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Dr. Kridel is a lymphoma specialist at the Princess Margaret Cancer Centre in Toronto, having previously completed his medical training in Europe (Switzerland) and Canada (Vancouver). His research focuses on the delineation of distinct patient populations based on integrative genomic profiling of tumour biopsies, aiming to identify vulnerabilities that will lead to biology-adjusted therapeutic approaches. In addition, his research group explores means to overcome treatment resistance through functional genomic approaches.

Moving beyond Chemotherapy in the Management of Follicular Lymphoma

Introduction

Follicular lymphoma (FL) is the most common indolent lymphoma. It is estimated that approximately 2,000 Canadians are newly diagnosed with FL each year; however, this is an underestimation of the disease burden due to the indolent nature of FL. Indeed, the life expectancy for most patients can be measured in decades, with slow but constant improvement in survival estimates having been achieved over time.

Traditionally, FL has been considered a chemo-sensitive disease and, for the last 15 years, antibodies targeting the CD20 surface epitope on B cells have become a compelling adjunct to induce long-lasting remission in the frontline setting.[1] Outcomes are favourable for most patients; a long-term follow-up from the seminal PRIMA trial showed that the median progression-free survival (PFS) was 10.5 years in patients treated with immunochemotherapy as part of an initial induction regimen followed by rituximab maintenance, as compared with just over 4 years in the control arm (initial induction regimen followed by observation).[2] In terms of chemotherapy backbone, bendamustine has established itself as the preferred standard in Canada and induces durable response in the majority of patients.[3]

This article will focus on patients with high-tumour burden disease in need of treatment, as opposed to patients with limited-stage disease who may benefit from localized radiation or patients with advanced-stage with low-tumour burden disease who may benefit from observation or single agent rituximab.

Reasons to Move Beyond Chemotherapy

The phrase "chemotherapy-free" has gained popularity in recent years to connote a new, modern era of treating FL. It is important to note that the term chemotherapy-free does not equate with an absence of side effects as novel therapeutics can have their own set of adverse effects. In addition, these therapies should not be viewed as "natural," given that they are either chemical probes or highly engineered immune therapies that do not exist as such in the natural world.

There exist multiple reasons to move beyond chemotherapy. Approximately 20% of patients experience early progression after immunochemotherapy and are at increased risk of lymphoma-related mortality.[4] Especially with bendamustine-based treatment, the majority of progression events are due to histological transformation.[5] Preventing early progression and/or transformation should be an important goal with the use of novel therapies.

Secondly, FL tends to become less chemo-sensitive with each successive round of recurrence, and treatment guidelines are not well defined in cases of relapse.[6]

Thirdly, chemotherapy is undoubtedly associated with both acute and long-term toxicity. For example, the GALLIUM trial demonstrated that obinutuzumab significantly prolonged progression-free survival (PFS) in previously untreated patients with follicular lymphoma relative to rituximab (R) when combined with cyclophosphamide (C), doxorubicin, vincristine (V), and prednisone (P; CHOP); CVP; or bendamustine. However, an unexpected risk of fatal adverse events associated with the use of bendamustine was observed which may reflect a difference in baseline patient risk profile.[7] The use of bendamustine and rituximab has also become more controversial in the last two years as the double hit of impairing both humoral and cellular immunity puts patients at risk of severe COVID-19.[8]

Lastly, but importantly, chemotherapy is associated with long-term complications including an increased risk of cardiovascular events and secondary cancers, and, more generally, premature aging.[9] Accordingly, there are compelling reasons to study novel therapeutic agents that may improve outcomes for FL patients. The results from selected trials in relapsed/refractory (R/R) FL are summarized in **Table 1**.

Chemotherapy Alternatives

The most studied chemo-free regimen in both the front-line and relapsed setting is the combination of rituximab with lenalidomide (R2). The latter is a targeted agent that leads to the degradation of the Ikaros and Aiolos lymphoid transcription factors.[10] Despite its selective mode of action on the molecular level, lenalidomide has pleiotropic effects including both direct anti-tumour and also immune-modulating effects.

Therapeutic agent	Phase	N	ORR (%)	CRR (%)	Median PFS (months)
Immunomodulator-based					
Lenalidomide + rituximab (R2) vs. placebo + rituximab[13]	III	147 vs. 148	80% vs. 55%	35% vs. 20%	39 vs. 14
PI3K inhibition					
Idelalisib[16]	II	72	56%	17%	11
Duvelisib[17]	II	83	42%	1%	10*
Umbralisib[20]	IIb	117	45%	5%	11
Copanlisib[18]	II	104	59%	20%	13#
Copanlisib + rituximab vs. placebo + rituximab[19]	III	184 vs. 91	85% vs. 54%	37% vs. 21%	22 vs. 19
BTK inhibition					
Ibrutinib[34]	II	110	21%	11%	5
Epigenetic					
Tazemetostat[24]	II	99	69% (*EZH2*^{mut}) 35% (*EZH2*^{wt})	13% (*EZH2*^{mut}) 4% (*EZH2*^{wt})	14 (*EZH2*^{mut}) 11 (*EZH2*^{wt})
BCL2 antagonist					
Venetoclax[14]	I	29	38%	14%	11
mTOR inhibitors					
Everolimus[35]	II	23	61%	not reported	7*
Temsirolimus[36]	II	39	54%	26%	13
Checkpoint inhibitor					
Nivolumab[37]	II	92	4%	1%	2
Bispecific antibodies					
Mosunetuzumab[28]	I	65	69%	51%	12*
Glofitamab[29]	I	44	71%	48%	12
Epcoritamab[30]	I	11	82%	45%	not reported
Odronextamab[31]	I	40	78%	63%	17&
CAR T-cell therapy					
Axicabtagene ciloleucel[38]	II	86$	94%	79%	not reached
Tisagenlecleucel[39]	II	94^	86%	69%	not reached
CD47 blockade					
Magrolimab (previously referred to as 5F9)[33]	Ib/II	28	66%**	24%**	not reported

Table 1: *Results from selected trials of novel therapies in relapsed/refractory FL*

N, number; ORR, overall response rates; CRR, complete response rate; PFS, progression-free survival; mut, mutated; wt, wild-type. The column with patient numbers specifically refers to FL patients. It is important to note that patient populations may vary between the trials and direct comparisons can be misleading. Only controlled trials can answer the question of head-to-head efficacy.

**, these PFS results include patients with small lymphocytic lymphoma and marginal zone lymphoma; #, these PFS results include patients with small lymphocytic lymphoma, marginal zone lymphoma and lymphoplasmacytic lymphoma/Waldenström's macroglobulinemia; &, PFS refers to patients having received odronextamab doses of 5 mg or higher; $, evaluable for activity (out of 127 follicular lymphoma patients enrolled); ^, efficacy set (out of 98 patients enrolled); **, combined outcomes for 28 patients with follicular lymphoma and 1 patient with marginal zone lymphoma.*

A seminal phase III trial (RELEVANCE) compared the R2 regimen to immunochemotherapy (rituximab plus chemotherapy) in over 1,000 patients.[11] While this study was designed as a superiority trial, the primary endpoints of complete response (CR) at 120 weeks and progression-free survival were ultimately similar in both groups of patients. Study results demonstrated rates of confirmed or unconfirmed complete response at 120 weeks to be 48% in the rituximab–lenalidomide group and 53% in the rituximab–chemotherapy group (P=0.13). The interim 3-year rate of progression-free survival as measured both by independent review committee and as assessed by the investigator was 77% and 78%, respectively. Immunochemotherapy led to a higher rate of neutropenia and febrile neutropenia, while R2 was associated with a higher rate of skin rashes. Thus, overall, R2 can be considered a non-superior alternative to immunochemotherapy; unfortunately, it is not reimbursed in Canada.

A more recent phase II trial (GALEN) studied lenalidomide in combination with obinutuzumab and found that oral lenalidomide plus obinutuzumab was well tolerated and effective in patients with R/R FL.[12] While obinutuzumab may be more effective than rituximab for many indolent lymphomas, including FL, a direct comparison with obinutuzumab-chemotherapy is needed to draw conclusions as to the relative efficacy of an obinutuzumab-lenalidomide combination.

R2 is also a useful regimen in the relapsed setting where it has been studied in comparison with single-agent rituximab in a phase III trial (AUGMENT).[13] R2 was found to be superior, with a median duration of response of 39.4 months, as compared to 11.4 months with rituximab monotherapy. Unfortunately, R2 is also not typically reimbursed in Canada in the relapsed setting.

Given that the t(14;18) translocation, leading to upregulation of anti-apoptotic BCL2, is found in ~85% of all FL cases, it is appealing to hypothesize that BCL2 degradation may have therapeutic benefits in FL akin to those seen in chronic and acute leukemias. Unfortunately, the response rate to venetoclax was lower than expected in a phase I trial of 106 patients with relapsed or refractory NHL receiving venetoclax once-daily until progressive disease or unacceptable toxicity, with only 38% of FL patients responding, and a median PFS of 11 months.[14] In the CONTRALTO study, a chemo-free regimen with venetoclax and rituximab led to a complete response in only 17% of patients with relapsed/refractory FL, and the addition of venetoclax to bendamustine and rituximab was associated with a high rate of grade 3/4 adverse events.[15] It is possible, however, that judicious combination with other targeted therapies may improve upon these results.

FL usurps signaling pathways from normal B cells and their inhibition has been studied, for example by targeting the PI3K pathway using idelalisib,[16] duvelisib,[17] copanlisib[18,19] or umbralisib,[20] with response rates ranging between 42-59% and median PFS between 10-13 months.[21] While the respective side effect profiles of these agents differ, some of the side effects, such as hepatotoxicity, colitis and pneumonitis, can be severe, which has dampened the enthusiasm for this class of agents. Clinicians should note that no PI3K molecule is currently funded for FL in Canada.

Pathogenetic Approach to Therapy

The genetic basis of FL is characterized by mutations in epigenetic modifiers, (i.e. enzymes that catalyze the post-translational modification of histones) resulting in aberrant transcriptional programs. Historically, FL was among the first types of cancer in which mutations of epigenetic modifiers were described.[22] The mutations affecting enhancer of zeste homolog 2 (*EZH2*) are seen in ~20-25% of FL cases and result in gain-of-function of its methyltransferase activity.[23] Consequently, EZH2 has rapidly emerged as a target for pharmacological inhibition.

The most robust data available are for tazemetostat therapy, with response rates of 69% and 35%, and median PFS of 13.8 versus 11.1 months in *EZH2*-mutated and *EZH2*-wildtype FL, respectively.[24] While the PFS results observed in this study may be perceived as underwhelming relative to other treatment regimens, the approach of inhibiting EZH2 has some clear advantages. First of all, tazemetostat is generally well-tolerated, which is important for the quality of life of our patients and is also important because it may portend safe combination with other therapeutic agents. Secondly, *EZH2* mutations represent the first predictive biomarker for FL, allowing identification of those patients with the highest probability of clinical benefit.

Immunocentric Approach to Therapy

FL cells grow in a cellular ecosystem in which they closely interact with their microenvironment, relying on cues from immune and stromal cells to grow, evade immune escape and induce a tumour-promoting microenvironment.[25] FL cells can be conceptually thought of as parasitic colonizers of the germinal centre. Accordingly, the therapeutic disruption of these tumour-immune interactions should reduce the growth of FL.

Unfortunately, the response rate to immune checkpoint inhibition has proven to be very low.[26] This lower clinical response does not mean that immune responses cannot have therapeutic effects. For example, in situ vaccination with a TLR9 agonist, combined with low-dose radiation has been shown to lead to tumour responses in non-treated sites, suggesting that strengthening the immune surveillance through antigen-specific immune responses may be beneficial.[27]

However, the most promising advances in the FL field come from the development of immune therapies that are based on recognition of B-cell epitopes, coupled with activation of T cells in the immediate vicinity of malignant cells. The efficacy of at least 4 different CD20×CD3 bispecific antibodies (mosunetuzumab,[28] glofitamab,[29] epcoritamab[30] and odronextamab[31]) has been reported in early phase trials, with promising CR rates of 69-82%.[32] Longer follow-up of these studies is required in order to fully determine the durability of response. The toxicity profiles of these agents include cytokine release syndrome (CRS), that is often low-grade and mostly confined to the period of treatment initiation, and thus can be mitigated by an appropriate titration schedule.

Chimeric antigen receptor-modified T cells (CAR T-cells) have similarly been studied in R/R FL, with high rates of CR (79% with axicabtagene ciloleucel in the ZUMA-5 trial and 69% with tisagenlecleucel in the ELARA trial) and median PFS results of 18 and 12 months, respectively.[32] These therapies are not currently funded in Canada for FL patients.

Beyond immune therapies that ultimately rely on T cells for anti-tumour effects, blocking the "do-not-eat-me" signals produced by FL cells has been shown to enhance the phagocytic function of macrophages. An early phase trial showed a response rate of 66% and CR rate of 24% in patients with relapsed/refractory indolent lymphomas.[33]

These results highlight the potential of novel immune therapies to induce high response rates in R/R FL, with emerging data providing answers with regards to the durability of these responses.

Conclusion

In summary, the role of chemo-free treatment options for FL patients is rapidly evolving, with an increasing number of novel therapies being investigated in clinical trials, as monotherapy or as part of combination treatments. Simultaneously, our understanding of the pathobiological underpinnings of FL is expanding at a fast pace. Ideally, predictive biomarkers will facilitate decision-making in the future, beyond the current individualized decision-making criteria involving factors such as frailty or comorbidities. While the cost of approved novel therapies will likely be significant, a cost-effective approach to FL treatment can be rationalized through the prioritization of the most effective therapy for a given patient, ultimately improving patient outcomes. However, to fully evaluate the relative efficacy of novel therapies, comparative clinical trials are urgently needed.

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