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New drugs for follicular lymphoma

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ABSTRACT

Despite the improvement in prognosis since the advent of rituximab, follicular lymphoma is still incurable and remains the cause of death of most afflicted patients. With the expanding knowledge of the pathogenesis of B-cell malignancies, in the last few years a plethora of new therapies acting through a variety of mechanisms have shown promising results. This review attempts to analyze the evidence available on these new drugs, which include new monoclonal antibodies and immunoconjugates, the anti-angiogenic and immunomodulatory agent lenalidomide, the proteasome inhibitor bortezomib, inhibitors of B-cell receptor pathway enzymes, such as ibrutinib, idelalisib, duvelisib and entospletinib, BCL2 inhibitors and checkpoint inhibitors. We conclude that despite the high expectations around the new therapeutic options for patients with refractory disease, these new drugs have side effects that require caution with their use, particularly in light of the still short follow up and the lack of both randomized trials and data on combination regimens.

1. Introduction

Follicular lymphoma (FL) is a lymphoproliferative disorder originating in germinal center B-cells. It is the most common indolent lymphoproliferative disorder in the western world, and it is biologically characterized by the translocation t(14;18), which leads to a constitutive overexpression of BCL2, an anti-apoptotic protein, which, in turn, leads to cellular immortality [1]. Clinically, FL responds well to therapy, but relapses occur in almost all instances, responses are shorter to each successive line of treatment, and lymphoma progression is the eventual cause of death of most patients [2,3]. The prognosis of FL has notably improved since the introduction of the anti-CD20 agent rituximab, and, at present, median overall survival (OS) exceeds 10 years [4]. The Follicular Lymphoma International Prognostic Index (FLIPI) is a prognostic score that includes 5 clinical and analytical variables (age >60 years, hemoglobin >120 g/L, elevated serum lactate dehydrogenase, advanced stage and involvement of >4 nodal sites) and distinguishes prognostic groups with 5-year OS probabilities between 88% and 43% before the introduction of rituximab [5] and 95% and 70% since then [6].

2. Current treatment of follicular lymphoma

Patients with localized disease (stage I and most with stage II) should receive radiotherapy [3,7,8]. Involved-field or involved-site 24-Gy radiotherapy are preferable to higher doses and extended-field radiotherapy as they seem to be as effective but less toxic [3,9]. The benefits of combined treatment (i.e., the addition of chemotherapy or immunotherapy to radiotherapy) are unclear as it seems to improve progression-free survival (PFS) but not OS [10].

In patients with advanced stage but asymptomatic and low tumor burden disease, active treatment at diagnosis does not improve the OS over watchful waiting, and therefore delaying treatment is a valid option for these patients [3,7,8]. Few patients present with symptomatic but low tumor burden FL and, in these cases, an alternative cause of the symptoms should be sought. If no other cause is found and they are finally attributed to lymphoma, treatment is appropriate. Patients with high tumor burden should be treated at diagnosis [3,7]. There are several chemotherapy regimens available, and they should be combined with rituximab since OS is improved compared with the same regimens without rituximab [3]. After response, which occurs in >85% of patients treated with immunochemotherapy (ICT) [3,11,12], they should receive

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one of several post-induction therapies, which increase PFS and delay the eventual relapse. Among the options available, including interferon maintenance, autologous stem cell transplantation, consolidation with radioimmunotherapy or bimonthly maintenance with rituximab for 2 years, the latter is the standard because of its effectiveness and safety profile [3,7,8].

After relapse, treatment should be tailored to each patient. Several factors should be considered, including the duration of response (in early relapses non-cross resistant regimens are recommended), accumulated past and potential future toxicities, and clinical and biological factors, such as age, comorbidities and stage and FLIPI at relapse. Given all these, therapeutic options range from watchful waiting and local radiotherapy to clinical trials. However, chemotherapy combined with rituximab is the standard salvage treatment except in refractory disease (progression or relapse before 6 months of first line treatment) in which case immunotherapy is not recommended [3,7].

In the last few years, expanding knowledge of the neoplastic FL cells and the molecules and metabolic pathways involved in malignization and therapeutic resistance have allowed the development of drugs targeted to some of these molecules. The purpose of this manuscript is to review the results obtained with the drugs with the most clinically advanced development in FL. Tables 1 and 2 summarize the evidence that has already been published with these drugs.

3. New drugs in the treatment of follicular lymphoma

3.1. Monoclonal antibodies

Ofatumumab is a humanized, class I anti-CD20 agent (such as rituximab), but with an increased complement dependent cytotoxicity compared with the latter. It binds to a different CD20 epitope resulting in higher affinity and, theoretically, a higher activity in cases with low CD20 surface expression [13]. In a phase 3 trial including 116 FL patients previously treated with rituximab or rituximab-containing chemotherapy, it was well tolerated (grade 3 infusion reactions and infections occurred in <5% of patients) but ofatumumab monotherapy showed an overall response rate (ORR) of only 10% in the 86 patients who received the highest dose (1000 mg, 8 weekly doses) [14]. However, in first-line, in a phase 2 trial with FL patients, ofatumumab was given at 1000 mg per week for a month and subsequently 1000 mg every 2 months for 8 months and obtained an ORR of 86% (Complete response [CR] in 13%) with a 1-year PFS probability of 97% and a safety profile similar to rituximab [15]. It has also been administered as part of combination treatment; 59 patients with advanced-stage, previously untreated FL received ofatumumab plus CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) and attained an ORR of 100%, with CR in 62% of patients [16].

Obinutuzumab (GA101) is another humanized anti-CD20 agent. It is a class II agent, and therefore, it has a higher antibody-dependent cellular cytoxicity and induces B-lymphocyte apoptosis more effectively than rituximab [13]. In patients with relapsed/refractory (R/R) indolent non-Hodgkin lymphoma (iNHL), 8 cycles of obinutuzumab were administered (days 1 and 8 of the first cycle and day 1 of each subsequent cycle) [17]. One arm received 1600 mg in the first cycle and 800 mg subsequently, while the other arm received 400 mg (flat dose), obtaining an ORR of 55% and 17% and a median PFS of 11.9 and 6 months, respectively. In a phase II study including R/R iNHL patients, an induction and maintenance courses of obinutuzumab (4 weekly doses of 1000 mg and then every 2 months for 2 years) were superior in terms of ORR (45% vs. 27%) but not PFS to induction and maintenance with rituximab at the standard 375 mg/m^2 [18]. Severe adverse events were

Table 1
Published studies with new drugs for follicular lymphoma acting on the cell surface: monoclonal antibodies, immunoconjugates and checkpoint inhibitors.

Drug (mechanism of action)	Regimen	Study (Refs.)	Study phase	Setting	N (FL)	OR (CR)	PFS/DFS	OS
Ofatumumab (anti-CD20)	Ofatumumab	Czuczman et al. [14]	Phase III	Relapsed FL	116	10% (1%)[a]	6.1 mts	–
	Ofatumumab + CHOP	Czuczman et al. [16]	Phase II	Untreated FL	59	100% (38%)[a]	NR	NR
Obinutuzumab (anti-CD20)	Obitunuzumab	Salles et al. [17]	Phase II	Relapsed indolent NHL	40 (34)	55% (9%)[a]	11.9 mts[a]	–
	Obinutuzumab + CHOP	Radford et al. [19]	Phase Ib	Relapsed FL	28	100% (64%)[a]	–	–
	Obinutuzumab + FC				28	86% (21%)[a]	–	–
	Obinutuzumab (induction and maintenance)	Sehn et al. [18]	Phase II	Relapsed indolent NHL	88 (74)	66.2% (41.9%)[b,c]	45.8% at 2 yrs[c]	–
	Rituximab (induction and maintenance)				87 (75)	64% (22.7%)[b,c] (p = 0.006 for CR)	50.3% at 2 yrs[c] (NS)	–
	Obinutuzumab + Bendamustine	Sehn et al. [21]	Phase III	Relapsed indolent NHL	194 (155)	69% (11%)[e]	NR	–
	Bendamustine				202 (166)	63% (12%)[e]	14.9 mts (p = 0.0001)	–
Galiximab (anti-CD80)	Galiximab + Rituximab	Leonard et al. [22]	Phase I/II	Relapsed FL	73	66% (19%)	12.1 mts	NR
	Galiximab + Rituximab	Czuczman et al. [23]	Phase II	Untreated FL	61	72% (41%)	2.9 yrs	–
Epratuzumab (anti-CD22)	Epratuzumab + Rituximab	Leonard et al. [24]	Phase II	Relapsed indolent NHL	48 (41)	54% (24%)[c]	10 mts[c]	–
	Epratuzumab + Rituximab	Grant et al. [25]	Phase II	Untreated FL	59	88% (42%)	60% at 3 yrs	91% at 3 yrs
Inotuzumab Ozogamicin (Anti-CD22-Calicheamicin)	Inotuzumab + Rituximab	Fayad et al. [28]	Phase I/II	Relapsed NHL	118 (39)	87% (62%)[c]	68% at 2 yrs	90% at 2 yrs
	Inotuzumab	Goy et al. [29]	Phase II	Relapsed indolent NHL	81 (72)	71% (35%)[c]	14.7 mts[c]	–
Polatuzumab (anti-CD79-MMAE)	Polatuzumab[d]	Palanca-Wessels et al. [31]	Phase I	Relapsed NHL	95	46% (20%)[e]	7.9 mts[e]	–
Pidilizumab (anti-PD1)	Pidilizumab + Rituximab	Westin et al. [76]	Phase II	Relapsed FL	30	66% (52%)	18.8 mts	–
Nivolumab (anti-PD1)	Nivolumab	Lesokhin et al. [77]	Phase I	Relapsed hemaatological malignancies	81 (10)	40% (10%)[c]	NR[c]	–

OR: Overall response, CR: complete response, PFS: progression-free survival, DFS: disease-free survival, OS: overall survival, FL: Follicular lymphoma, NR: Not reached, NHL: non-Hodgkin lymphoma, CHOP: cyclophosfamide, adriamycin, vincristin, prednisone, FC: fludarabine, cyclophosphamide, MMAE: Monomethy Auristatin E, PD1: Programmed cell death protein 1.

[a] With the higher dose (1000 mg for Ofatumumab and 1600 mg for Obinutuzumab in the first cycle and 800 mg in all others).

[b] response rate after the maintenance treatment.

[c] rates for follicular lymphoma.

[d] A minority of patients (n = 9) also received rituximab.

[e] rates for indolent NHL.