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Treatment of follicular NHL: The old and the new

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Abstract

Despite remaining an incurable disease, overall survival improvements have been noted in patients with advanced stage follicular lymphoma. The Follicular Lymphoma International Prognostic Index (FLIPI) is a robust prognostic index in this disease, and continues to provide prognostic information in the rituximab era. Rituximab has significantly changed the management of follicular lymphoma, and the most dramatic impact of rituximab is observed in combination with cytotoxic chemotherapy. However, resistance to rituximab remains a problem, and standard therapy in the rituximab-refractory setting includes radioimmunotherapy, autologous stem cell transplantation, and allogeneic stem cell transplantation. In addition, several novel agents show encouraging activity in FL, including bendamustine, lenalidomide, bortezomib and other proteasome inhibitors, and BCL2 inhibitors.

Introduction

Follicular lymphoma is the most common of the indolent non-Hodgkin's lymphomas. Like many lymphomas, it is increasing in incidence with over 24,000 new cases diagnosed each year. It remains incurable with standard treatment options. Follicular lymphoma has been associated with the translocation of chromosomes 14 and 18, which results in constitutive activation of the *BCL2* oncogene and the subsequent inhibition of apoptosis.

Several datasets have demonstrated that the overall survival of patients with follicular lymphoma is improving. In a review of several Southwest Oncology Group (SWOG) studies, [1] patients that were initially diagnosed with follicular lymphoma from 1998 to 2000 were treated with CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) and a monoclonal antibody, either rituximab or ^{131}I-tositumomab. The patients in this group had significantly higher rates of progression-free survival (PFS) (P=0.005) and overall survival (OS) (P<0.001) than patients in previous studies from 1974 to 1983 and from 1988 to 1994. Patients treated with monoclonal antibodies had a PFS of 61% and an OS of 91%, compared to PFS rates of 46% and 48%, and OS rates of 69% and 79% in the earlier trials. It is likely that the addition of monoclonal antibody therapy to the chemotherapy regimen contributed to these improvements.

Prognostic Indexes

The Follicular Lymphoma International Prognostic Index (FLIPI) was derived from the International Prognostic Index (IPI), which has 5 components, including extranodal sites, performance status, age, stage, and lactate dehydrogenase (LDH) level. However, when the

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IPI is used to assess prognosis in patients with follicular lymphoma, very few patients are in the high-risk group.[2] This is because many patients with follicular lymphoma have a favorable performance status, and few have significant extranodal disease. The FLIPI was designed to be more predictive of outcome and a more robust prognostic scheme than the IPI.[3] FLIPI substitutes low hemoglobin (Hgb) levels and a large number of nodal sites for performance status and extranodal sites. These substitutions resulted in a prognostic index whereby approximately 1/3 of the patients are low risk and at 10 years have a 71% survival and another 1/3 are high risk and have a 36% survival.[3]

Though the FLIPI was initially devised in the era before the advent of treatment with monoclonal antibodies, such as rituximab, a recently published study by Buske et al[4] demonstrated that the FLIPI maintains its prognostic value even when patients are treated with regimens containing rituximab.

The National LymphoCare study is continuing to assess treatments and outcomes in patients with follicular lymphoma.[5] It is a prospective observational study conducted in the United States to evaluate prognosis, treatment, and outcomes in FL. Between 2004 and 2007, the study enrolled over 2700 patients newly diagnosed with follicular lymphoma. Most (85%) of these patients were enrolled from community oncology sites, and only 15% were enrolled from academic sites. The FLIPI scores from the patients in the LymphoCare study[6] mirrored the paper by Solal-Celigny et al[3], reinforcing the utility of the FLIPI as a prognostic scheme. However, 31% of the patients in the LymphoCare study did not have all the criteria available at diagnosis. This resulted in an inability to calculate FLIPI scores. To choose the best treatment available for patients, it is important for practicing oncologists to gather all the data necessary, including LDH level, to calculate a FLIPI score for each newly diagnosed FL patient.

Front-line Treatment

The treatment of FL may last for 20 or more years. Radiation therapy is an appropriate front-line therapy for some patients with early stage disease. Other first-line therapy choices include observation, clinical trials, single agents, or combination therapies. In a relapsed setting, it is appropriate to repeat some modalities, such as combination chemotherapy, radioimmunotherapy, and transplant.

Several studies have recently demonstrated progression-free survival benefit and suggested potential overall survival benefit when rituximab is combined with chemotherapy.[7–12]. In a phase 2 study by Hiddemann and colleagues that evaluated CHOP with and without rituximab, [7] R-CHOP was found to significantly prolong the time to treatment failure ($P<0.001$) and to produce a significantly higher overall response rate (ORR) (96% vs 90%; $P=0.011$) and prolonged duration of remission ($P=0.001$). Additionally, overall survival (OS) was significantly higher ($P=0.016$) in the R-CHOP group in the first 3 years.[7] In another study by Hiddemann, patients with follicular lymphoma treated with interferon and R-CHOP as an initial therapy had a significantly longer PFS compared to those treated with CHOP (63% vs 84%, $P=0.0004$).[8] In a study comparing CHVP-I (cyclophospamide, doxorubicin, vindesine, prednisone and interferon-alpha) with and without rituximab, event-free survival (EFS) and OS were significantly higher in the R-CHVP-I arm (81% vs 62%, $P=0.002$; and 91% vs 84%, $P=0.029$, respectively).[9] A study comparing CVP (cyclophosphamide, vincristine, and prednisone) with and without rituximab[10] found significant improvements in overall and complete response rates in the R-CVP arm (81% vs 57%, and 41% vs 10%, respectively, $P<0.0001$). Patients on the R-CVP arm also had significantly prolonged time to progression ($P<0.0001$) and a longer median time to treatment failure ($P<0.0001$). A 2006 follow-up to that study,[11] found a significantly longer time to progression or death in the R-CVP arm (34 months vs 15 months, $P<0.001$). Patients in the R-CVP arm also had significantly improved

OS (P=0.03). In a study comparing MCP (mitoxantrone, chlorambucil, and prednisolone) with and without rituximab, Herold and colleagues[12] found that patients in the R-MCP arm had significantly higher response rates (92.4% vs 75%, P=0.0004) and complete responses (49.5% vs 25%, P=0.0009). Median PFS and EFS were not reached in the R-MCP arms but still reached significance (P<0.0001 for median PFS and EFS). These studies prove the benefit of adding rituximab when treating follicular lymphoma patients with chemotherapy.

Of the 2700 patients in the National LymphoCare study, 18% received observation only as the initial treatment, 14% received rituximab as a single agent, and 53% received chemotherapy and rituximab.[13] Most patients receiving chemotherapy and rituximab were on an R-CHOP regimen (59%), 19% received R-CVP, and 11% an R-fludarabine-based regimen.

While it is clear that rituximab prolongs PFS and OS, relapse patterns continue to be observed. Maintenance rituximab may improve PFS, but many unanswered questions remain. What is the role of watchful waiting in the rituximab antibody therapy era? What is the role of maintenance therapy after rituximab-containing chemotherapy? What is the role of FLIPI in stratifying a patient for therapy?

Ongoing Trials in Indolent Lymphoma

Currently 3 important studies in the upfront treatment of FL are underway. The first is the Eastern Cooperative Oncology Group's (ECOG) RESORT trial (Rituximab Extended Schedule or Re-treatment Trial),[14] which is a phase 3 randomized trial of rituximab in patients with low-tumor-burden indolent lymphoma. The study aims to determine whether it is better to give rituximab continuously on a maintenance schedule, or to get re-treated at the time of progression. The study's endpoints are time to rituximab failure and time to first cytotoxic therapy.

The PRIMA (Primary Rituximab and Maintenance) study[15] is another important trial in indolent lymphoma. Results from this trial should be available in the next year. The study, composed of almost 1000 patients, used 4 different rituximab-containing chemotherapy regimens, although close to 75% of these patients were treated with the R-CHOP regimen. Patients were then randomized to maintenance rituximab or observation. The study aims to determine whether maintenance has a role after rituximab-containing chemotherapy.

The third trial, the Southwest Oncology Group's SWOG 0016 trial,[16] is investigating the role of upfront radioimmunotherapy. The randomized study is comparing R-CHOP vs CHOP plus tositumomab and iodine-131 tositumomab in untreated patients with grades 1 to 3 and stages III to IV FL. This study is expected to have mature results in about a year and a half.

Relapsed Follicular Lymphoma

Despite all the upfront treatment successes, all patients with advanced stages of disease still relapse. Rituximab-refractory disease is the new problem emerging in patients who are treated with rituximab-containing regimens. A 2005 study compared the benefit of maintenance rituximab therapy vs rituximab re-treatment at progression in previously treated indolent non-Hodgkin's lymphoma patients.[17] Half of the FL patients treated upfront with either rituximab on a schedule or rituximab when necessary became refractory to rituximab within 2 to 3 years. Therefore, the duration of rituximab benefit is limited for a large number of patients.

A few standard options are available for rituximab-refractory disease: radioimmunotherapy, which has a very high response rate with variable time to progression, autologous stem cell transplant, and, for a very small group of young patients who have a donor, allogeneic stem

cell transplant. If available, allogeneic stem cell transplant should be discussed, particularly if these patients are refractory to rituximab and chemotherapy regimens.

The response rate to radioimmunotherapy is high, but for the majority of patients, the response duration is relatively short (approximately 1 year). In one study on the efficacy of tositumomab and iodine-131 tositumomb and relapsed or refractory FL patients, 17% of the patients experienced 5-year PFS, and 21% had ≥ 2-year PFS.[1] However, it is difficult to predict which patients will have a long remission. Frequently, these patients had been refractory to 4 or 5 previous chemotherapy regimens. Response rates were encouraging, ranging from 47% to 68%, and complete response rates ranged from 20% to 38%.[1] This modality is underutilized and should be considered, due to its favorable outcomes and low morbidity.

Autologous transplant is applicable in a minority of patients and may be difficult given the extensive prior therapy or marrow involvement that many patients have. However, it is experiencing a resurgence due to a retrospective analysis by Rohatiner et al.[18] This study is a long-term follow-up of patients treated at the Dana-Farber Cancer Institute (Boston) and St. Bartholomew's Hospital (London). The patients had relapsed indolent lymphomas and underwent autologous transplant. At the 12-year follow-up, 48% of the patients remain in remission.[18] This suggests that the treatment modality may be potentially curative for a group of highly selected patients.

Though radioimmunotherapy and autologous stem cell transplant have the potential for long-term PFS, some questions remain. Is autologous transplant potentially a curative option, and how does allogeneic transplant fit in? The morbidity of allogeneic transplant is high in many centers, and a new system for appropriately choosing patients must be developed.

Only 3 agents have been formally tested in the rituximab-refractory setting: bendamustine and the radioimmunoconjugates, ^{90}Y ibritumomab and ^{131}I tositumomab (Table 1). In small studies, both radioimmunoconjugates have high response rates with relatively short PFS,[19, 20] suggesting that high response rates are possible in the rituximab-refractory setting. Most of the patients were refractory to single-agent rituximab. A recent phase 2 study of single-agent bendamustine[21] shows a very high response rate (77% ORR) in heavily pretreated patients with rituximab-refractory disease.

Several new agents are being studied for indolent lymphomas. Proteosome inhibitors are an exciting class of agents that have been used in multiple myeloma and mantle cell lymphoma. Proteasome inhibitors disrupt the pathways involved in the pathogenesis of non-Hodgkin's lymphoma, and preclinical models show sensitivity in lymphoma cell lines to proteasome inhibitors.[22–24] Bortezomib and carfilzomib are currently under study for indolent lymphomas.[25–28] See Table 2 for a summary of these agents.

A 2006 study by de Vos and colleagues compared weekly and twice weekly schedules of bortezomib in combination with rituximab in a group of patients who were sensitive to rituximab.[29] Eighty-six percent of the patients had FL. Toxicities differed between the 2 arms, with the twice-weekly arm experiencing more grade 3 adverse events (54% vs 35%), but the outcomes were similar. The twice-weekly and weekly arms had response rates of 57% and 53% and median times to progression of 9.9 months and 9 months, respectively. However, without a rituximab-alone arm, it is hard to determine the degree to which the bortezomib is contributing to these response rates. As there is not yet a good control population for the patients who have relapsed FL, this combination is now in a randomized trial comparing combination bortezomib and rituximab to rituximab alone.

Lenalidomide, another drug used to treat myeloma, has numerous mechanisms of action. It is still unclear exactly how lenalidomide works, but it has antiangiogenic and immunomodulatory

properties.[30] In one small phase 2 trial that was presented at the American Society of Clinical Oncology in 2007,[31] lenalidamide showed some activity in a variety of indolent lymphoma subtypes, including follicular lymphoma. Of 12 patients with follicular lymphoma, 3 (25%) experienced a response. This agent has potential to combine with other standard treatments, making it an attractive option for study.

The BCL2 inhibitors are some of the most exciting new agents. As mentioned above, BCL2 is an important player in the molecular basis of FL.[32,33] BCL2 small molecules, such as oblimersen sodium, obatoclax mesylate, and ABT-263, have been developed that look promising in preclinical models (Table 3).[34] In early phase clinical trials, these agents are showing hints of activity.[35–38] Many more studies on BCL2 inhibitors in indolent lymphoma will likely be initiated in the future.

There is great potential for combining these new agents with monoclonal antibodies and chemotherapy for patients with indolent lymphomas. However, clinical trial design for these drugs is challenging. It is difficult to know who should compose the control group, and it is hard to interpret results on these drugs without randomized trials. Synergy may not be predicted from single-agent activity, which was the case with bevacizumab in solid tumors.[39] The response rate may be exceedingly high when lenalidomide is combined with other agents. Furthermore, there are too many agents to investigate in a small number of patients, making it imperative to encourage patients with FL to enroll in clinical trials.

Summary

Currently, transplantation must be considered when FL becomes refractory to rituximab, Radioimmunotherapy is a low-morbidity and highly active option that is underutilized. Promising novel agents and combinations under development are likely to significantly change treatment approaches in the next few years. One new agent, bendamustine, is likely to be approved in the United States in the year 2008, adding to the treatment arsenal. Finally, clinical trial accrual must be encouraged in order to definitively answer the key questions about optimal therapy of follicular lymphoma.

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Table 1

Compounds studied in rituximab-refractory population

Compound	Study	N	CR/CRu (%)	ORR (%)
Bendamustine	Friedberg et al. J Clin Oncol 2008	74	34	77
^{90}Y ibritumomab	Witzig et al. J Clin Oncol 2002	54	15	74
^{131}I tositumomab	Horning et al. J Clin Oncol 2005	40	38	65

CR, complete response; CRu, unconfirmed complete response; ORR, overall response rate

Table 2

Summary of proteasome inhibitors in indolent NHL

Agent	Type of inhibitor	Clinical status
Bortezomib	Reversible	Approved for use in MCL
Carfilzomib (PR-171)	Irreversible	Phase 1 testing
NPI-0052	Irreversible	Early phase 1 testing

MCL, mantle cell lymphoma.

Table 3

Summary of new BCL2 inhibitors

Agent	Phase	Disease
Oblimersen sodium	2	FL, DLBCL, WM, MM, NHL
	3	MM
Obatoclax mesylate	1	MCL
	2	MDS, FL, HL
ABT-263	2	CLL, FL (combined with rituximab)

CLL, chronic lymphocytic leukemia; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; HL, Hodgkin's lymphoma; MCL, mantle cell lymphoma; MDS, myelodysplastic syndrome; MM, multiple myeloma; NHL, non-Hodgkin's lymphoma; WM, Waldenstrom's macroglobulinemia