Novel agents in indolent lymphomas

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Abstract: Indolent non-Hodgkin's lymphomas (iNHLs) include follicular lymphomas (FL), marginal-zone lymphoma, lymphoplasmacytic lymphoma/Waldenström macroglobulinemia and small lymphocytic lymphoma. First-line standard therapy in advanced, symptomatic iNHL consists of rituximab-based immunochemotherapy. The recent rediscovery of the 'old' chemotherapeutic agent bendamustine, an alkylating agent with a peculiar mechanism of action, has added a new effective and well-tolerated option to the therapeutic armamentarium in iNHL, increasing response rates and duration. However, patients invariably relapse and subsequent active and well-tolerated agents are needed. In recent years a large number of new targeted agents have been tested in preclinical and clinical experimentation in FL and indolent nonfollicular lymphoma (iNFL), including the new monoclonal antibodies binding CD20 or other surface antigens, immunoconjugates and bispecific antibodies. Moreover novel agents directed against intracellular processes such as proteasome inhibitors, mTOR inhibitors and agents that target the tumour microenvironment, notably the immunomodulatory agent lenalidomide, are under active clinical investigation. The development of these new drugs may change in the near future the approach to iNHL patients, leading to better tolerated and effective therapy regimens.

Keywords: bendamustine, bortezomib, indolent lymphomas, lenalidomide, mTOR inhibitors, novel agents, obinutuzumab, ofatumumab

Introduction

The term 'indolent lymphoma' is commonly used to describe the clinical behaviour of lymphomas that tend to grow and spread slowly and have few symptoms for long periods. Indolent non-Hodgkin's lymphomas (iNHL) encompass the following low-grade histologic subtypes of B-cell non-Hodgkin's lymphoma (NHL) included in the recent World Health Organization (WHO) classification of lymphoid neoplasm published in 2008: follicular lymphoma (FL), small lymphocytic lymphoma (SLL), lymphoplasmacytic lymphoma (LPL), which is defined as Waldenström's macroglobulinemia (WM) when associated with a monoclonal IgM component and bone marrow involvement, splenic marginal-zone lymphoma (SMZL), primary nodal marginal-zone lymphoma (NMZL) and marginal-zone lymphoma of mucosa-associated lymphoid tissue (MALT) [Campo *et al.* 2011]. FL is the second most common subtype of NHL, accounting for approximately 25% of newly diagnosed cases of NHL [The Non-Hodgkin's Lymphoma Classification Project, 1997], followed by MALT lymphoma (7% of all NHL, including 'gastric' and 'nongastric' cases), while other subtypes are rather rare, with SLL, LPL, SMZL and NMZL accounting for 3%, 2%, 2% and 1% of NHL patients, respectively [The Non-Hodgkin's Lymphoma Classification Project, 1997]. For this reason, given their infrequency with respect to FL, these entities are frequently grouped altogether under the category of 'indolent nonfollicular lymphoma' (iNFL).

Overall, iNHLs are highly responsive to standard chemotherapy regimens, but still remain incurable, showing a relentless progressive–relapsing course. In the pre-rituximab era median survival for advanced iNHL was around 8–10 years and after relapse it became around 4–5 years. In the last decade, however, the advent of rituximab-based immunochemotherapy not only increased overall response rate (ORR) and complete response (CR)

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Table 1. Novel agents in indolent lymphomas.

Drug class	Representative drugs	Targets
Alkylating agents	Bendamustine	DNA
Type I anti-CD20 monoclonal antibodies	Ofatumumab	CD20
Type II anti-CD20 monoclonal antibodies	Obinutuzumab	CD20
Anti-CD22 monoclonal antibodies	Epratuzumab	CD22
Anti-CD80 monoclonal antibodies	Galiximab	CD80
Immunoconjugated monoclonal antibodies	Inotuzumab Ozigamicin	CD22 and DNA
Bispecific antibodies	Blinatumumab	CD3 and CD19
Proteasome inhibitors	Bortezomib Carfilzomib	Proteasome
Signalling pathway inhibition	Temsirolimus	mTOR
mTOR inhibitors	Everolimus	
PI3K inhibitors	CAL-101	PI3K
BTK inhibitors	PCI-32765	BTK
Bcl-2 inhibitors	AT-101 ABT-263 Obatoclax	Bcl-2 family
Immunomodulatory drugs	Lenalidomide	Microenvironment

rates, but prolonged progression-free survival (PFS) and overall survival (OS) [Herold *et al.* 2007; Hiddemann *et al.* 2005; Marcus *et al.* 2005]. Furthermore, the introduction of the radio-immuno-conjugates yttrium-90 (^{90}Y)–labelled ibritumomab tiuxetan and iodine-131 (^{131}I)–labelled tositumomab has shown promising results in terms of efficacy and safety in either front-line, consolidation or relapsed/refractory settings, inducing in some cases long-term remissions. In addition, the increasing understanding of molecular mechanisms involved in the pathogenesis of iNHL has opened the door to the discovery and development of several new targeted therapies that in the near future could challenge the current scenario (Table 1).

This review focuses on novel agents recently introduced in the treatment of iNHL and analyses the available data separating results obtained in FL from other entities.

Chemotherapeutic agents

Bendamustine. Bendamustine is an 'old' alkylating agent that has been 'rediscovered' recently and has undergone extensive clinical development. It was first synthesized in 1963 by Ozegowski and it has been used in Germany since 1971 for the treatment of several haematologic malignancies [Cheson and Rummel, 2009]. The chemical structure of bendamustine consists of a nitrogen mustard (mechlorethamine) linked to a benzimidazole ring, which is thought to confer purine-analogue properties, and a butyric acid side chain. Experimental evidence of its unique mechanism of action has demonstrated: (1) a potent ability to induce sustained double strand breaks; (2) the induction of unique DNA repair pathways, i.e. base-excision DNA repair; (3) the induction of apoptosis via extrinsic and intrinsic pathways (p53, NOXA, caspases cascade); (4) the deregulation of the cell cycle through the inhibition of mitotic checkpoints; and (5) the induction of apoptosis-independent forms of cell death ('mitotic catastrophe') [Leoni *et al.* 2008]. As a result, bendamustine displays significant mechanistic differences from other alkylating agents, exhibiting greater stability and slower repair of DNA damage [Leoni *et al.* 2008]. In preclinical models bendamustine demonstrated significant synergism with rituximab [Chow *et al.* 2002].

Beginning in the late 1990s, many German groups have performed an increasing number of pilot trials evaluating bendamustine in NHL. These studies showed a remarkable activity and a very favourable side-effect profile, characterized primarily by moderate haematological toxicity,

Table 2. Clinical trials evaluating bendamustine in indolent lymphomas.

Study	Number of patients (histotypes)	Population	Treatment schedule	ORR% (CR)	PFS (months)
Friedberg *et al.* [2008]	76 (46 FL, 12 SLL, 1 LPL, 2 MZL, 15 transf. NHL)	Rituximab-Ref	B 120 mg/m^2 d 1-2, q21	77 (34)	6.7
Kahl *et al.* [2010a]	102 (63 FL, 21 SLL, 1 LPL, 16 MZL)	Rituximab-Ref	B 120 mg/m^2 d 1-2, q21	75 (17)	9.3
Rummel *et al.* [2005]	63 (24 FL, 17 LPL, 6 MZL, 16 MCL)	Rel/Ref	R 375 mg/m^2 d 1 + B 90 mg/m^2 d 2-3, q28 [BR]	90 (60)	24
Robinson *et al.* [2008]	66 (40 FL, 10 SLL, 2 LPL, 2 MZL, 12 MCL)	Rel/Ref	R 375 mg/m^2 d 1 + B 90 mg/m^2 d 2-3, q28 [BR]	91 (55)	23
Rummel *et al.* [2012]	514 (283 FL, 93 iNFL, 138 MCL)	1st-line	BR *versus* R-CHOP	93.8 (40.1) *versus* 93.5 (30.8)	69.5 *versus* 31.2
Rummel *et al.* [2010]	208 (96 FL, 71, 41 MCL)	Rel/Ref	BR *versus* FR	83.5 (38.5) *versus* 52.5 (16.2)	30 *versus* 11

FL, follicular lymphoma; SLL, small lymphocytic lymphoma; LPL, lymphoplasmacytic lymphoma; MZL, marginal-zone lymphoma; transf. NHL, transformed non-Hodgkin's lymphoma; MCL, mantle-cell lymphoma; iNFL, indolent nonfollicular lymphoma; Rel/Ref, relapsed/refractory; B, bendamustine; R, rituximab; ORR, overall response rate; CR, complete remission; PFS, progression-free survival

mild nausea and a quite inconsistent rate of alopecia [Cheson and Rummel, 2009]. The results of major clinical trials evaluating bendamustine in iNHL are summarized in Table 2. Two large US phase II multicentre studies investigated bendamustine monotherapy in patients with rituximab-refractory iNHL [Friedberg *et al.* 2008; Kahl *et al.* 2010a]. In the first, bendamustine showed a favourable side-effect profile with good clinical activity: grade 3–4 toxicities were prevalently haematological, including reversible neutropenia (54%) and thrombocytopenia (25%); the ORR was 77% (CR/CRu 34%), with a median duration of response (DOR) of 9 months. The second study showed similar results (ORR 75%, CR/CRu 17%; median PFS 9.3 months) [Kahl *et al.* 2010a]. Of note, the efficacy of bendamustine was comparable between the different indolent histological subtypes: the ORR was 74% in FL, 71% in SLL, 86% in MALT-MZL and 78% in NMZL patients. Taken together, these studies demonstrated a promising clinical activity and good safety profile for bendamustine in patients with rituximab-refractory iNHL. However, the duration of remission was rather short.

To improve these results, the logical next step was to combine bendamustine with rituximab (BR). Two similar trials investigated this combination in relapsed/refractory iNHL. In the first study, Rummel and colleagues treated 63 patients with FL, iNFL or MCL with the BR regimen [Rummel *et al.* 2005]. Leukopenia was the most common side-effect (16% grade 3–4); no evidence of cumulative myelosuppression was found. None of the patients suffered from alopecia and no organ toxicity was seen. The response rate was promising (ORR 90%, CR 60%) and, importantly, responses were fairly durable, with median PFS of 24 months. Notably, PFS in FL and LPL patients was even higher (median not reached). The second trial showed almost identical results, in terms of toxicity profile (36% grade 3–4 neutropenia) and efficacy (median PFS of 23 months) [Robinson *et al.* 2008].

As a consequence of these results in the relapsed/refractory setting, the StiL group performed a phase III randomized study comparing six cycles of BR with six cycles of R-CHOP as first-line therapy in 514 patients with FL, iNFL and MCL. The final results of this study were reported at the ASH meeting in 2009 [Rummel *et al.* 2009] and updated at the last ASCO meeting [Rummel *et al.* 2012]. BR was more effective than R-CHOP, with a median PFS of 69.5 months *versus* 31.2 months. The advantage in term of PFS was evident in all risk groups and histologic subtypes, with the exception of the small subgroup of MZL. OS was not significantly different between the two treatment regimens. Concerning adverse events, R-CHOP was more toxic than BR (grade 3–4 neutropenia 46.5% *versus* 10.7%). In addition, a sub-analysis of this study showed that the BR combination did not impair the collection of stem cells for subsequent transplant, since the mobilization performed at the end of the treatment course allowed a similar rate of success in both arms [Burchardt *et al.* 2009].

Table 3. Clinical trials evaluating ofatumumab in indolent lymphomas.

Study	Number of patients (histotypes)	Population	Treatment schedule	ORR% (CR)	PFS (months)
Hagenbeek *et al.* [2008]	40 (FL)	Rel/Ref	Ofatumumab (300 to 1000 mg x4, q7)	43	8.8
Czuczman *et al.* [2012a]	116 (FL)	Rituximab-Ref	Ofatumumab (500 or 1000 mg x8, q7)	13 *versus* 10	5.8
Czuczman *et al.* [2012b]	58 (FL)	1st-line	Ofatumumab (500 *versus* 1000 mg + CHOP x6, q21)	90 (24) *versus* 100 (38)	

FL, follicular lymphoma; Rel/Ref, relapsed/refractory; ORR, overall response rate; CR, complete remission; PFS, progression-free survival

In a similar way, the StiL group performed a phase III study that compared six cycles of BR and fludarabine–rituximab in 208 patients with relapsed/refractory iNHL or MCL [Rummel *et al.* 2010a]. BR showed a superior efficacy, with a better ORR (83.5% *versus* 52.5%), CR (38.5% *versus* 16.2%) and PFS (30 *versus* 11 months), without any difference in terms of toxicity.

Since bendamustine is an alkylating agent, a great deal of attention has been focused on the issue of secondary malignancies. To date, the two StiL studies did not show an increased rate of MDS/AML or solid tumours in the BR arm [Rummel *et al.* 2010b]; however, a longer follow up is still warranted to draw definitive conclusions.

For the future directions, bendamustine is now being evaluated in relapsed/refractory iNHL in conjunction with a great variety of other agents (i.e. IMIDs, proteasome inhibitors, monoclonal antibodies [mAbs]).

Agents that target the cell surface

Novel mAb anti-CD20

As mentioned previously, the introduction of the chimeric human–mouse mAb anti-CD20 rituximab actually changed the outcome of B-cell NHL and the combination of rituximab and chemotherapy is now the standard treatment in iNHL. Nevertheless, a significant number of patients affected by iNHL develop recurrent disease and become refractory to first or subsequent immunochemotherapy treatment [Davis *et al.* 2000]. In these cases retreatment with rituximab-based therapy is not considered useful and new agents potentially able to overcome rituximab-resistance mechanisms are recommended. For this reason, several novel mAbs, either directed against CD20 or other antigens, were specifically designed by incorporating structural modifications that are hoped to overcome mechanisms of rituximab resistance. Many of these new mAbs are currently under different preclinical and clinical phases of assessment.

Ofatumumab. Ofatumumab is a fully humanized anti-CD20 mAb. Classified as a type I mAb, ofatumumab displays greater complement-dependent cytotoxicity (CDC) with respect to rituximab [Teeling *et al.* 2004]. Ofatumumab binds to a novel epitope of CD20, which encompasses the small extracellular loop and the *N*-terminal region of the second large extracellular loop. Ofatumumab binds to the CD20 with greater avidity than rituximab and his action is carried out even at lower density of this cell surface antigen [Cillessen *et al.* 2007; Teeling *et al.* 2004].

In the field of iNHL, Ofatumumab has been initially tested in FL, as summarized in Table 3. In the first phase I/II study, Hagenbeek and coworkers enrolled 40 patients (37,5% previously treated with rituximab) affected by relapsed or refractory FL [Hagenbeek *et al.* 2008]. The best response rate across all dose groups was 43%, without direct correlation with ofatumumab dose. Previous rituximab-treated patients had a response rate of 64%. The median time to progression (TTP) was 8.8 months for all patients and 32.6 months for responders, with median DOR of 29.9 months. Ofatumumab was generally well tolerated and toxicity was similar to that of rituximab (reversible grade 3–4 infusional reactions occurring during first infusion). Immunological tests showed that ofatumumab induced a longer lasting depletion of B cells (6–10 months) compared with rituximab [Teeling *et al.* 2004]. However,

Table 4. Clinical trials evaluating obinutuzumab (GA-101) in indolent lymphomas.

Study	Number of patients (histotypes)	Population	Treatment schedule	ORR% (CR)	PFS (months)
Salles *et al.* [2012]	21 (13 FL, 2 LPL, 1 SLL, 4 MCL, 1 DLBCL)	Rel/Ref	Obinutuzumab (50 to 2000 mg x9, q7)	43	
Salles *et al.* [2011]	40 (34 FL, 6 iNFL)	Rel/Ref	Obinutuzumab (1600/800 *versus* 400/400 mg x9, q7)	60 (20) *versus* 35 (7)	11.8 *versus* 6
Sehn *et al.* [2012]	22 (10 FL, 2 SLL, 5 CLL, 1 MCL, 4 DLBCL)	Rel/Ref	Obinutuzumab (100 to 2000 mg x4 q7 + 8 q12)	22	
Sehn *et al.* [2011]	175 (149 FL, 26 iNFL)	Rel/Ref	Obinutuzumab (1000 mg) *versus* Rituximab 375 mg/m^2) x4, q7	43 *versus* 28	
Radford *et al.* [2011]	56 (FL)	Rel/Ref	[G-CHOP] *versus* [G-FC] (Obinutuzumab 1600/800 *versus* 400/400 mg)	96.4 (39) *versus* 92.9 (50)	

FL, follicular lymphoma; SLL, small lymphocytic lymphoma; LPL, lymphoplasmacytic lymphoma; MCL, mantle-cell lymphoma; iNFL, indolent nonfollicular lymphoma; DLBCL, diffuse large B-cell lymphoma; CLL, chronic lymphocytic leukemia; Rel/Ref, relapsed/refractory; G, GA-101 (obinutuzumab); R, rituximab; ORR, overall response rate; CR, complete remission; PFS, progression-free survival

infections were infrequent and generally mild (18 grade 1–2 and 2 grade 3).

To assess whether this novel anti-CD20 mAb might overcome rituximab resistance, ofatumumab was tested in 116 rituximab-refractory FL patients in a double-blind study evaluating two dose levels [Czuczman *et al.* 2012a]. Patients were heavily pretreated: 65% had chemotherapy-refractory disease and the median number of previous treatments was 4. The subjects who received the higher dose experienced an ORR of 10% (1 CR, 8 PR) while 50% had stable disease (SD). Median DOR was 6 months. The limited activity in this setting suggests it should be combined with chemotherapy (CHOP or bendamustine).

A subsequent phase II study explored the combination of ofatumumab with CHOP in 58 patients with previously untreated FL [Czuczman *et al.* 2012b]. In the higher dose group ORR was 100% (CR 38%). The most common grade 3–4 adverse events were leukopenia and neutropenia.

In conclusion, ofatumumab has demonstrated efficacy as a single agent in relapsed/refractory FL patients, with less evident effect in true rituximab-refractory patients. The combination of ofatumumab and CHOP appears highly active in previously untreated FL and opens the way to further studies.

Obinutuzumab (GA-101). Obinutuzumab (GA-101) is a third-generation, fully humanized, type II anti-CD20 mAb, that was glyco-engineered to display afucosylated Fc region carbohydrates, resulting in enhanced antibody-dependent cell-mediated cytotoxicity (ADCC) activity and superior direct B-cell killing compared with rituximab and other type I mAbs, despite lower complement-dependent cytotoxicity (CDC) activity [Ashraf *et al.* 2009; Mossner *et al.* 2010]. GA-101 was investigated as a single agent in two phase I studies (Table 4). In the first trial, 21 patients with relapsed/refractory B-cell NHL were treated with escalating doses of GA-101. All patients were heavily pretreated; 20 (95%) were previously exposed to rituximab and 9 (43%) were rituximab-refractory. No dose-limiting toxicity was observed, and side-effects consisted primarily of grade 1–2 infusion-related reactions. An overall response was observed in nine patients (43%), including five CR/CRu. All responding patients belonged to the FL subgroup (ORR 69%, CR 38%) [Salles *et al.* 2012]. The phase II part of this study compared two different doses of GA-101 in 40 patients with relapsed/refractory FL. Better results were obtained in the higher dose group (ORR 60%, 33% CR/CRu; median PFS 11.8 months). These preliminary data indicate that GA-101 monotherapy display encouraging efficacy with higher response observed at higher dose [Salles *et al.* 2011]. In the second phase I

trial, 22 subjects with B-cell NHL or chronic lymphocytic leukemia (CLL) received four weekly doses followed by maintenance therapy. Half of patients were refractory to prior rituximab. Toxicity was similar to the previous trial. After completion of induction, 5 patients obtained a PR (22%) and 12 had SD; 8 patients received maintenance treatment, that lead to improvement of response in 3 patients. In the subset of FL, the best ORR was 40% (4/10 including 1 CR) [Sehn *et al.* 2012].

Preliminary results of the first head-to-head trial of obinutuzumab against rituximab in relapsed/refractory iNHL patients have been presented at the last ASH meeting in San Diego (2011) and updated at the last EHA meeting in Amsterdam (2012) [Sehn *et al.* 2011]. A total of 175 patients were randomized to receive four weekly infusions of either GA-101 or rituximab. Patients had received a median of two prior treatments (prior rituximab in 99). Safety analysis did not reveal any difference between the two treatments. Based on blinded central radiology review, ORR was significantly in favour of GA-101 (44.6% *versus* 26.7%); however, at the time of analyses (median observation time: 15 months), PFS and OS were not different between the two arms. Longer follow up is probably needed to establish whether the higher response rate of GA-101 with respect to rituximab could be able to translate also in better survival.

Given its encouraging antilymphoma activity, particularly in FL, obinutuzumab has been evaluated also in combination with chemotherapy in relapse/refractory FL setting [Radford *et al.* 2011]. In a phase I study (GAUDI), 56 patients were randomized to receive either 6–8 CHOP or 4–6 FC cycles, in combination with GA-101. All patients (28/28) in the G-CHOP arm and 22/28 in the G-FC arm completed the treatment. Grade 3–4 neutropenia was reported in 39% and in 50% of patients treated with G-CHOP and G-FC, respectively. ORR at the end of induction was 96.4% in G-CHOP group (39% CR) and 92.9% in G-FC group (50% CR). The response rate with G-CHOP compared favourably with the R-CHOP arm of a similar previous trial (EORTC 20981). In conclusion GA-101 can be combined safely with CHOP, demonstrating a high level of activity compared with historical controls, while G-FC showed worse tolerability.

Following these promising results, obinutuzumab is currently being explored in combination with chemotherapy (CHOP, CVP or bendamustine) as first-line therapy in a randomized phase III study against the current standard of care rituximab chemotherapy in patients with advanced untreated iNHL [ClinicalTrials.gov identifier: NCT01332968].

Antibodies against targets other than CD20

CD22 is an antigen widely expressed on normal and malignant B cells and plays a role in B-cell receptor (BCR) activation and signal transduction. Epratuzumab is a humanized anti-CD22 antibody that demonstrated ADCC and direct cytotoxicity in preclinical studies [Leonard *et al.* 2005]. Phase I/II studies showed that epratuzumab is well tolerated, and has significant single-agent clinical activity across various dose levels in relapsed/refractory FL [Leonard *et al.* 2003], suggesting its combination with rituximab should be explored. In the relapsed/refractory setting this combination demonstrated promising results, with an ORR of 54% in FL patients (CR 24%) and a median DOR of 13.4 months [Leonard *et al.* 2008]. Also in first-line setting this regimen seems to be quite effective, showing an ORR of 84% (CR 33.3%) in 57 FL patients [Grant *et al.* 2010].

Galiximab is a chimeric human–primate anti-CD80 mAb with single-agent activity and excellent tolerability in previous treated FL [Czuczman *et al.* 2005]. A phase I/II study evaluating the combination of galiximab and rituximab in patients with relapsed/refractory FL showed an ORR of 66% and a median PFS of 12.1 months [Leonard *et al.* 2007]. In 61 untreated FL patients, this regimen appeared efficacious (ORR 72%, CR/CRu47%), particularly in patients with low-risk Follicular Lymphoma International Prognostic Index (FLIPI) score (ORR 92%, CR/CRu 75%, 75% 3-year PFS 75%) [Czuczman *et al.* 2012c].

Immunoconjugates. Another mechanism to induce cell killing beyond the direct antibody effect is represented by the use of a toxin conjugated to B-cell mAbs. Differently from naked antibodies, which exert their effects largely from the cell surface, conjugated antibodies often benefit from internalization. Inotuzumab ozigamicin (CMC-544) is a humanized anti-CD22 antibody conjugated to calicheamicin. In a phase I study the main toxicities included thrombocytopenia, asthenia, nausea, neutropenia and elevated

aspartate transaminase (AST) [Ogura *et al.* 2010]. The ORR for all patients was 39%; 68% of patients with FL responded at the maximum tolerated dose. A phase II study evaluating the combination of inotuzumab ozigamicin and rituximab enrolled 110 patients with refractory or recurrent FL or aggressive NHL. In 38 patients with FL, ORR was 87% and median PFS was 23.6 months [Dang *et al.* 2009].

Bispecific antibodies. Bispecific antibodies are antibodies that target two antigens. Blinatumomab is an anti-CD3/anti-CD19 antibody that engages cytotoxic T cells and malignant B cells, enhancing tumour lysis. Phase I studies have demonstrated tolerability and clinical activity in B-cell NHL [Bargou *et al.* 2008]. Further studies are now evaluating this promising new treatment in different NHL subtypes.

Agents that target intracellular processes

Proteasome inhibitors

Bortezomib. Bortezomib is a first-in-class drug designed to target the ubiquitin–proteasome complex, i.e. the regulatory pathway that exerts intracellular protein degradation in eukaryotes [Orlowski, 2005], resulting in impairment of apoptosis, that is considered one of the most involved pathways in the pathogenesis of iNHL. For this reason bortezomib has been evaluated with great interest in FL and iNFL (especially WM).

Early phase II trials revealed striking variation of efficacy in different histologies: while significant response rates to bortezomib were shown in MCL [Fisher *et al.* 2006; Goy *et al.* 2009], the results in other iNHLs were less impressive [O'Connor *et al.* 2005]. The results of clinical studies evaluating bortezomib as single agent or in combination with other drugs are summarized in Table 5. The first trial addressing the efficacy of biweekly (biw) single-agent bortezomib at standard dose (1.3 mg/m^2) in FL showed dismal results, with a median TTP of 5.1 months [Di Bella *et al.* 2010]. Best response rates were found with higher dose (1.5 mg/m^2) in 18 patients with FL, with 50% ORR (22% CR), similar to the MCL group; however, the toxicity of this schedule, mainly in terms of grade 3–4 peripheral neuropathy (PN) (8%) and thrombocytopenia (27%) was not negligible and led to drug discontinuation in 33% of subjects [O'Connor *et al.* 2005]. In order to ameliorate toxicity, a weekly (qw) bortezomib schedule (1.8 mg/m^2) was studied in 26 iNHL patients; however, the ORR was low (18%) and PFS was not improved (6.7 months) [Gerecitano *et al.* 2009]. The weekly *versus* twice-weekly debate was answered by the GELA in a randomized phase II trial comparing the two schedules of single-agent bortezomib in 87 relapsed/refractory FL patients. At planned interim analysis the weekly dosing arm demonstrated insufficient responses (ORR 23% *versus* 32%) and the twice-weekly schedule was recommended for furthers studies [Ribrag *et al.* 2010]. However, given the unsatisfactory response rates of single-agent bortezomib, the focus moved to the combination of bortezomib with rituximab or immunochemotherapy regimens in the hope of improving efficacy in FL and iNFL.

The combination of bortezomib and rituximab is an attractive area of investigation because of the different mechanisms of action and side-effect profiles; moreover, *in vitro* and *in vivo* murine studies showed synergistic activity [Smolewski *et al.* 2006]. One of the first studies addressing this combination explored again the weekly *versus* twice-weekly bortezomib schedule with the association of rituximab in 81 patients with relapsed/refractory FL or MZL [de Vos *et al.* 2009]. As expected, the weekly schedule was better tolerated (grade 3–4 PN 5% *versus* 10%) and given the noninferiority in terms of efficacy, it was chosen for further development. To this purpose, a large international randomized phase III trial (LYM-3001) allocated 676 patients with relapsed/refractory FL to receive rituximab either alone or with bortezomib [Coiffier *et al.* 2011]. Median PFS was 12.8 months in the bortezomib–rituximab arm and 11 months in the rituximab-only arm; this also coincided with a better ORR (63% *versus* 49%). However, the clinical benefit did not reach the anticipated prespecified improvement of 33% in PFS and the safety profile revealed higher rates of PN in the combination arm [Coiffier *et al.* 2011]. Another phase II trial (BRIL-06) evaluating rituximab and bortezomib combination in 49 patients with relapsed/refractory iNFL and MCL, showed encouraging results: ORR 53% (CR, 26.5%), 1-year PFS 50% for MZL and 37% for LPL [Chiappella *et al.* 2009].

Many studies addressing feasibility and efficacy of adding bortezomib to an immunochemotherapy

Table 5. Clinical trials evaluating bortezomib in indolent lymphomas.

Study	Number of patients (histotypes)	Population	Treatment schedule	ORR% (CR)	PFS (months)
O'Connor *et al.* [2005]	18 (FL)	Rel/Ref	Bor 1.5 mg/m^2 biw	50 (22)	
Gerecitano *et al.* [2009]	26 (18 FL; 8 iNFL)	Rel/Ref	Bor 1.8 mg/m^2 qw x4	18	6.7
Ribrag *et al.* [2010]	87 (FL)	Rel/Ref	Bor 1.6 mg/m^2 qw x6 *versus* Bor 1.5 mg/m^2 biw x8	23 *versus* 32	
de Vos *et al.* [2009]	81 (70 FL, 11 MZL)	Rel/Ref	R 375 mg/m^2 x 4 qw + Bor 1.3 mg/m^2 biw x4 or Bor 1.6 mg/m^2 qw x3	49 *versus* 43	5 *versus* 10
Coiffier *et al.* [2011]	676 (FL)	Rel/Ref	R 375 mg/m^2 x8 qw alone *versus* R + Bor 1.6 mg/m^2 qw	49 *versus* 63	11 *versus* 12.8
Chiappella *et al.* [2009]	49 (25 MCL, 8 MZL, 16 LPL)	Rel/Ref	R 375 mg/m^2 x8 + Bor 1.6 mg/m^2 qw	53 (26.5)	45% (1 y)
Ribrag *et al.* [2009]	49 (11 FL)	1st-line	R-CHOP + Bor (1 or 1.3 mg/m^2; qw or biw	(82)	
Sinha *et al.* [2012]	19 (10 FL, 3 MZL, 2 LPL)	1st-line	R-CHOP (VCR NTE 1.5 mg) + Bor 1 or 1.3 or 1.6 mg/m^2 qw (d 1 and 8)	100 (68)	89.5 (3 y)
Fowler *et al.* [2011]	73 (FL)	Rel/Ref	Bor 1.6 mg/m^2 qw + B 50, 70 or 90 mg/m^2 d 1-2 + R 375 mg/m^2 x4 qw (1st-cycle) than d 1 q28 x up to 5 cycles	88 (55)	14.9
Friedberg *et al.* [2011]	31 (16 FL, 3 MZL, 3 SLL, 2LPL, 7 MCL)	Rel/Ref	Bor 1.3 mg/m^2 biw + B 90 mg/m^2 d 1,4 + R 375 mg/m^2 d 1 x up to 6 cycles	83	47% (2 y)
Roy *et al.* [2012]	9 (FL)	Rel/Ref	Bor 1 or 1.3 or 1.6 mg/m^2 qw (d 1, 8, 15) + ^{90}Y-Ibr.T. 0.4mCi/kg d 15 + Bor 1.6 mg/m^2 qw (d 1, 8, 15) x up to 3 cycles	89	6.5

FL, follicular lymphoma; SLL, small lymphocytic lymphoma; LPL, lymphoplasmacytic lymphoma; MZL, marginal-zone lymphoma; MCL, mantle-cell lymphoma; iNFL, indolent nonfollicular lymphoma; Rel/Ref, relapsed/refractory; Bor, bortezomib; B, bendamustine; R, rituximab; ORR, overall response rate; CR, complete remission; PFS, progression-free survival; qw, weekly (day 1,8,15,22); biw, biweekly (day 1,4,8,11); NTE, not to exceed; ^{90}Y-Ibr.T., ^{90}Y ibritumomab tiuxetan

regimen in iNHL patients have been performed in recent years. In a randomized phase II trial of the GELA, patients with B-cell NHL were allocated to receive frontline standard R-CHOP with addition of bortezomib either with the biweekly or weekly schedule [Ribrag *et al.* 2009]. A total of 49 patients were enrolled, with a CR/CRu rate of 82%. The ORR appeared higher in the biweekly arm (90% *versus* 79%) and at the higher doses. However, since grade 3 neurologic toxicity was excessively increased at the higher doses in both arms, the investigators concluded that the biweekly doses of bortezomib in combination with R-CHOP should not exceed 1 mg/m^2. A recent phase I trial in untreated iNHL demonstrated, however, that weekly bortezomib, combined with modified R-CHOP with vincristine capped at 1.5 mg, is able to produce high response rates without substantial increase in PN development (grade 3–4: 11%) up to the maximum tolerated dose of 1.6 mg/m^2 [Sinha *et al.* 2012].

Recently, two phase II trials investigating the combination of bortezomib, bendamustine, and rituximab (VBR) have been completed. In the larger VERTICAL trial, 73 patients with relapsed/refractory FL were enrolled to receive up to five cycles of VBR [Fowler *et al.* 2011]. The ORR was 88% (53% CR) and the median PFS was 14.9 months. Myelosuppression was the main toxicity (25% and 14% of patients experienced grade 3–4 neutropenia and thrombocytopenia, respectively), while transient grade 3–4 neuropathy occurred in 11% of patients. Although the primary endpoint of CR >60% was not accomplished, this regimen demonstrated to be effective in this highly pretreated population. The second study (31 patients) showed comparable results: although ORR was encouraging (83% for all subtypes; 93% for FL), the 2-year PFS of 47% did not meet the primary endpoint of 25% improvement with respect to historical results of bendamustin–rituximab only [Friedberg *et al.* 2011]. In conclusion, neither of these trials demonstrated a significant

improvement in ORR and PFS with the addition of bortezomib in relapsed/refractory FL and other iNHL.

As preclinical studies suggested that bortezomib, through inhibition of NF-κB, may act as a radiosensitizer, a phase I study was designed to explore the feasibility of weekly bortezomib combined with radioimmunotherapy (^{90}Y ibritumomab tiuxetan) in relapsed/refractory FL: despite the high rate of haematologic toxicities, this regimen resulted safe, well tolerated and effective [Roy *et al.* 2012].

Combination regimens including bortezomib seem to be an attractive option in WM. Recently, Treon and colleagues reported efficacy of bortezomib, dexamethasone and rituximab in 23 previously untreated patients with symptomatic WM [Treon *et al.* 2009]. As a best response, median bone marrow disease involvement declined from 55% to 10%, serum IgM levels declined from 4830 to 1115 mg/dl, and haematocrit increased from 29.8% to 38.2%. The ORR was 96%, and at a median follow up of 22.8 months, 18 out of 23 patients remained free of disease progression. The most common toxicity was PN, which led to discontinuation of treatment in 61% of patients.

Other proteasome inhibitors. Bortezomib is a reversible proteasome inhibitor that exhibits a lower affinity for target-binding sites, resulting in practical limitations because of drug schedule and intensity. Carfilzomib is a second-generation irreversible and selective proteasome inhibitor: recent data showed that carfilzomib is highly active in relapsed/refractory MM patients, especially if bortezomib-naïve [Vij *et al.* 2012]. Notably this agent is associated with only minimal painful PN, while its dose-limiting toxicity is myelosuppression. Moreover recent data provided evidence of significant preclinical activity of carfilzomib in WM [Sacco *et al.* 2011].

mTOR inhibitors

The PI3K/AKT/mTOR signalling pathway is one of the most deregulated in human cancer [Samuels *et al.* 2004] and it has been extensively studied as a molecular target in NHL therapy [Tay *et al.* 2010]. This pathway regulates cell growth and survival in response to growth factor receptor signalling and metabolic status [Bunney and Katan, 2010]. The activation of AKT through PI3KT leads to the stimulation of the mammalian target of rapamycin (mTOR) that is a serine/threonine kinase that regulates translation of proteins involved in cell growth, protein synthesis and cell cycle progression; mTOR exerts its action as a part of two complexes, mTORC1 and mTORC2, involved in the translation of oncogenes such as c-MYC or Cyclin D1 [Hay and Sonenberg, 2004].

PI3K/AKT/mTOR activation has been described mainly in MCL [Peponi *et al.* 2006]; however, preclinical studies have also demonstrated activation of mTOR pathways in indolent lymphomas such as FL [Garcia-Martinez *et al.*; Gulmann *et al.* 2005; Gupta *et al.* 2009; Leseux *et al.* 2008] and WM [Roccaro *et al.* 2010; Sacco *et al.* 2010]. For these reasons, many drugs targeting PI3K/AKT/mTOR pathway, and in particular rapamycin-analogue (rapalog) mTOR inhibitors, are under investigation in iNHL treatment.

Rapamicyn is a macrolide antibiotic that exerts its activity on mTORC1 complex causing a conformational change in its active site. New molecules with improved bioavailability are temsirolimus and everolimus.

Temsirolimus. Temsirolimus is a water soluble rapalog that is rapidly converted to the parent compound rapamycin after intravenous administration. It has been mainly studied in MCL for which is now a treatment option in relapsed/refractory disease [Hess *et al.* 2009].

Temsirolimus has been evaluated also in other NHL histotypes: Smith and colleagues published a phase II trial in which temsirolimus was used as a single agent in patients with relapsed aggressive and indolent lymphomas [Smith *et al.* 2010]. FL patients reached an ORR and a CR rate of 54% and 26%, respectively, and median PFS of 12.7 months; median OS has not yet been reached; CLL/SLL, and other iNHL patients obtained a PR rate of 11% with no complete responders. If we consider the results obtained by Hess and colleagues in MCL (ORR 22%; median PFS 4.8 months) [Hess *et al.* 2009], the results in FL seem promising. This was the first study to establish single-agent activity of temsirolimus in patients with B-cell lymphomas other than MCL, showing that mTOR inhibition is a rational target also in other subtypes of lymphomas.

Everolimus. Everolimus, an orally available ester derivative of rapamycin, has been tested in a phase

I study in advanced haematologic malignancies by Yee and colleagues [Yee *et al.* 2006]: no dose-limiting toxicities were observed and although no objective response were observed in lymphoid malignancies, four of six patients with CLL had a reduction in lymphocytosis or lymphadenopathy. A recently Japanese phase I study evaluating everolimus in relapsed or refractory NHL confirmed no dose-limiting toxicities [Tobinai *et al.* 2010]. Witzig and colleagues recently published a phase II study in which everolimus was tested in relapsed lymphoma [Witzig *et al.* 2011], with an ORR of 30% with no major differences between DLBCL, MCL and FL. In relapsed/refractory WM, Ghobrial and colleagues demonstrated an ORR of 70% (42% PR) [Ghobrial *et al.* 2010].

In conclusion, rapalogs show a certain degree of activity in relapsed/refractory NHL; however, with the exception of WM, a relatively low percentage of complete and durable responses has been reported. For these reasons, new mTOR inhibitor molecules are under evaluation and in particular the association with other classes of drugs is warranted to increase their efficacy.

CAL-101. The PI3K/AKT/mTOR pathway is essential in the survival of several different B-cell NHLs and therefore represents an attractive therapeutic target [Cantley, 2002]. The most important member in upstream part of this pathway is the p110d isoform of PI3K, which is restricted to cells of haematopoietic origin. CAL-101 is an oral potent p110d-selective PI3K inhibitor. Kahl and colleagues reported a phase I trial with this agent in 56 patients with B-cell malignancies, including 28 iNHL, with an ORR of 62% [Kahl *et al.* 2010b]. Notably, the most important dose-limiting toxicity was represented by reversible abnormalities in transaminases (33%). Further studies are planned for combinations of this with other agents including rituximab and bendamustine.

BTK inhibitors

Bruton's tyrosine kinase (BTK) is a key component of the BCR signalling pathway [Contri *et al.* 2005; Honigberg *et al.* 2010]. The orally bioavailable compound PCI-32765 is a selective and permanent inhibitor of BTK, resulting in block of BCR-stimulated activation of NF-κB and ERK, inhibition of growth and induction of apoptosis of B cells [Honigberg *et al.* 2010]. Fowler and colleagues [Fowler *et al.* 2010a] presented the results of an ongoing phase I trial of PCI-32765 in relapsed/refractory B-cell malignancies. In 35 patients with iNHL, ORR was 40% (1 CR and 13 PR) and responses were detected across all histologic subtypes and were quite durable. Side-effects were mild, with few grade 3 (9/47) and no grade 4 toxicities at this point in the dose escalation.

BCL-2 inhibitors

The Bcl-2 family is a group of proteins that may be either anti-apoptotic (e.g. Bcl-2, Bcl-X_L) or pro-apoptotic (Bax, Bak). The t(14;18), which occurs in the majority of FL, results in the juxtaposition of the BCL-2 gene next to the immunoglobulin heavy chain gene, leading to its constitutive expression and to signalling unbalance in favour of survival of malignant cells. AT-101, an orally active Bcl-2 inhibitor, demonstrated some activity in patients with CLL, but was associated with dose-limiting hepatic and gastrointestinal toxicity [Balakrishnan *et al.* 2009] The orally available Bcl-X_L-inhibitor ABT-263 showed activity primarily in CLL, with thrombocytopenia being the main toxicity [Wilson *et al.* 2009]. Obatoclax is a novel Bcl-2 inhibitor that appears to sensitize rituximab-resistant lymphoma cells to treatment with bortezomib; this agent is currently undergoing clinical investigation in combination with other agents in FL [Joudeh and Claxton, 2012].

Agents that target the microenvironment

Lenalidomide. Lenalidomide is an immunomodulatory drug (IMiD) which is 10,000 times more potent and displays a better safety profile than its parent compound thalidomide [Vallet *et al.* 2012]. The key to the therapeutic potential of lenalidomide lies in the fact that it has multiple mechanisms of action, resulting in anti-inflammatory, anti-angiogenic and antitumour effects in a wide spectrum of haematological malignancies, such as myelodysplastic syndromes, multiple myeloma (MM) and B-cell NHL [Kotla *et al.* 2009]. To date, lenalidomide has been associated with TNF-α inhibitory, T-cell costimulatory and anti-angiogenic effects [Teo, 2005].

With respect to thalidomide, lenalidomide displays single-agent better efficacy, has a better safety profile and does not cause significant somnolence, constipation or peripheral neuropathy. However, myelosuppression can be a serious problem, and frequently a reduction of doses and/or granulocyte growth factor support is required.

Table 6. Clinical trials evaluating lenalidomide in indolent lymphomas.

Study	Number of patients (histotypes)	Population	Treatment schedule	ORR% (CR)	PFS (months)
Witzig *et al.* [2009]	43 (22 FL, 18 SLL, 3 MZL)	Rel/Ref	Len 25 mg/d 1-21, q28	23 (7)	4.4
Fowler *et al.* [2010b]	48 (30 FL)	First line	R 375 mg/m2 d 1 + Len 20 mg/d 1 -21, q28 x up to 6	86 (79)	91% at 20 months
Leonard *et al.* [2012]	94 (FL)	Rel/Ref	Len 15 (1st) or 20 (≥2nd) mg/d 1-21, q28 x12 alone *or* + R 375 mg/m2 q7 x4	49 (13) *versus* 75 (32)	14 *versus* 24*

FL, follicular lymphoma; SLL, small lymphocytic lymphoma; MZL, marginal-zone lymphoma; Rel/Ref, relapsed/refractory; Len, lenalidomide; R, rituximab; ORR, overall response rate; CR, complete remission; PFS, progression-free survival.
*Event-free survival.

Both lenalidomide and thalidomide have comparable incidences of venous thrombotic disease (deep vein thrombosis or pulmonary embolism) [Vallet *et al.* 2012].

Lenalidomide has shown promising results in the treatment of patients with iNHL (Table 6). In a perspective phase II study evaluating the safety and the efficacy of lenalidomide monotherapy in 43 patients with relapsed/refractory iNHL the ORR was only 23% (3 CR and 7 PR); however, responses were quite durable (more than 16 months) [Witzig *et al.* 2009]. The median time to antitumor response was 3.6 months and the median PFS for the whole group was 4.4 months. Adverse events were predictable and manageable; the most common grade 3–4 adverse events were neutropenia (46%) and thrombocytopenia (19%).

Based on preclinical studies demonstrating synergistic activity between rituximab and lenalidomide in lymphoma models, several investigators are evaluating the efficacy and the tolerability of lenalidomide in combination with rituximab in iNHL. Results of a randomized CALGB study, evaluating lenalidomide alone *versus* lenalidomide and rituximab (RR or R^2 regimen) in 94 patients with recurrent FL (previously exposed to rituximab), were presented at the last ASCO meeting (2012). Briefly, RR was more active than lenalidomide alone and demonstrated a significantly longer EFS, with similar haematological toxicity [Leonard *et al.* 2012]. Recently, Fowler and colleagues reported the preliminary results of treatment with RR in newly diagnosed iNHL patients (n = 48; 30 FL). The ORR was 86% for the entire cohort (CR 79%) and 93% for FL patients (CR 86%). At a median follow up of 20 months PFS was 91% [Fowler *et al.* 2010b]. Adverse events were similar to those observed in lenalidomide single-agent studies. Of interest, no significant tumour-flare reactions were observed. Results of currently ongoing randomized trials evaluating the activity of this chemotherapy-free regimen in comparison with the current standard immunochemotherapy in iNHL are eagerly awaited.

Conclusions

In recent years, the introduction of rituximab and the rediscovery of bendamustine have provided significant benefits for patients with iNHL. Now that these agents are used more often in the front-line setting, the need remains for new and more effective drugs for progressive disease. Fortunately, an increasing number of active targeted new agents, targeting either cell surface antigens, intracellular pathways or the microenvironment, are now available for study in iNHL. However, many challenges exist in determining the optimal use of novel agents in iNHL: for example, the combination of multiple new agents should rely on scientific rationale and tolerability profile; more homogenous study populations are greatly needed, especially with reference to histologic subtypes and prognostic stratification; correlative studies focusing on enhancing the understanding of mechanism of action and resistance of the drugs are essential; randomized trials with current gold standards (such as a comparison with rituximab for novel mAbs) should be warranted; the incorporation of the use of new agents as part of initial therapy may be explored; finally, the issue of costs cannot be eluded. To address these questions, since iNHLs are still considered incurable diseases, it is of great importance to encourage patients to participate to clinical trials whenever these agents become available. In fact, the growing body of data emerging

from well-designed clinical studies would facilitate the development of better tolerated and effective combinations of these targeted therapies, which will increasingly improve the outcome of patients affected by iNHL in the near future.

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Conflict of interest statement

The authors declare no conflicts of interest in preparing this article.

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