

ADVANCES IN LLM

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Current Status of Rituximab Maintenance Therapy

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H&O What is the status of maintenance therapy with rituximab in patients with follicular lymphoma?

JV The anti-CD20 monoclonal antibody rituximab (Rituxan, Genentech/Biogen Idec) has changed the treatment paradigm for follicular lymphoma and other B-cell non-Hodgkin lymphomas. In patients with follicular lymphoma who achieve stable disease or an objective response with single-agent upfront rituximab, maintenance therapy with rituximab offers a statistically significant increase in median progression-free survival over re-treatment with rituximab. Although each patient's individual situation differs, rituximab maintenance therapy appears to prolong progression-free survival by as much as 1 year. A small number of studies show an overall survival advantage with this regimen, and long-term data in this regard are expected in the future. The data on progression-free survival seen with rituximab maintenance therapy following rituximab plus chemotherapy are not yet available. The large Primary Rituximab and Maintenance (PRIMA) study in Europe, which has finished accruing patients, is expected to elucidate the important question of whether rituximab in combination with chemotherapy upfront followed by rituximab maintenance therapy confers a survival advantage. In the setting of relapsed/refractory follicular lymphoma, Dr. Marinus van Oers and colleagues showed that maintenance rituximab improves progression-free and overall survival following chemotherapy with or without rituximab. Furthermore, maintenance therapy produces better rates of complete remission than re-treatment at disease progression; significantly longer continu-

ous remissions and progression-free survival are seen with rituximab maintenance. The optimal dose, schedule, and duration of maintenance therapy still remain to be identified (Table 1). Overall, however, rituximab maintenance therapy is typically associated with approximately 2 years of symptom-free life.

H&O Has rituximab been combined with other agents in the maintenance setting?

JV There are studies currently assessing rituximab-based combinations in the maintenance setting such as with bortezomib (Velcade, Millennium) or lenalidomide (Revlimid, Celgene). However, no results are currently available.

H&O What are the data on maintenance therapy with rituximab in patients with chronic leukemia?

JV Rituximab is used in the upfront treatment of chronic lymphocytic leukemia (CLL) in combination with chemotherapy, a setting in which significant positive frontline results have been achieved. Patients with small lymphocytic leukemia (SLL) or CLL do not appear to achieve a significant survival advantage, however, with maintenance rituximab therapy. Standard-dose and -schedule single-agent rituximab is active in the first-line treatment of patients with CLL or SLL, which are morphologically and clinically similar diseases, producing substantially higher response rates than reported in relapsed or refractory patients. Re-treatment with rituximab at 6-month intervals is well tolerated. The progression-free survival

Table 1. Ongoing Trials of Rituximab Maintenance Therapy in the Treatment of Lymphoma

ClinicalTrials.gov Identification Number	Disease	Official Title	Phase
NCT00209209*	Mantle-cell lymphoma	Efficacy of Maintenance Therapy With Rituximab After Induction Chemotherapy (R-CHOP vs R-FC) for Elderly Patients With Mantle Cell Lymphoma Not Suitable for Autologous Stem Cell Transplantation	III
NCT00400478*	Diffuse large B-cell lymphoma; follicular lymphoma grade 3b	A Multicentre, Randomized Phase III Study of Rituximab as Maintenance Treatment Versus Observation Alone in Patients With Aggressive B-Cell Lymphoma: NHL-13	III
NCT00081146	Diffuse large B-cell lymphoma	Randomized Study of ICE Plus Rituximab (R-ICE) Versus DHAP Plus Rituximab (R-DHAP) in Previously Treated Patients With CD20 Positive Diffuse Large B-Cell Lymphoma, Eligible for High-Dose Chemotherapy and Transplantation Followed by Randomized Maintenance Treatment With Rituximab	III
NCT00078949	Non-Hodgkin lymphoma	A Phase III Study of Gemcitabine, Dexamethasone, and Cisplatin (GDP) Compared to Dexamethasone, Cytarabine, and Cisplatin (DHAP) as Salvage Chemotherapy for Patients With Relapsed or Refractory Aggressive Histology Non-Hodgkin's Lymphoma Prior to Autologous Stem Cell Transplant and Followed by Maintenance Rituximab Versus Observation	III
NCT00430352	Non-Hodgkin lymphoma	A Study to Evaluate the Safety of MabThera (Rituximab) Maintenance Therapy in Patients With Follicular Non-Hodgkin's Lymphoma Who Have Responded to Induction Therapy	IV
NCT00137995	Diffuse large B-cell lymphoma	Randomized Study of ICE Plus RITUXIMAB Versus DHAP Plus Rituximab in Previously Treated Patients With Diffuse Large B-Cell Lymphoma, Followed by Randomized Maintenance With Rituximab	III
NCT00290511	Follicular lymphoma	A Phase II Study of R-FND, Followed by Zevalin Radioimmunotherapy, and Subsequent Maintenance Rituximab for Advanced Stage Follicular Lymphoma With High-Risk Features	II

* Europe only.

observed in patients with CLL/SLL seems shorter than the 36- to 40-month median progression-free survival reported with first-line rituximab followed by maintenance rituximab in patients with follicular lymphoma. There are no data to indicate whether overall survival in patients with CLL is improved by maintenance therapy with rituximab.

H&O Could you discuss the use of rituximab in the setting of stem cell transplantation?

JV In the setting of stem cell transplantation, there are not as many randomized trials of rituximab as maintenance therapy as there are of rituximab as initial therapy. Retrospective analyses show that if patients receive rituximab within 3 months before undergoing transplantation, the outcome is improved. However, there has been only

a single trial, conducted in Europe, assessing the use of rituximab as maintenance therapy after transplantation, which found an improvement in progression-free survival but no improvement in overall survival.

H&O What is the status of maintenance therapy with rituximab in other types of non-Hodgkin lymphoma?

JV Maintenance rituximab has been tested in diffuse large B-cell lymphoma, and the findings were negative. Any benefit achieved with rituximab maintenance therapy was limited to patients who received cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) as initial therapy without rituximab, but the combination of CHOP and rituximab upfront is
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standard therapy in this setting. Rituximab maintenance therapy has also been tested in mantle-cell lymphoma, where there was a slight improvement in progression-free survival but not a notable long lasting improvement in overall survival. Trials are examining the best approaches to maintenance therapy in other types of lymphoma; for example, whether therapy should be continued until relapse or for a set period of time, and what doses and schedules are ideal.

H&O What further controversies remain with rituximab maintenance therapy?

JV There is controversy regarding the increased risk of infection due to neutropenia in patients who receive rituximab for a long period of time. Certain rare infections have been observed in patients receiving rituximab, such as reactivation of hepatitis B or progressive multifocal leukoencephalopathy. Another controversy is whether maintenance therapy leads to increased resis-

tance to rituximab. All patients who receive rituximab appear to develop resistance eventually, but the concern is whether maintenance therapy causes patients to develop this resistance sooner.

Suggested Readings

Cheson BD. Anti-CD20 monoclonal antibodies in the treatment of indolent lymphoma and CLL. *Clin Adv Hematol Oncol.* 2007;5(2 suppl 3):1-16.

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