REVIEW ARTICLE

A SYSTEMATIC REVIEW OF THE MANANGEMENT OF RELAPSED/REFRACTORY FOLLICULAR LYMPHOMA

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SUMMARY

Refractory follicular lymphoma is an indolent malignancy of follicular center cells where a subgroup of disease presents with relapse and refractoriness to treatment or transformation to aggressive diffuse large B cell lymphoma. Improved knowledge of the disease biology is expected to provide means of identifying refractory disease at diagnosis and new approach to their treatment. This systematic review of emerging treatment modalities was done with a view to identifying appropriate treatment of refractory or relapsed follicular lymphoma in resource poor settings.

A systematic search of the database of MEDLINE, COCHRANE and EMBASE was done using the following words: relapse/refractory follicular lymphoma, follicular lymphoma clinical trials, follicular lymphoma treatment guideline. Randomized controlled phase II/III trials were selected for review. National Comprehensive Cancer Network and European Society for Medical Oncology recent guidelines were also reviewed. The promising potentials of recently approved novel targeted therapy were dampened by toxicity and drug resistance.

Keywords: Follicular lymphoma, refractory indolent lymphoma, targeted therapy, genetic diversity.

INTRODUCTION

Follicular lymphoma (FL) is an indolent malignancy of follicular center B cells characterized by a peak incidence after the sixth decade of life, non-tender lymphadenopathy, rearrangement of BCL2 gene {t (14;18)} in the majority of cases and cells with positive CD20 and CD10.[1] It represents 22-25% of non-Hodgkin lymphomas in the Western Hemisphere while it represents 3-7% in Sub-Saharan Africa being over shadowed by diffuse large B cell lymphoma and endemic Burkitt lymphoma.[2-5]

TREATMENT

The StiL-1 and BRIGHT trials, of symptomatic advanced FL (Table 1), have shown that addition of rituximab (R) to chemotherapy combinations followed by maintenance rituximab (2-monthly rituximab for 2 years) or radio-immunotherapy (^{90}Y-ibritumomab tiuxetan) consolidation particularly for patients in partial remission, have increased median overall survival from 8-10 years to over 15 years while bendamustine-rituximab (BR) and maintenance with rituximab have improved mean progression free survival with less toxicity.[6,7] Further analysis of the BRIGHT study showed that 3% of patients given BR and 9% of those given R- Cyclophosphamide, Doxorubicin, Oncovin, Prednisolone (R-CHOP) or R-Cyclophosphamide, Oncovin, Prednisolone (R-CVP) were refractory to immunochemotherapy.[7] These refractory and early relapse follicular lymphomas are a subset of disease with poor prognosis.[8]

TABLE 1: STAGING OF FOLLICULAR LYMPHOMA

STAGE	LYMPH NODE	EXTRANODAL
EARLY (10% to 15% of cases)		
I	One node of a group of adjacent nodes	Single extranodal lesions without nodal involvement
II	Two or more nodal groups on the same side of the diaphragm	Stage I or II by nodal extent with limited contiguous extranodal involvement
Advanced plus constitutional symptoms		
II bulky	II as above with “bulky” disease (>5cm)	Not applicable
III	Nodes on both sides of the diaphragm; nodes above the diaphragm with spleen involvement	Not applicable
IV	Additional noncontiguous extralymphatic involvement	Not applicable

Tonsils, Waldeyer’s ring, and spleen are considered nodal tissue

FL patients will ultimately relapse after first line therapy. The European Society for Medical Oncology (ESMO) guideline of 2016 recommends watchful waiting strategy in the absence of the Groupe d’Etudes des Lymphomes Folliculaires [GELF-Table 2] or German Low Grade Lymphoma Study Group (GLSG) or British National Lymphoma Investigation (BNLI) criteria for treatment and a re-biopsy to exclude transformation, if there is intention to treat.[9,10,11]

Positron Emission Tomography (PET) scan may be helpful in identifying a node in transformation for biopsy (Table 3) using the Standardised Uptake Values (SUV between 10 and 13 are suggestive, but above 13 is indicative).[12,13] The National Committee Cancer Network (NCCN) recommends that patient on watchful waiting should have clinical and laboratory evaluation done every 3-6 month for 5 years and annually thereafter, while ultrasound/CT surveillance can be done every 6 months in the first 2 years and annually thereafter.[14]

Follow up measures in ESMO guidelines included thyroid function tests at 1, 2 and 5 years after radiotherapy to the neck.[9] Unfortunately, response rate in relapsed disease is lower and the possibility of a second relapse exists in which case the treatment options are limited. The heterogeneity and variability in the course of disease are unmet needs in the management of relapsed/refractory follicular lymphoma. The authors therefore embarked on a systematic review of treatment options in refractory and multiply relapsed FL with a view of exploring evidence-based guidelines in a resource poor practice.

TABLE 2: Follicular Lymphoma International Prognostic Index (FLIPI)/GELF Criteria

FLIPI	FLIPI -2	GELF CRITERIA
age >60yrs	age >60 yrs	Nodal/ extra nodal size >7cm
Haemoglobin <12g/l	Haemoglobin <12g/l	>3 nodal areas with >3cm diameter
LDH >ULN	$\beta_2$microglobulin >ULN	Systemic symptoms
>4 lymph nodes areas	largest node >6cm	Serous effusion
Stage 4	bone marrow involved	Local compression cytopenia/leukaemia

LDH-Lactate dehydrogenase; ULN- Upper limit of normal; FLIPI 1: 0-1 low risk; 2-intermediate risk; >3 high risk (10-year overall survival- 71%, 51%, 36% respectively)

METHODS

A systematic review of the management of relapsed / refractory follicular lymphoma was done between January and March 2019 using predetermined protocol of literature search. Articles published between 2010 and 2019 were sought from the following database: EMBASE, MEDLINE and COCHRANE with the following key words: relapse/refractory follicular lymphoma, follicular lymphoma clinical trials, follicular lymphoma treatment guideline. Abstracts of randomized controlled phase II/III clinical trials published after 2010 were reviewed. The trials with end points showing response rate (RR), progression free survival (PFS), overall survival (OS) and adverse events (AE) were selected based on PICOS-T criteria (participants, interventions, comparison or control, outcomes, study design, time period). Where there were no randomized trials, less stringent retrospective analysis was considered. Using Google Scholar search engine, recent NCCN and ESMO guidelines from 2016 were also studied.

DATA ANALYSIS

The reporting was in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analysis (PRISMA) guidelines.

RESULTS

Initial search using ‘relapsed or refractory follicular lymphoma’ yielded 5,739 publications. Secondary search using ‘lymphoma’ yielded 2212 publications. Further interrogations with ‘phase II/III clinical trials’ yielded 378 publications. On review of the abstracts, repeated reporting and phase 1 trials were dropped and the 49 articles that reported RR, PFS, OS and AE were selected for full article review. The results are shown in Tables 4 and 5. A meta-analysis of complete response rates as an indicator of longer overall survival was not done due to inconsistencies in protocols, primary outcomes and controls.

DISCUSSION

Data from the National LymphoCare Study showed that 20% of patients will progress or relapse within 2 years of first line immunochemotherapy.[8] This group of patients had poorer outcomes compared to patients that relapsed after 2-3 years (5-year overall survival was 50% vs. 90%).[8] Similarly, FL that are refractory to first line immunotherapy or that relapsed within 6 months of rituximab treatment are resistant to rituximab.[15] In addition, a second challenge with rituximab results in 60% resistance.[15] Based on these findings,

TABLE 3: WHO Grading of Follicular Lymphoma

GRADE	CENTROBLAST
1	0-5 centroblasts per hpf (40x objective)
2	6-15 centroblasts per hpf
3A	>15 centroblasts per hpf
3B	Solid sheets of centroblasts
Reporting of pattern	Proportion follicular
Follicular	>75%
Follicular and diffuse	25%-75%
Focally follicular	<25%
Diffuse	0%(*Diffuse areas containing >15 centroblasts per hpf are reported as Difuse Large B Cell Lymphoma with follicular lymphoma*)

18 mm field of view ocular, count 10 hpf and divide by 10. If using a 20 mm field of view ocular, count 8 hpf and divide by 10. If using a 22 mm field of view ocular, count 7 hpf and divide by 10. Low grade FL – grades 1 and 2 ± grade 3A

this study has stratified treatment into: refractory and rituximab resistant disease; early relapse disease; late relapse disease; multiply relapse disease and disease in elderly and frail patients. The guiding principles were: improving overall survival; sustaining good quality of life by using maintenance immunotherapy especially in patient with partial remission;[16,17] early detection of transformation to diffuse large B cell lymphoma as predicted by rapidly growing lymph node, high lactate dehydrogenase, new extranodal site, hypercalcaemia and new B symptoms for appropriate intervention; [14,18] minimizing the chance of developing myelodysplastic syndrome or acute leukaemia by restricting multiple use of doxorubicin or fludarabine based chemotherapy; [19,20] delaying Stem Cell Transplant (SCT) until first or second relapse and avoiding repeated radiotherapy; limiting marrow depression so that high risk patients that are fit and young may benefit from high dose therapy followed by autologous SCT at relapse; offering palliative therapy to elderly and frail high risk patients with palliative radiotherapy, repeated rituximab monotherapy, targeted novel therapies, radioimmunotherapy or drug conjugated immunotherapy.[9,14]

Refractory of Early Relapse within Six Months of Treatment: Refractory disease was defined as failure to respond to, or progression within 6 months of rituximab-based treatment. Since these patients are resistant to rituximab and first line chemotherapy, it is appropriate to treat with an alternative non-cross resistant immunotherapy.[9,14]

Immuno-Chemotherapy:
Options that have been tried are: Obinutuxumab (GA) plus alternative chemotherapy, radio-immunotherapy, conjugated immunotherapy, autologous stem cell transplant or allogeneic stem cell transplant and CAR-T cell therapy. Summary of the results of phases II/III clinical trials are in Table 4. Obinutuzumab (GA) is a humanized glycol engineered type II anti CD 20 monoclonal antibody with an enhanced caspase dependent and antibody mediated cell cytotoxicity.[21,22] However, Obinutuzumab is associated with more infusion related adverse events, neutropenia and cough than rituximab.[21,22] The possibility of a progressive multifocal leukoencephalopathy is also a drawback.[23] It is, therefore, indicated in refractory and early relapsed FL (GADOLIN Trial with bendamustine; Table 4).[24] The optimum dose of Obinutuzumab is 1000mg intravenous monthly for 6 months followed by 2-monthly maintenance treatment for 2 years.[21] Alternative chemotherapy may be combination of fludarabine and cyclophosphamide or combination of CHOP/CVP (Table 4).[25] Bendamustine (B) is an alkylating agent with attached purine analogue which makes it both cycle and non-cycle dependent chemotherapy. Bendamustine has minor cross resistance with other alkylating agents and may therefore be effective in alkylating agent resistance.[26] Dosage of bendamustine in combination is 90mg/m^2 on days 1 and 2 of a 28 day cycle.[24] The GADOLIN trial (Table 4) demonstrated that combination of GA and bendamustine significantly increased the minimal residual disease rate (MRD) and the median progression free survival (PFS).[24] Patients that respond to obinutuzumab plus bendamustine may benefit from obinutuzumab maintenance or consolidation with radio-immunotherapy or autologous stem cell transplant at first relapse since this sub set of patients have poor prognosis. Patients that are refractory to obinutuzumab plus chemotherapy may benefit from radio-immunotherapy, targeted therapy, combination of plain immunotherapy and conjugated immunotherapy with or without ASCT (Table 4).

Radioimmunotherapy:
Radio-immunotherapy is a monoclonal antibody conjugated to a radioactive substance where radioactivity destroys attached and adjoining cells. Trials with ^{90}Yttrium-ibritumomab tiuxetan and ^{131}I-tositumumab earned USA and European approval, but ^{131}I-tositumumab is no longer in the market. ^{90}Y-ibritumomab tiuxetan is a murine IgG1 kappa anti CD20 monoclonal antibody conjugated to tiuxetan, a linker-chelator of ^{90}Y radionuclide. It is a beta emitter with a short half-life (27 hrs) and wider penetration. It, therefore, requires the gamma emitter ^{111}I for dosimetry to assess safe radioactivity in other organs.[27] Therapy is convenient in that it may be given as outpatient with minimal effect on co-inhabitant.[27] Phase II/III ^{90}Y-ibritumomab tiuxetan controlled trials (Table 4), which included rituximab refractory FLs showed an impressive overall response rate (ORR) ranging from 74% to 80% and complete response (CR) of 15 -30%.[28,29] The major adverse event was severe marrow suppression and for this reason it is only recommended in non-bulky tumor and if the marrow involvement is less than 25%, platelet count is >100,00/µl and neutrophil count >1500/µl.[30-32] Radioimmunotherapy is also associated with increased risk of myelodysplasia or acute leukaemia if preceded by multiple chemotherapy but it is active in rituximab resistance.[32,33] It is, therefore, best suited for elderly/frail patients in early relapse with low tumor burden who may not tolerate chemotherapy nor high dose therapy (HDT) with autologous stem cell transplantation (ASCT).

Conjugated Immunotherapy:
Conjugated immunotherapy trials included: inotuzumab ozogamicin, which is an immune-conjugate of calicheamicin (an receptor) and pinatuzumab vedotin an anti-CD22 antibody both of which are antibiotic causing double strand DNA breaks) and inotuzumab (humanised anti-CD22 antibody), polatumumab vedotin an anti CD79b (a component of B cell conjugated

to the same anti mitotic agent monomethylaurastatin E (MMAE).[34-37] These antigens on B lymphocytes are internalized on binding thereby internalizing the conjugated cytotoxic drug.[34] A phase II trial of inotuzumab ozogamicin in rituximab refractory indolent lymphomas showed an ORR of 67% with CR of 31% and median progression free disease of 12.7 months.[35,36] However, the rate of adverse events was high and there was high treatment discontinuation rate although an earlier trial had posted better results (Table 4).[35,36] In a phase 1/II ROMULUS trial that compared polatumumab plus rituximab (R) with pinatuzumab vedotin plus rituximab, R-polatumumab was more effective (Table 4) with better adverse event performance which has justified inclusion in other trials.[37,38] The major adverse events were fatigue, diarrhea, nausea, transaminitis and haematological toxicities which have discouraged clinical application.[34-37] Preliminary data from studies combining immunoconjugate with bendamustine and obinutuzumab or rituximab are however encouraging.[39] In essence, immunoconjugates may be used in bridging multiply refractory diseases with SCT or as alternative treatment for transplant ineligible patients.

Patients that respond to either of these three options and are young and fit or patients that relapsed after 2nd line immunochemotherapy may be offered the option of HDT ± radioimmunotherapy followed by ASCT and immunotherapy maintenance.[40-44] There was improved OS in patients offered ASCT compared to no transplant in early relapse, the improvement was more prolonged in patients that relapsed within one year (Table 4).[45] An analysis of a cohort of 121 patients with relapsed FL who had ASCT at St. Bartholomew's Hospital in London and Dana-Faber Cancer Institute in Boston, showed that about 50% of transplant patients are still in remission 10 to 15 years after transplant.[45,46] The possibility of cure with ASCT after early relapse (1 year) may, therefore, alter the paradigm in the management of FL.

Chimeric Antigen Receptor (CAR) T-Cell Therapy:
Cytotoxic T cells engineered to react to a lineage specific antigen on the tumor cell binds to the cells with cytotoxic effect. In FL, the antigen is CD19 and the adoptive receptor is expressed on the CD3 zeta domain of T-cell receptor coupled to a co-stimulatory signal determinant (CD28 or CD137) and a cytokine domain.[47,48] The activities of T cells are boosted by pre-treating patients with intermediate dose of chemotherapy (cyclophosphamide, fludarabine or bendamustine) 4 days before CAR-T cell infusion. This effect is due to increase in IL-15 and growth factor associated with pre-chemotherapy.[48] A study of CAR-T cell therapy in 14 double relapsed or refractory FL showed an impressive response (Table 4).[49] However, 18% and 11% of patients developed severe cytokine release syndrome and serious encephalopathy respectively. A patient with severe cytokine release syndrome responded to tocilizumab an anti-IL-6 antibody while the neurotoxic events were self-limiting, but for one that was fatal.[49] Recovery of B cells, IgG, IgM and IgA took place within 6 to 18months. The patients that failed to respond had either increased immune check point ligands (PD-L1, PD1, LAG3, TIM3) or loss of CD19 on tumour cells.[49] Therefore, Trials involving immune check point inhibitors administered within 3 months of CAR-T cells are in progress. The authors therefore recommended CAR-T cell trial in patients that are refractory or relapse within 6 months of a second line immune- chemotherapy or after an autologous stem cell transplant.[49]

Early Relapse, but Rituximab Sensitive:
Some patients relapsed after six months of stopping rituximab, but within two years of treatment. This is a likely scenario in resource poor centres due to inability to complete rituximab maintenance for financial reasons. This subset will respond to rituximab, but may be resistant to the first line chemotherapy. Going by the ESMO and NCCN guidelines, the options are: rituximab plus an alternative chemotherapy or radio-immunotherapy.[9,14]

TABLE 4: Clinical Trials in Early Relapse or Refractory Follicular Lymphoma

Intervention	**Trial**	**Sample Size**	**Control**	**OR (%)**	**CR (%)**	**PFS (%)**	**OS (%)**	**AE (%)**
Obin + bend	2014 Gadolin	194/202	Bend	78.7 vs 74.7 MRD-82 vs 43	15.5 vs 18,7	NR vs 14.9 mth	NR	Neutr- 33 vs 26 IRR-11.3 vs 6 (Cost 108,571 Euros)
Obin +CHOP	2013 Gaudi	28 vs 28	Obin +FC	96 vs 93	39 vs 50			68 vs 82
Obin	2015 Gauss	74 vs 74	Ritux	66.2 vs 64	49.1 vs 22.7	17.6 vs 25.4 mth		11 vs 5
Obin + chemo	2017 Gallium	601/601	Ritux +chemo	88.5 vs 86.5		80 vs 73.3		74.6 vs 67.8
^{90}Y-Ibritum omab tiuxetan	2002	143	Ritux	80/56	30/ 16	15mth vs 10mth		35 Grd4 neutr
Ibritum omab	2002 Ritux. Refr	57		74	15	6.8 mths		35 Grd 4 neutr
Inotuz	2016	81		67	31	12.7 mths	NR	58
Inotuz	2009	38		87		23.6 mth		48
Polatuz + Ritux	2014 Romulus	20/21	Pinatu+ Ritux	70 vs 62	40 vs 10			36/43
ASCT <2yrs	2018	175 vs 174	no ASCT				67 vs 60	
ASCT <1 yr	2018	123	no ASCT				73 vs 60	
CAR-T (19) cell		14			71.4	At 29 mth 89		29
Blinatu zumab		15		80	40	>20 mths 40		

Obin: obinutuzumab; bend:bendamustine; MRD: minimal residual disease; NR: not reached; Neutr: neutropenia; IRR: infusion related reaction; Ritux: rituximab; mth: month; Chemo: chemotherapy; Grd: grade; Inotuz: inotuzumab; polatuz: polatumumab; pinatu: pinatuzumab; CHOP: cyclophosphamide, doxorubicin, oncovin, prednisolone; FC: fludarabine, cyclophosphamide

The StiL-2 trial compared the alternative non-alkylating chemotherapy combinations i.e. R-Bendamustine with R-Fludarabine in relapse Fl setting. The ORR were 82% vs 51%; median PFS were 34.2 months vs 11.7 months; OS were 109.7 months vs 49.1 months in RB and RF respectively.[50] Fludarabine combination, therefore has an inferior activity with higher toxicity and propensity for myelodysplasia.

Late Relapse:
Patients that relapse after 2-3 years of first line therapy will respond to the first line immunochemotherapy. Therefore, the first line combination may be repeated with maintenance immunotherapy (i.e. rituximab) as recommended by NCCN and ESMO guidelines.[9,14] Responding young and fit patients may benefit from ASCT.[9,14] However, 60% may be rituximab resistant and will thereby require alternative immunotherapy with obinutuzumab plus alternative chemotherapy followed by maintenance immunotherapy ± ASCT in young and fit patients.[9,14]

Multiple Relapse and Refractory Disease:
NCCN recommends the use of High Dose Therapy (HDT) plus ASCT in 2ND relapsed/refractory FL in post-rituximab era.[14] Randomized Stem Cell Transplant trials had accrual shortcomings. Therefore, evidence is limited to retrospective analysis by NCCN and Center for International Bone Marrow Transplant Research (CIBMTR) that compared ASCT with Allogeneic Stem Cell Transplantation (Allo-SCT). They showed that ASCT has higher OS while Allo-SCT is associated with higher non-relapse mortality (NRM), but a lower relapse rate (Table 4).[51-53] ASCT is, therefore, preferred to Allo-SCT after 2nd relapse. Introduction of reduced intensity conditioning (RIC) and improved transplant care are expected to reduce the NRM, improve OS in Allo-SCT as a result of graft versus lymphoma effect and make Allo-SCT available to older patients.[52] Allo-SCT has the advantage of reduced haematological malignancies, improved PFS and OS after 2 years of transplant (achieving a plateau after 2-3 years).[52] Allo-SCT may therefore be an option in relapse post ASCT, where peripheral stem cell collection is difficult or in heavily chemotherapy treated patients. In a multivariate Cox regression analysis, age >60 years and number of prior therapies >3 were significant risk factors for Event Free Survival (EFS) and OS in auto-SCT patients, whereas age >50 years and resistant disease emerged as prognostic factors in the allo-SCT cohort.[51] In the CIBMTR analysis, performance status was an additional prognostic factor.[52] Hence SCT is better introduced after a second relapse, at age below 50 years, after good response to immune-chemotherapy and in patients with good performance status.

Multiply relapsed FL patients are characterized by: old age, accumulated organ dysfunctions due to repeated chemotherapy, increased risk of myelodysplasia/leukaemia and resistance to immuno-chemotherapy. These make most patients ineligible for SCT. Therefore, novel drugs targeting cell survival and proliferative pathways have been tried in combination with immunotherapy or other targeted small molecules to avoid repeated chemotherapy. The target drugs are: drugs targeting the phosphatidyl inositol-3 kinase and its downstream pathways like AKT pathway, NFkB signal and mammalian target of rapamycin (mTOR) i.e. idelalisib, duvelisib, copanlisib, temsirolimus; drugs targeting the Bruton tyrosine kinase pathway like ibrutinib; drugs targeting the BCL2 anti-apoptotic pathway like venetoclax; drugs targeting the 20S proteolytic core unit of 26S proteasome e.g. bortezomib and carfizomib; drugs targeting the microenvironment like lenalidomide or PD-1 pathway; histone deacetylase inhibitors like vorinostat and abexinostat; histone methyl transferase related inhibitor of EZH2 like tazemetostat and drugs targeting the T regulatory cells.[54-65]

TABLE 5: Targeted therapy in multiply relapsed/refractory FL

DRUG	**YEAR**	**SAMPLE SIZE**	**CR (%)**	**ORR (%)**	**PFS (%)**	**OS (%)**	**AE** Neutr- **(%)**
Idelalisib	2017	72	13.9	55.6	11.2 mths	NR	22
Copanlisib	CHRONOS1	104	14.4	58.7			26
Duvelisib	DYNAMO 2017	83		41	8.3	11.1	
Lenalidomide plus ritux vs lenalidomideor rituximab	ALLIANCE TRIAL	46 vs 45	39 vs 20	76 vs 53	24 mths vs 11mths		20 vs 16
Len + ritux vs Ritux	AUGMENT 2018	295	44 vs NA	78 vs 53	39.4mths vs 14.1 mths	95 vs 86(2yr)	8 vs 4
Len + obinut	GALEN 2017	86	44.2	74.4	75.5 (1yr)	8.8 (1yr)	28.4
Len + ritux	MAGNIFY 2017	117	36	67	66 (1 yr)		NA
Bortezomib + ritux vs ritux	Coiffier et al in LYMPH 3001 Study	676	25 vs 18	63 vs 49	12.8 mths vs 11mths		11 vs 4
Ibrutinib	CONSORTIUM TRIAL	40	2.5	30	9.9mths		8

Len: lenalidomide; ritux: rituximab; obinut: obinutuxumab; NR: not reached: NA: not available; neutr: neutropenia

The activities of monotherapy with these agents in relapsed/refractory FL are modest, therefore, phase II/III trials using these agents in combination with immunotherapy in relapsed/refractory cases or as first line choices are in progress (Table 5).

Idelalisib, an oral inhibitor of the delta isotype of PI3K, has an impressive ORR of 55% and CR of 6% as a single agent in a phase II clinical trial but the median PFS is short at 11 months.[54,55] Given at 150mg twice daily, significant adverse events such as severe infections, pneumonitis, transaminitis and gastroenteritis are drawbacks. Moreover, trials using combinations with immune-chemotherapy have been associated with fatalities. However as single agent, Idelalisib is recommended in multiply relapsed/refractory FL with a proviso that prophylaxis for cytomegalovirus and *Pneumocystis Jiroveci* are provided and patients are monitored closely for early detection of other infections or immunological reactions so as to treat and reduce dosage or suspend treatment early.[55,56] Copanlisib, an intravenous inhibitor of the alpha and delta isotypes of PI3K, has similar activity in relapsed /refractory FL (ORR-59%; CR-14%) with reduced toxicity at a dose of 60mg on days 1, 8, 15 of a 28 day cycle as evidenced by the phase II/III CHRONOS trial (Table 5).[57,58] The major adverse events

observed were diabetes and hypertension, while others were diarrhea and leucopenia.[57,58] Therefore blood sugar and blood pressure should be controlled before the commencement of therapy and concomitant administration of strong CYP3A inhibitors or inducers is discouraged.

Lenalidomide is an oral immunomodulator that down regulates growth promoting factors like tumor necrosis factor alpha (TNF-α), IL-6, IL-4, epidermal growth factor and it activates T cell cytotoxicity and natural killer cells by enhancing immune synapse and reduction of T-regulatory cell activities. It exerts an antiproliferative effect by binding to cereblon, an E3 ubiquitin ligase, to downregulate interferon regulatory factor 4 (IRF4), myc oncogene and increases P21 expression while its anti-angiogenetic effect is mediated via depletion of macrophages and monocytes lymphangiogenesis.[59] In combination with either rituximab or obinutuzumab, lenalidomide demonstrated ORR ranging between 67% and 78% with complete response varying from 36% to 44% in four phase II/III clinical trials (Table 5).[60-63] Major adverse events observed at a dose of 20mg daily for 21days in a 28 day cycle for 12 cycles in these trials were neutropenia and thrombocytopenia (8% to 28%).[61,62] Combination with rituximab is undergoing trial as first line therapy (RELEVANCE Trial) and this may be utilized in elderly patients in future.[63]

Another targeted agent that has shown promising result in phase II/III trial is the combination of Bortezomib and Rituximab in multiply relapsed FL with an ORR of 63% (Table 5).[64,65] Bortezomib binds reversibly to inhibit proteasome-ubiquitin degradation of cellular proteins/enzymes thus modulating cell cycle, nuclear factor-kappa B activities and apoptotic enzymes in favor of inhibition of proliferation and tissue growth.[64,65] Other phase II studies combining bortezomib with chemoimmunotherapies (R-CVP, RCHOP, RB) were done based on the impression that a proteasome inhibitor would increase CD20 expression and increase apoptosis induced by chemotherapy. However, the modest improvements in ORR and CR rates were overshadowed by high grade 3-4 adverse events (neuropathy, neutropenia and thrombocytopenia), though, a weekly dose was associated with fewer adverse events.[64,65]

CONCLUSION

The favorable prognosis observed in follicular lymphoma is sublimed by its refractory nature and recurrent relapse of the disease. Unfortunately, means of identifying this group at diagnosis are not yet validated despite increase in knowledge of the disease biology. In resource limited settings, emerging treatment options are either not available or beyond the budget of the patients. Randomized clinical trials using available and affordable novel drugs are desirable.

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Authors' Contributions:
All authors participated in the review of selected articles and final editing, while DAO lead in the conceptualization and writing of the first draft.

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