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Evolving Immunotherapy to Improve Survival for Patients With Non-Hodgkin Lymphoma

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Abstract Recent studies have investigated the role of immunotherapy and other chemotherapy alternatives in various settings in the treatment of lymphoma, including as initial treatment in aggressive lymphoma and as components of combination therapy for relapsed and refractory disease. Radioimmunotherapy is being evaluated as both induction therapy and as consolidation after first-line induction therapy in patients with indolent non-Hodgkin lymphoma (NHL). Various treatments are also being evaluated in the maintenance setting to prolong response duration of therapy. Whereas maintenance rituximab has demonstrated a clear benefit in indolent lymphoma, rituximab maintenance has not demonstrated a significant benefit in patients with aggressive lymphoma. Newer strategies, including small-molecule inhibitors and immunomodulatory agents, are being assessed in the maintenance setting based on promising activity demonstrated in patients with relapsed/ refractory disease. Investigations into the molecular characteristics of NHL are revealing lymphoma subtypes with different gene expression patterns and different responses to therapy. Further investigations into these biomarkers may lead to the development of individualized therapy to optimize outcomes. In this monograph, leading lymphoma experts Drs. Martin H. Dreyling, Myron S. Czuczman, Peter McLaughlin, and Thomas E. Witzig provide insights based on recent and ongoing clinical research.

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Issues in Maintenance Therapy for Aggressive Lymphoma

Martin H. Dreyling, MD, PhD

Although maintenance therapy has demonstrated a clear benefit in indolent lymphoma, the role of maintenance therapy in improving outcomes in aggressive lymphoma is unclear. Studies investigating novel maintenance approaches in aggressive lymphoma are limited. These trials use different criteria, such as long-term safety and convenience, than those used in trials evaluating agents in the frontline setting. A limited number of agents qualify for maintenance trials. Recent studies have explored the use of newer molecular compounds, including monoclonal antibodies, small-molecule inhibitors, and other agents as maintenance therapy in this setting.

Rituximab Maintenance Therapy

Maintenance therapy with the anti-CD20 antibody rituximab has demonstrated a clear progression-free survival (PFS) benefit in patients with indolent follicular lymphoma (FL), both in the relapsed/refractory setting and, most recently with the presentation of the PRIMA (Primary Rituximab and Maintenance) trial, after first-line induction therapy.[1,2] However, rituximab maintenance therapy has shown no benefit in aggressive lymphoma. In the Intergroup E4494/C9793 study of 415 older patients with diffuse large B-cell lymphoma (DLBCL), maintenance rituximab had no effect on outcomes in patients receiving induction therapy with rituximab plus cyclophosphamide, hydroxydaunorubicin, vincristine, and prednisone (R-CHOP), with a median time to treatment failure (TTF) of 5.6 years versus 5.4 years with R-CHOP followed by observation.[3] However, maintenance rituximab did improve outcomes in patients who received CHOP alone as induction therapy, with a median TTF of 5.2 years versus 1.6 years with CHOP followed by observation (P=.0004). These results indicate that once rituximab is included as part of induction, additional rituximab in the maintenance setting confers no benefit to patients with DLBCL.

The international, multicenter, phase III trial NHL-13 will reinvestigate the role of rituximab maintenance in patients with aggressive lymphoma in the context of standard induction therapy.[4] In this ongoing study, patients attaining successful induction therapy with rituximab plus CHOP-like chemotherapy are randomly assigned to maintenance rituximab or observation. Results are expected in late 2012.

Enzastaurin as Maintenance Therapy

After gene profiling studies demonstrated overexpression of protein kinase C (PKC)-beta in refractory DLBCL,[5] studies were undertaken to investigate the use of the PKC-beta inhibitor enzastaurin in aggressive lymphoma. A phase II trial of single-agent enzastaurin in 55 patients with relapsed or refractory DLBCL showed only modest activity; 22% of patients had freedom from progression for 2 cycles and 15% had freedom from progression for 4 cycles.[6] Safety data for this agent have been favorable. In an analysis of 135 patients included in phase I and phase II trials, no deaths were related to enzastaurin.[7] The most common drug-related event, chromaturia, occurred in 14% of patients. There were no reports of drug-related bone marrow suppression or of grade 3 neutropenia, thrombocytopenia, or anemia. Edema, migraine, and peripheral motor neuropathy were observed in 1 patient each.

The reported prolongation of freedom from progression, combined with the agent's favorable safety profile, supported investigations into enzastaurin as maintenance therapy after chemotherapy induction in aggressive lymphoma. The ongoing randomized, placebo-controlled, phase III PRELUDE (Study to Investigate the Prevention of Relapse in Lymphoma Using Daily Enzastaurin) trial is investigating the role of daily enzastaurin for preventing relapse in patients with DLBCL who are in remission after recently completing R-CHOP induction therapy.[8]

Lenalidomide as Maintenance Therapy

Lenalidomide is an immunomodulatory agent that is also being evaluated for the treatment of aggressive non-Hodgkin lymphoma (NHL) both as part of a novel combination and in the maintenance setting. Two phase II trials demonstrated activity with lenalidomide in relapsed/refractory aggressive lymphoma. An overall response rate (ORR) of 35% was achieved both in the US pilot study with 49 heavily pretreated patients who had failed a median of 4 prior

therapies,[9] as well as in a large international study with 217 patients.[10] In the US study, the most common grade 4 adverse events were neutropenia (8.2%) and thrombocytopenia (8.2%). The most common grade 3 adverse events were neutropenia (24.5%), leukopenia (14.3%), and thrombocytopenia (12.2%). In the international study, grade 3/4 adverse events included neutropenia (41%), thrombocytopenia (19%), anemia (9%), and leukopenia (7%).

A phase I/II trial demonstrated the feasibility of combination therapy with lenalidomide plus R-CHOP in the first-line treatment of aggressive lymphoma.[11] Phase I data showed that the addition of lenalidomide did not affect hematologic recovery and did not require a single delay in R-CHOP administration. The phase II portion of the study, evaluating dose and schedule, is ongoing. Another ongoing phase I dose-escalation study is determining the optimal dose of lenalidomide and R-CHOP in patients with B-cell lymphomas.[12]

Despite a high level of myelosuppression associated with lenalidomide, treatment did not appear to translate into an increase in infection rates. This tolerability profile suggests that lenalidomide may be a good candidate for use in the maintenance setting. The REMARC (Double Blind Randomized Phase III Study of Lenalidomide Maintenance Versus Placebo in Responding Elderly Patients With DLBCL and Treated With R-CHOP in First Line) trial[13] by the Groupe d'Etude des Lymphomes de l'Adulte (GELA) is evaluating lenalidomide maintenance therapy after R-CHOP in elderly patients, who are generally less tolerant of dose-intensified chemotherapy. This phase III trial is enrolling patients ages 60–80 years with an age-adjusted International Prognostic Index (IPI) score greater than 1.

Maintenance Therapy for Mantle Cell Lymphoma

Mantle cell lymphoma (MCL) is characterized as an aggressive lymphoma, as it can progress quickly. However, similar to other lymphomas with an indolent histology, current treatment options do induce a survival plateau in patients with MCL, and the disease remains incurable with high rates of relapse. Although R-CHOP is associated with a high ORR (94%, with 34% complete remissions), patients generally relapse within several years.[14] New maintenance approaches are necessary to maintain remission.

Lenalidomide has emerged as a potential option for maintenance therapy based on results from phase II studies indicating promising activity with the agent in relapsed or refractory MCL,[9,10,15] as well as on data for the duration of response, which was a median of 6.2 months in the US pilot study[9] and a median of 11.6 months in the international trial.[10] In a subgroup analysis by Habermann and colleagues of 15 patients with MCL, single-agent lenalidomide was associated with an ORR of 53% (3 complete responses [CR] and 5 partial responses [PR]).[15] The ongoing phase III, multicenter, randomized, double-blind, placebo-controlled RENEW (Study to Evaluate the Efficacy of Lenalidomide as Maintenance Therapy After Completion of First-line Combination Chemotherapy in Patients With Mantle Cell Lymphoma [MCL]) trial is evaluating the use of lenalidomide as maintenance therapy after first-line chemotherapy with rituximab.[16]

One important factor in the development of successful maintenance therapies for aggressive lymphoma will be the inclusion of representative patients in clinical trials. Many studies have enrolled only young, fit patients, although the majority of patients with aggressive lymphoma are elderly with various comorbidities. For these poor-risk patients, it is hoped that the addition of a molecular approach, either as maintenance therapy after chemotherapy, or simultaneously with chemotherapy, will improve outcomes.

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Unmet Needs in the Treatment of Aggressive Lymphoma

Myron S. Czuczman, MD

Currently, the standard upfront immunochemotherapy regimen for DLBCL is R-CHOP, which is associated with a complete remission rate of approximately 76% and a 2-year PFS rate of 50–60%.[1] Unfortunately, a significant percentage of patients are either refractory to R-CHOP, or their disease relapses after first-line therapy.[2] The initial treatment strategy for relapsed DLBCL is high-dose chemotherapy and autologous stem cell transplantation (ASCT) in chemotherapy-sensitive and transplant-eligible patients. In the 1995 trial from the PARMA group studying patients with chemosensitive relapsed NHL, ASCT was associated with a 5-year event-free survival rate of 46%.[3] Thus, a significant number of patients remain uncured after upfront therapy or aggressive salvage therapy with ASCT.

The variation in clinical outcomes in DLBCL may be partly due to differences in the disease at the molecular level. Genetic studies have shown that DLBCL represents a heterogeneous group of malignancies. The main variants are germinal center B-cell (GCB) type or non-GCB type (which includes primarily activated B-cell [ABC] type, as well as mediastinal large B-cell lymphoma [a more rare subtype that occurs predominantly in young women]).[4]

Prognosis in DLBCL is significantly better in patients with GCB type than in patients with non-GCB type, with 5-year overall survival rates of 76% and 34%, respectively (P<.001).[5] Among patients receiving R-CHOP, 3-year overall survival is longer in those with the GCB type than the ABC type. Whereas ABC-type DLBCL is characterized by activation of nuclear factor-kB (NF-kB),[6] the primary oncogenic mechanism in GCB-type DLBCL is B-cell leukemia/lymphoma 2 translocation.[7] Clinical trials have been investigating whether specific therapies are more effective in certain lymphoma subtypes.[8]

Therapeutic Options in Relapsed/Refractory DLBCL

Treatment options for patients with relapsed/refractory DLBCL are limited, and often include chemotherapeutic agents that the patients may have already been exposed to earlier in treatment. These may include single-agent gemcitabine, etoposide, oxaliplatin, and rituximab. However, response rates in this setting reach only 20–30% and typically are associated with short remission duration and overall survival.[9] Trials investigating newer agents, including the proteasome inhibitor bortezomib,[10] have shown similarly modest responses.

Lenalidomide in Relapsed/Refractory Aggressive Lymphoma

One agent demonstrating promising activity in aggressive lymphoma is the immunomodulatory agent lenalidomide. In a large international phase II trial with 217 patients, single-agent lenalidomide demonstrated significant activity in the subset of patients with relapsed/refractory DLBCL, with an ORR of 28%, including 7% CRs.[11] Although median PFS was 3.5 months, median duration of response was 11.6 months.

A retrospective analysis showed that lenalidomide was particularly active in patients with non–GCB-type lymphoma, who tend to have poorer outcomes after CHOP.[12] The ORR with lenalidomide in these patients was 77% versus 11% in patients with GCB-type lymphoma (P=.011). Among non-GCB patients, 44% achieved a CR versus 11% of GCB patients. Median PFS was 336 days in the non-GCB subgroup versus 72 days in the GCB subgroup (P=.008). Median overall survival for non-GCB patients was 420+ days compared with 73 days for GCB patients; this difference did not reach statistical significance (P=0.4). Additional samples are being acquired to validate these findings in a larger analysis.

Based on these preliminary findings, a phase II/III registration trial was initiated to evaluate lenalidomide in patients with relapsed/refractory DLBCL who are stratified according to molecular subtype. Researchers will first examine whether lenalidomide is particularly effective in patients with the non-GCB subtype (in phase II of the trial). If efficacy is confirmed, then a subsequent phase of the trial (phase III) will focus on evaluating the safety and efficacy of lenalidomide in this subpopulation of patients.

Bortezomib

The proteasome inhibitor bortezomib has also demonstrated activity in relapsed/recurrent DLBCL. Because bortezomib inhibits NF-kB activity, it was hypothesized that bortezomib may sensitize ABC-type DLBCL to chemotherapy. Indeed, Dunleavy and colleagues found that while bortezomib has minimal single-agent activity in 49 patients with recurrent DLBCL, combination therapy with bortezomib and dose-adjusted etoposide, vincristine, doxorubicin, cyclophosphamide, and prednisone (EPOCH) chemotherapy is significantly more effective in ABC-type versus GCB-type DLBCL, in regard to response rate (83% vs 13%; $P<.001$) and median overall survival (10.8 vs 3.4 months; $P=.003$).[8] However, the regimen is associated with significant toxicity, especially in patients in the post-transplant setting. Therefore, agents associated with less toxicity—particularly hematologic toxicity—may be more beneficial in this population.

Galiximab

The monoclonal antibody galiximab is also being investigated for the treatment of refractory lymphoma. The agent binds to CD80, an immune costimulatory molecule that is constitutively expressed on the FL cell surface. A phase II trial demonstrated the activity of galiximab in combination with rituximab in patients with relapsed/refractory FL, demonstrating an ORR of 64%, including 17% CR.[13] The median PFS after a median follow-up of 45 months was 12.2 months, and the PFS exceeded 2 years in 20% of patients. No serious infections or secondary malignancies were observed with this combination.

Galiximab has also been evaluated in patients with relapsed Hodgkin lymphoma. The agent was well tolerated but had minimal activity in these heavily pretreated patients, with an ORR of 7%.[14] Although more must be learned about the potential of galiximab, it is possible that it may play a potential role in the future treatment of aggressive lymphoma.

As these new agents are evaluated, it will be important to continue to explore biomarkers associated with responses to treatment. Researchers are investigating a number of molecular pathways to determine which may be more predominant in certain subtypes of lymphoma. Such studies could lead to the development of individualized treatment based on molecular characteristics.

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Novel Immunotherapy Combinations for the Treatment of Indolent Non-Hodgkin Lymphoma

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Although effective therapies for FL are available, the likelihood of relapse remains high. New strategies that will either prevent relapse or prolong the duration of response are needed. Clinical trials have been investigating new combinations of biologic and chemotherapeutic agents, consolidation with radioimmunotherapy (RIT), and maintenance approaches using immunotherapy as well as other novel agents.

Rituximab and Lenalidomide in Indolent Lymphoma

The immunomodulatory drug lenalidomide is being evaluated in both aggressive and indolent lymphomas. Although this thalidomide analog is best categorized as a biologic agent, it has some chemotherapy-like characteristics, including its association with myelosuppression. The agent has demonstrated single-agent activity in patients with indolent NHL[1] and has more recently been evaluated in combination with rituximab.

Preclinical studies suggest that the combination of lenalidomide and rituximab is synergistic. Indeed, lenalidomide appears to upregulate natural killer (NK) cell numbers and activation state. Moreover, in vitro studies have shown that lenalidomide enhances NK cell–mediated, antibody-dependent cellular cytotoxicity.[2] In animal studies, eradication of NK cells results in a loss of synergy between lenalidomide and rituximab, supporting the role of NK cells in this process. Based on this preclinical evidence, lenalidomide plus rituximab combination therapy is being evaluated in clinical trials.

In 2010, Fowler and colleagues presented results from a phase II study of lenalidomide plus rituximab in the first-line treatment of stage III/IV indolent NHL.[3] Patients received lenalidomide (20 mg/day) on days 1–21 and rituximab (375 mg/m^2) on day 1 of each 28-day cycle for up to 6 cycles. Among the 45 patients evaluable for response, the ORR was 89% (73% CR/unconfirmed CR [CRu]). Among the 48 patients included in the intention-to-treat analysis, 5 achieved stable disease and 7 achieved PR. The most common grade 3/4 adverse events in the 48 patients who completed 6 cycles of therapy were neutropenia (n=10), rash (n=6), thrombocytopenia (n=6), myalgia (n=4), and thrombosis (2). Among the 3 patients who discontinued treatment due to adverse events, 1 patient developed a severe reaction to rituximab prior to lenalidomide dosing during cycle 2, 1 patient developed grade 3 rash during cycle 1 (skin biopsy showed leukocytoclastic vasculitis), and 1 patient developed arterial thrombosis during cycle 1.

Combination therapy with lenalidomide and rituximab is also feasible in patients with relapsed/refractory MCL. A phase I/II trial studied a treatment regimen of lenalidomide administered once daily on days 1–21 of a 28-day cycle and rituximab 375 mg/m^2 IV administered weekly for 4 weeks.[4] Four doses of lenalidomide were evaluated: 10 mg, 15 mg, 20 mg, and 25 mg. The phase I results of 13 patients, presented in 2007, showed no responses in patients receiving the 10 mg or 15 mg doses of lenalidomide. In the 6 patients who received the 20 mg dose, after 2 cycles, 5 achieved a response (1 CR, 1 PR, 3 minor responses), and only 1 progressed. The patient with a PR achieved a CR after 6 cycles. The maximally tolerated dose was 20 mg. Among the 2 patients in the 25 mg arm, 1 developed grade 3 hypercalcemia and 1 developed grade 4 neutropenic fever and died of sepsis (grade 5) during the first cycle. Grade 3 hematologic adverse reactions included neutropenia (4 events) and thrombocytopenia (2 events). Grade 1/2 hematologic adverse reactions included neutropenia (20 events), thrombocytopenia (6 events), and anemia (6 events). This ongoing phase I/II trial is also enrolling patients with DLBCL, transformed large cell lymphoma, and/or grade 3 FL.[5]

A 2009 study examined a regimen of lenalidomide 20 mg/day on days 1–21 of a 28-day cycle, which was continued until disease progression.[6] Rituximab 375 mg/m^2 IV was initiated on day 15 of cycle 1 and repeated weekly for a total of 4 doses. After cycle 2, if the patient achieved less than a CR, then 4 additional doses could be administered at the discretion of the treating physician. Among the 16 patients evaluable for response, 12 responded to treatment, including 5 patients with a CR/CRu and 7 patients with a PR. Responses occurred in 4 of 7 patients with rituximab-refractory disease, and in 7 of 10 patients who had been heavily pretreated. Of 13 patients with relapsed/refractory FL, the ORR was 85%; 5 achieved a CR/CRu, and 6 achieved a PR. The estimated median PFS for all patients was 12 months. Among patients who received more than 5 cycles of lenalidomide, PFS had not been reached. The most common grade 3/4 adverse events were lymphopenia (occurring in 25%), neutropenia (occurring in 18%), hyponatremia (occurring in 18%), and fatigue (occurring in 12%).

Feasibility of Chemotherapy-free Treatments

Given the high relapse rates with today's treatments for FL, many patients will use every available treatment option, including chemotherapy. However, a growing understanding of molecular mechanisms, prognostic factors, and treatment efficacy in different patient populations may increasingly allow us to identify patients who may be eligible for initial treatments with biologic agents only.

At our institution, we are leaning toward initial biologic approaches for patients with low-risk features as determined by Follicular Lymphoma International Prognostic Index (FLIPI) or FLIPI-2 scores. I believe that other institutions are also beginning to stratify treatment strategies, using initial chemotherapy approaches only in patients in the higher-risk categories. However, in spite of the advances in nonchemotherapeutic strategies, we are still not promising cures to any patients, including those with lower-risk scores. Many patients will eventually need chemotherapy or transplant strategies, as well as biologic treatments, over the course of their disease. Although my hope is that we can continue to develop effective biologic approaches, chemotherapy will continue to play an important role in the care of patients with lymphoma.

Rituximab Maintenance Therapy in Indolent NHL

Maintenance rituximab has shown a significant benefit in patients with relapsed or refractory FL. In long-term follow-up of the randomized, phase III European Organisation for Research and Treatment of Cancer (EORTC) 20981 intergroup trial,[7] rituximab maintenance significantly improved PFS compared with observation (median, 3.7 years vs 1.3 years; hazard ratio [HR], 0.55; $P<.001$), both after CHOP induction (HR, 0.37; $P<.001$) and R-CHOP (HR, 0.69; $P=.003$).[8] Similar benefit from rituximab maintenance has been reported following salvage immunochemotherapy with rituximab, fludarabine, cyclophosphamide, and mitoxantrone (R-FCM).[9]

The use of rituximab maintenance following frontline therapy has recently been addressed by the phase III, international, randomized PRIMA trial, which compared 2 years of maintenance rituximab versus observation in 1,018 patients with FL responding to first-line rituximab plus chemotherapy. In data presented in 2010, maintenance rituximab was associated with a significant 50% improvement in PFS (HR, 0.50; $P<.0001$), with 2-year PFS rates of 82% and 66%, respectively.[10]

These findings suggest that monoclonal antibody-based maintenance therapy is beneficial in FL, even in patients already exposed to monoclonal antibodies during induction therapy.

Bortezomib in Indolent NHL

The proteasome inhibitor bortezomib is also being evaluated as an alternative to conventional chemotherapy in NHL. Like lenalidomide, bortezomib could be categorized as a biologic agent, though it has features of chemotherapeutic agents. In either case, bortezomib does fit nicely into combination therapies for lymphoma. Recently, Friedberg and colleagues[11] presented phase II data on the combination of bendamustine, bortezomib, and rituximab in patients with relapsed/refractory indolent lymphoma and MCL. In the 25 patients evaluable for response, the ORR was 84%, including 52% CR/CRu and 32% PR. Similar results were also reported by Fowler and coworkers for patients with recurrent FL.[12] The addition of bortezomib, however, was associated with higher rates of toxicities than are seen with bendamustine and rituximab alone.

Role of RIT in Indolent NHL

RIT has been evaluated as both induction therapy and as consolidation therapy in patients with indolent NHL. In 2005, Kaminski and colleagues published results from a phase II trial of the anti-CD20 radioimmunotherapeutic agent iodine ^{131}I-tositumomab as initial therapy for FL.[13] In 76 patients with previously untreated stage III or IV FL, a single course of treatment with iodine ^{131}I-tositumomab therapy was associated with an ORR of 95%, including 75% CR. In 2009, the investigators provided long-term follow-up results from this study. After a median of 10 years of follow-up, the median duration of response was 6 years, and 40% of patients remained progression-free.[14] The 10-year overall survival rate was 82%. Thus, this study showed that a single 1-week course of iodine ^{131}I-tositumomab therapy can produce excellent, durable responses in FL.

RIT has also demonstrated impressive results as consolidation therapy for patients with FL in first remission after chemotherapy. In the international, randomized, phase III FIT (First-line Indolent Trial) study in 414 patients with CD20-positive advanced-stage FL, consolidation therapy with yttrium-90-ibritumomab tiuxetan was associated with a significant prolongation of remission compared with no further treatment in patients attaining an objective response after first-line induction treatment.[15] After a median follow-up of 3.5 years, the median PFS was 36.5 months versus 13.3 months in the control arm (HR, 0.465; $P<.0001$). The improvements were significant regardless of whether patients had achieved PR or CR after induction therapy, and regardless of risk subgroups. After consolidation therapy, 77% of patients originally in PR converted to CR or CRu, resulting in a final CR/CRu rate of 87%.

Because rituximab had not yet been endorsed by European regulatory agencies when the FIT trial was designed, most patients had not received rituximab as part of their induction therapy. Although patients with rituximab-containing induction therapy were included in the study as a late modification to the trial, the benefit of ibritumomab tiuxetan consolidation was primarily seen in a patient population not previously exposed to anti-CD20 therapy. Given the positive results in the PRIMA trial, it would be interesting to investigate whether a single dose of ibritumomab tiuxetan consolidation would yield comparable outcomes to those achieved with 2 years of rituximab maintenance.

Immunotoxin-based Therapy

Another class of agents that have recently gained interest for the treatment of lymphoma is the immunotoxins. These agents consist of a monoclonal antibody linked to a toxin; binding of the antibody to the target cell delivers the cytotoxic molecule. One such agent being evaluated in clinical trials is CMC-544 (inotuzumab ozogamicin), which consists of an anti-CD22 antibody linked to calicheamicin. In 2009, Dang and associates presented results on the clinical activity of CMC-544 in combination with rituximab in patients with relapsed/refractory CD20-positive/CD22-positive B-cell NHL.[16] In 112 evaluable patients, the ORR was 87% in FL (38 patients), 80% in relapsed DLBCL (40 patients), and 20% in rituximab-refractory NHL (25 patients). Median PFS was 23.6 months, 15.1 months, and 2 months, respectively.

Novel Anti-CD20 Monoclonal Antibodies

Multiple new humanized anti-CD20 antibodies are now being evaluated in lymphoma; how they compare with rituximab is still a matter of study. One such agent that has been widely studied is ofatumumab, which binds to a different CD20 epitope than rituximab does.[17] Despite this theoretical distinction from rituximab, a disappointing ORR of 11% was seen in a single-agent ofatumumab trial in patients with rituximab-refractory FL.[18] However, Czuczman and colleagues presented encouraging results from a phase II trial evaluating the safety and efficacy of 2 dose levels of ofatumumab in combination with CHOP chemotherapy in 58 patients with previously untreated FL. The ORR was 90% at the higher evaluated ofatumumab dose and 100% at the lower dose, with CR/CRu rates of 69% and 55%, respectively.[19] The regimen appeared effective across risk groups, with a CR/CRu rate of 76% in the 21 patients with FLIPI scores of 3–5. The most common grade 3/4 adverse events by laboratory assessments were leukopenia (72% and 83% at dose levels 1 and 2) and neutropenia (90% in each group).

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Immunotherapy for the First-line Treatment of B-cell Non-Hodgkin Lymphoma

Thomas E. Witzig, MD

Although rituximab plus CHOP chemotherapy has emerged as the standard initial treatment for DLBCL, several approaches are under investigation for improving upon results with this regimen. These include the addition of novel monoclonal antibodies, immunomodulatory agents, and other agents. The goal of these new strategies is to improve both response rates and duration of response after initial therapy.

Epratuzumab, a Novel Anti-CD22 Antibody

Several agents that have previously demonstrated activity in patients with relapsed disease are being evaluated in the frontline setting. One such agent is the investigational antibody epratuzumab, which is directed against CD22, a B-cell antigen expressed on almost all DLBCLs. Thus, combining epratuzumab with R-CHOP allows targeting of both CD20 and CD22 on the B-cells. In patients with relapsed NHL, epratuzumab has demonstrated an ORR of 15% as a single agent[1] and 47% in combination with rituximab.[2] This demonstrated activity in the relapsed setting led to investigations of epratuzumab and rituximab in the first-line setting.

In the multicenter phase II study North Central Cancer Treatment Group (NCCTG) N0489, 78 patients with previously untreated DLBCL received a standard-dose CHOP regimen plus epratuzumab and rituximab (ER-CHOP).[3] Based on the revised IPI scale, 50% of patients were characterized as poor/high risk (IPI 3–5). The addition of epratuzumab did not significantly increase the treatment burden, adding approximately 1 hour to the overall infusion time. The ER-CHOP regimen was associated with an ORR of 95% in both the low-risk and high-risk IPI groups, with a CR rate of 71% by computed tomography analysis and 87% by positron emission tomography assessment using functional CR. This study was not designed to be a randomized trial comparing R-CHOP with epratuzumab versus R-CHOP without epratuzumab. Historical data, however, suggest that the addition of epratuzumab to R-CHOP is associated with a 10% improvement in response rate.

Although ER-CHOP has the potential to improve outcomes over R-CHOP, a large, randomized phase III trial is needed to quantify potential benefits over the current standard protocol. However, designing and conducting such trials is challenging in the current era, when the standard regimen already produces a 70–80% response rate. Although these large studies require an investment of time and resources, they must be performed in order to gain further improvements over our current therapies.

Lenalidomide as an Addition to R-CHOP

The immunomodulatory drug lenalidomide is also active in the relapsed setting, demonstrating an ORR of 27% in patients with relapsed FL.[4] Along with Nowakowski and others,[5] I recently reported phase I findings for an ongoing phase I/II trial evaluating lenalidomide plus R-CHOP in patients with newly diagnosed DLBCL. The 12 enrolled patients were not selected for lymphoma subtype (ABC or GCB). Patients were assigned to 1 of 3 dose levels of lenalidomide plus a standard R-CHOP schedule, with growth factor support. No dose-limiting toxicities were observed at any dose level, suggesting that the highest lenalidomide dose evaluated (25 mg/day for 10 days per cycle) can safely be added to R-CHOP. The phase II portion of this study is ongoing.

In 2009, Fowler and colleagues presented preliminary results of a phase II trial of lenalidomide plus rituximab as the initial treatment for indolent lymphoma, demonstrating an ORR approaching 100% in these patients.[6] However, upfront therapies often produce excellent response rates in these patients. In spite of this caveat, it is promising that a nonchemotherapy upfront regimen has the potential to produce such a high response rate, suggesting that this could be a very interesting regimen to study in larger trials in the future.

The work by Dr. Czuczman and others showing that lenalidomide is more effective in the ABC subtypes, in which response rates to R-CHOP are typically lower, may provide a greater impetus for designing a phase III trial of a lenalidomide-containing initial regimen.

RIT

Two radioimmunotherapeutic agents, yttrium-90-ibritumomab tiuxetan and ^{131}I-tositumomab, are currently

approved by the US Food and Drug Administration for use in patients with relapsed or refractory low-grade or transformed lymphoma. More recently, clinical trials have investigated the use of RIT as consolidation treatment after first-line induction therapy. The goal of this approach is to prolong time-to-progression, which may translate into improved outcomes for patients with FL. As Dr. McLaughlin discussed, RIT is being adopted as consolidation after chemotherapy induction based on results of the phase III FIT trial, which showed a significant progression-free benefit with yttrium-90-ibritumomab tiuxetan consolidation therapy in patients with FL after first-line induction therapy.[7] In September 2009, the US Food and Drug Administration approved ibritumomab tiuxetan as a consolidation dose of RIT for patients with follicular NHL who achieve a response with induction therapy.

mTOR Inhibitors

The mammalian target of rapamycin (mTOR) helps regulate cellular pathways that lead to growth, proliferation, and angiogenesis. The intravenous mTOR inhibitor temsirolimus, which is currently approved for use in renal cell carcinoma in the United States, has also demonstrated activity in lymphoma. Single-agent temsirolimus is associated with a response rate of 40% in patients with relapsed or refractory MCL,[8,9] which increases to 48% when temsirolimus is administered in combination with rituximab.[10]

The oral mTOR inhibitor everolimus also appears active in lymphoma, demonstrating single-agent response rates of 47% in relapsed Hodgkin lymphoma,[11] 18% in recurrent/refractory small lymphocytic lymphoma,[12] and 70% in relapsed/refractory macroglobulinemia.[8,13] A study evaluating single-agent everolimus in 145 patients with various types of relapsed lymphoma showed response rates of 30% in DLBCL, 32% in MCL, 50% in FL, and 63% in T-cell lymphoma.[14]

Based on these findings, I believe that the rapamycin analogs will be evaluated as a part of initial therapy for macroglobulinemia and, potentially, in combination with other commonly used therapies for B-cell lymphoma.

In summary, the future holds much promise for improving the standard therapy for lymphoma, with the next generation of cooperative trials evaluating the addition of immunomodulatory agents, antibodies, and other agents to a chemotherapy backbone. It will be important to evaluate rational combinations based on how agents with different mechanisms of action may interact to have additive or synergistic effects.

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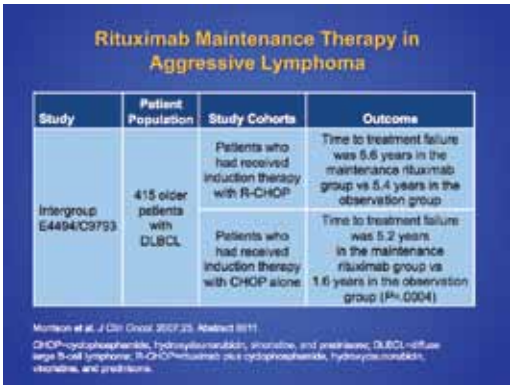

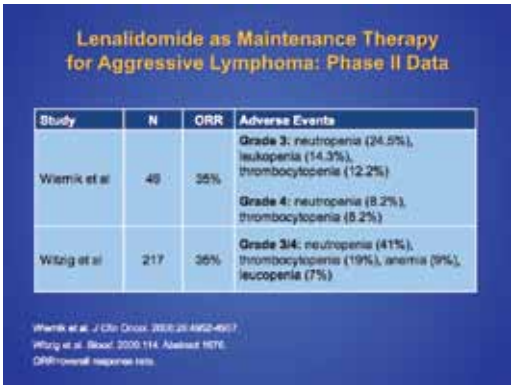

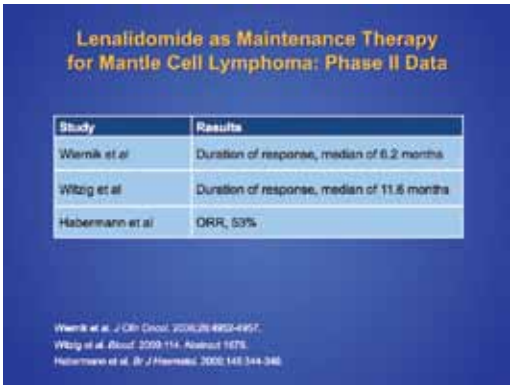

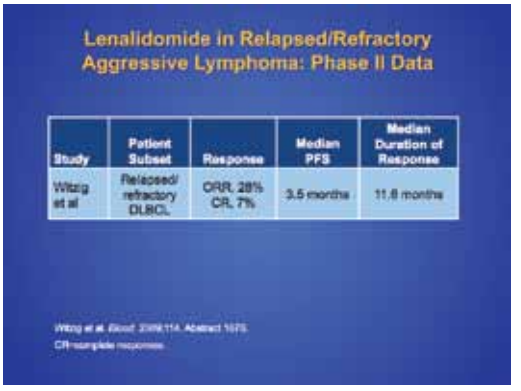

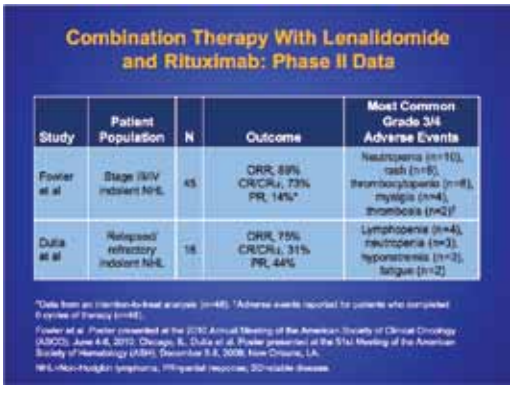

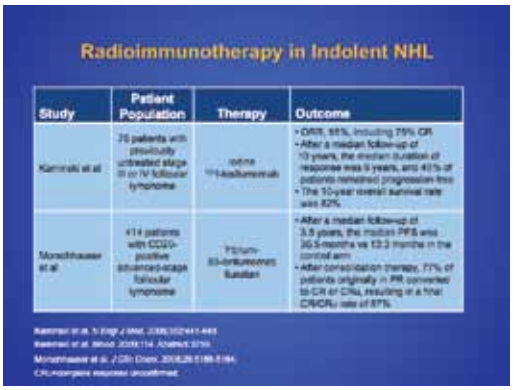

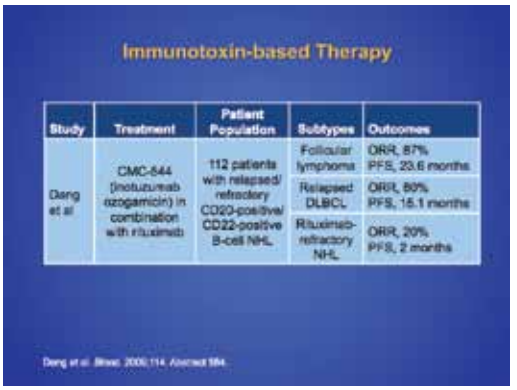

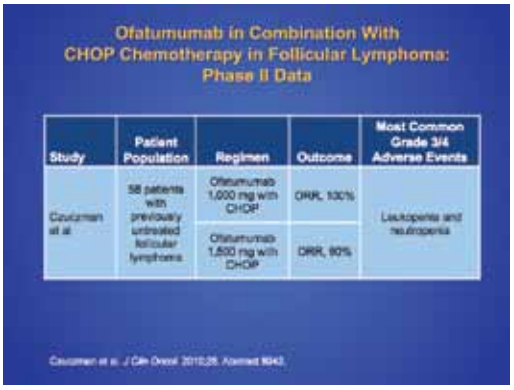

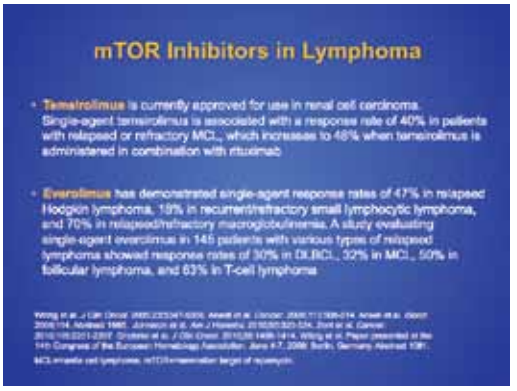

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