

Optimizing the Treatment of Patients With Rituximab-pretreated Recurrent Indolent Non-Hodgkin Lymphoma

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Abstract: Indolent non-Hodgkin lymphomas (NHLs) are among the most prevalent hematologic malignancies; their incidence has been increasing over the last several decades. Because advanced-stage indolent lymphoma is generally incurable, therapy for this group of patients is geared toward chronic management over years. Recently, numerous trials have demonstrated that the combination of chemotherapy and the anti-CD20 monoclonal antibody rituximab can provide superior efficacy to chemotherapy alone. Thus, rituximab-containing regimens are the standard approach for primary therapy in patients with symptomatic advanced disease. As these patients progress and receive multiple rituximab-based regimens over time, new treatment options are needed for this new group of rituximab-pretreated patients. This review focuses on the development of novel therapies for rituximab-pretreated, relapsed or refractory indolent NHL.

Indolent non-Hodgkin lymphomas (NHLs) are B-cell malignancies that are generally associated with long survival times, but these malignancies are typically considered incurable by conventional therapies.¹ Follicular lymphoma (FL) is the most common form of indolent lymphoma and constitutes approximately 35% of adult cases in the United States and 22% of cases worldwide.^{2,3} In patients diagnosed between 1978 and 1995, there was a reported 16–22% increase in the incidence of FL among white patients and a dramatic, 77% increase among black males.⁴ More recent data from the Surveillance Epidemiology and End Results (SEER) registries for patients diagnosed between 1992 and 2001 have demonstrated a 1.8% annual increase in the incidence of FL occurring among the elderly. However, overall incidence rates may be plateauing.⁵

Treatment Options for Indolent NHL

The majority of patients with FL present with advanced-stage disease; however, they are often asymptomatic.⁶ Among patients with advanced asymptomatic disease, therapy is commonly delayed until the onset of progressive, symptomatic disease (watchful waiting). In studies comparing immediate therapy to delayed treatment, no difference in survival was observed.⁷ Once the onset of symptoms occurs, single-agent chemotherapy (chlorambucil, cyclophosphamide, cladribine, or fludarabine) or combination chemotherapy (cyclophosphamide, vincristine, prednisone [CVP] or cyclophosphamide, doxorubicin, vincristine, prednisone [CHOP]) with rituximab (Rituxan, Genentech/Biogen Idec) is commonly used.^{2,8-10} Generally, indolent lymphomas are very sensitive to chemotherapy, with complete response (CR) rates as high as 96%.¹¹⁻¹⁶ However, relapse is expected, often within 2–3 years of completing chemotherapy, although more durable responses are not uncommon.¹ As patients experience cycles of response and relapse, it has been observed that response durations commonly shorten with each sequential therapy.

The anti-CD20 monoclonal antibody rituximab has become a standard component of therapy for NHL. Rituximab has been shown to produce overall response rates of approximately 50% as a single agent in patients with relapsed or refractory disease, with median response durations of approximately 1 year.¹⁷ The current most commonly employed initial approach for FL is a combination of rituximab and chemotherapy (R-CVP, R-CHOP), which provides overall response rates of 81–100%, with durations of approximately 32–82.5 months.^{18,19}

Although rituximab has increased response durations in patients with indolent NHL, patients will typically relapse. A subpopulation of these patients will be truly refractory to rituximab, defined as either failure to respond to treatment or disease progression within 6 months of treatment.^{20,21} However, some patients with relapsed rituximab-pretreated lymphoma will respond to another course of rituximab alone or as part of a rituximab-containing chemotherapeutic regimen.²²⁻²⁴ As patients continue through the usual course of indolent NHL, at each relapse, they are commonly given different chemotherapies in combination with rituximab. The percentages of patients who have undergone multiple treatments with rituximab plus chemotherapy and develop some form of resistance to rituximab over time is unclear, and the outcomes of these patients have not been carefully investigated. It is evident, however, that novel therapeutic options are needed for rituximab-pretreated patients in various settings.

Some efforts to improve patient outcomes have involved the development of next-generation anti-CD20 antibodies. These humanized antibodies have been engineered to improve their pharmacokinetic properties and immunogenicity, as well as to optimize their capacity to mediate complement-dependent cytotoxicity, antibody-mediated cellular cytotoxicity, or direct antitumor effects.²⁵ Examples of these agents include ofatumumab (HuMax-CD20, Genmab)^{26,27} PRO70769 (Genentech/Roche/Biogen Idec),²⁸ IMMU-106 (Immunomedics),²⁹ AME-133 (Applied Molecular Evolution),³⁰ and GA-101 (Roche/Glycart).³¹ These agents are now being tested in early phase clinical trials.²⁵ Monoclonal antibodies directed against other cell surface receptors including CD22, CD40, CD80, CD52, CD2, and the tumor necrosis factor receptor family, and vascular endothelial growth factor are being developed for the treatment of NHLs.^{32,33} Some of these have demonstrated activity in patients with rituximab-relapsed disease, though their activity in the rituximab-refractory population has undergone little study to date.

Radioimmunotherapy

Anti-CD20 radioimmunoconjugates are highly effective in the treatment of indolent NHLs. These agents deliver targeted immunotherapy to CD20-expressing tumor cells using iodine-131 (¹³¹I) or yttrium-90 (⁹⁰Y). Radioimmunoconjugates currently approved by the US Food and Drug Administration (FDA) for the treatment of NHL include the CD20-targeted agents ibritumomab tiuxetan (Zevalin, Cell Therapeutics) and tositumomab (Bexxar, GlaxoSmithKline). ⁹⁰Y-ibritumomab is approved for the treatment of patients with relapsed or refractory, low-grade, follicular, or transformed B-cell NHL, including patients with rituximab-refractory follicular NHL,³⁴ whereas ¹³¹I-tositumomab is approved for the treatment of patients with CD20-expressing relapsed or refractory, low-grade, follicular, or transformed NHL, including patients with rituximab-refractory NHL.³⁵

⁹⁰Y-ibritumomab tiuxetan was investigated in a phase III study that led to its approval in the relapsed/refractory setting (Table 1).³⁶ In this trial, 143 patients with relapsed, refractory, or transformed NHL, including 113 patients with follicular histology, were randomized to receive a single dose of ⁹⁰Y-ibritumomab tiuxetan (0.4 mCi/kg) or a standard dose of rituximab (375 mg/m² weekly for 4 weeks).³⁶ Ibritumomab resulted in a significantly improved overall response rate (ORR; 80% vs 56%; *P* = .002). The primary toxicity was reversible myelosuppression.

Due to its success in the relapsed/refractory setting, ⁹⁰Y-ibritumomab tiuxetan has been investigated as part of therapy in the frontline setting (Table 2).³⁷⁻³⁹ A nonrandomized phase II clinical trial investigated

Table 1. Radioimmunotherapy in Relapsed/Refractory Indolent Lymphoma

| First Author | N | Treatment | Median No. of Prior Therapies | ORR,% (CR,%) | Durability |
|-----------------------|--------------------|--|-------------------------------|--------------------|-----------------------------------|
| Witzig ³⁶ | 143 | Rituximab ⁹⁰ Y-ibritumomab | 2 | 56 (16) 80 (30) | TTP, 10.1 mo TTP, 11.2 mo (NS) |
| Wiseman ⁷¹ | 30 | ⁹⁰ Y-ibritumomab | 2 | 83 (37) | TTP, 9.4 mo |
| Gordon ⁷² | 51 | ⁹⁰ Y-ibritumomab | 1–2 regimens | 73 (51) | TTP in responders, 12.6 mo |
| Fisher ²¹ | 250 in 5 trials | ¹³¹ I-tositumomab | 4 | 47–68 (20–38) | 5-yr PFS, 17% |
| Vose ⁴⁶ | 47 | ¹³¹ I-tositumomab | 4 | 57 (32) | OS, 36 mo |
| Davies ⁴⁷ | 41 | ¹³¹ I-tositumomab | 1–2 regimens | 76 (49) | OS, not reached |

CR=complete response; NS=not significant; ORR=overall response rate; OS=overall survival; PFS=progression-free survival; TTP=time to progression.

Table 2. Radioimmunotherapy in First-line Indolent Lymphoma

| First Author | N | Treatment | Response, % | Durability |
|------------------------------|-----|---|---|--|
| Kaminski ⁴² | 76 | ¹³¹ I-Tositumomab | ORR, 95 CR, 75 | PFS, 6.1 yr estimated 5-yr OS, 89% estimated 5-yr PFS, 59% |
| Leonard ⁴³ | 35 | Fludarabine, then ¹³¹ I-tositumomab | After fludarabine: ORR, 89 CR, 9 After tositumomab: ORR, 100 CR, 86 | Estimated 5-yr PFS 60% |
| Press/ SWOG ⁴⁴ | 90 | CHOP, then ¹³¹ I-tositumomab | ORR, 91 CR, 69 | Estimated 5-yr PFS, 67% Estimated 5-yr OS, 87% |
| DeMonaco ³⁷ | 19 | R-CHOP, then ⁹⁰ Y-ibritumomab | After R-CHOP: ORR, 75 CR, 25 After ibritumomab + rituximab: CR, 87.5 | NR |
| Jankowitz ³⁹ | 60 | R-CHOP, then ⁹⁰ Y-ibritumomab | After R-CHOP: CR, 68 After ibritumomab: CR, 96 | 1-yr PFS, 98% 2-yr PFS, 77% |
| Hagenbeek ³⁸ | 414 | Induction, then placebo or ⁹⁰ Y-ibritumomab | After ibritumomab: CRu, 87 | PFS, placebo 13.5 mo PFS, ibritumomab 37 mo |

CHOP=cyclophosphamide, doxorubicin, vincristine, prednisone; CR=complete response; CRu=unconfirmed complete response; NR=not reported; ORR=overall response rate; OS=overall survival; PFS=progression-free survival; R-CHOP=rituximab + CHOP; SWOG=Southwest Oncology Group.

⁹⁰Y-ibritumomab tiuxetan following R-CHOP in previously untreated patients (N=60) with symptomatic or grade III FL.³⁹ At a median follow-up of 14.5 months, the rates of CR by positron emission tomography scan following R-CHOP and ⁹⁰Y-ibritumomab tiuxetan were 68% and 96%, respectively; the 1- and 2-year progression-free survival (PFS) rates were 98% and 77%, respectively. The predominant toxicity was myelosuppression. An ongoing phase III randomized clinical trial is evaluating a single

treatment of ⁹⁰Y-ibritumomab tiuxetan (250 mg/m² rituximab on days -7 and 0, followed on day 0 by 0.4 mCi/kg ibritumomab, maximal dose 32 mCi) or placebo following a partial response (PR) or CR to induction therapy in patients (N=414) with advanced-stage FL.³⁸ Preliminary results obtained at a median follow-up time of 2.9 years showed that ibritumomab-treated patients experienced a significantly longer PFS than placebo-treated patients (37 vs 13.5 months; *P*<.0001; hazard ratio, 0.463). There

Table 3. Radioimmunotherapy in Rituximab-refractory Indolent Lymphoma

| First Author | N | Treatment | Median No. of Prior Therapies | ORR, % (CR, %) | Survival, mo |
|-----------------------|----|--------------------------------------|-------------------------------|----------------|--------------|
| Witzig ²⁰ | 57 | ⁹⁰ Y-ibritumomab tiuxetan | 4 | 74 (15) | mTTP: 6.8 |
| Horning ⁴⁰ | 40 | ¹³¹ I-tositumomab | 4 | 65 (38) | mPFS: 10.4 |
| Ogura ⁴¹ | 45 | ⁹⁰ Y-ibritumomab tiuxetan | 3 | 83 (63) | mPFS: 9.6 |

CR=complete response; mPFS=median progression-free survival; mTTP=median time to progression; ORR=overall response rate.

was a higher incidence of grade 3–4 infections in the ibritumomab arm (8% vs 2%).

⁹⁰Y-ibritumomab tiuxetan has also been tested in patients with rituximab-refractory disease (Table 3).^{20,40,41} A phase II study enrolled 57 patients with a median of four prior therapies, including 54 patients with FL.²⁰ Patients were required to be nonresponders to rituximab or to have had a time to progression (TTP) of less than 6 months following rituximab therapy. The ORR was 74% for patients with FL, with 15% CRs and 59% PRs. Median TTP was 6.8 months; among the 40 responders, the median TTP was 8.7 months. Adverse events were primarily hematologic and transient in nature and included grade 4 neutropenia (35%), thrombocytopenia (9%), and anemia (4%). The majority of nonhematologic adverse events were grade 1/2. Like ibritumomab, tositumomab has been studied in previously untreated patients (Table 2).^{42–44} In a phase II trial, previously untreated patients (N=76) with stage III or IV FL received a single dose of tositumomab/¹³¹I-tositumomab.⁴² The ORR was 95%, with a 75% CR rate. At a median follow-up of 5.1 years, the actuarial 5-year PFS for all patients was 59% and the median PFS was 6.1 years. Hematologic toxicity was reported to be moderate and no patient required hematopoietic growth factors or transfusions. Like any single-arm, single-center study in untreated lymphoma, the relative role of patient selection cannot be determined without a randomized comparison group.⁴⁵

Another phase II clinical trial evaluated tositumomab/¹³¹I-tositumomab following an abbreviated course of fludarabine in 35 patients with previously untreated FL.⁴³ Following administration of fludarabine, the response rate was 89%, with 9% of patients exhibiting a CR. The response rate increased to 100%, with 86% of patients exhibiting a CR, following administration of tositumomab/¹³¹I-tositumomab. The estimated 5-year PFS was 60% and the primary toxicities were manageable and hematologic. The largest phase II clinical trial (N=90) tested six cycles of CHOP followed by tositumomab/¹³¹I-tositumomab in patients with previously untreated advanced-stage FL.⁴⁴ In this study, the ORR was 91%, with 69% of patients

exhibiting CRs. At a median follow-up of 5 years, the estimated PFS and overall survival rates were 67% and 87%, respectively. Eighty-two patients were assessable for toxicity after tositumomab/¹³¹I-tositumomab and 34% (n=28) experienced grade 3 or lower toxicity, whereas 12% (n=10) experienced grade 4 or lower toxicity.

Although it is currently under extensive evaluation as part of initial treatment for indolent lymphoma, including studies led by the Southwest Oncology Group (SWOG), the most established role for ¹³¹I-tositumomab is in patients with relapsed or refractory NHL (Table 1),^{21,46,47} including rituximab-refractory disease (Table 3).⁴⁰ Most relevant to this review, an analysis of five clinical trials enrolling a total of 250 patients with relapsed or refractory indolent NHL or transformed low-grade NHL who had received one dose of ¹³¹I-tositumomab was recently reported by Fisher and colleagues.²¹ Patients had received a median of four prior therapies; 40 patients had rituximab-resistant disease. The ORRs ranged from 47% to 68%, with 20–38% CRs. At a median follow-up of 5.3 years, 5-year PFS was 17% in this heavily pretreated patient population. In a phase II trial enrolling 40 patients, including 24 rituximab nonresponders and 11 with a response to rituximab lasting less than 6 months, an ORR of 65% was achieved after a single dose of ¹³¹I-tositumomab.⁴⁰ Of these responses, 38% of patients achieved a confirmed CR, and the median PFS was 10.4 months. Grade 3/4 hematologic toxicities occurred in 50% of these patients. Within 12 weeks of therapy, 22 patients developed infections. Of these patients, 15 developed grade 1/2 viral or upper respiratory infections, and 2 serious cases of pneumonia were reported.

These data demonstrate that radioimmunotherapy with either approved agent remains an important treatment option for patients with indolent lymphoma recurrent after prior therapy with rituximab.

Bortezomib

Bortezomib (Velcade, Millennium) is a potent, selective, and reversible small-molecule inhibitor of the proteasome and is the first of its class to be evaluated in human stud-

Table 4. Bortezomib in Recurrent Follicular Lymphoma

| First Author | N | Median No. of Prior Therapies | CR/Cru, n | PR, n | ORR, % |
|------------------------|----|-------------------------------|-----------|------------------------|--------|
| O'Connor ⁵¹ | 16 | NR | 1/1 | 7 | 56 |
| Goy ⁵² | 8* | 3.5 | 0/1 | 0 | 12.5 |
| Strauss ⁵³ | 11 | 4 | 0 | 2 late PR [†] | 18 |

*Includes 3 patients with transformed FL.

[†]73% and 55% tumor disease reductions were observed 3 months after stopping therapy.

CR=complete response; CRu=unconfirmed complete response; NR=not reported; ORR=overall response rate; PR=partial response.

ies.⁴⁸ It is currently approved in the United States for the treatment of multiple myeloma and mantle cell lymphoma (MCL) in patients who have received at least one prior therapy. Proteasome inhibition results in the disruption of protein biology, which affects a variety of pathways, resulting in cell death.^{49,50} Thus, preclinical and clinical data indicate that proteasome inhibition is a rational strategy for further clinical evaluation in lymphoma.

Though bortezomib has not been tested specifically in the population of rituximab-refractory indolent NHL patients, it has been investigated as a single agent in FL patients who received multiple prior treatments (including prior rituximab) in multiple phase II studies (Table 4).⁵¹⁻⁵³ In a multi-institutional phase II trial enrolling 74 patients with relapsed indolent NHL or MCL, bortezomib 1.5 mg/m² was given on days 1, 4, 8, and 11 every 3 weeks.⁵⁴ Bortezomib treatment resulted in an ORR of 43%. Among the 16 assessable patients with FL, the ORR was 56%, which included 1 CR, 1 unconfirmed CR (CRu), and 7 PRs. The same schedule of bortezomib was tested in a separate phase II study that enrolled 60 patients with a median of 3.5 prior regimens.⁵² Patients were enrolled by histology, including one trial arm that had 21 non-MCL patients with various indolent B-cell lymphomas, including 5 patients with FL. An ORR of 19% was reported in this group, divided among 1 patient with Waldenström macroglobulinemia (1 PR), 1 patient with small lymphocytic lymphoma (CR), and 1 patient with FL (CRu). The estimated PFS at 6 months for this study was 36% among patients with non-MCL lymphomas (95% confidence interval, 20–64%). Overall grade 3 toxicities included thrombocytopenia (47%), gastrointestinal (20%), fatigue (13%), neutropenia (10%), and peripheral neuropathy (5%). Grade 4 toxicity was reported in 15% of patients and there were 3 deaths from disease progression within 30 days of study withdrawal. In a third phase II study, a total of 51 patients were enrolled. These patients with relapsed/refractory NHL were treated with a lower dose of bortezomib

1.3 mg/m² twice weekly for 2 of 3 weeks.⁵³ The median number of prior treatments was four, with 34 patients having received at least four prior therapies. Among the 11 evaluable FL patients, 2 achieved a PR 3 months after stopping therapy, which suggests that time to response in FL might be longer than in other subtypes and that more extended treatment may be necessary. Additionally, the lower response observed in this study compared with the previously described studies could be due to the lower dose of bortezomib used. In this study, grade 3–4 toxicities were thrombocytopenia (n=22), fatigue (n=10), and peripheral neuropathy (n=3).

Based on synergy observed in preclinical studies, several trials are currently ongoing that combine bortezomib with chemotherapy or other agents in relapsed/refractory indolent NHL.⁴⁸ Bortezomib combined with rituximab was tested in a phase II study in patients with disease that was rituximab-naïve or -relapsed (ie, not refractory to rituximab).⁵⁵ Patients were treated with either bortezomib 1.3 mg/m² twice weekly for 2 weeks in each 3-week cycle plus rituximab 375 mg/m² weekly for the first 4 weeks only (n=41) or bortezomib 1.6 mg/m² weekly for 4 weeks in each 5-week cycle plus rituximab 375 mg/m² weekly for the first 4 weeks only (n=40). The majority of patients enrolled had FL (33 and 37 patients in the 2 arms, respectively). In a preliminary report of investigator-assessed response, 57% of patients treated with twice-weekly bortezomib responded, whereas 53% of those receiving weekly bortezomib responded. In addition, the weekly schedule appeared to have a more favorable safety profile. No grade 4 adverse events were reported for the bortezomib-weekly arm whereas 7% of patients in the twice-weekly arm experienced grade 4 toxicity. Grade 3 or higher events were more frequent in the twice-weekly bortezomib arm (54% vs 35% in the weekly bortezomib arm). Grade 3 or higher hematologic toxicities were also more frequent in the twice-weekly bortezomib arm, including thrombocytopenia (10% vs 0%) and neutropenia (10% vs 3%). Several other trials are ongoing

Table 5. Ongoing Combination Trials With Bortezomib in Recurrent Lymphoma⁴⁸

| Regimen | NHL Subtype |
|--|--|
| Bortezomib + 17-AAG | Relapsed/refractory hematologic malignancies |
| Bortezomib + flavopiridol | Recurrent/refractory indolent B-cell lymphoma |
| Bortezomib + cyclophosphamide + prednisone | Relapsed/refractory indolent lymphoma |
| Bortezomib + fludarabine | Relapsed/refractory indolent NHL, CLL |
| Bortezomib + rituximab | Recurrent FL, MCL, Waldenström macroglobulinemia |
| Bortezomib + bendamustine | Refractory NHL or B-CLL |
| Bortezomib + EPOCH | Relapsed/refractory DLBCL |

17-AAG=tanespimycin; CLL=chronic lymphocytic leukemia; DLBCL=diffuse large B-cell lymphoma; EPOCH= etoposide, vincristine, doxorubicin, cyclophosphamide, prednisone; FL=follicular lymphoma; MCL=mantle cell lymphoma; NHL=non-Hodgkin lymphoma.

(Table 5),⁴⁸ as well as studies investigating bortezomib as a potential frontline therapy for NHL.

Bendamustine

Bendamustine (Treanda, Cephalon) is a chemotherapeutic compound containing a nitrogen mustard group, similar to the alkylating agents chlorambucil and cyclophosphamide, and a benzimidazole ring, which may act similarly to a purine analog.⁵⁶ This molecule was developed in East Germany in the 1960s, though it was more systematically

studied in patients in the 1990s.⁵⁷ A phase II multicenter trial⁵⁸ investigated single-agent bendamustine 120 mg/m² given on days 1 and 2 every 21 days for a total of six cycles (Table 6).^{56,58-60} This study enrolled 75 patients with indolent or transformed rituximab-refractory NHL who had received a median of 2 prior chemotherapies. The overall response rate was 74% and included 25% CRs and 49% PRs. The most common adverse events reported were nausea (63%), fatigue (39%), vomiting (38%), fever (25%), and diarrhea (22%); however, most events were grade 1 or 2. Grade 3–4 adverse hematologic events included neutropenia (47%), thrombocytopenia (29%), and anemia (11%).

Bendamustine has also been investigated in combination with rituximab in two phase II studies. Rummel and colleagues reported an ORR of 90% among 63 patients with either MCL or low-grade NHL.⁵⁶ Bendamustine 90 mg/m² was given on days 1 and 2, and rituximab 375 mg/m² was given on day 1 for a maximum of four cycles every 4 weeks. Patients were less heavily pretreated, in that most enrolled patients had received one prior therapy, and patients were not required to be refractory to rituximab. As seen with single-agent bendamustine, the major toxicity reported was myelosuppression, including grade 3–4 leukopenia (16%). A similar study was reported that enrolled 66 patients, including 40 patients with FL.⁵⁹ An ORR of 94% was noted, with a CR/CRu of 41%. Similar to the previous study, the majority of patients (62%) had received one prior chemotherapy regimen, with 56% having received prior rituximab.

Bendamustine combined with mitoxantrone and rituximab was investigated in patients with relapsed or refractory indolent lymphoma in a German phase II trial.⁶⁰ This trial enrolled 57 patients, including 29 with FL and 18 with MCL. Approximately 60% of patients had received one prior chemotherapeutic regimen, and

Table 6. Bendamustine in Relapsed or Refractory Follicular Lymphoma

| First Author | N | Treatment | Median No. of Prior Therapies | ORR, % |
|----------------------------|-----------------|---|-------------------------------|----------------|
| Friedberg ⁵⁸ | 75* | Bendamustine | 2 | 74 (25 CR) |
| Van der Jagt ⁵⁹ | 40 [†] | Bendamustine + rituximab | 1 | 94 (41 CR/CRu) |
| Weide ⁶⁰ | 29 [‡] | Bendamustine + mitoxantrone + rituximab | 1 (59%) | 92 (50 CR) |

*Number of patients with rituximab-refractory disease; study enrolled patients with B-cell non-Hodgkin lymphoma.

[†]56% of patients were previously treated with rituximab.

[‡]39% of patients were previously treated with rituximab.

CR=complete response; CRu=unconfirmed complete response; ORR=overall response rate.

23% had received two prior therapies. Prior rituximab had been given to 39% of patients. Of the patients enrolled in the trial, 89% responded to treatment, with 35% achieving a CR and 54% achieving a PR. Among patients with FL, 50% achieved a CR and 42% achieved a PR. The ORR among rituximab-pretreated patients was 76%. The 2-year overall survival was 60% for patients with FL or MCL. Myelosuppression was the major adverse event reported; grade 3/4 events included anemia (10%), leukocytopenia (78%), granulocytopenia (46%), and thrombocytopenia (16%). Bendamustine is currently being investigated as a single agent in a multicenter, open-label phase III study specifically in patients with rituximab-refractory disease and 1–3 prior regimens. This study is currently closed to further enrollment, and analysis is ongoing. In addition, two phase III trials investigating bendamustine plus rituximab versus R-CHOP in previously untreated patients or bendamustine plus rituximab versus R-fludarabine in patients with relapsed disease are ongoing.⁶¹

Lenalidomide

Lenalidomide (Revlimid, Celgene) is an immunomodulatory agent that has recently been approved by the FDA for the treatment of relapsed or refractory multiple myeloma and myelodysplastic syndromes. Recent studies have investigated the utility of lenalidomide in the treatment of NHL. The preliminary results of two phase II studies (Table 7)^{62,63} were reported at the 2007 annual meeting of the American Society of Clinical Oncology. The first trial reported the results from the first 27 evaluable patients, 12 of whom had FL, 12 had small lymphocytic lymphoma, and 3 had nodal marginal zone B-cell lymphoma.⁶² The median number of prior therapies was three and patients were not required to be rituximab-refractory. Lenalidomide 25 mg was given daily on days 1–21 every 28 days. Of these patients, 3 achieved a CR/CRu (11%; 2 FL), 4 achieved a PR (1 FL), and 9 achieved stable disease (3 FL). The most common grade 3 adverse events were neutropenia (16%) and thrombocytopenia (14%). Grade 4 neutropenia occurred in 5 (19%) patients. Similar activity and safety results were reported in a separate phase II study using the same dosing schema in other histologies.⁶³

Preclinical data have suggested that lenalidomide may augment the efficacy of therapeutic monoclonal antibodies in both rituximab-sensitive and resistant B-cell lymphoma cell lines.⁶⁴ A phase II study currently being conducted by the Cancer and Leukemia Group B randomizes patients with FL and recurrent disease after rituximab to receive lenalidomide alone or with rituximab. These data should provide some sense of the activity of the combination and the single-agent treatment.

Table 7. Lenalidomide in Relapsed/Refractory Indolent Lymphoma

| First Author | N | No. of Prior Therapies | ORR, % |
|-----------------------|------------|------------------------|--------------|
| Wiernik ⁶³ | 22 3 FL | 2 | 32 1/3 FL |
| Witzig ⁶² | 27 | 3 | 26 |

FL=follicular lymphoma; ORR=overall response rate.

Stem Cell Transplantation

Stem cell transplantation (SCT) offers potentially curative therapy in selected patients with indolent lymphoma. Autologous SCT is sometimes employed in patients with refractory or recurrent indolent NHL.⁶⁵ Although the mortality rate associated with autologous SCT is now less than 5%,^{66,67} a convincing survival benefit has not been demonstrated and there remains a significant relapse risk.⁶⁵ Patients treated with allogeneic SCT have lower relapse rates than those treated with autologous SCT, but they experience higher treatment-related mortality.⁶⁵ The use of reduced-intensity or nonmyeloablative conditioning regimens has decreased the risk of treatment-associated mortality and allows older patients or patients with comorbidities to be treated with autologous SCT.^{33,68,69} With minimal conditioning regimens, the majority of antitumor activity must originate from the graft-versus-tumor (GVT) effect.³³ Because it is difficult to obtain GVT activity while avoiding graft-versus-host disease (GVHD), allogeneic SCT involving minimal conditioning regimens is associated with late, nonrelapse deaths from acute and chronic GVHD or immunosuppression.³³ However, the risk of early death from conditioning toxicity has declined with minimal conditioning regimens. Due to the risks associated with SCT and the limited randomized data, the optimal timing of using SCT options versus other regimens remains to be fully determined.

Conclusions

The typical course of indolent NHL involves repeating cycles of relapse and re-treatment, with decreasing durations of response expected over time. The clinical development of rituximab-containing chemotherapeutic regimens has improved outcomes for patients; these regimens are an accepted treatment of choice for most patients.⁷⁰ However, as patients receive multiple rituximab-containing regimens during the course of their disease, the development of rituximab-refractory tumors eventually is

expected to occur in most patients, and ongoing efforts are focused on the best way to treat these individuals. Several novel agents are currently being investigated for this patient population. The use of radioimmunotherapy is clearly effective, specifically in patients with rituximab-refractory disease. The novel agent bortezomib has shown promise in pretreated patients, including those who have received prior rituximab. Bendamustine, a novel chemotherapeutic agent, clearly is effective in this patient population, and lenalidomide is currently being investigated in this setting as well. Further studies will be needed to elucidate the optimal strategies to sequence therapies over the extended course of patients with indolent lymphoma in order to deliver the maximal benefit.

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