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Follicular lymphoma: the diminishing role of chemotherapy

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Abstract

Follicular lymphoma (FL) is the most common indolent non-Hodgkin lymphoma, accounting for 70% of cases in Western countries. Despite this unique name, FL is an extremely heterogeneous disease, both clinically and biologically. The basis of FL heterogeneity lies in the different biological pathways which can be activated, because of the variety of gene mutations that can occur. Today, there is a growing interest in the knowledge of these activated pathways, which is also testified by the presence of a new model that incorporates FL mutations to define patient's prognosis (m7-FLIPI). These evaluations are also appealing because of the recent possibility of using "targeted therapies". Targeted therapies are new tools, currently applicable in the setting of relapse/refractory (R/R) disease, where we can find a great variety of "chemo-free" combinations. As in other hematologic malignancies, "cellular therapy" enriches FL drug scenario, including T-cell dependent bispecific antibodies and chimeric antigen receptor (CAR) T-cell. Since FL heterogeneity is the basis of the difference in therapeutic efficacy and disease course among patients, the hope for the future is to understand FL biology more deeply, to better comprehend how to obtain more representative samples and pre-treatment prognostic information in order to individualize the treatment strategy as early as frontline therapy.

Keywords: Follicular lymphoma, POD24, target therapies, chemo-immunotherapy, biological heterogeneity



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INTRODUCTION

Follicular lymphoma (FL) is the most common indolent non-Hodgkin lymphoma, accounting for 70% of cases in Western countries^[1]. Median age at presentation is 65 years old^[2] and the disease course is typically made of remissions (even spontaneous ones in 5%-10% of cases^[3]) but multiple relapses over time. Patients typically present with painless lymphadenopathies, reported to have slowly enlarged over a few weeks or months. Bone marrow involvement is present in about 70% of patients at diagnosis, whereas B symptoms characterize only 20% of them^[1]. Sometimes the presentation is aggressive, because lymphadenopathies are already bulky at diagnosis, determining consequences due to organ compression or infiltration in the chest or the abdomen.

In this paper, we highlight the main features of FL heterogeneity and emphasize how this biological heterogeneity could be connected to a different clinical behavior. If we start to look at FL in this way, nothing will appear more obsolete than using the same treatment, without distinctions, in all the patients.

FOLLICULAR LYMPHOMA: A BIOLOGICALLY HETEROGENEOUS DISEASE

Despite the presence of a unique name, FL is an extremely heterogeneous disease, both clinically and biologically. In fact, it is characterized by a wide range of clinical presentations, with a very well-known possibility of transformation into diffuse large B-cell lymphoma (DLBCL) in 2% of cases/year^[1]. The basis of FL heterogeneity lies in the different biological pathways which can be activated in this disease, and it is partly, but not fully, captured by the histologic classification into Grades I-III, each associated with increasing aggressiveness in the disease behavior^[1,4,5].

In the last years, significant improvements have been made in our understanding of FL biology. A multistep pathogenesis and the crosstalk between FL cells and tumor microenvironment (TME) are emerging as crucial steps of disease evolution. FL cells represent the malignant counterparts of normal germinal center (GC) B cells: they are CD10 and BCL6+ and they show ongoing processes of class-switch recombination and somatic hypermutation^[6,7]. The t(14;18) (q32;q21) translocation is considered the genetic hallmark and founding lesion in FL, occurring in more than 85% of patients. It results in B-cell lymphoma 2 (BCL2) constitutive overexpression and therefore protection of lymphocytes from apoptosis^[8]. However, the presence of t(14;18) alone is insufficient for lymphomagenesis. In fact, healthy adult individuals can display mono- or oligo-clonal t(14;18)-positive B cells in peripheral blood, without having FL diagnosis^[9]. These cells are thought to represent a pre-malignant pool of “FL-like cells” (FLLCs). Although it is not clearly understood which cases subsequently progress into FL, it is postulated that FLLCs go through secondary lymphoid tissue GCs repeatedly, acquiring additional genomic aberrations, while evading apoptosis, via BCL2 constitutive expression^[10].

Genetic profiles of FL tumors can evolve longitudinally over the disease course, explaining the dramatic changes in disease clinical behavior, but also spatially, at different sites of involvement in the same moment. *Araf and colleagues* demonstrated that, in a single patient, samples coming from different involved lymph nodes could express different gene mutations^[11]. This heterogeneity increases as FL progresses from Grade I-II to Grade 3 and more and more as it transforms into DLBCL^[11-13].

In this “heterogeneity context”, there are mutations other than Bcl-2 that occur early in FL history, such as those affecting epigenetic regulation. Epigenetic mutations typically occur on histone post-translational modifying genes, including cAMP response element-binding protein binding protein (CREBBP), histone-lysine N-methyltransferase 2D (KMT2D), enhancer of zeste homologue 2 (EZH2), and E1A binding protein P300 (EP300)^[13-15]. KMT2D^[16,17] and CREBBP^[18] are the most commonly mutated genes (70%-80% of

patients), whereas EZH2 and EP300 are involved in 25% and 15% of cases, respectively^[19]. The sum of loss of function mutations affecting KMT2D, CREBBP, and EP300, together with EZH2 gain of function mutations, are transcriptionally repressive, leading to lymphoma development via GC cells proliferation, impairment differentiation, and immune evasion with major histocompatibility complex (MHC) downregulation^[20]. Since most FL carry multiple epigenetic lesions, mutation timing, type, and degree become important variables that can help us understand the clinical heterogeneity of FL patients. Furthermore, other pathways can be disrupted, including immune recognition, nuclear factor κB, mammalian target of rapamycin (mTOR), and Janus-kinase signal transducers and activators of transcription (JAK-STAT) signaling: these alterations concur, together with epigenetic mutations, to lymphomagenesis. In addition to genetic changes, TME is the other leading actor in FL pathophysiology, as the pabulum of non-neoplastic cells determinate the immune response suppression and facilitate tumor cells' growth^[21].

Beside the longitudinal genetic heterogeneity, another layer of complexity is our understanding of the existence of spatial genetic heterogeneity within a single patient at different disease sites, posing challenges for precision medicine approaches. A relatively recent method consists in detecting circulating tumor cells (CTCs) and circulating cell-free DNA (cfDNA) in the patient's peripheral blood through polymerase chain reaction. This allows for an extensive studying of the lymphoma's genetic characteristics and for the monitoring of its spatial and temporal heterogeneity without the need for repeated invasive biopsies^[7,22]. This knowledge is important, as some mutations are now included in prognostic models, such as EZH2 and EP300 that are integrated into the m7-FLIPI score (FL International Prognostic Index), and can be easily missed with a single sample^[23]. Furthermore, in the near future, increasingly free from chemotherapy, the failure to detect the corresponding predictive biomarker in a tumor biopsy could prevent some patients from receiving specific targeted therapies. In this setting, the early identification of patients with high-risk biology becomes necessary for guiding treatment selection and sequencing.

PROGNOSTIC MODELS IN FOLLICULAR LYMPHOMA: ARE WE READY TO IDENTIFY THE POOREST RISK SUBSET OF PATIENTS?

Several interesting models have been developed to predict progression-free survival (PFS) and overall survival (OS) of FL patients. FLIPI, built in the pre-rituximab era, and FLIPI2, developed when chemo-immunotherapy had become the standard for first-line treatment, both include an evaluation of tumor burden in terms of Ann Arbor stage, number of nodal sites, lymph node size, and lactatedehydrogenase (LDH)^[24,25]. Recently, *Batlevi and colleagues* identified the increased FLIPI-score between diagnosis and first-line treatment as markers of high-risk biology in FL patients. In particular, patients whose FLIPI increased during observation time had inferior PFS and OS^[26].

A new model, where gene mutations are included for the first time to predict failure-free survival, is m7-FLIPI. It was validated in over 100 patients, and it considers FLIPI score, *Eastern Cooperative Group* performance status (PS), and the mutational status of seven genes (EZH2, ARID1A, MEF2B, EP300, FOXO1, CREBBP, and CARD11) to predict a subset of patients at high risk of treatment failure. Particularly, it divides a low-risk group (78% of patients) with a five-year failure-free survival of 68% versus 25% in a high-risk group (22% of patients)^[23]. The high-risk m7-FLIPI is enriched in those patients with recurrence or progression of disease within 24 months of frontline treatment (POD24 positive patients),^[23] introducing the concept of early relapse as poor prognostic factor. More recent studies have highlighted the role of 23 genes involved in DNA response pathways, immune regulation, cell cycle, and cell migration pathways as well as tumor microenvironmental components as independent predictors of PFS status at 24 months and POD24 in FL patients^[27].

POD24 is nowadays a very appealing tool, and it is considered the most important prognostic factor. A study by *Casulo and colleagues*, considering patients treated in first line with R-CHOP regimen (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone), demonstrated that POD24-positive patients have shorter OS (five-year OS of 34%-50% vs. 93%) and higher risk of histologic transformation compared to those without early disease recurrence^[28]. POD24 is thus able to identify a small subset of FL patients (around 20%) at very high risk, who might be candidate for intensive treatment strategies at first relapse^[28-32].

A recent pooled analysis of 13 randomized clinical trials of patients in both pre- and post-rituximab era identified male gender, poor PS, high FLIPI score, and elevated baseline B2M as predictors of early progression or death^[32]. It is also increasingly evident that the impact of an early relapse or progression is greater in patients treated in first line with chemo-immunotherapy than in those treated with rituximab or observation only^[32,33]. Moreover, there is growing evidence about the importance of metabolic response - evaluated by positron emission tomography (PET) scan - at the end of induction therapy. Particularly, as demonstrated in a secondary analysis in the PRIMA and GALLIUM studies, 2.5-year PFS is 87% in complete metabolic responders and 55% in non-complete metabolic responders^[34,35].

Despite being largely used to this day, neither of the existing pre-treatment prognostic indices is able to reliably identify those highest risk patients who will relapse within two years of frontline chemo-immunotherapy^[36]. Current staging methods, i.e., PET and computed tomography (CT) scans, can provide the functional and anatomical data necessary to determine the viable portion of the tumor mass [total metabolic tumor volume (TMTV)], which has already emerged as an interesting tool in baseline evaluation of other types of lymphoma^[36]. *Meignan and colleagues* recently demonstrated its strong independent predictive value in FL: patients with a high TMTV > 510 cm³ had significantly inferior five-year PFS and a median PFS of three years, compared to median PFS of six years in patients with TMTV below that level^[36]. *Delfau-Larue and colleagues* explored the connection between the metabolic and the circulating tumor burden in untreated FL through evaluation of TMTV, obtained from PET/CT scans, and either the number of CTCs or the plasmatic cell-free tumor DNA obtained from peripheral blood. The cutoff for high TMTV in this study was confirmed at 510 cm³, whereas a high load of cfDNA was defined as >2500 Eqg/mL of plasma. The combination of these biomarkers allowed for the identification of a very good prognosis subgroup (TMTV < 510 cm³ + cfDNA < 2500 Eqg/mL) with 94% four-year PFS, and a poor prognosis subgroup with four-year PFS of 65% (TMTV > 510 cm³ + cfDNA > 2500 Eqg/mL)^[22].

The authors suggested that TMTV and cfDNA should not replace the more traditional prognostic tools, such as FLIPI2 and metabolic response at the end of treatment, but will probably be helpful in refining the existing scores^[22,36].

For sure, understanding the clinical and biological features of high-risk FL patients is necessary to improve their therapeutic sequence and allow the use of novel therapies earlier in their therapeutic path.

FRONTLINE STRATEGIES IN FOLLICULAR LYMPHOMA PATIENTS

Early stage (I/II) FL represents a rare occurrence, consisting in less than 10% of all FL patients. In this population, first-line treatment is involved field radiotherapy (IF-RT), which can induce long lasting remissions with prolonged OS^[37]. At our Institution, we perform four courses of rituximab (375 mg/m², once a week) followed by IF-RT in Stage I/II FL. The aim of rituximab addiction is to eventually treat undetectable disease and thus prevent relapses in different sites. Moreover, this approach provided good PFS in a study considering this specific population, without additional toxicity^[38].

Most FL patients have advanced-stage disease, but these patients do not all require therapy immediately after diagnosis. Today, the most used criteria to decide when therapy is needed are the GELF criteria (*Groupe d'Etude des Lymphomes Folliculaires*), based on a large study resulting in no significant OS difference with the “wait and see” strategy vs. treatment upfront^[39]. For some researchers, the “watch and wait” attitude is questionable in the rituximab era^[40], but, as no conclusive evidence is available, we prefer to reserve therapy for when it is really needed.

When it is time to start first-line treatment, the road traveled generally consists of chemo-immunotherapy, which is almost worldwide the standard of care. The alkylating agent bendamustine, in combination with rituximab (BR), remains the first choice, considering its superiority in terms of PFS and complete response (CR) rates over R-CHOP/R-CVP (rituximab, cyclophosphamide, and prednisone)^[41-43]. In those patients who obtained at least a partial response after a frontline rituximab containing regimen, 24 months of rituximab maintenance prolongs the time to disease progression, although no improvement in OS has been demonstrated^[44].

In the phase III GALLIUM study, obinutuzumab, a Type II anti-CD20 monoclonal antibody, whose Fc region is defucosylated in order to have greater affinity for receptors FcRIIIa on effector cells and increased antibody-dependent cell-mediated cytotoxicity (ADCC), was combined with chemotherapy^[45]. The association was compared to rituximab-based chemo-immunotherapy. A longer PFS was seen with obinutuzumab than with rituximab (estimated three-year PFS: 80% vs. 73.3%), although no statistical differences were observed in terms of CR and OS rates^[45]. The obinutuzumab plus chemotherapy combination resulted in a higher rate of adverse events (AEs) in comparison to the rituximab arm. In particular, the obinutuzumab - CHOP association was characterized by Grade > 3 cytopenia, while the association with bendamustine led to a higher rate of Grade > 3 infections and deaths^[45]. For this reason, we prefer not to associate obinutuzumab with bendamustine, and we believe that this combination must be used with caution. In frontline setting, we reserve obinutuzumab treatment for those patients in whom we can choose CHOP as the chemotherapy backbone, such as young, fit patients with intermediate- to high-risk disease, as per FLIPI score.

In the last decades, following the development of novel immunotherapies and targeted agents, a chemotherapy-free approach has been explored, initially for relapsed/refractory patients but also in the frontline setting.

Other attempts to spare chemotherapy to FL patients at diagnosis have included using frontline epratuzumab combined with rituximab. Epratuzumab is a humanized monoclonal IgG1 antibody targeting the B cell = specific transmembrane phosphoglycoprotein CD22. The drug showed significant activity both as a single agent and in combination with rituximab in heavily pre-treated FL patients^[46-48]. A phase II study by *Grant and colleagues* published in 2013 demonstrated the efficacy of its association with rituximab even in the frontline setting (CALGB 50701), with 88% overall response rate (ORR) and 42.4% complete response rate (CRR). After a three-year follow-up, PFS was 60%^[49].

Although the RELEVANCE study failed to reach its first endpoint, demonstrating a comparable clinical efficacy of rituximab-lenalidomide compared to standard R-chemotherapy, it showed the safety and efficacy of immunomodulating agents also in the first-line setting, paving the way to chemo-free regimens in FL patients at frontline^[50].

At present, a phase II study (GALEN) is evaluating the efficacy and safety of lenalidomide plus obinutuzumab in previously untreated advanced FL patients, with promising preliminary results as the combination yields an ORR of 94% and a CR of 80%; three-year PFS is 82%^[51].

Some attempts are also ongoing to explore the possibility of a risk-adapted approach based on metabolic response or minimal residual disease (MRD) at the end of induction therapy. The Italian FOLL12 study (NCT02063685), for example, compares a standard rituximab-maintenance arm to a PET- and MRD-based approach, dividing patients into three groups: MRD-negative, PET-negative patients, who will be observed; MRD-positive, PET-negative patients, who will receive rituximab maintenance; and MRD-positive, PET-positive patients who will undergo consolidative radioimmunotherapy (RIT) with ⁹⁰Y ibritumumab tiuxetan and rituximab maintenance^[52].

TREATMENT OF RELAPSED/REFRACTORY FOLLICULAR LYMPHOMA PATIENTS: A PATH TOWARDS NOVEL AND CHEMO-FREE REGIMENS

When to use high dose salvage chemotherapy and autologous stem cell transplantation

Although the majority of FL patients respond well to rituximab-containing frontline chemo-immunotherapy, the disease course is inevitably punctuated by subsequent relapses and most patients need multiple lines of treatment. Moreover, the duration of remission tends to decrease with each successive line of therapy. As already discussed, one of the main prognostic indicators for relapsed patients is time to disease progression: about 20% of patients are POD24-positive, and this has been proven to be the strongest independent risk factor for poor survival thus far^[29,32].

Patients who relapse after the first two years of first-line treatment (POD24-negative patients) do not necessarily require immediate treatment and clinicians can apply the same criteria used for patients with newly diagnosed diseases^[53]. Those who do not meet the GELF criteria, in other words, patients with low tumor burden and asymptomatic disease, can initially be managed by a watchful waiting approach^[53]. In the case of symptomatic, localized disease, low-dose radiotherapy can be a valid option, whereas cases presenting with symptomatic, low tumor burden systemic disease can be addressed with single-agent rituximab^[53]. Moreover, clinicians should always be aware of the possibility that FL transforms into an aggressive form of lymphoma. It is therefore strongly recommended, whenever possible, to obtain histologic confirmation of the diagnosis before starting salvage treatment, since aggressive B-cell lymphomas must be treated accordingly.

As previously said, POD24-positive patients are believed to have a biologically distinct disease, characterized by clinical and genetic factors that confer resistance to standard chemo-immunotherapy^[29,32]. No specific treatment approach is currently recommended for this population, although some clinical trials are ongoing to address the role of novel therapies in this setting.

Young patients (under 65 years) with a good PS should be considered for high-dose chemotherapy (HDT) followed by consolidative autologous stem-cell transplantation (ASCT). This approach can yield prolonged remissions in a subset of patients, provided they respond to salvage chemotherapy, and its survival benefit seems to be greater within one year of treatment failure^[54]. *Casulo and colleagues* recently reported a 73% five-year OS for patients receiving ASCT in this setting compared to those treated otherwise (five-year OS: 60%). Similar results were also obtained by a German group (77% vs. 46%)^[30,31]. Overall, available data (largely retrospective in nature) suggest that patients with early treatment failure that achieve a second CR (or a first CR following a salvage regimen) with HDT benefit from ASCT in terms of both PFS and OS.

Older patients and people with comorbidities that contraindicate ASCT should, whenever possible, be enrolled in clinical trials. Alternatively, a different, non-cross-resistant chemotherapy schedule can be employed, such as bendamustine in those previously treated with an anthracycline-containing regimen. Single-agent bendamustine can achieve ORR of approximately 75%-80% in this setting, but with disappointing median PFS of 7-9 months^[55]. The bendamustine-rituximab association, on the other hand, showed a similar ORR of approximately 74% in the phase II study by *Rueda and colleagues*, with a 48% CRR and five-year PFS of 40%^[56]. Some patients, however, present with disease progression within six months of completing a rituximab-containing frontline treatment (rituximab-refractory patients). Obinutuzumab has shown activity in relapsed FL patients, both as a single agent and in association with chemotherapy^[57-59]. The Gadolin study, in particular, demonstrated the superiority of the obinutuzumab-bendamustine regimen compared to bendamustine alone in rituximab-refractory FL patients, with ORR of 69% and median PFS not reached after a median follow-up time of 21.9 months (vs. 14.9 months in the bendamustine arm)^[59]. The updated analysis published in 2018 also demonstrated a significant OS benefit^[60]. These results led to the approval of the obinutuzumab-bendamustine regimen for the treatment of this subgroup of patients. The association can therefore be considered a suitable second-line option for ASCT-ineligible patients with FL who received CHOP-like chemotherapy and rituximab as a frontline therapy.

In recent years, the introduction of multiple novel agents has transformed our approach to relapsed-refractory FL, progressively confining chemotherapy to the earliest phases of the disease course. The treatment of multiple-relapsed FL is now largely chemo-free and based on several effective biological agents.

Chemo-free strategies for relapsed/refractory follicular lymphoma patients

Despite the prolonged PFS and OS achieved with chemo-immunotherapy, it has by now been established that hardly any patient with FL can be cured through this approach. New therapeutic strategies are therefore being pursued, which should not only be able to increase the patients' life expectancy but also minimize toxicity, ensuring them a good quality of life. The long-term side effects of frontline chemotherapy are also a concern, which is why many efforts are being made to find adequate alternatives; the most significant advances, however, can be seen in the setting of relapsed and refractory patients, where many novel targeted and immunomodulatory agents are being tested.

Monoclonal antibodies

The radical change that rituximab brought to the management of NHL led to the development of various other monoclonal antibodies (mAb) targeting different antigens. We discussed the anti-CD22 epratuzumab previously^[46-49]. Galiximab is a chimeric anti-CD80 mAb whose linking to the costimulatory molecule CD80 on the surface of B lymphocytes inhibits cell proliferation, upregulates proapoptotic molecules, and induces ADCC. The drug showed a favorable safety profile in pre-treated FL patients, with modest single-agent activity (ORR 11%)^[61] but good efficacy when associated with rituximab (ORR of 63% with a median PFS of 11.7 months)^[62]. Seen these promising results, the combination of rituximab plus galiximab was also explored in the frontline setting (CALGB 50402), obtaining a 72% ORR and 41% CRR in 61 previously untreated FL patients. Notably, the trial showed that FLIPI score correlated with response and PFS: low-risk patients had a 92% ORR, 75% CRR, and three-year PFS of 75%^[63].

Interestingly, a retrospective pooled analysis of patients enrolled in three phase II trials evaluating the aforementioned frontline chemo-free regimens (CALGB 50402, CALGB 50701, and CALGB 50803) confirmed the adverse prognostic role of POD24 even in this setting, stressing the need for early identification of higher risk patients^[64].

Tafasitamab is another mAb, recently developed for targeting the B-lymphocyte antigen CD19. This surface antigen is broadly expressed during B-cell development, highly preserved across most B-cell malignancies, and still detectable in relapsed diseases. Tafasitamab monotherapy showed encouraging results in a phase IIa study published in 2018, where 29% of the participating R/R FL patients obtained an objective response (CRR 9%); median PFS in this cohort was 8.8 months at a median follow-up of 21 months^[65]. Considering these results, several clinical trials are now ongoing to evaluate the efficacy of tafasitamab in combination with other target drugs such as lenalidomide (NCT04680052) and the phosphatidylinositol 3-kinase (PI3K δ) inhibitor piasclisib (NCT04809467).

Radioimmunotherapy

Given the high radiosensitivity of FL cells, combined with the constant and intense expression of CD20 on their surface, anti-CD20 RIT drugs have been developed for treatment of relapsed patients. ⁹⁰Y ibritumomab tiuxetan, in particular, was associated with high ORR of approximately 80% after a single administration and 12-month PFS. Patients obtaining a CR tend to have longer PFS, lasting up to four years in around 30% of cases^[66]. The drug received Food and Drug Administration (FDA) and Italian medicine agency (Agenzia Italiana del Farmaco, AIFA) approval for consolidation of CR in FL patients after first-line therapy and for the treatment of FL that is R/R after rituximab. Nevertheless, the use of RIT is limited by adequate bone marrow cellularity and reduced bone marrow infiltration by lymphoma.

Lenalidomide

The immunomodulatory agent (imid) lenalidomide acts through a variety of mechanisms; in vitro studies demonstrated its ability to synergize with rituximab through enhancement of ADCC^[67]. This led to the hypothesis of the possibility to overcome rituximab-refractoriness by combining the anti-CD20 monoclonal antibody with lenalidomide. The phase II study published by Chong *et al.* in 2015 demonstrated the efficacy of lenalidomide both as monotherapy and in combination with rituximab (R²), with an ORR of 63% and PFS of 24 months for responders^[68]. Shortly after, Leonard and colleagues published the results of a randomized multicenter trial (Alliance) demonstrating the superiority of R² compared with lenalidomide single agent (ORR 76% vs. 53%, CRR 20% vs. 39%); median time to progression (TTP) was significantly longer for the R² arm than lenalidomide alone (2 vs. 1.1 years)^[69]. In 2019, the results of the Augment trial showed that R² was also associated with a statistically significant improvement in ORR and PFS (39.4% vs. 14.1%) compared with rituximab monotherapy^[70], leading to FDA, European Medicine Agency (EMA), and AIFA approval of this combination in the setting of relapsed or refractory FL after at least one previous therapy. The MAGNIFY trial (NCT01996865) is currently exploring the effect on PFS of maintenance with R² vs. rituximab alone after 12 cycles of lenalidomide plus rituximab in patients with indolent NHL, with particular attention on POD24-positive patients.

Moreover, as stated above, a phase III clinical trial (NCT04680052) is testing the efficacy and safety of R² compared to R² plus tafasitamab, a humanized anti-CD19 monoclonal antibody that has already shown promising results as a single agent in R/R FL^[65].

Tazemetostat

Tazemetostat is a first-in-class inhibitor of the enhancer of zeste homolog 2 (EZH2) histone methyltransferase, an enzyme that has a fundamental role in the formation of GCs^[71]. The molecule harbors a mutation in approximately 25% of FL^[19]. The drug blocks both the mutant (mut) and wild-type (wt) forms of EZH2, but the results of the phase II study in which it was evaluated showed better outcomes in EZH2mut patients: ORR was 69% in this population versus 35% in EZH2wt patients, with 13% vs. 4% CRR, respectively. Median PFS was 13.8 months in EZH2mut patients and 11.1 months in the EZHwt group^[71].

Moreover, tazemetostat showed a favorable safety profile in clinical trials. This led the FDA to approve the drug for third-line therapy of patients with EZH2mut FL, as well as for patients with R/R FL with no other satisfactory treatment choice. A few studies are currently evaluating the role of tazemetostat in combination with other agents, namely anti-CD20 mAbs (rituximab, ublituximab, and obinutuzumab), lenalidomide, umbralisib, and atezolizumab, in order to improve the results obtained with its single-agent use. This may lead tazemetostat to gain a prominent role in the landscape of third-line therapy for FL.

PI3K-inhibitors

The PI3K-AKT-mTOR is crucial for the survival, growth, and proliferation of lymphoma cells. In 2014, the first-in-class, orally bioavailable inhibitor of the δ subunit of PI3K δ idelalisib received accelerated FDA approval for the treatment of FL patients relapsing after ≥ 2 lines of therapy. The pivotal trial by Gopal *et al.* showed 57% ORR with 6% CRR in a population of 125 heavily pre-treated patients with indolent lymphomas, among whom 72 (i.e., 58%) had FL^[72]. The median PFS was 11 months and OS at one year was 80%. Two subsequent subgroup post hoc analysis were performed on FL patients and, specifically, on high-risk FL patients who experienced early relapse after initial chemo-immunotherapy^[73,74]. Both investigations reported efficacy and safety results that were consistent with those obtained in the entire study population. In particular, the significant antitumor activity shown by the drug in POD24-positive FL patients warrants the development of prospective studies, in order to optimize the use of PI3K-inhibitors (PI3Ki) in this setting^[74]. However, whereas the first studies reported a favorable toxicity profile, several phase III trials of idelalisib showed relevant safety issues. Idelalisib treatment is mainly associated with immune-mediated AEs (in particular, diarrhea, transaminitis, and pneumonitis), secondary to organ infiltration by dysregulated CD8+ T lymphocytes, and opportunistic infections, especially *Pneumocystis jirovecii* pneumonia (PJP) and human Cytomegalovirus (CMV) reactivation^[75,76]. Therefore, PJP prophylaxis and CMV viremia monitoring are considered mandatory for patients receiving idelalisib^[76]. Since idelalisib approval was based on the results of a phase II trial, continued approval for FL [as well as for small lymphocytic lymphoma (SLL)] depended on the results of confirmatory phase III studies. However, the therapeutic landscape of FL has widely evolved over the last few years and has incorporated novel promising agents, many of which are significantly more manageable than PI3Ki. This has made enrolment in confirmatory studies harder, leading to the company's decision to withdraw the FDA indications of idelalisib for FL and SLL. Duvelisib, an oral dual inhibitor of PI3K δ and γ , suffered the same fate. The drug had been approved by the FDA for the treatment of FL after at least two prior lines of therapy. Approval came after the publication of the DYNAMO phase II study, in which 83 patients with FL obtained an ORR of 42% with a toxicity profile similar to idelalisib^[77].

Coplanlisib is the only PI3Ki that currently maintains FDA indication for FL from the third line of therapy. Copanlisib, an intravenous, pan-class PI3Ki targeting mostly the p110 α and δ isoforms of the enzyme, has been approved by the FDA following a phase II study conducted on 141 NHL patients (104 of them having FL) where it showed an ORR of 59% and CRR of 14%; PFS was 11 months^[78]. The drug displays a peculiar safety profile, mainly characterized by hyperglycemia, hypertension, and skin rash but with lower rates of gastrointestinal toxicities and infections compared to idelalisib^[78]. The intermittent dosing and the i.v. administration, which reduces the gut concentration of the drug and the first-pass metabolism, may partly be responsible for this difference; hyperglycemia, however, seems to be an on-target effect secondary to the p110 α inhibition. Umbralisib is a dual inhibitor of both PI3K δ and casein kinase-1 ϵ ; the drug was investigated in the phase IIb UNITY study, where 117 FL patients obtained a 45% ORR and 5% CRR; median PFS was 10.6 months and median time to next treatment was 4.6 months^[79]. Neutropenia, diarrhea, and transaminase elevation were the most common toxicities, while immune-related events such as non-infectious colitis and pneumonitis were reported very rarely^[79]. In April 2022, TG Therapeutics announced

umbralisib withdrawal for chronic lymphocytic leukemia (CLL), SLL, and for the two other approved indications of FL and marginal zone lymphomas (MZL). The decision was based on the recently updated results of the UNITY-CLL phase III trial, which showed an increasing imbalance in OS in favor of the control arm (obinutuzumab+ chlorambucil) in CLL and SLL. Currently, additional molecules are undergoing clinical evaluation and showing promising results: piasclisib and zandelisib are highly selective and potent inhibitors of the PI3K δ isoform^[80]. The high selectivity for the enzymatic target helps reducing the immune-mediated AEs and the risk for infections, although an attentive monitoring is always required.

Recently, a matching-adjusted indirect comparison was conducted between tazemetostat and idelalisib, duvelisib, copanlisib, and umbralisib. A systematic literature review allowed for the identification of six published trials that were sufficiently comparable in terms of study design and eligibility criteria. Despite the many limitations of such an analysis, after adjusting for baseline population differences, tazemetostat emerged as the safest and most tolerable option with comparable efficacy outcomes^[81].

BTK-inhibitors

The idea of treating FL by blocking the B-cell receptor (BCR) signaling pathway has also been pursued by employing the inhibitors of the Bruton tyrosine kinase (BTK). Ibrutinib, however, has shown unsatisfactory activity in phase II clinical trials, with the DAWN study achieving only 21% ORR and median PFS of five months^[82]. Responses seem to be higher in CARD11WT patients and in those harboring mutations of FOXO1 and KMT2D^[83]. Overall, ibrutinib does not represent an effective strategy for R/R FL. Nevertheless, new generations of highly selective and potent BTK-inhibitors (BTKi) are undergoing evaluation in this setting. Zanubrutinib, for instance, is an irreversible and orally bioavailable BTKi, which proved safe and effective in combination with obinutuzumab in a phase I study^[84]. The trial enrolled a cohort of 36 patients with FL, among whom the ORR was 72% [with 14 cytokine release syndrome (CRS)]; upper respiratory tract infections (39%), contusion (28%), fatigue (25%), and cough (22%) were the most common AEs among FL patients^[84]. A phase II study is currently ongoing comparing zanubrutinib plus obinutuzumab and obinutuzumab monotherapy in R/R FL patients (NCT03332017). Furthermore, a third generation of BTKi has recently been developed with the aim of overcoming the resistance that lymphoproliferative diseases can put up against traditional (irreversible) BTKi. Pirtobrutinib is the first-in-class, orally available non-covalent BTKi, and it is capable of blocking the enzyme even in the presence of epitope alterations such as the C481 mutation^[85]. The BRUIN phase I/II study enrolled 323 patients, including 12 FL patients; among the eight FL patients who were evaluable for efficacy, ORR was 50%^[85]. Pirtobrutinib also displays a 98% selectivity for BTK versus 370 other kinases, reducing the risk for off-target toxicities. The results of the BRUIN study show that the drug is very well tolerated, and no dose-limiting toxicities were registered; the most common AEs were fatigue, diarrhea, and contusion, while the most common Grade ≥ 3 AE was neutropenia^[85]. Overall, both covalent and non-covalent BTKi show great results in the treatment of chronic lymphocytic leukemia (CLL), Waldenstrom macroglobulinemia (WM), and mantle cell lymphoma (MCL), whereas their role in FL remains to be clarified and their use is currently not recommended outside of clinical trials^[86].

Venetoclax

Venetoclax is a BH3-mimetic small molecule that impairs the anti-apoptotic activity of BCL-2, thus restoring apoptosis in lymphoma cells. The drug has largely entered the therapeutic armamentarium of CLL and MCL, where it shows significant antitumor activity with a favorable safety profile both alone and in combination with other agents^[87-89]. Despite being characterized by the overexpression of the antiapoptotic protein BCL-2, FL did not show the expected sensitivity to venetoclax in clinical trials. Among 29 patients with FL enrolled in the phase I trial by Davids *et al.* the ORR was 38% with a CRR of 14%; median PFS was 11 months^[90]. Recent studies have begun to clarify the mechanisms by which PI3K δ -inhibitors interfere with

FL microenvironment, which plays a key role in the pathogenesis of the disease. In particular, these agents increase the dependence of tumor cells on the activity of BCL-2 over different anti-apoptotic proteins: this leads to an improved efficacy of venetoclax in FL preclinical models^[91]. This finding may provide a rationale for investigating the combination of PI3Ki and venetoclax in clinical trials. The recently published Contralto study^[92] explored the safety and efficacy of venetoclax in association with the BR regimen (Arm B), comparing this combination with BR (Arm C) and with the chemo-free arm R-venetoclax (Arm A). While the combination arm showed the highest rates of toxicity, with increased need of dose reductions and treatment interruptions, response rates were similar to Arm C: ORR was 84% and CRR was 75% at primary response assessment (PRA); after one year of follow-up, ORR was 49% and CRR was 43%. The chemo-free R-venetoclax arm, on the other hand, showed only modest anti-lymphoma activity, with ORR of 35% and CRR of 17% at PRA. Notably, most patients in this cohort had received several prior therapy lines and presented high-risk features such as refractoriness to last treatment and advanced stage disease. Responding patients, however, seem to achieve durable remissions: at one-year follow-up, an ORR of 27% was registered, with 19% CRR^[92]. Based on these results, other trials are currently studying the best way to optimize the combination of venetoclax with chemo-immunotherapy; one study in particular is exploring obinutuzumab-bendamustine in association with a non-continuous dosing schedule of venetoclax (NCT03113422).

Antibody-drug conjugated

The last two decades saw the development of another new category of drugs, namely antibody-drug conjugates (ADC), which allow the administration of antineoplastic agents while minimizing their AEs thanks to their targeted mechanism of action. The compounds consist of a monoclonal antibody moiety, responsible for the selective binding to the lymphoma cell, linked to a cytotoxic molecule, which is conveyed directly into the malignant cell.

Studies of ADCs in FL include the anti-CD22 pinatuzumab vedotin and the anti-CD79b polatuzumab vedotin, both harboring as a cytotoxic agent a molecule of monomethyl auristatin E (MMAE)^[93,94]. The ROMULUS study proved that both agents, associated with rituximab, can induce objective responses in pre-treated FL lymphoma patients (ORR 62% for R-pina vs. 70% for R-pola), with significantly higher CRR for R-pola (45% vs. 5% with R-pina). Median PFS was 15 months for patients receiving R-pola^[95]. Several trials have been designed that combine polatuzumab with obinutuzumab and various different agents, such as lenalidomide, venetoclax, and mosunetuzumab, in order to test the potential synergy of these targeted molecules in treating FL.

Loncastuximab tesirine is an anti-CD19 ADC whose cytotoxic molecule is represented by a pyrrolobenzodiazepine dimer. The drug has recently received accelerated FDA approval for the treatment of R/R DLBCL following the results of the LOTIS 2 phase II trial^[96]. The phase I study in which the drug was evaluated included 14 FL patients, who obtained an ORR of 79% with 64% CRR; mDOR was not reached in this cohort^[97]. Ninety-eight percent of patients had at least one treatment-emergent adverse event, which was generally manageable and reversible with dose delays and/or reductions. Hematologic toxicities were common, whereas fatigue was the most common non-hematologic AE (42.6%); other significant toxicities were represented by nausea (32.2%), peripheral edema and effusions (47%), skin- and nail-related alterations (54%, mainly represented by skin rash in sun-exposed areas), and increase of liver enzymes (31%)^[97]. The ongoing LOTIS 6 randomized phase II study (NCT04699461), comparing the efficacy of loncastuximab tesirine with idelalisib in R/R FL, may lead to approval of the ADC in this setting. It remains to be seen, however, whether the recent developments in PI3Ki applications in FL will impair the success of the trial.

CAR T-cell therapy

In the last years, anti-CD19 Chimeric antigen receptor (CAR) T-cell therapy proved to be a valuable addition to the therapeutic armamentarium of R/R acute lymphoblastic leukemia and DLBCL. More recently, this treatment strategy has shown promising results in the setting of indolent B-cell lymphomas. The phase II ZUMA-5 study, for instance, has explored the efficacy and safety of axicabtagene ciloleucel (axi-cel) in R/R FL and MZL. Among 124 patients with FL, 84 were evaluable for efficacy: ORR was 94% with 80% of patients achieving a CR; the 12-month PFS and OS were 74% and 93%, respectively, while median OS was not reached^[98]. The most common AEs related to CAR T-cell therapy, namely CRS and immune effector cell-associated neurotoxicity syndrome (ICANS), were experienced by 77% and 55% of patients, respectively. However, only 6% CRS and 15% ICANS were considered Grade ≥ 3 ^[98]. Based on these results, axi-cel has received FDA approval for the treatment of R/R FL after two or more lines of therapy, adding to its indication for R/R DLBCL. Another phase I/II trial has confirmed the efficacy of anti-CD19 CAR T-cells in FL, testing a second-generation CAR, with 4-1BB co-stimulation and formulated at 1:1 CD4+:CD8+ CAR T-cell ratio^[99]. The study enrolled eight patients with FL, seven of whom responded, all of them obtaining a CR (88%). All responding patients remained in CR for a median follow-up of 24 months, with remissions lasting up to three years after CAR T-cell infusion. No Grade ≥ 3 CRS or ICANS was registered^[99].

Bispecific monoclonal antibodies

In the 1960s, some researchers demonstrated the possibility of combining two different univalent Fab' fragments into a bivalent antibody construct harboring specificity for two different antigens^[100]. Bispecific antibodies (BsAbs) are single polypeptides comprised of two different monospecific antigen-binding regions: one of the binding sites recognizes the neoplastic cell, while the other part binds T or natural killer (NK) cells. The BsAbs employed in B-cell neoplasms generally recognize tumor cells through an anti-CD20 or anti-CD19 binding region, while the other site binds to T-cells through the CD3 surface antigen^[100]. This leads to recruitment, activation, and expansion of T lymphocytes in an MHC-independent way; effector cells can then direct their cytotoxicity against the malignant cells expressing the target antigen. Four CD20/CD3 BsAbs constructs are currently being studied for the treatment of FL: odronextamab, mosunetuzumab, glofitamab, and epcoritamab.

Odronextamab is a first-in-class, intravenously administered, human IgG4-base BsAb. The FL patients enrolled in the phase I study obtained a 93% ORR with 75% CRR; mPFS was 12.8 months^[101]. CRS was one of the most frequent AEs and was reported to be Grade ≥ 3 in 11% of cases. A phase II study is ongoing to confirm the role of odronextamab in NHL, including 112 patients with FL (NCT03888105).

Mosunetuzumab is a fully humanized IgG1 BsAb, which has received FDA breakthrough designation for R/R FL. The drug, which is given intravenously, achieved a 68% ORR with 50% CRR on 62 FL patients treated in a phase I/Ib study. The results were consistent among all high-risk groups. Median DOR and mPFS were 20 and 11.8 months, respectively; among patients obtaining a CR, 74% are still in remission. The safety profile proved to be favorable, with neutropenia as the most common AE, and only 23% of patients experienced CRS (of which only 1.6% were considered to be serious AEs)^[102]. The drug is also being studied in a subcutaneous formulation, which seems to be associated with an even lower rate of relevant AEs, namely Grade 2 CRS and neurologic toxicity^[103]. The results reported by Matasar and colleagues show an 86% ORR with CRR of 29% in the indolent NHL subgroup^[103].

Epcoritamab is a humanized mouse IgG1-based heterodimeric antibody, which is currently undergoing evaluation in a phase I/II trial in R/R NHL patients, including 12 patients with FL (NCT03625037). The

drug is given subcutaneously. All eight FL patients who received the BsAb at a dose ≥ 0.76 mg obtained an objective response (100% ORR) with 25% CRR^[104].

Glofitamab is an intravenously administered, humanized mouse IgG1-based BsAb with a 2:1 configuration: its CD3-binding region is connected to one of the two CD20-binding regions through a flexible linker, thus enabling bivalent binding to CD20 on B cells and monovalent binding to CD3 on T-cells. CD20 bivalency enhances the potency of glofitamab even in the setting of pre- or co-treatment with anti-CD20 agents^[105]. Moreover, the drug shows a longer half-life compared to the other BsAbs constructs. The phase I study (NCT03075696) in which the drug was evaluated included 44 patients with FL, who achieved 70.5% ORR and 47.7% CRR. Responders showed an mDOR of 10.8 months; in particular, 90.5% patients in CR remained in remission up to 22.9 months^[105]. Toxicities were manageable, with low rates of Grade ≥ 3 CRS^[105].

Overall, BsAbs display promising results in pre-treated patients with FL, even among high-risk groups, although their ability to provide sustained remissions similar to those observed after CAR T-cell therapy still needs to be confirmed. A considerable advantage they have over CAR T-cells is their availability as off-the-shelf products, as well as not requiring administration of lymphodepleting chemotherapy. Moreover, their toxicity profile seems much more favorable compared to CAR T-cells, with lower rates of Grade ≥ 3 CRS and neurotoxicity.

Checkpoint inhibition

Currently, the application of anti-programmed cell death protein (PD) 1 and programmed cell death ligand (PD-L) 1 to FL is confined to clinical trials, although responses to these agents have been largely reported.

A novel immune checkpoint inhibitor targeting CD47 has recently shown promising results in combination with rituximab in a phase Ib/II study enrolling patients with FL and DLBCL^[106]. CD47 is overexpressed on the surface of cancer cells in multiple malignancies and works as a “do not eat me” signal to phagocytic cells. The binding of the blocking antibody (Hu5F9-G4) to the receptor induces the phagocytosis of lymphoma cells; their destruction is enhanced by the concomitant exposure to rituximab, which induces complement and NK cell-mediated, antibody-dependent, cellular cytotoxic effect. Among patients with FL, the ORR was 71% with three patients (43%) obtaining a CR; the median DOR was not reached at a median follow-up of 8.1 months^[106].

CONCLUSION: THE FUTURE OF FOLLICULAR LYMPHOMA

FL is the most common indolent lymphoma in Western countries; thus, it represents a field where the still present unmet medical needs must be solved as soon as possible. As expressed above, the biggest failure to date is the absence of methods able to easily depict the biological and clinical heterogeneity of a disease that encloses many different conditions under a unique name. Consequently, in clinical practice, the standard therapeutic induction approach is composed of a chemotherapy backbone (mainly bendamustine or CHOP) and an anti-CD20 immunotherapy drug (rituximab or obinutuzumab), while small molecules, BsAbs, CAR T-cells, and everything we call “targeted therapies” are licensed for R/R patients or available up-front only in the context of clinical trials.

Since the keywords of the contemporary era are “targeted therapy” and “personalized medicine”, we think that FL represents a great model where we can strive to achieve this future direction. As stressed in the manuscript, heterogeneity is very high among different patients, but it can also be present in the same patient at different sites. On the other side, as the drug armamentarium is huge, the goal should be to select

the right therapy, for the right patient. How do we reach this very appealing but also difficult target?

First, we must consider that the milestone of the heterogeneity concept lies in the possibility of having representative samples of every single patient, collected in the diagnostic moment. These samples should be able to show not only which different biological pathways are activated in that patient but also what potential role they play in favoring the development of the disease. Since performing different biopsies of different disease sites is hardly ever possible, we think that efforts should be made to improve diagnosis through CTCs and cfDNA. By improving these techniques, we will be able to obtain large amounts of information with a noninvasive sample of peripheral blood.

Second, we encourage clinical trials where targeted therapies are used up-front. Only in this way, we can compare the newer and often less toxic molecules to the older chemotherapy schemes that still represent the basis of FL initial therapy. Ideally, if we could promptly and reliably identify the patients who are more likely to be POD24-positive, we could design appropriate frontline treatment strategies that minimize the risk of early relapse.

Another extremely relevant matter is how to define the most appropriate succession of treatments, given all of the innovative agents that are available nowadays, in order to obtain the best possible results from each of them without exposing patients to unnecessary toxicity.

Ongoing clinical experience with PI3Ki, for instance, has unveiled their scarce manageability, particularly when compared to newer agents such as tazemetostat, together with unsatisfactory response rates compared to immunotherapies such as BsAbs and CAR T-cells.

BsAbs, differently from autologous CAR T-cells, are “off-the-shelf” products, and therefore a potentially more convenient choice for symptomatic patients who would have trouble waiting for the manufacturing process of CAR T-cells to be completed. Moreover, the absence of lymphodepleting chemotherapy and their favorable safety profile make them a more promising option for older or unfit patients. The association between BsAb and other target agents, such as lenalidomide or the anti-CD79b antibody-drug conjugated, polatuzumab vedotin^[107] (NCT05169658, NCT03671018, and NCT03533283), shows promising results in B-cell NHL, also in those who failed CAR T-cell treatment.

Consequently, in the near future, third-line therapy of FL could be dominated by CAR T-cells, whenever possible to use them depending on the characteristics of the disease (aggressiveness, CD19 antigen expression), and BsAbs, which could become the option of choice in symptomatic, older, or unfit patients not suitable for chemotherapy conditioning or who cannot wait for the T-cell manufacturing procedures.

Randomized trials comparing HDT and ASCT with immunotherapies (CAR T-cells and BsAbs) could also help clarify the actual role of transplantation in FL patients at first relapse, which would be especially relevant for POD24-positive patients who are at the highest risk of being chemoresistant.

To conclude, even if for now it is probably still a dream, the hope for the future is to build new diagnostic strategies capable of identifying the right therapeutic choice for every single patient. In this way, hopefully, we will be able to spare the less effective therapies for that single patient *a priori*. Moreover, by using only targeted therapies, we will also avoid chemotherapy’s intolerable traditional side effects.

DECLARATIONS

Authors' contributions

Conceptualization: Casadei B, Nanni L, Lolli G, Zinzani PL

Methodology: Casadei B, Zinzani PL

Writing - original draft preparation: Casadei B, Nanni L, Lolli G, Zinzani PL

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