Therapy of newly diagnosed follicular lymphoma

Jason R. Westin and Sattva S. Neelapu*
University of Texas MD Anderson Cancer Center, Houston, TX, USA

INTRODUCTION

Follicular lymphoma is the second most common subtype of lymphoma, with nearly 15,000 new cases annually in the United States (Siegel et al., 2011). For unclear reasons, the incidence of FL continues to increase in the United States and Europe (Cartwright et al., 1999; Groves et al., 2000). FL arises from germinal-center B cells with the genetic hallmark of an acquired t(14;18) (q32;q21) translocation, leading to deregulation of BCL2, a key gene in the regulation of apoptosis and cell death. The t(14;18) translocation is found in the normal B cells of over half of healthy individuals, and thus is insufficient alone for lymphomagenesis (Staudt, 2007). Occasionally, an in situ type of FL is identified with t(14;18) and BCL2 expression in a lymph node without other sites of disease. Patients with in situ FL rarely progress to disseminated FL and generally can be observed (Limpens et al., 1991; Cong et al., 2002; Roulland et al., 2006; Staudt, 2007; Jaffe, 2009). Historically, cells harboring the t(14;18) translocation in the peripheral blood of healthy individuals were thought to represent naïve B cells, but recent work suggests these cells have many similarities to FL cells, including class-switch recombination, and surface expression of IgM and IgD (Roulland et al., 2006). It is not clear if the presence of the t(14;18) translocation in healthy individuals has any prognostic or therapeutic value, but suggests a possible common pre-malignant stage.

PROGNOSTIC SYSTEMS

Nearly five of every six patients with newly diagnosed FL will have advanced disease, either due to a long asymptomatic phase prior to diagnosis or early dissemination. Follicular lymphoma is staged by the Ann Arbor system, originally devised in the 1970s to account for radiation field size in Hodgkin lymphoma. The system accounts for a stepwise progression to adjacent lymph node chains, a pattern often not found in non-Hodgkin lymphomas (NHL), and thus its validity in this population has been questioned (Staudt and Dave, 2005). Clinical outcomes vary within stages, suggesting that clinical factors other than location of disease affect outcomes. In 2000, the Intergroupo Italiano Linfomi attempted to account for these additional factors by proposing a model incorporating age, sex, number of extranodal sites of disease, B symptoms, serum lactate dehydrogenase (LDH), and erythrocyte sedimentation rate (ESR; Federico et al., 2000). This model was further improved by an international cooperative effort evaluating over 4000 patients, creating the Follicular Lymphoma International Prognostic Index (FLIPI, Figure 1). Based on the number of adverse features present, patients were classified into three groups with 10-year overall survival (OS) rates of 70.7, 50.9, and 35.3% (Solá-Celgny et al., 2004). The FLIPI was widely adopted, but had several important limitations. It was created from a retrospective database analysis of patients not treated with current chemomunotherapy, was missing significant amounts of data (ESR, β2M, and performance status), and had an endpoint of OS. OS is difficult to model in an indolent disease such as FL due to the duration of follow-up required, a relapsing and remitting disease course, and multiple lines of effective therapy. To account for these weaknesses, the International Follicular Lymphoma Prognostic Factor Project launched the F2 study in 2003 (Federico et al., 2009). The primary endpoint of the model was progression-free survival (PFS), now the preferred metric in lymphoma clinical trials (Cheson et al., 2007). The factors identified as significant in the F2 study, now referred to as the FLIPI2, are relatively similar to those included in the FLIPI score (Figure 1). Based on the number of factors present, the FLIPI2 classifies patients into three groups with 5-year PFS of 79.5, 51.2, and 18.4%.

It is important to note that the vast majority of patient data utilized to generate these models is from patients with grades 1 and 2 disease. Grade 3 FL is split into A and B categories by the WHO classification. The B category lacks centrocytes and has similar biology and outcomes to diffuse large B cell lymphoma (DLBCL; Jaffe, 2009). Grade 3B FL is generally treated like DLBCL, however this remains an area of controversy. The discussion in this paper refers to FL grades 1–3A, unless otherwise stated.

As the majority of patients have a responding and relapsing course, the option of not treating immediately after diagnosis, often referred to as “watch and wait,” was explored and found to have no detrimental effect on OS (Hornung and Rosenberg, 1984;
O’Brien et al., 1991). More concerning, early retrospective reviews found that multiple single agents and chemotherapy combinations, though initially effective, had little or no effect on the OS of patients with FL (Horning, 1993). Newer studies which include therapy with targeted agents have demonstrated improvements in survival; however cure remains elusive for the vast majority of FL patients. Thus, newer treatments which prolong remission duration with minimal toxicity are needed.

**INDICATIONS FOR THERAPY**

Most cases of FL demonstrate an indolent nature, and when treated are highly responsive to therapy (Cheson, 2010). Nearly all advanced FL will eventually relapse after response to initial therapy, and thus FL is currently considered incurable in most cases.

After appropriately staging a newly diagnosed patient with FL, the most important initial decision is “Does this patient require therapy now?” To assist in answering this question, several risk stratification classification systems have been generated for FL. The Groupe d’Etude des Lymphomes Folliculaires (GELF) criteria (Figure 1) were developed in a prospective clinical trial randomizing patients to observation, chemotherapy, or interferon (Brice et al., 1997). In this trial, patients with a high tumor burden had a significantly worse OS (5-year: 78 vs. 57%). Based on these data, patients with ≥3 nodal sites with diameters of ≥3 cm or one mass ≥7 cm are typically not candidates for delayed therapy.

**WANT AND WAIT**

Deferred therapy with serial observation, or “watch and wait,” has been employed in asymptomatic patients with low disease burden due to the typically indolent nature of FL, occasionally even demonstrating regression or long periods of disease stability without therapy (Horning and Rosenberg, 1984). Spontaneous regressions, occurring in 3–25% patients, are thought to be related to the immune responsive nature of FL (Kannan and Neelapu, 2009). In the GELF-06 trial, patients with newly diagnosed FL were randomized to receive interferon, the oral alkylating agent prednimustine, or observation until clinically meaningful progression (Brice et al., 1997). The overall response rate (ORR) to therapy was 70 and 78% in the early treatment arms, and 70% once therapy was indicated in the observation arm, and OS at 5 years was similar in all three arms. In another immediate vs. delayed therapy clinical trial, nearly 10% of the patients randomized to the observation arm did not require systemic therapy with at least 10 years of follow-up (Ardeshna et al., 2003). Several other trials have demonstrated similar outcomes with initial and delayed therapy (Abramson et al., 2009; Kloo et al., 2011). Even with modern therapies yielding improved survival, there are no conclusive data yet which suggest “watch and wait” results in inferior long-term survival outcomes.

The risk of transformation to a more aggressive form of lymphoma is a dreaded event in FL patients, as even intensification of therapy typically results in poor outcomes with the majority of patients dying within 2 years (Yuen et al., 1995). A large retrospective observational study found the annual risk of transformation to be an estimated 3% per year in patients initially treated with chemotherapy, radiotherapy, or observation (Al-Tourah et al., 2008).

An important factor to consider with the “watch and wait” strategy is patient anxiety. It is certainly understandable that some patients may find it difficult to receive a diagnosis of cancer and be given a follow-up visit in lieu of cancer therapy. Patient anxiety is often lessened when hearing the rationale behind “watch and wait,” and the advantages of deferring exposure to potential treatment-associated toxicities.

**RADIOTHERAPY**

Limited stage FL (stage I and contiguous stage II) is potentially curable with radiotherapy alone. Several series have reported dramatic long-term disease-free survival (35–50% at ≥10 years, with 100% local control in the radiation field), likely representing cure, in patients who were treated with involved field radiotherapy with minimal long-term toxicities (Mac Manus and Hoppe, 1996; Wilder et al., 2001). A large trial of aggressive chemotherapy (prior to rituximab) with 30–40 Gy involved field radiotherapy resulted in a 10-year time to treatment failure and OS rates of 72 and 80%, respectively (Seymour et al., 2003). A randomized trial is currently evaluating radiotherapy with and without chemotherapy in this population. As neither chemotherapy nor immunotherapy are currently able to achieve this degree...
of long-term disease control, radiotherapy is considered the standard of care and should be strongly considered in this patient population.

**IMMUNOTHERAPY**

The immune responsive nature of certain malignancies, including FL, has been successfully manipulated for therapeutic benefit using multiple strategies. In the late nineteenth century, Dr. William Coley used a mixture of bacterial toxins as an initial attempt at immunotherapy and reportedly achieved dramatic results in lymphomas. Unfortunately, these results could not be replicated (Thotathil and Jameson, 2007). The immune stimulant interferon-α demonstrated significant activity in follicular lymphoma, either in combination with chemotherapy or alone, but did not have a clear impact on OS and is not commonly utilized due to treatment related toxicities (Price et al., 1991; Solal-Celigny et al., 1993; Solal-Celigny et al., 1998; Herold et al., 2007; Baldo et al., 2010).

Dr. Levy and others proposed using monoclonal antibodies, a passive immunization strategy, to target lymphoma cell surface markers. In 1994, the phase I trial of a monoclonal antibody targeting the B cell marker CD20 (IDEC-C2B8, rituximab) displayed tumor regression in 40% of heavily pre-treated B cell lymphoma patients (Maloney et al., 1994). The mechanism of action of rituximab is thought to be a combination of complement-mediated cytotoxicity, antibody-dependent cellular cytotoxicity, and direct signaling. Rituximab has shown significant single agent activity in both the frontline and relapse settings (Table 1; Maloney et al., 1997; McLaughlin et al., 1998; Witzig et al., 2000). Importantly, these multicenter trials also found rituximab to be well tolerated with major toxicities essentially limited to infusional reactions.

In an attempt to directly address “watch and wait” vs. immediate immunotherapy, an intergroup trial randomized newly diagnosed FL patients with stage ≥ II, asymptomatic non-bulky disease to observation, weekly rituximab × 4 doses, or weekly rituximab × 4 doses followed by maintenance rituximab (MR) every 2 months for 2 years (Ardeshna et al., 2010). The primary endpoints were time to initiation of new therapy and quality of life. Preliminary results show the estimated median time to initiation of new therapy was 33 months in the observation arm and not reached at 4 years in the rituximab arms. Perhaps not surprisingly, no difference in OS was found between the groups. It remains unclear if the delay in time to initiation of new therapy achieved by

---

**Table 1 | Clinical outcome with various therapeutic regimens in newly diagnosed FL (top) and promising experimental therapies in development in FL (bottom).**

| Rituximab | ORR | CR | PFS (month) | Reference |
|-----------|-----|----|-------------|----------|
| Previously treated | 46-48 | 6-8 | 10-13 | Maloney et al. (1997), McLaughlin et al. (1998) |
| Untreated | 29 | 23 | 26 | Witzig et al. (2000) |
| R-CHOP | 96% | 20% | NR, 30 months ≥ 75% | Hiddemann et al. (2005) |
| CHOP | 90% | 17% | 30 months | Hiddemann et al. (2005) |
| BR | 92.7% | 39.8% | 69.5% | Rumelt et al. (2012) |
| R-CHOP | 91.3% | 30% | 312 | Rumelt et al. (2012) |
| R-CHOP | 85% | 41% | NR, 2 years ≥ 76% | Press et al. (2011) |
| CHOP+IVRT | 83% | 46% | NR, 2 years ≥ 80% | Press et al. (2011) |
| R-IVIG | 98% | 87% | NR, 14 months ≥ 94% | Fizler et al. (2011) |

| Experimental therapies | Target | Current development | Reference |
|------------------------|--------|---------------------|----------|
| Brutinib | BTK | Phase II | Advani et al. (2012) |
| CAL-101 | P13K | Phase II | de Vos et al. (2011) |
| ABT263 | Bcl2 | Phase III | Wilson et al. (2009) |
| Epratuzumab | CD22 | Phase II | Leonard et al. (2008) |
| Inotuzumab | CD22 | Phase III | Ogura et al. (2010) |
| SAR3419 | CD19 | Phase I | Younes et al. (2009) |
| SGH-40 | CD40 | Phase I | Adami et al. (2006) |
| Bintuzumab | CD19/IT cell | Phase I | Viale et al. (2009) |
| PID112Zumab | PO-1 | Phase II | Westin et al. (2010) |
| PF05825866 | 4-1BB | Phase I | Fisher et al. (2012) |
| BiovaxID | Idiotypic | Phase III | Schuster et al. (2011) |

ORR, overall response rate; CR, complete response; PFS, progression free survival; IVRT, radioimmunotherapy.
initial rituximab will ultimately change the natural history of the disease, future responses to rituximab, or time to second line therapy. The PRIMA study demonstrated the value of continued exposure to rituximab in a less frequent schedule, commonly referred to as maintenance therapy (Oglesby et al., 2011). Over a thousand patients with newly diagnosed FL who achieved CR or PR after chemotherapy were randomized to observation or rituximab every 2 months. At 2 years, 75% of patients treated with rituximab maintenance were free from progression, as opposed to 58% of observation patients (p < 0.0001). The RESORT trial randomized newly diagnosed FL patients who responded to rituximab weekly × 4 to receive indefinite MR or rituximab retreatment (RR) at the time of disease progression (Kahl et al., 2011). The median time to treatment failure was 3.9 years with MR and 3.6 years with RR, and 93% of MR and 86% of RR did not require cytotoxic chemotherapy at 3 years. The mean number of rituximab doses were quite different: the MR group received 15.8 (range 5–31) and RR 4.5 (range 4–16) doses, raising the question of the cost effectiveness of the maintenance approach. No difference in OS was observed in either the PRIMA or RESORT trials.

Lenalidomide, an immunomodulatory agent that is FDA approved to treat multiple myeloma, has recently shown very promising efficacy in both newly diagnosed and relapsed FL. Witzig et al., 2009; Fowler et al., 2010; Zhu et al., 2011; Leonard et al., 2012. A phase II study of lenalidomide with rituximab in newly diagnosed FL patients revealed an impressive preliminary ORR of 98% and CR of 87% (Fowler et al., 2009, 2010, 2011). An international randomized trial comparing rituximab with either lenalidomide or chemotherapy in newly diagnosed FL is currently underway.

CHEMOTHERAPY
Follicular lymphoma is a chemosensitive disease, with numerous combinations successfully utilized over the past 30 years. A retrospective review spanning 25 years from our institution found that with each subsequent intensification of initial therapy, both failure-free survival (FFS) and OS improved (Liu et al., 2006). The 1972–1982 cohort was treated with cyclophosphamide, doxorubicin, vincristine, prednisone (CHOP), and bleomycin, which resulted in a 15-year FFS and OS of 13 and 27%, respectively. In contrast, the 1988–1992 cohort was treated with intensive alternating triple therapy and interferon, and achieved a 15-year FFS and OS of 32 and 50%, respectively. Newer therapies, including those with rituximab, had not yet reached their median FFS and OS at the time of publication but appeared to result in further improvements. As with any study measuring long-term outcomes over different eras, a caveat is required for the possible influence of improved supportive care and subsequent therapies on survival.

The addition of rituximab to less intensive chemotherapy regimens, including CHOP and CV, has proven in multiple studies to be superior to chemotherapy alone (Cruzcan et al., 2004; Marcus et al., 2008). A randomized trial by the German Low-Grade Lymphoma Study Group of CHOP with or without rituximab found superior response rates, duration of response, and OS in the rituximab arm (Table 1; Hiddemann et al., 2005). As a result, rituximab is now established as a core component of nearly every therapy for FL, both as a single agent and combined with chemotherapy.

The combination of rituximab and bendamustine, an unique drug with activity similar to alkylating agents and purine analogs, has demonstrated significant activity in untreated and relapsed FL (Table 1; Rummel et al., 2005; Cheson and Rummel, 2009). A randomized study of rituximab combined with bendamustine or CHOP in newly diagnosed FL reported a superior FFS of 69.5 vs. 31.2 months favoring bendamustine (Rummel et al., 2012). Although the final report of this trial has not been published to date, the combination of bendamustine and rituximab is now commonly used for newly diagnosed patients requiring therapy.

RADIOIMMUNOTHERAPY
In patients with newly diagnosed advanced stage FL treated with CHOP chemotherapy (without rituximab), a single dose of 131I-tositumomab resulted in an ORR of 95% and CR of 69% (Press et al., 2006). A randomized phase III study of R-CHOP vs. CHOP followed by 131I-tositumomab achieved similar results (2-year PFS of 76 and 80%, OS 97 and 93%, respectively, Press et al., 2011). An ongoing trial of R-CHOP followed by radioimmunotherapy consolidation and MR aims to determine if efficacy can be further improved by combining multiple anti-CD20 therapeutic modalities. A single course of 131I-tositumomab in newly diagnosed FL without chemotherapy resulted in an ORR of 95%, CR of 75%, and a median PFS of 6.1 years, an approach which may be valuable to elderly patients who fail rituximab monotherapy and decline chemotherapy (Kaminski et al., 2005).

POST-THERAPY FOLLOW-UP
According to the NCCN guidelines, patients with initially treated FL should be followed with physical exam and laboratory assessment every 3–6 months for at least 5 years. Surveillance CT scans should be performed no more than every 6 months for the first 2 years, then annually if indicated. Patients and physicians may feel more comfortable with frequent imaging, but the associated cost and radiation exposure are not likely more advantageous than early diagnosis of relapse in this indolent disease. When relapse is identified, immediate therapy is not required and the same general criteria used in newly diagnosed patients can aide in determining when to start therapy.

If a patient appears to have relapsing disease with a rapidly enlarging site, significantly elevated LDH, or new B symptoms, it is possible they have transformed into an aggressive lymphoma (Wong and Dickinson, 2012). In this setting, it is imperative to obtain a biopsy of the concerning site, as the most accessible lymph node may still represent low-grade FL. Patients with FL which has undergone transformation have a poor prognosis and should be considered for a clinical trial.

OUTCOMES
The National LymphoCare Study evaluated treatment practices of academic and community oncologists and found that 17% opted for initial observation, 13.9% rituximab monotherapy, 51.9% rituximab with chemotherapy, 5.6% radiation therapy, and only 6.1% on a clinical trial. These data were obtained prior
to the data regarding bendamustine, and thus the majority of chemotherapy-treated patients received R-CHOP. With the perception that bendamustine has less toxicity than CHOP, these data have likely shifted to include more use of chemotherapy overall, with CHOP making up a smaller proportion. Of note, only 23% of stage I patients received radiation therapy – a potentially curative approach (see Radiation).

Newly diagnosed FL patients often are confused regarding their long-term prognosis, as FL is often considered “incurable.” It is important to clarify the important difference between incurable and untreatable. Patients may read information on the Internet and not understand this difference, and thus be unnecessarily concerned or question the recommendations of their doctor. The median OS for all newly diagnosed FL patients is ~10 years, and these data are not likely representative of modern therapy as they are based on patients diagnosed in the pre-rituximab era (Liu et al., 2006).

INVESTIGATIONAL APPROACHES

The LymphoCare study found that only 6.1% of patients were enrolled on a clinical trial for newly diagnosed FL. This may be due in part to the perception that FL is easily treated with standard therapies that achieve satisfactory outcomes. Although we agree with these assumptions, we recommend all newly diagnosed patients be considered for clinical trial enrollment.

Follicular lymphoma remains an incurable disease that requires costly, and occasionally toxic, recurrent treatments. An impressive assortment of new targeted agents and immunotherapy are currently undergoing clinical evaluation (Table 1, Advani et al., 2006, 2012; Leonard et al., 2008; Wilson et al., 2009; Younes et al., 2009; Ogura et al., 2010; Viardot et al., 2010; Westin et al., 2010; de Vos et al., 2011; Schuster et al., 2011; Fisher et al., 2012). The ultimate goal of these potential advances can improve outcomes for patients with FL depends upon having a sufficient number of both newly diagnosed and relapsed patients enroll on clinical trials.

CONCLUSION

Follicular lymphoma is a common disease due to its incidence and relatively long life expectancy. Despite it being currently considered incurable, many effective treatments exist with many more under evaluation. Patients with early stage disease should be treated with radiotherapy, which is potentially curative. Newly diagnosed advanced stage disease patients should not reflexively be treated unless they are symptomatic or meet standardised criteria. When treatment is necessary, immunotherapy or immunomodulation therapy are very effective, but eventual relapse is common. We recommend all newly diagnosed FL patients be considered for a clinical trial to accelerate the development of the next generation of therapy.

REFERENCES

Abrahamson, J. S., Chen, W., Jaczynski, P., Talebally, H., Neuberg, D., Kunkel, J. L., et al. (2009). The heat shock protein 90 inhibitor IP-104 induces apoptosis of AIT-dependent diffuse large B-cell lymphoma. Br. J. Haematol. 153, 273–284.

Abrams, R., Forte-Torre, A., Furman, R. B., Rosenblatt, J. D., Younes, A., Shipp, M. A. (2006) 562–567 (anti-bcma mAb) monotherapy induces durable objective responses in patients with relapsed aggressive non-Hodgkin’s lymphoma: evidence of antitumor activity from a phase I study. Blood 108, abstr. 695.

Adragna, K. M., Smith, P., Nor- ton, A., Hansesci, B. W., Haidon, P. J., Macleman, R. A., et al. (2010). Long-term effect of a watch and wait policy versus immediate systemic treatment for asymptomatic advanced-stage non-Hodgkin’s lymphoma: a randomised controlled trial. Lancet 376, 516–521.

Balbo, P., Repoli, M., Compagnoni, A., Lanarini, R., Bore, A., Canusinovaro, R., et al. (2010). Interferon-alpha for maintenance of follicular lymphoma: Cochrane Database Syst. Rev. CD004629.

Bici, P., Baston, V., Lepage, E., Breuze, N., Hainem, C., Morera, P., et al. (1997). Comparison in low-grade and high-grade follicular lymphomas between an initial no-treatment policy and immediate chemotherapy: a randomized controlled trial of the Groupe d’ Etude des Lymphomes Folliculaires. Group of Study of the Lymphomas of the Adult. J. Clin. Oncol. 15, 1110–1117.

Cartwright, R., Benczer, H., Carli, P. M., Clisen, D., Cossu, C., Jadh, A., et al. (1999). The rise in incidence of follicular lymphomas in Europe 1985–1992. Eur. J. Cancer 33, 627–633.

Cheson, B. (2010). Targeted treat- ment and new agents in follicular lymphoma. J. Hematol. 92, 5–11.

Cheson, B. D., Pfeifer, B., Jewell, M. E., Gancayco, R. D., Specht, L., Horrow, S. J., et al. (2007). Revised response criteria for malignant lymphomas. J. Clin. Oncol. 25, 579–596.

Cheson, B. D., and Rummel, M. J. (2019). Bendamustine or abatacept in newly diagnosed aggressive non-Hodgkin’s lymphoma: 8 year follow-up of a phase III study. Blood 133, 4550–4556.

Coutre, S. E., Leonard, J. P., W agner-Franz, C., Jaffe, E. S., et al. (2000). In situ localization of follicular lymphoma: a predictive model based on a retrospective analysis of 597 cases. Blood 95, 783–789.

Criscuolo, M. S., Weaver, R., Alkisiomos, B., Reikle, J., and Golli- Lopez, J.A. (2004). Prolonged clinical and molecular remission in patients with low-grade or follicular non- Hodgkin’s lymphoma treated with rituximab plus CHOP chemotherapy: 9-year follow-up. J. Clin. Oncol. 22, 4659–4664.

de Vos, S., Schneider, T. M., Hahn, J. W., Conte, S. L., Leonard, J. P., Wagner- Johnstone, N. D., et al. (2011). A phase 1 study of the selective phosphotyrosine de- nes- 5-hydroxy-5-deaza (THD5dela) inhibitor, Cal-101 (GS-1101), in combination with rituximab and/or bendamustine in patients with previ- ously treated, indolent non-Hodgkin’s lymphoma (INHIBIT). Blood 118, abstr. 2699.

Faderec, M., Bellet, M., Marchessoli, L., Luminari, S., Lopez-Guillermo, A., Vitolo, U., et al. (2008). Follicular lymphoma international prognostic index: a new prognostic index for follicular lymphoma developed by the international follicular lymphoma prognostic factor project. J. Clin. Oncol. 27, 4505–4512.

Faderec, M., Vitolo, U., Zinzani, P. L., Chieci, T., Cio, B., Bellet, M., et al. (2008). Prognosis of follicular lym- phoma: a predictive model based on a retrospective analysis of 567 cases. Blood 95, 783–789.

Fisher, T., Kampenbroeck, C., Ohlunte, T., Love, V., Lira, P., Dorosman, B., et al. (2012). Targeting of 4-1BB by monoclonal antibody PR-0582906 enhances T-cell function and pro- motes anti-tumor activity. Cancer Immunol. Immunother. 61, 1721–1735.

Fowle, N., Hagenmeister, F. B., Mischak- lin, P., Reik, L., Romagnara, J., Funa, M., et al. (2011). Lenalidoci- mide plus rituximab is a highly effective and well-tolerated bio- logic therapy in untreated in- dolent B-cell non-Hodgkin’s lymphoma.
Marcus, R., Innes, K., Solé-Català, P., Catellano, J. V., Dimsoritis, A., Raepo, J. C., et al. (2008). Phase III study of R-CHP compared with cyclophosphamide, vincristine, and prednisone alone in patients with previously untreated advanced follicular lymphoma: final analysis. J Clin Oncol 26, 4579–4586.

McLaughlin, P., Grillo-Lopez, A., Link, B., Levy, R., Cruzman, M., Williams, M., et al. (1998). Rituximab chimeric anti-CD20 monoclonal antibody therapy for relapsed indolent lymphoma: half of patients respond to a four-dose treatment program. J Clin Oncol 16, 2823–2835.

O'Brien, M., Esterbroek, P., Powell, J., Blackledge, G., Iason, L., McMullan, L., et al. (1991). The natural history of low grade non-Hodgkin's lymphoma and the impact of a no initial treatment policy on survival. J Q Med 80, 651–660.

Ortmann, M., Tishbi, K., Hatake, K., Ushila, T., Kani, M., Oyama, T., et al. (2010). Phase I study of tositumomab-yspin (C2B8-α-2b) combined with etoposide and rituximab. Blood 116, 1098–1104.

Pascual, C., Arnaiz, V., García-Valdecasas, P., Ballesteros, M., et al. (2007). Rituximab maintenance for 2 years in patients with high tumour burden follicular lymphoma responding to rituximab plus chemotherapy (PRIMA): a phase III, randomised controlled trial. Lancet 372, 42–52.

Perren, H., S. J., N. D., G., A. N., S., B., and L. R., A., G., M., et al. (2010). Vaccination with patient-specific tumor-derived antigen in first remission improves disease-free survival in follicular lymphoma. J Clin Oncol 29, 2707–2714.

Seymour, J. F., Pro, B., Pallier, L. M., Manning, J. T., Hagemann, F. B., Romaguera, J., et al. (2005). Long-term follow-up of a prospective study of combined modality therapy for stage I-II indolent non-Hodgkin's lymphoma. J Clin Oncol 23, 2115–2122.

Solal-Céligny, P., Lepage, E., Brousse, N., et al. (1991). The natural history of indolent non-Hodgkin's lymphoma. J Natl Cancer Inst 83, 75–88.

Herskind, A., Christensen, E., and Rosenberg, S. A. (1984). The natural history of indolent, untreated low-grade non-Hodgkin's lymphomas. N Engl J Med 315, 1473–1477.

Jaffe, E. S. (2008). The 2008 WHO classification of lymphomas: implications for clinical practice and translational research. Hematology 2009, 525–31.

Kabli, B., S., Høeg, H., Williams, M. E., Gavewicz, R. D., Winger, L. I., Kraus, J. C., et al. (2011). Results of Eastern Cooperative Oncology Group Protocol E4402 (RESORT): a randomized phase III study comparing two different rituximab dosing strategies for low-grade follicular lymphoma. Blood 118, 3105–3113.

Kaminski, M. S., Al-Batran, S. E., Kim S-Z, Welslau, M., Hecker, R., Kofahl-Krause, D., et al. (2005). Randomized phase II trial of rituximab plus rituximab (R-R) versus CHOP plus rituximab (RCHOP-R) as first-line treatment in patients with indolent and mantle cell lymphomas (MCL): updated results from the StiL NHL1 study. J Clin Oncol 23, abstr 5.

Söll, S., Seymour, J. F., Offner, F., López-Guillermo, A., Belzera, D., Xirr, L., et al. (2011). Rituximab maintenance for 2 years in patients with high tumour burden follicular lymphoma responding to rituximab plus chemotherapy (PRIMA): phase III, randomised controlled trial. Lancet 377, 42–52.
Arranz-Saez, R., et al. (2004). Follicular lymphoma international prognostic index. Blood 104:1258–1265.

Straif, L. M. (2007). A closer look at follicular lymphoma. N. Engl. J. Med. 356:741–2.

Strahl, L. M., and Dave, S. (2005). The biology of human lymphoid malignancies revealed by gene expression profiling. Adv. Immunol. 87:163–288.

Thoratik, Z., and Jamieson, M. B. (2005). Early experience with novel immunomodulators for cancer treatment. Expert Opin. Investig. Drugs 14:1391–1405.

Vaidel, A., Goswami, M., Schmida, J. S., Zangane, G., Neppeney, R., Knop, S., et al. (2010). Treatment of patients with non-Hodgkin lymphoma (NHL) with CD19/CD3 bispecific antibody M2M4295. Blood 114, abstr. 2880.

Westin, J. R., Chu, F., Foglietta, M., Rotem-Yehudar, R., and Neelapu, S. S. (2010). Phase II safety and efficacy study of CT-011, a humanized anti-PD-1 monoclonal antibody, in combination with rituximab in patients with relapsed follicular lymphoma. J. Clin. Oncol. 28(Suppl.), abstr. TPS509.

Widler, R. B., Jones, D., Tackett, S. L., Fuller, L. M., Hu, C. S., McLaughlin, P., et al. (2001). Long-term results with radiotherapy for stage I–II follicular lymphomas. Int. J. Radiat. Oncol. Biol. Phys. 51:1219–1227.

Winston, W., O'Connor, O., Cramer, M., LaCoccia, A., Gentetakis, J., LaRocca, J., et al. (2009). Phase 1/2a study of ABT-263 in relapsed or refractory lymphoid malignancies. Blood 114, abstr. 1711.

Witzig, T. E., Vukov, A. M., Habermann, T. M., Greer, L., Kattner, P. J., Fraundborg, W. R., et al. (2005). Rituximab therapy for patients with newly diagnosed, advanced-stage, follicular grade 1 non-Hodgkin’s lymphoma: a phase II trial in the North Central Cancer Treatment Group. J. Clin. Oncol. 23:1105–1109.

Witzig, T. E., Wermut, P. H., Mose, T., Renier, C., Cole, C., Justice, G., et al. (2009). Lenalidomide oral monotherapy produces durable responses in relapsed or refractory indolent non-Hodgkin’s lymphoma. J. Clin. Oncol. 27:5404–5409.

Wong, E., and Dickenson, M. (2012). Transformation in follicular lymphoma biology, prognosis, and therapeutic options. Curr. Opin. Oncol. 24:426–432.

Youse, A., Gooden, L., Kim, S., Romagnesi, J., Copeland, A. R., de Castro Farial, S., et al. (2009). Phase I multi-dose escalation study of the anti-CD19 maytansinoid immunoconjugate SAR419 administered intravenously (IV) infusion every 3 weeks to patients with relapsed/refractory B-cell non-Hodgkin’s lymphoma (NHL). Blood 114, abstr. 585.

Yuen, A. R., Kamel, O. W., Halpern, J., and Horning, S. J. (1995). Long-term survival after histologic transformation of low-grade follicular lymphoma. J. Clin. Oncol. 13:1728–1733.

Zhu, Y. X., Braggio, E., Shi, C.-X., Bruins, L. A., Schmidt, J. E., van Wier, S., et al. (2011). Cereblon expression is required for the antilymphoma activity of lenalidomide and pomalidomide. Blood 118, 4771–4779.

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.