a median PFS from second randomisation of 51.5 months versus 14.9 months with observation (HR, 0.40; p<0.001). Improved PFS was found both after induction with CHOP (HR, 0.30; p<0.001) and R-CHOP (HR, 0.54; p=0.004). Rituximab maintenance also improved OS from second randomisation: 85% at 3 years versus 77% with observation (HR, 0.52; p=0.011). This is the first trial showing that in relapsed/resistant FL rituximab maintenance considerably improves PFS, irrespective of induction regimen.

Long-term data from the EORTC trial have been reported, showing the effect of rituximab maintenance treatment on PFS at a median 6-year follow-up from the second randomisation.[8] Median PFS was significantly improved with rituximab maintenance compared with observation (3.7 years vs 1.3 years; HR, 0.55; p<0.001); 5-year OS was 74.3% for the rituximab maintenance arm and 64.7% for the observation arm (HR, 0.70; p=0.07).

Long-term safety, tolerability data

Rituximab maintenance was well tolerated with minimal toxicity in the EORTC trial. Important between-group differences included a higher incidence of grade 3–4 neutropenia (10.8% vs 5.4% for observation) and grade 3–4 infections, mostly upper/lower respiratory tract and viral (9.0% vs 2.4%, respectively). Rituximab maintenance had no appreciable effect upon IgG levels, which remained stable throughout the 2-year period.

PRIMA phase III study

The Primary Rituximab Maintenance (PRIMA) phase III study is the first reported trial that investigated maintenance rituximab in patients with FL responding to first-line immunochemotherapy consisting of either (according to the investigator's choice) 8 cycles of rituximab plus CVP (cyclophosphamide, vincristine and prednisone), or 6 cycles of R-CHOP or R-FCM (rituximab plus fludarabine, cyclophosphamide and mitoxantrone, plus 2 additional rituximab infusions).[9] A total of 1,217 patients with untreated FL were enrolled worldwide between December 2004 and April 2007. Patient demographics and tumour characteristics were evenly matched between the arms throughout the trial. The majority (75%) received R-CHOP induction (22% R-CVP, 3% R-FCM). The 1,018 patients who responded to induction therapy were randomised (stratified by regimen and response to induction) to observation or rituximab maintenance, 375 mg/m^2 IV every 8 weeks for 2 years. The primary endpoint of PFS was met at the planned interim analysis (ITT: 513 observation, 505 rituximab maintenance). Median follow-up was 25 months from randomisation (31 months from study entry). As with the EORTC trial, rituximab maintenance was associated with a significant (p<0.0001) improvement in the primary endpoint PFS (HR, 0.50; 2-year PFS 82% vs 66% for observation). An independent response review committee confirmed the significant improvement in PFS in the rituximab maintenance arm (HR, 0.53). Time to next anti-lymphoma treatment, as well as response rate at the end of maintenance or observation, were significantly improved in the rituximab maintenance arm. Maintenance rituximab was beneficial in all major subgroups evaluated (younger and older age, FLIPI score, chemotherapy regimen, CR or PR). Safety outcomes were similar to those with the EORTC trial: rituximab was well tolerated, with an observed trend towards a slight increase in grade 3–4 infections in the maintenance rituximab group.

Impact of clinical trial results on treatment of indolent NHL in clinical practice in BC

1) R-CVP was adopted as routine induction for indolent NHL in 2004
2) Rituximab maintenance has been routinely administered for untreated/relapsed indolent NHL following response to induction since 2006
3) R-CVP x 8 cycles then rituximab maintenance (every 3 months for 2 years) has been administered since 2006.

Concluding remarks

Overall, current data seem to indicate that maintenance rituximab in indolent NHL improves the quality of response and PFS, delays the need for next chemotherapy and is well tolerated with minimal side effects. However, several unresolved questions remain such as optimal schedule (every 2 or 3 months), duration of maintenance, benefit in non-follicular indolent histologies and benefit of repeat maintenance. Results from two ongoing clinical trials, i.e. the SAK 35/03 study and the RESORT study, may provide answers to some of these questions.

References

1. Hainsworth JD, et al. Rituximab as first-line and maintenance therapy for patients with indolent non-Hodgkin's lymphoma. J Clin Oncol. 2002;20(20):4261-7.
2. Ghielmini M, et al. Prolonged treatment with rituximab in patients with follicular lymphoma significantly increases event-free survival and response duration compared with the standard weekly x 4 schedule. Blood. 2004;103(12):4416-23.
3. Hainsworth JD, et al. Maximizing therapeutic benefit of rituximab: maintenance therapy versus re-treatment at progression in patients with indolent non-Hodgkin's lymphoma – a randomized phase II trial of the Minnie Pearl Cancer Research Network. J Clin Oncol. 2005;23(6):1088-95.
4. Hochster HS, et al. Maintenance rituximab after CVP results in superior clinical outcome in advanced follicular lymphoma (FL): results of the E1496 phase III trial from the Eastern Cooperative Oncology Group and the Cancer and Leukemia Group B. Blood. 2005 (ASH Annual Meeting Abstracts);106:349.
5. van Oers MH, et al. Rituximab maintenance improves clinical outcome of relapsed/resistant follicular non-Hodgkin's lymphoma, both in patients with and without rituximab during induction: results of a prospective randomized phase III intergroup trial. Blood. 2006;108(10):3295-301.
6. Forstpointner R, et al. Maintenance therapy with rituximab leads to a significant prolongation of response duration after salvage therapy with a combination of rituximab, fludarabine, cyclophosphamide and mitoxantrone (R-FCM) in patients with relapsed and refractory follicular and mantle cell lymphomas – results of a prospective randomized study of the German Low Grade Lymphoma Study Group (GLSG). Blood. 2006;108(13):4003-8.
7. Martinelli G, et al. Long-term follow-up of patients with follicular lymphoma receiving single-agent rituximab at two different schedules in trial SAKK 35/98. J Clin Oncol. 2010;28(29):4480-4.
8. van Oers MH, et al. Rituximab maintenance treatment of relapsed/resistant follicular non-Hodgkin's lymphoma: long-term outcome of the EORTC 20981 phase III randomized intergroup study. J Clin Oncol. 2010;28(17):2853-8.
9. Salles G, et al. Rituximab maintenance for 2 years in patients with untreated high tumor burden follicular lymphoma after response to immunochemotherapy. 2010 ASCO Annual Meeting Proceedings (Post-Meeting Edition). 2010;28(15) (May 20 Supplement): 8004.

Roche

Publication of this article was supported by an educational grant from Roche Products (New Zealand) Limited. [does Dr Sehn provide research support or serve in any capacity for pharmaceutical companies, such as Roche Canada (Hoffmann-La Roche), and did she accept financial support from Roche to present at this meeting?]