Frontline strategy for follicular lymphoma: are we ready to abandon chemotherapy?

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Chemotherapy combinations have been the backbone of therapy for follicular lymphoma, and are associated with high initial response rates. Unfortunately, toxicity and secondary malignancies remain concerns, and most advanced-stage patients still relapse within 5 years, regardless of the regimen. Advances in the understanding of lymphoma biology have resulted in a new generation of noncytotoxic therapeutics with significant activity in follicular lymphoma. Recent studies exploring biological and targeted combinations in the frontline have shown promise, with response rates similar to chemotherapy. However, these regimens are also associated with significant cost as well as a unique toxicity profile. Large randomized studies are underway to compare noncytotoxic regimens with chemotherapy in the frontline, and several new combinations are being tested in the phase 2 setting. Ongoing work to identify predictive biomarkers and investment in mechanistic studies will ultimately lead to the personalization of therapy in the frontline setting for follicular lymphoma.

Learning Objectives

- To describe the evolution of standard frontline therapy in follicular lymphoma and the outcomes associated with common cytotoxic regimens
- To understand the rationale for emerging noncytotoxic combinations and the activity of several regimens currently under study

Introduction

> *Chemotherapy* n. *[kee-moh-ther-uh-pee]: the therapeutic use of chemical agents to treat disease > ; especially: the administration of one or more cytotoxic drugs to destroy or inhibit the growth and division of malignant cells in the treatment of cancer.*

Traditional chemotherapy has remained the mainstay of therapy for follicular lymphoma (FL) for the past 50 years. Recently, improved understanding of the impact of the immune microenvironment and the role of key signaling pathways in B-cell malignancies has led to a new generation of targeted, biological agents with activity in follicular lymphoma. Can these new agents displace traditional cytotoxic chemotherapy, and how will a deeper understanding of disease biology inform treatment strategies to integrate these agents into frontline therapy? This review will examine the progress of cytotoxic chemotherapy regimens in follicular lymphoma, summarize select advances in targeting the immune microenvironment and cellular pathways, and suggest ways to integrate novel agents into standard practice to improve long-term outcomes.

Follicular lymphoma is the second most common subtype of non-Hodgkin lymphoma (NHL) in the Western world, with ~14 000 new cases diagnosed in the United States annually.[1] The disease follows a heterogeneous course, and untreated patients are often presented with multiple treatment options including observation, single-agent rituximab, radiotherapy, and various combinations of chemo-immunotherapy. The decision to initiate therapy, and the regimen employed is often informed by an individual's performance status and the characteristics of each patient's disease. Today, the goal of frontline therapy is typically the prevention of disease-related complications, and disease control. Several standard combinations often result in prolonged progression-free survival (PFS), and long-term follow-up suggests a small minority of patients may be cured with aggressive approaches.[2] Utilization of improved combinations of chemoimmunotherapy in the frontline and at relapse, coupled with improvements in supportive care, have translated into a significant prolongation of expected median overall survival in FL, which now approaches 20 years.[3] However, despite these advances, the majority of patients continue to relapse within 5 years of initial therapy and chemotherapy is associated with immediate and enduring toxicities, including secondary malignancies and organ dysfunction.

A short history of chemotherapy in follicular lymphoma

Before discussing how to move novel treatments into the frontline, it is important to review the successful evolution of therapy in FL, and the current goals of initial management. Approximately 10% to 15% of patients with FL will present with low-volume, asymptomatic disease. Because of a perceived lack of long-term benefit with early intervention, most patients with low tumor burden are currently observed. This treatment pattern arose from historical studies that compared chemotherapy to initial observation in low-tumor-burden patients.[4] Although these studies indeed failed to show a clear

Conflict-of-interest disclosure: The author has received research funding from Gilead, Jannsen, Celgene, Roche, and Infinity and has consulted for Jannsen, Celgene, Roche, Infinity, and TG Therapeutics.

Off-label drug use: None disclosed.

survival benefit with early intervention, the potential impact of introducing newer agents earlier in the disease course is unknown. Ardeshna et al conducted a study comparing early use of single-agent rituximab to observation in low-tumor-burden, asymptomatic patients. When compared with observation, rituximab use resulted in an improved time to a new treatment, but a survival benefit has yet to be reported.[5] When most patients eventually receive treatment, the goals of therapy include palliation of symptoms, control of bulky disease, and preservation of organ function. Based on these goals, several large cooperative groups such as the Groupe d'Etude des Lymphomes Folliculaires (GELF), and the British National Lymphoma Society (BNLI) have developed standardized criteria to define patients in need of therapeutic intervention.

Patterning the success of multi-agent chemotherapy in aggressive lymphoma, the past several decades have been marked by a series of attempts to develop regimens that could achieve a high level of disease control and potentially eradicate minimal residual disease. Alkylators formed the backbone of most combinations and resulted in high response rates. Unfortunately, most studies have failed to demonstrate long-term survival improvements with the addition of multi-agent chemotherapy to this backbone. In 1980, the Cancer and Leukemia Group B (CALGB) conducted a randomized study of 228 patients with untreated FL, comparing cyclophosphamide alone to cyclophosphamide, adriamycin, vincristine, prednisone, and bleomycin (CHOP-B). Surprisingly, at 10-year follow-up, there was no advantage in either failure-free survival (FFS) or overall survival (OS) with a combination approach.[6] A randomized Italian study enrolled 170 untreated indolent (nonfollicular) patients to receive either chlorambucil monotherapy or chlorambucil with epirubicin. The addition of an anthracycline failed to show a benefit in response rate, FFS, or OS.[7] Rummel and colleagues reported a study in untreated advanced-stage FL, which also demonstrated no benefit in either PFS or OS with combination cytotoxic therapy (CHOP) compared with an effective alkylator backbone (bendamustine).[8] In the 1990s, our center conducted a series of studies exploring aggressive combinations of cytotoxic therapy including alternating triple therapy (ATT) with cyclophosphamide, doxorubicin, vincristine, dexamethasone, and bleomycin (CHOD-Bleo); etoposide methylprednisolone, cytarabine, and cisplatin (ESHAP); and mitoxantrone, vincristine, prednisone, and procarbazine (NOPP) with interferon maintenance. This approach resulted in an impressive 95% overall response rate (ORR) including 65% of patients who achieved complete remission (CR).[9] The median FFS ranged from 4.1 to 4.8 years, with a significant subset of patients (33%-44%) in remission at 15 years.[10] The nucleoside analog fludarabine used alone or in combination is highly active in FL. Based on encouraging results with fludarabine, mitoxantrone, and dexamethasone (FND) in relapsed FL, we conducted a randomized study to compare FND with ATT. One-hundred forty-two patients with untreated advanced-stage indolent lymphoma were enrolled (73 on FND, 69 on ATT). The ORRs were 97% for both regimens. ATT was associated with a longer FFS than was FND (50% vs 41% at 5 years) but was significantly more toxic. Severe cytopenias were observed in both groups, including grades 3-4 neutropenia and thrombocytopenia in 94% vs 81% and 78% vs 12%, respectively. Twenty-seven percent of patients also developed grade 3 or greater infections in the ATT group.[11] Despite significant toxicity, long-term follow-up again demonstrated ~40% of patients who remained in persistent remission at 10 years.[10]

The first and only agent to repeatedly confer a survival advantage when added to chemotherapy in FL is the biological agent rituximab. Unlike traditional chemotherapy, direct cytotoxicity is only a minor action of this immunotherapeutic, and the ability to augment antibody-mediated cellular cytotoxicity (ADCC) likely explains its high level of activity in FL. Using rituximab as monotherapy, studies have also reported long-term remissions in a minority of patients.[12,13] Multiple large, randomized studies have now demonstrated a benefit in PFS, and OS with the addition of immunotherapy to various chemotherapy backbones.[14-16]

A recent Italian randomized study compared different rituximab-containing frontline regimens in the up-front setting. As expected, the use of either rituximab, cyclophosphamide, vincristine, and prednisone (R-CVP); R-CHOP; or rituximab, fludarabine, and mitoxantrone (R-FM) resulted in a high level of initial disease control, with ORR rates ranging from 88% to 91% and CR rates from 67% to 73%. Despite high response rates, 37% to 48% of patients relapsed within 3 years of treatment. In addition, although PFS was longer with the addition of an anthracycline to a cyclophosphamide or fludarabine backbone, no survival benefit was observed when either combination was compared with R- CVP. Increased cytopenias and infections were reported with both R-FM and R-CHOP, and fludarabine was associated with the highest rate of secondary malignancies (8%).[17]

Bendamustine plus rituximab (BR) has been widely adopted as a standard front-line option based on an improved tolerability profile and potential clinical benefit compared with R-CHOP. A randomized noninferiority study conducted by the German Study Group for Indolent Lymphoma (StiL) compared BR with R-CHOP in 549 patients with newly diagnosed stage III or IV indolent and mantle NHL. At a median follow-up of 45 months, the median PFS was not reached in the 179 patients with FL who received BR compared with 40.9 months in the R-CHOP arm (hazard ratio [HR] 0.61; $P = .0072$).[8] These observations were further confirmed by a noninferiority international study that reported similar ORR and CR for BR compared with R-CHOP/R-CVP, 99% vs 94% and 30% vs 25%, respectively.[18]

Can we cure advanced stage follicular lymphoma?

The simple answer is yes. Nearly every aforementioned regimen will result in a subset of patients who attain a molecular response and achieve durable remissions.[10] Long-term follow-up of several studies suggest that ~30% to 40% of patients will not experience relapse despite decades of follow-up.[2,9,10] Furthermore, the rate of relapse appears to plateau between 8 and 10 years in most trials.[19] We recently presented the long-term follow-up of 157 indolent NHL patients who received rituximab plus FND as part of a phase 2 frontline study. With a median follow-up of nearly 12 years, the 10-year remission rate was 47%, with a secondary myelodysplasia rate of 4%.[20] In the relapsed setting, both autologous and allogeneic stem cell transplant (SCT) have been associated with durable remission in a large percentage of patients.[21,22] Although most studies have been small or retrospective, several centers have now reported a plateau in relapse rate ranging between 30% to 50% at 5 to 15 years with autologous SCT.[23] Rohatiner and colleagues reported the long-term follow-up of 121 patients with FL who received cyclophosphamide and total-body irradiation followed by autologous bone marrow transplantation. In this multicenter retrospective analysis of patients with at least 12 years of follow-up, 41 patients (34%) remained in remission. The approach was also associated with significant toxicity, and >10% (15 patients) died secondary to myelodysplasia or secondary leukemia.[21]

Allogeneic transplant is perhaps the single most effective curative strategy in FL and some studies have reported durable CR in >70%

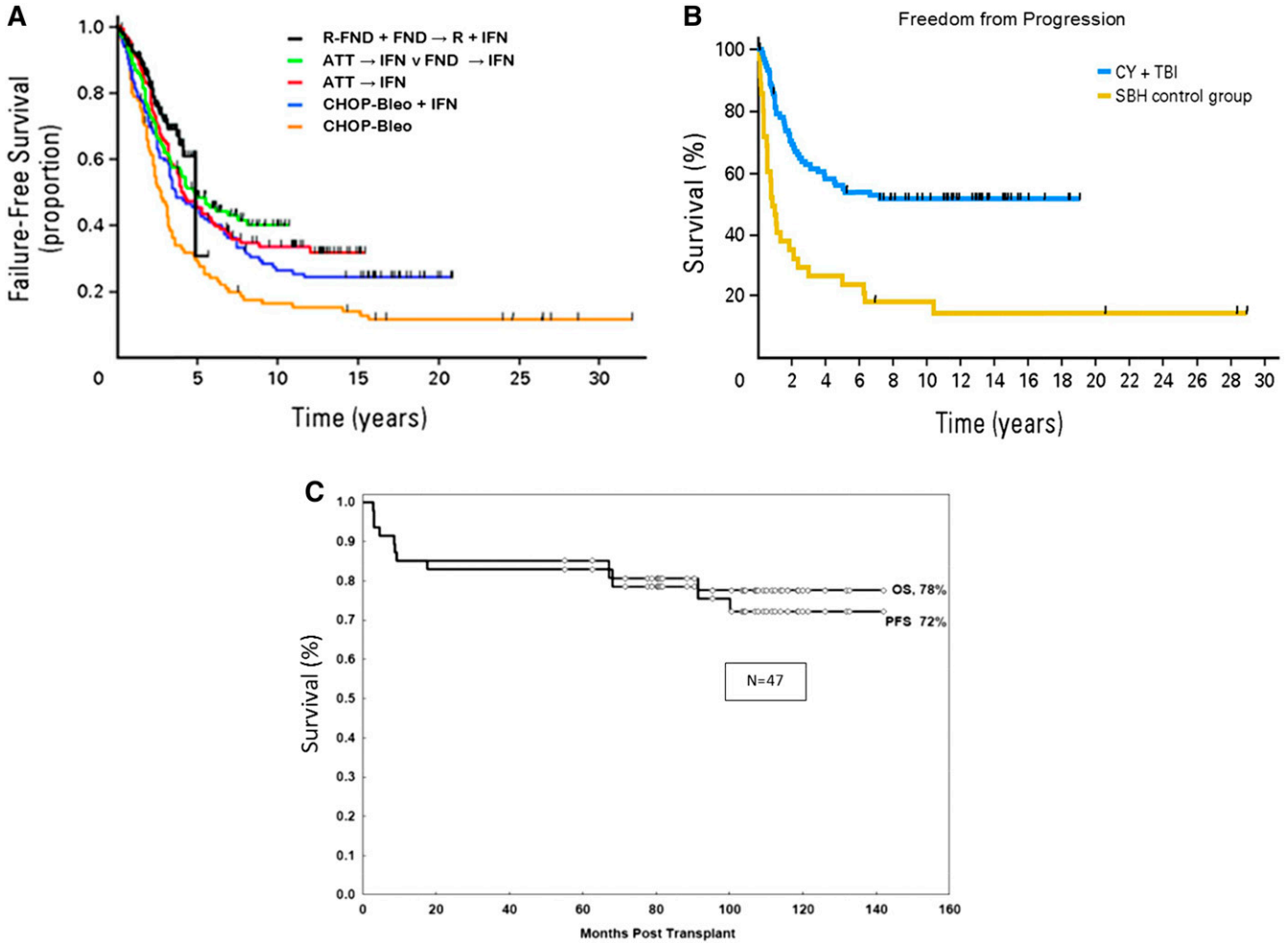

Figure 1. Long-term outcomes after aggressive therapy. (A) Failure-free survival (FFS) of FL patients treated with frontline chemotherapy regimens at MD Anderson Cancer Center.[10] Most regimens resulted in a plateau of FFS curves between 8 and 10 years. Data adapted. (B) Long-term follow-up of patients (N = 121) who received cyclophosphamide and total-body irradiation followed by autologous bone marrow transplantation compared with matched control group.[19] Data adapted. (C) Long-term follow-up of FL patients (N = 47) treated with nonmyeloablative allogeneic transplantation.[20] Data adapted.

of patients, with only rare relapses beyond 2 years. In 2012, Khouri et al reported long-term results of 47 relapsed and refractory FL patients who underwent nonmyeloablative allogeneic transplantation with FCR (30 mg/m^2 of fludarabine plus 750 mg/m^2 of cyclophosphamide for 3 days plus 375 mg/m^2 of rituximab on day −13 and 1000 mg/m^2 on days −6, +1, and +8). Nineteen percent of patients had relapsed after prior auto-SCT, and only 38% were in CR before conditioning. With a median follow-up of 107 months, the estimated OS and PFS rates at 11 years were 78% (95% confidence interval [CI] 62%-87%) and 72% (95% CI 56%-83%), respectively. The 3-year cumulative incidence of chronic graft-versus-host disease was 58%, and 6 (13%) patients died as a result of infection (Figure 1).[22]

Despite significant efficacy, chemotherapy and transplant are clearly not an option for all patients. The average age at diagnosis for patients with FL is 60 years, and many present with comorbid conditions or compromised organ function, which prohibits intensive approaches.[24] The majority of patients still relapse after standard induction regimens, and a validated method for predicting those who will attain a prolonged remission after cytotoxic therapy has yet to be identified. Allogeneic transplant, although effective, is only available to a select few, and toxicity remains significant. Better options are needed. Fortunately, recent advances in the understanding of lymphoma biology have unveiled approaches that could not only increase the efficacy of induction therapy, but potentially decrease associated toxicity.

Evolving understanding of the target

Although the t(14;18) translocation is characteristic of FL and occurs early in lymphomagenesis, multiple additional genetic aberrations are required for a malignant phenotype. Nearly all FLs have additional somatic mutations affecting oncogenic signaling pathways, resulting in further cell deregulation. The mutational makeup in FL is highly complex, and new efforts using deep sequencing are now deciphering a unique but heterogeneous landscape. Recently, inactivating mutations of MLL2 were found in 80% of FL, suggesting that epigenetic dysregulation may also play a key role in lymphomagenesis. Further mutations have been described in CREBBP, EZH2, and MEF2B in 33%, 27%, and 15% of FL, respectively.[25]

It is highly likely that genomic changes contribute to aberrant signaling through the B-cell receptor (BCR) in FL. Levy and researchers at Stanford University demonstrated that stimulated FL cells displayed

greater levels of BCR-induced phosphorylation of SYK, BTK, and MAPK compared with normal nonmalignant tumor-infiltrating B cells. Furthermore, in cases where >40% of cells exhibited an active BCR pathway, an inferior prognosis was found, independent of FLIPI scores.[26] Interestingly, it appears that BCR signaling in FL can occur in the absence of exogenous antigen, and ~20% of FLs have BCRs that bind to a common vimentin autoantigen.[27] Activation may also occur through mutations of the IgH, allowing for increased signaling through the binding of ubiquitous microenvironmental lectins.[28,29]

It is now well understood that the composition and activity of nonmalignant cells within the immune microenvironment in indolent lymphoma is altered, and plays a key role in determining clinical outcomes after frontline therapy, including survival, progression, and resistance. Although the make-up of immune cells in the microenvironment can be variable, it mirrors the normal tissue at the site of development, and FL cells retain dependence on interactions with nonmalignant cells and stromal elements for survival.[30] Landmark work by Dave et al underscored the importance of this signaling and its impact on survival. Examining biopsies in treatment-naïve patients, gene expression signatures derived from stromal elements revealed distinct immune response signatures, which predicted dramatically different clinical outcomes.[31] In retrospect, this is not surprising, because nearly 50% of the cell mass in FL is made up of tumor-infiltrating T cells, normal B cells, dendritic cells, and macrophages. Ongoing work from several centers now suggests that the pattern and composition of these $CD68^+$ macrophages and regulatory T cells, as well as the ratio of $CD4^+/CD8^+$ T cells can have a profound effect on the natural history of FL. Unfortunately, efforts to develop prognostic or predictive models based on immunohistochemical findings have been contradictory, further highlighting the difficulty of replicating results across centers and the impact of heterogeneous therapy on immune cell subsets.

Integrating novel combinations into frontline therapy

Notwithstanding the success of rituximab-based combinations, no other noncytotoxic agent has been approved for frontline therapy or has been shown to improve OS. Despite the significant hurdles associated with moving novel approaches into early lines of therapy, there are hints that noncytotoxic therapy may provide alternatives to standard chemotherapy as an initial management strategy. Early studies combining monoclonal antibody doublets proved safe, with a suggestion of improved benefit. The anti-CD80 antibody galiximab was combined with rituximab in a phase 2 study by Czuczman et al, with an ORR of 79% and a reported PFS of 2.9 years.[32] Grant and colleagues reported an ORR of 88%, with 60% of patients remaining in remission at 3 years with the anti-CD22 antibody epratuzumab combined with rituximab.[33]

The immunomodulatory drug lenalidomide has both direct antineoplastic activity and affects the tumor microenvironment through mediation of B, T, natural killer (NK), and dendritic cells. In experimental B-cell models, lenalidomide appears synergistic with multiple agents, including rituximab, dexamethasone, and BCR pathway inhibitors.[34] Based on the premise that augmentation of NK cell activity could enhance rituximab-mediated ADCC, investigators at MD Anderson Cancer Center launched a study in 2008 to explore lenalidomide and rituximab (a regimen referred to as "R squared") in previously untreated indolent lymphoma. The study enrolled 110 patients who received up to 12 months of oral lenalidomide with monthly rituximab. The ORR was 90%, including 63% patients who attained CR. In patients with FL (N = 46), the ORR and CR rates were 98% and 87%, respectively. The 3-year PFS was 79% in FL, and 93% of patients attained PET negativity at the end of therapy. Grades 1 and 2 fatigue were common but rarely led to dose interruption. Grade three or greater neutropenia was reported in 35% of patients, and rash in the first 2 cycles was seen in >40%.[35] Recently, Martin et al reported similar findings from the CALGB 50401 study, which also enrolled and treated advanced-stage untreated FL patients with lenalidomide and rituximab for up to 12 cycles. The study reported a similar ORR of 93%, with 72% of patients attaining CR. With a median follow-up of 2.3 years, the 2-year PFS was 89%. The adverse event profile was also similar to the previously reported phase 2 study with the combination.[36] These impressive results led to the initiation of a large international phase 3 study (RELEVANCE) comparing lenalidomide and rituximab with rituximab plus chemotherapy. The study's objective is to compare a noncytotoxic combination with several standard frontline regimens, and the control arm allows physicians to choose R + bendamustine, R-CHOP, or R-CVP. Enrollment of 1000 patients is now complete and results are eagerly awaited.

Recently the PI3K inhibitor idelalisib received regulatory approval in relapsed FL. The pivotal phase 2 study enrolled 125 patients with relapsed and refractory indolent lymphoma. In this heavily pretreated population, the ORR was 57% with a 6% CR rate reported. The median duration of response was 12.5 months and the median PFS was 11 months. Treatment was associated with grade 3 or greater diarrhea, colitis, or both in 16% of patients, and emergence of these events was found to be somewhat unpredictable and occurred later in treatment, at a median of 6 months.[37] Despite single-agent activity, combination studies have been problematic. Combining idelalisib with lenalidomide was associated with severe and, in some cases, fatal hepatotoxicity and immune dysregulation.[38] A recent frontline study of idelalisib plus rituximab in previously untreated elderly patients with indolent lymphoma was also halted because of unexpected infections. Alternate PI3K inhibitors are currently in development and may result in improved response and/or reduced toxicity, but frontline studies have yet to be conducted.

As single agent, the Bruton tyrosine kinase inhibitor, ibrutinib, is active in relapsed FL with ORRs of 28% to 55% in heavily pretreated patients.[39,40] At pharmacologic levels, ibrutinib has been shown to augment ADCC and enhance the activity of anti-CD20 monoclonal antibodies such as rituximab.[41] The combination of ibrutinib and rituximab as frontline therapy for FL was recently explored in a phase 2 study. In a cohort of 60 treatment-naïve patients, the ORR was 80% with a CR rate of 27%. At 12 months, 86% of patients remained in remission. Grade 3 or greater adverse events were reported in 48% of patients, with the most common being fatigue, diarrhea, and nausea.[42]

The Alliance Cooperative Group recently presented their experience with the triplet of lenalidomide, rituximab, and ibrutinib in untreated indolent patients. The ORR reported was 94%, with 63% of patients attaining CR. Although no dose limiting toxicities were observed in the 22 patients enrolled, rash was noted in 73%, including 32% who had a grade 3 or greater event.[43] Several other small studies have been exploring biological combinations in the frontline setting with mixed success (Table 1).[44,45]

The road ahead

Although it is tempting to quickly move novel agents into frontline therapy, replacing highly active chemotherapy-based regimens should be done with caution and only in the setting of a clinical study. In fact, several studies exploring novel-novel biological regimens in relapsed disease have encountered unexpected and occasional serious toxicities.[46] When considering how to test next-generation

Table 1. Select ongoing or completed combination studies in untreated FL

Regimen	Phase	N	ORR (CR)	PFS	Ref.
Lenalidomide + rituximab	2	50	98% (87%)	75% (3 y)	26
Lenalidomide + rituximab	2	65	96% (71%)	89% (2 y)	27
Lenalidomide + rituximab*	2	77	81% (36%)	NR	44
Lenalidomide + rituximab vs R-Chemo	3	1000	TBD	TBD	Clinicaltrials.gov
Ibrutinib + rituximab	2	60	80% (27%)	86% (12 mo)	33
Ibrutinib + rituximab + lenalidomide	1	22	91% (63%)	84% (12 mo)	34
Idelalisib + rituximab*	2	—	NR	NR	Terminated
Sargramostim + rituximab	2	52	74% (42%)	54% (2 y)	45
Galiximab + rituximab	2	61	72% (48%)	58% (2 y)	32

*Single-arm results from randomized study.

regimens in the frontline setting, it is important to consider the lessons of the past 30 years:

- Chemotherapy is initially effective, but is associated with significant toxicity and most patients ultimately relapse.
- Follicular lymphoma is highly dependent on survival signals from the immune microenvironment.
- Many patients have defective antitumor immune response at diagnosis.
- Immunomodulatory approaches (IMiDs, allogeneic SCT) have high activity in FL.
- Novel combinations have been associated with unexpected and occasionally serious toxicities.

Despite encouraging early results with some immune-based and targeted agents in the frontline, it appears that a subset of patients still continue to relapse after induction, and the optimal combination is unknown. Ideally, methods to predict patients likely to attain long-term remission or cure with chemotherapy vs those that would benefit most from immunotherapy or novel targeted agents could improve outcomes. Unfortunately, personalization of therapy has been hampered by a lack of validated predictive biomarkers, poor understanding of the mechanism of several emerging agents, and the complex biological heterogeneity observed across patients. A recent study by Westin et al explored the safety and activity of a presumed PD-1 inhibitor, pidilizumab, plus rituximab in relapsed FL. Interestingly, gene-expression profiling of pretreatment biopsies predicted PFS after immunotherapy. This pretreatment "immune signature" consisted partially of genes upregulated during T-cell activation, or genes repressing regulatory T cells, suggesting that antitumor immunity at baseline predicted outcomes to the checkpoint inhibitor.[47] Multiple teams at our center and others are currently working to develop a comprehensive "immunoscore" to further categorize patients into subsets based on their pretreatment tumor immunogenicity. If such a scoring system could be validated, lymphomas that are highly immunogenic could be targeted with immune-based combinations such as IMiDs, checkpoint inhibitors, or vaccine therapy, whereas patients with a low immunoscore would be treated with combinations of evolving cytotoxic agents, targeted antibodies, CAR-T cells, or BiTE-like agents.[48]

Logistic issues have also been a major hurdle blocking efficient integration of emerging agents into initial therapy. Drug development in the frontline setting currently requires overwhelming time and investment to show a significant benefit of a new agent vs R-Chemo. Currently designed frontline studies in FL can take 2 to 3 years to complete accrual, and another 8 to 10 years to reach a primary end point of PFS. In an era of rapid drug discovery, these timelines are unacceptable. Clearly, by the time the study answer is revealed, the question posed by a trial is at risk of being irrelevant or outdated. To accelerate novel drug development, academic and industry partners have begun to explore surrogate end points in FL that predict PFS. Recently the Follicular Lymphoma Analysis of Surrogacy Hypothesis (FLASH) group analyzed data for 13 randomized induction studies in FL. After analyzing data from >3500 patients, the group found a highly significant correlation between CR rate at 30 months after initiation of treatment (CR30) and PFS.[49] If accepted by regulatory bodies, surrogate end points in FL have the potential to dramatically increase the time to drug approval of emerging agents and further accelerate the study of potential novel combinations in the frontline setting.

Conclusion

Improvements in the understanding of the immune microenvironment and intracellular signaling pathways have resulted in a new generation of therapeutics with activity in low-grade lymphoma. Several early studies exploring these novel chemotherapy-free combinations in the frontline suggest high levels of activity, but will require longer follow-up to determine whether a subset of patients will achieve outcomes comparable with existing regimens. Furthermore, several novel regimens are associated with a unique toxicity profile and may not be ideal for all patients. Quality-of-life comparisons conducted as part of ongoing phase 3 studies will also further help clinicians individualize treatment. Although it is not yet time to abandon chemotherapy, the next generation of studies has the greatest potential yet to identify biological combinations with not only increased efficacy and decreased toxicity, but ultimately higher cure rates. Future studies should focus on identifying predictors of response to specific agents/classes, selecting regimens based on validated biomarkers, and recognizing patients at high risk for early response.

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