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Chemotherapy Combinations With Monoclonal Antibodies in Non-Hodgkin's Lymphoma

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Abstract

Although the use of monoclonal antibodies as single agents has had a tremendous impact on the care of patients with non-Hodgkin's lymphoma (NHL), the greatest benefit has been generated by the addition of monoclonal antibodies to conventional cytotoxic chemotherapy. Rituximab is the monoclonal antibody responsible for all clinical improvement noted to date. The addition of rituximab to cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) chemotherapy (R-CHOP regimen) improves the response rate, progression-free survival (PFS), and overall survival (OS) in diffuse large B-cell lymphoma (DLBCL). Adding rituximab to CHOP chemotherapy improves response rates and PFS in mantle cell lymphoma (MCL). Finally, the addition of rituximab to a variety of chemotherapy regimens improves the response rates, PFS, and OS in follicular lymphoma (FL). Several other (epratuzumab, bevacizumab, alemtuzumab) monoclonal antibody–chemotherapy combinations are currently under study in NHL. This review will summarize the data supporting the addition of rituximab to chemotherapy in NHL and discuss preliminary data regarding the use of other monoclonal antibodies in combination with chemotherapy.

It is well established that combining rituximab (Rituxan, Genentech, South San Francisco, CA) to most (perhaps all) chemotherapy regimens produces a major clinical benefit when treating $CD20^+$ B-cell lymphoma. Improvement in most efficacy end points, without added toxicity, has been consistently demonstrated in most B-cell histologies. Exactly how this benefit is achieved remains unclear. It is generally accepted that rituximab "sensitizes" the cells to killing by chemotherapy. Whether this is a synergistic effect or an additive effect is controversial. Limited preclinical data suggest a synergistic interaction.[1] A proposed model hypothesizes that rituximab binding to CD20 initiates a signal transduction pathway leading to downregulation of interleukin-10 (IL-10) expression, which results in downregulation of bcl-2 expression, increasing the cell's sensitivity to cytotoxic therapy. Consistent with this hypothesis, two studies suggest rituximab added to chemotherapy overcomes the negative prognostic effect of bcl-2 overexpression.[2–3] Whether there are different mechanisms and differential sensitization dependent on the cytotoxic agent administered remains uncertain.

Rituximab Plus CHOP for Diffuse Large B-Cell Lymphoma

Three randomized clinical trials (RCT) and one population-based registry trial have shown a significant improvement in cure rate when rituximab is added to cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP, R-CHOP regimen) or CHOP-like

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chemotherapy.[4–7] Two of the RCTs (Group d'Etude des Lymphomas de l'Adulte [GELA] and E4494) were conducted in patients older than 60 years of age with advanced-stage diffuse large B-cell lymphoma (DLBCL). In an update of the original GELA report, the 5-year overall survival (OS) rate was 58% in patients who received rituximab plus CHOP (R-CHOP) compared to 45% (P <.007) in those receiving CHOP.[8] The US intergroup trial, E4494, confirmed these results and demonstrated a 3-year OS of 67% in R-CHOP patients compared to 58% (P = .05) in CHOP patients.[6] No additional benefit for maintenance rituximab after R-CHOP therapy was observed. The third RCT was conducted in patients under the age of 60 who had one or fewer adverse prognostic factors.[7] The chemotherapy was either CHOP or cyclophosphamide, doxorubicin, vincristine, etoposide, and prednisone (CHOEP). The estimated 3-year OS was 93% in the rituximab–chemotherapy patients compared to 84% (P = .0001) in the chemotherapy-alone patients. Population-based analysis, performed in the province of British Columbia, revealed a marked improvement in 2-year OS after the introduction of R-CHOP therapy: 78% versus 52% (P <.0001). In summary, these studies show that the addition of rituximab to CHOP chemotherapy improved the OS in the three RCTs by 9% to 13% in absolute terms (Table 1). Since OS can be influenced by factors unrelated to the treatment under investigation (such as the effectiveness of salvage regimens), progression-free survival (PFS) is considered a better end point for evaluating the efficacy of a regimen. When analyzed by PFS, the impact of rituximab is even more striking, with absolute improvements ranging from 13% to 24% (Table 1).

Rituximab Plus CHOP for Mantle Cell Lymphoma

Only one relatively small RCT has compared R-CHOP to CHOP in previously untreated mantle cell lymphoma (MCL).[9] The impact of rituximab appears to be less dramatic in this disease compared with DLBCL and follicular lymphoma (FL), as no improvement in OS was demonstrated. R-CHOP was superior to CHOP in terms of overall response rate (94% *v* 75%), complete response rate (34% *v* 7%) and median time to treatment failure (21 months *v* 14 months). All differences were statistically significant. No additional toxicity was noted with the addition of rituximab.

Rituximab Plus Chemotherapy for Follicular Lymphoma

Previous clinical trials incorporating anthracyclines or autologous stem cell transplantation as part of first-line therapy in FL were able to demonstrate improved PFS but failed to improve the OS. Since these strategies were associated with increased toxicity, the tradeoff did not seem justified and these approaches have not been routinely adopted. However, after the introduction of rituximab, major improvements in PFS without increased toxicity were demonstrated in frontline RCTs, and the incorporation of rituximab was widely adopted. With longer follow-up, somewhat surprisingly, four of these RCTs have now demonstrated a small but statistically significant improvement in OS favoring the addition of rituximab to frontline chemotherapy.[10–13] That the improvement in OS represents a major milestone in the management of FL is a testament to the contribution of rituximab (Table 2).

The first published study to show an impact on OS was published by the German Low-Grade Lymphoma Study Group.[10] In this trial, rituximab was added lo standard CHOP chemotherapy. Responding patients went on to receive either autologous stem cell transplantation or interferon maintenance therapy. The estimated probability of survival at 2 years was 95% for R-CHOP patients and 90% for CHOP patients. Because the absolute difference was small and the study follow-up short, and due lo the potential confounding effects of the post remission therapy, many investigators were initially skeptical regarding the reported OS advantage. This skepticism soon dissipated.

Reported at the 2006 American Society of Clinical Oncology meeting was the second RCT demonstrating an OS advantage for the inclusion of rituximab.[11] This study, FL2000, was a combined effort from the GELA and the Groupe Ouest Est des Leucemies et Autres Maladies du Sang (GOELAMS) study groups. Rituximab was added to the cyclophosphamide, doxorubicin, vindesine, and prednisone (CHVP) chemotherapy regimen and with 3.5 years of follow up, major improvements in PFS and OS were noted in the rituximab-containing chemotherapy arm. Six months later, at the 2006 American Society of Hematology meetings, two additional RCTs were reported, each demonstrating improved OS when rituximab was combined with first-line chemotherapy. The first was an update of a previously published international trial where rituximab was added to the cyclophosphamide, vincristine, and prednisone (CVP) chemotherapy regimen. The update revealed an improved 4-year OS (77% *v* 83%, $P < .05$). At the same meeting came a report from the East German Study Group Hematology and Oncology. In this study, rituximab added to the mitoxantrone, chlorambucil, prednisolone (MCP) regimen resulted in significant improvement in the 4-year OS (74% *v* 87%, $P < .05$). The differences in PFS in all four trials are even more striking (Table 2).

Based on these data, it is clear that rituximab added to chemotherapy provides major clinical benefit in the frontline treatment of FL. It is not clear if there is an “optimal” chemotherapy regimen to combine with rituximab, and for now the choice of chemotherapy will depend on physician preference and patient-specific factors. It is important to point out that eligibility for each of the four clinical trials required some features indicating necessity of therapy. The exact criteria varied from study to study, but the patients could not be considered candidates for a “watch and wait” approach. Therefore, at the present time we do not know if these data indicating an OS advantage for rituximab–chemotherapy can be extrapolated to the low tumor burden population.

Epratuzumab

Epratuzumab (Immunomedics, Morris Plains, NJ) is a humanized monoclonal antibody of the IgG1 subclass, directed against CD22, a B-cell specific antigen. CD22 is a 135-kd membrane sialoglycoprotein that is expressed on pre-B and mature B cells, and expression is lost upon maturation to plasma cells.[14] The exact role of the CD22 antigen is unclear, but it appears to be involved in cell adhesion and regulation of B-cell activation. Since it is lineage-restricted and present on most B-cell lymphomas (~85% of DLBCLs), it is an attractive target for antibody-based therapy. After binding epratuzumab, CD22 is rapidly internalized. Cell death does not appear to be mediated by complement, but modest antibody-dependent cellular cytotoxicity and direct killing effects have been demonstrated.[14–15] Epratuzumab is somewhat less potent than rituximab at inducing B-cell depletion. As a single agent, it has demonstrated a favorable safety profile and modest efficacy in both indolent and aggressive NHL.[16,17] Infusional toxicity appears to be less than that seen with rituximab and the efficacy was enhanced when combined with rituximab.[18,19]

There is one published pilot study evaluating the addition of epratuzumab to standard chemotherapy in untreated DLBCL.[20] Fifteen patients received R-CHOP plus epratuzumab at a dose of 360 mg/m^2 on day 1 of each 21-day cycle. The primary end point was the incidence of grade 4 neutropenia and grade 3 or 4 antibody infusional toxicity. The secondary end points included traditional measures of efficacy. The regimen proved to be feasible and safe. No grade 3 or 4 infusional toxicities were noted. Grade 4 neutropenia was reported in 30% of treatment cycles and three patients developed grade 3 or greater infection or fever. The overall response rate (ORR) was 87% (13/15) and the 2-year PFS and OS rates were both 86%. Based on these interesting results, a multicenter phase II study has been initiated by the North Central Cancer Treatment Group (NCCTG).

Bevacizumab

Bevacizumab (Avastin, Genentech) is a humanized monoclonal antibody directed against vascular endothelial growth factor (VEGF).[21,22] Targeting angiogenesis has long been a desired strategy in solid tumors and despite bevacizumab's lack of appreciable single-agent activity, it enhances the efficacy of standard chemotherapy in several settings. There is evidence that angiogenesis may be a rational target in certain lymphomas. Serum concentrations of VEGF have been shown to be a predictor of poor outcome in patients with NHL.[23] Gene expression profiling revealed the *VEGF* gene to be over-expressed in activated B-cell–like DLBCL relative to germinal center–like DLBCL.[24] Additionally, lymphoma patients with high expression of VEGF were shown to be less likely to respond to standard chemotherapy.[25]

A pilot study evaluating the addition of bevacizumab to the R-CHOP regimen in DLBCL has been published.[26] Bevacizumab was administered at a dose of 15 mg/kg intravenously on day 1 of each R-CHOP cycle, repeating every 21 days for eight cycles. The goal of the study was to obtain preliminary data on safety and efficacy. Thirteen patients, median age of 49 years (range, 26–63), were enrolled. Eight patients had stage 4 disease and nine patients had an elevated lactate dehydrogenase (LDH), suggesting this was a relatively high-risk group. Notable toxicities included four central line infections, two central line thromboses, one elevated transaminase, two episodes of transient hypertension, two episodes of febrile neutropenia, and one herpes simplex esophagitis. The ORR was 85% and the 1-year PFS was 77%. Plasma VEGF levels were higher in the two nonresponders compared to responders. Bevacizumab and rituximab levels were measured and the results suggested that combining the two monoclonal antibodies in the same regimen had no effect on the predicted pharmacokinetics.

There are at least three multicenter trials further evaluating the role of bevacizumab in the treatment of aggressive NHL. The Eastern Cooperative Oncology Group is conducting a phase II trial of bevacizumab combined with CHOP chemotherapy for untreated peripheral T-cell lymphoma (PTCL). The Southwest Oncology Group is conducting a phase II trial of bevacizumab combined with R-CHOP for untreated DLBCL. Finally, an international RCT is underway, comparing R-CHOP to bevacizumab plus R-CHOP for untreated DLBCL.

Alemtuzumab

Alemtuzumab (Campaih-1H, Bayer, Wayne, NJ) is a humanized IgG1monoclonal antibody that is approved for use in fludarabine-refractory chronic lymphocytic leukemia. It targets the CD52 antigen, which is present on normal B cells, T cells, monocytes, and macrophages. CD52 is expressed on most lymphoid malignancies, although to varying degrees. Expression is highest in T-prolymphocytic leukemia (T-PLL) and the expression in PTCL is present in approximately 50% of cases.[27] Despite the inconsistent expression of CD52 in PTCL, there has been interest in studying alemtuzumab in this disease group. This interest can be explained partly by the lack of other commercially available monoclonal antibodies available for study in PTCL and partly by the poor results in PTCL with standard therapies.

The Gruppo Italiano Terapie Innovative nei Linfomi (GITIL) has completed a multicenter prospective clinical trial evaluating the safety and efficacy of alemtuzumab added to the CHOP chemotherapy regimen for untreated PTCL.[28] Eligible patients received standard CHOP chemotherapy for eight cycles with 30 mg alemtuzumab administered subcutaneously on day – 1 of each cycle. Twenty-four patients, median age 52 years (range, 28–69), were enrolled. Histologic subtypes included PTCL unspecified (n = 14), angioimmunoblastic T-cell lymphoma (n = 6), anaplastic large cell lymphoma–ALK-negative (n = 3), and enteropathy-associated T-cell lymphoma (n = 1). The ORR was 71%

and the 2-year FFS was 48%. The investigators interpreted these outcomes as an improvement over standard CHOP therapy. However, the toxicities of the CHOP plus alemtuzumab regimen were considerable. Major infections included two instances of invasive aspergillosis, two instances of bacterial sepsis, two instances of bacterial pneumonia, one instance of *Pneumocystis carinii* pneumonia, one instance of J-C viral encephalitis, and one instance of suspected tuberculosis. RCTs are underway comparing CHOP to CHOP plus alemtuzumab in PTCL. Administration of this regimen outside of a clinical trial is not recommended at this time.

Summary

Rituximab's greatest impact on patient outcome is demonstrated when it is combined with conventional chemotherapy. The addition of rituximab to CHOP chemotherapy has improved the cure rate in DLBCL by 13% to 24% in absolute terms. Rituximab combined with chemotherapy improves the OS in FL, an end point no other previous therapy had been able to influence. Because of the remarkable therapeutic advances noted with these combinations, there is great interest in combining other monoclonal antibodies with chemotherapy. Additional study and time will tell if other antibody–chemotherapy combinations are able to further improve outcomes in NHL.

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Table 1

Published Trials Comparing Rituximab Plus CHOP to CHOP for Patients with DLBCL

				PFS		OS	
Study Group	**Study Type**	**N**	**Follow-up**	**R-CHOP**	**CHOP**	**R-CHOP**	**CHOP**
BCCA[5]	Registry	292	2yr	68%	51%	78%	52%
US intergroup[6]	RCT	632	3yr	52%	39%	67%	58%
International[7]	RCT	824	3yr	79%	59%	93%	84%
GELA[8]	RCT	399	5yr	54%	30%	58%	45%

NOTE. All differences in PFS and OS are statistically significant at the .05 level.

Abbreviations: BCCA, British Columbia Cancer Agency; GELA, Group d'Etude des Lymphomas de I'Adulte.

Table 2

Randomized Clinical Trials Comparing Rituximab Plus Chemotherapy to Chemotherapy Alone for Untreated Follicular Lymphoma

				PFS		OS	
Study Group	**Regimen**	**N**	**Follow-up**	**R-Chemo**	**Chemo**	**R-Chemo**	**Chemo**
GLSG[10]	CHOP	428	2 year	82%	64%	95%	90%
GELA-GOELAMS[11]	CHVP-IFN	358	3.5 year	67%	46%	91%	84%
International[12]	CVP	321	4 year	54%	17%	83%	77%
OSHO[13]	MCP	201	4 year	71%	40%	87%	74%

NOTE. All differences in PFS and OS are statistically significant at the .05 level.

Abbreviations: Chemo, chemotherapy; R, rituximab; GLSG, German Low Grade Lymphoma Study Group; GELA, Group d'Etude des Lymphomas de I'Adulte; GOELAMS, Groupe Ouest Est des Leucemies et Autres Maladies du Sang; OSHO, East German Study Group Hematology and oncology.