Best Practice & Research Clinical Haematology 31 (2018) 41–48

Contents lists available at ScienceDirect

Best Practice & Research Clinical Haematology

journal homepage: www.elsevier.com/locate/beha

Novel agents for relapsed and refractory follicular lymphoma

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ARTICLE INFO

Article history:
Received 7 November 2017
Accepted 10 November 2017

Keywords:
Follicular lymphoma
Treatment
Obinutuzumab
Idelalisib
Ibrutinib
Venetoclax
Lenalidomide

ABSTRACT

Follicular lymphoma is one of the most common non-Hodgkin's lymphomas. Although current frontline regimens are associated with high response rates, most patients still relapse. When progression is discovered, re-establishing the diagnosis and ruling out transformation in paramount. The outcomes following relapse have been improving due to the activity and increasing availability of novel agents with various mechanisms of action. Despite these advances, single agent activity is limited and the disease remains incurable in the majority of cases. Examples of drug classes with promising activity in relapsed disease include anti-CD20 monoclonal antibodies, immunomodulatory drugs (IMiDs), small molecule tyrosine kinase inhibitors, bcl2 inhibitors, epigenetic modifiers, conjugated antibodies, and checkpoint inhibitors. Many drugs in each class are associated with unique, variable and often surprising toxicity profiles. Combination studies are currently underway with novel-novel combinations and with traditional chemotherapy regimens. This overview will discuss the results of several recent studies exploring activity of novel drugs in relapsed follicular lymphoma.

1. Introduction

Follicular lymphoma (FL) is the most common indolent lymphoma with over 15,000 new diagnoses in the USA each year [1]. Response to frontline therapy is typical, however the disease inevitable relapses. FL is characterized by successive lines of therapy resulting in progressively shorter periods of disease-free survival followed ultimately by the development of either chemo-refractoriness, large cell transformation, or death from treatment related toxicities [2]. Although the median OS for FL has improved dramatically in recent years and now exceeds 12 years [3,4] most patients will require successive lines of treatment for their disease and treatment should ideally achieve both disease control and maintain high quality of life with minimal therapy related toxicity.

2. General considerations in relapsed/refractory FL

Repeat biopsy is recommended at time of suspected lymphoma relapse to exclude histologic transformation to diffuse large B-cell lymphoma (DLBCL). This may be directed by positron emission tomography with computed tomography (PET-CT) and is particularly relevant where there are clinical features of histologic transformation such as rapid discordant growth of a

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https://doi.org/10.1016/j.beha.2017.11.003
1521-6926/

single nodal site, B symptoms, marked increase in serum lactate dehydrogenase (LDH) or hypercalcemia. If these features are absent and repeat biopsy shows FL without transformation to DLBCL, our practice is in line with current guidelines that therapy can be safely deferred in the absence of threatened organ function, cytopenias due to lymphoma, bulky disease or constitutional symptoms [5–7]. For patients who do require treatment, we suggest enrolment to clinical trials evaluating novel therapies whenever possible. Outside of this, the choice of second line therapy depends on many factors including the age, fitness and comorbities of the patient, duration of remission following the first line of therapy, availability of novel agents and clinical trials. In the following section we will highlight on some of the agents under active development in FL with a focus on those in phase II/III studies.

3. Novel agents for FL

3.1. Anti-CD20 monoclonal antibodies

Rituximab, more than any other agent in the last two decades, has had a profound impact on the management of patients with FL. Rituximab is effective and well tolerated as a single agent [8,9]. The use of rituximab in combination with chemotherapy has resulted in substantial improvements in patient outcomes when added to induction chemotherapy [10,11] or as a maintenance after chemo-immunotherapy [12]. Although a number of new anti-CD20 molecules have been developed, the most promising in FL is obinutuzumab, a humanized type II IgG_1 mAb. This agent differs from rituximab by glcyoengineered non-fucosylated Fc fragments that result in higher affinity interaction with FcγR and enhanced antibody mediated cell mediate cytotoxicity (ADCC) [13]. Other key differences from rituximab are the lack of complement-dependent cytotoxicity [14] and the ability to potently evoke direct cell death [15]. It is worth noting that the dosing of obinutuzumab (1000 mg flat dose) differs considerably from rituximab (375 mg/m^2) and it remains unknown which molecule is more potent *in vivo* from an equimolar basis. Investigators exploring obinutuzumab in phase II studies in relapsed/refractory indolent lymphoma have demonstrated reasonable efficacy and safety both as single agent (ORR 55%) [16] and when combined with (ORR 93%) [17]. In the GAUSS study, Sehn et al. randomized 120 patients with previously treated indolent B-NHL to obinutuzumab or rituximab as induction, followed by maintenance with the same antibody, there was no difference in PFS [18]. In the phase III GADOLIN study, patients with rituximab-refractory indolent B-NHL were randomized to either six cycles of bendamustine alone (120 mg/m^2 IV D1,2) or six cycles of bendamustine (90 mg/m^2 IV D1,2) with obinutuzumab (1000 mg flat dose D1,8,15 in cycle (C)1 and D1 C2-6), followed by obinutuzumab maintenance for 2 years [19]. The study has attracted criticism for both the definition of rituximab-refractoriness and the lack of rituximab in the control arm, but nonetheless the investigators observed the addition of obinutuzumab did not impact ORR at the end of induction (69% vs 63%, P = 0.71) however despite this, it did result in near doubling of event free survival (EFS) (median 26.8 vs 13.2 months, hazard ratio [HR] 0.57, $P = 0.0001$) [19]. The results of this study were recently updated, and the difference in OS in patients randomized to receive obinutuzumab in addition to bendamustine had become significant with additional follow-up (median OS not reached vs. 53.9 mo [HR 0.58; 95% CI 0.39, 0.86; p = 0.0061]) [20]. On the basis of this study, obinutuzumab has been granted FDA approval for patients with rituximab-refractory relapsed/refractory indolent lymphoma in combination with bendamustine.

The results of a large, international multicenter phase III GALLIUM study in which 1202 patients with symptomatic indolent B-NHL (mostly FL) were randomized to induction with a chemotherapy backbone paired with either obinutuzumab or rituximab, with responders receiving the same antibody as maintenance for 2 years [21]. Briefly, although ORR at the end of induction were similar for both rituximab and obinutuzumab, after a median follow-up of 34.5 months, among patients with FL, there was an improvement in investigator assessed PFS at 3 years among patients treated with obinutuzumab relative to rituximab (80.0 vs 73.3%, HR 0.66, $P = 0.0012$). In terms of safety, obinutuzumab resulted in numerically higher rates of grade≥3 neutropenia (43.9 vs 37.9%) thrombocytopenia (6.1 vs 2.7%) infections (20.0 vs 15.6%) and infusion reaction (12.4 v 6.7%). In our opinion, the results from this study may lead to obinutuzumab replacing rituximab as the frontline mAb for FL in the future.

3.2. Lenalidomide

Lenalidomide is an oral immunomodulatory that exerts pleiotropic effects both directly on lymphoma cells and the immune microenvironment. Lenalidomide binds to the E3 ubiquitin ligase cereblon (CRBN) blocking survival signals to tumor cells increasing IL-2 production and enhancing of T-cell co-stimulation [22]. Further, lenalidomide induces Th1 polarization [23], reduces T_{reg} cells, increases antigen presentation to T_{eff} populations [24], repairs the immune synapse between tumor cells and cytotoxic T cells [25], restores impaired T-cell motility and interferes with communication between endothelial and tumor cells, reducing neo-angiongenesis [26]. Lenalidomide was explored as a single agent in patients with relapsed/refractory indolent lymphoma (mostly FL). In the NHL-001 study, 43 patients (22 FL) were treated with lenalidomide 25 mg daily for 21 days of a 28 day cycle [27]. The ORR was 23% (CR 7%) with a median PFS of 4.4 months. Although this activity was modest, preclinical data suggested lenalidomide augments the ADCC of anti-CD20 monoclonal antibodies [28,29], prompting investigators to combine lenalidomide with rituximab. Fowler et al. used the R2 combination (lenalidomide 20 mg D1-21 of 28 day cycle and rituximab 375 mg/m^2 IV day 1) as induction therapy in treatment-naïve patients with indolent NHL (mostly FL) in a phase II study performed at MD Anderson Cancer Center [30]. Among the FL patients, the CR/CRu rate was 87% and the 3-year estimated PFS 75%, making this one of the most promising chemotherapy-free combinations in this histologic subtype.