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Review

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BENDAMUSTINE: AN OLD DRUG IN THE NEW ERA FOR PATIENTS WITH NON-HODGKIN LYMPHOMAS AND CHRONIC LYMPHOCYTIC LEUKEMIA

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SUMMARY – The aim of this review is to present data on bendamustine, a non-cross resistant alkylating agent, alone or in combination for treatment of non-Hodgkin lymphoma (NHL) and chronic lymphocytic leukemia (CLL). Bendamustine is currently approved for rituximab-resistant indolent NHL and CLL in patients not fit for conventional chemotherapy. Recent studies have shown superiority of bendamustine combination with rituximab (B-R) in first line treatment of indolent NHLs and mantle cell lymphoma, suggesting a shift of the standard of care in this setting. B-R regimen has also shown efficacy in relapsed setting suggesting the possible treatment option for patients failing conventional chemotherapy. In rituximab-resistant NHL, the recent GADOLIN study exploring the addition of obinutuzumab to bendamustine has yielded impressive result changing the standard of care in this hard-to-treat population. Concerning CLL, despite inferiority to the standard of care in young fit patients, as defined in CLL10 study, B-R has yielded a more beneficial toxicity profile and its use in first line treatment should be decided individually. In relapsed setting, the addition of ibrutinib to B-R has shown superior results compared to B-R alone, possibly changing the paradigm of treatment of relapsed CLL. In conclusion, bendamustine as a single agent or in combinations has shown activity with acceptable toxic profile in the treatment of patients with indolent NHLs or CLL without del(17p) mutation.

Key words: *Bendamustine hydrochloride; Alkylating agents; Lymphoma, non-Hodgkin; Rituximab; Leukemia, lymphocytic, chronic, B-cell; Obinutuzumab*

Introduction

Non-Hodgkin lymphomas (NHL) represent the most common malignancy in hematologic oncology. According to the US SEER program, its incidence is 19.5 cases *per* 100 000 men and women, with 70.7% of patients surviving for 5 years[1]. Chronic lymphocytic leukemia (CLL) is the most common leukemia of elderly with the incidence of 4.6 cases *per* 100 000 men and women, with 82.6% of patients surviving for 5 years according to the SEER program[2]. In Croatia, the incidence of NHL is estimated to 6.96 *per* 100 000 men and 5.57 *per* 100 000 women[3]. The incidence of CLL is 2.59 *per* 100 000 men and 1.2 *per* 100 000 women. It is important to note that NHLs are heterogeneous disorders varying from aggressive type such as diffuse large B cell lymphoma (DLBCL) to indolent one such as follicular lymphoma (FL). In a recent international classification study on NHL in south-eastern Europe, the most common type of NHL was DLBCL (37%), followed by FL (20.2%)[4]. In this study, CLL was included as NHL with a prevalence of 12.5%.

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Bendamustine belongs to a group of alkylating agents, however, it has a distinct pharmacodynamic profile[5]. *In vitro*, it phosphorylates tumor suppressor p53 leading to apoptosis. Second mechanism is DNA repair by upregulation of EXO1 gene leading to a base excision repair pathway response. Third mechanism is inducing mitotic catastrophe causing downregulation of several genes involved in mitotic checkpoints leading to multinucleation or micronucleation and chromatin condensation (all events as hallmarks of mitotic catastrophe). It is important to note that the mechanism of bendamustine action still is not known and additional studies are needed to define the precise pharmacodynamic profile. Bendamustine also has a favorable pharmacokinetic profile regardless of sex, age and race[6]. Concerning hepatic dysfunction, no difference in pharmacokinetics has been found between normal function and mild hepatic impairment. Data on severe and moderate hepatic impairment are scarce, so caution is warranted when using bendamustine in this patient subpopulation. Concerning renal impairment, difference in the safety profile is not of clinical concern[7]. Patients with renal impairment defined as creatinine clearance <40 mL/min had only two higher adverse events, i.e. blood urea nitrogen and thrombocytopenia. These data are further supported by excellent tolerability in multiple myeloma patients with renal dysfunction treated by bendamustine[8,9]. Historically, bendamustine was first synthesized and used in Eastern Germany during the Soviet era, but with the fall of the Berlin Wall, further research made it available worldwide.

The main aim of this review is to assess data on the activity of bendamustine alone or in combinations in NHLs and CLL.

Bendamustine as First Line Therapy in NHL: the End of CHOP-R Era?

Anthracycline-based regimen in combination with rituximab, so called CHOP-R regimen (rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone) has been the mainstay of treatment in CD20 positive NHLs[10-12].

Based on *in vitro* studies where bendamustine produced apoptotic features in cell lines of indolent lymphomas and synergistic activity with rituximab, it has been established as a possible target drug in indolent NHLs, especially FL[13,14]. First frontline study examining bendamustine in combination with rituximab (B-R) *versus* CHOP-R regimen in indolent NHLs was performed by the Stil group for indolent lymphomas[15]. It was a phase III non-inferiority randomized clinical trial which included 549 patients with high tumor burden indolent NHLs and mantle cell lymphoma (MCL) randomized at a 1:1 ratio to receive either CHOP-R or B-R regimen for up to 6 cycles (dose of bendamustine 90 mg/m^2 on days 1 and 2). Despite the non-inferiority design, improvement of progression-free survival (PFS) favored B-R with median PFS of 69.5 months as compared with only 31.2 months for CHOP-R. Additional analysis was based on histology. In FL, PFS in the B-R arm was not reached as compared with 40.9 months in the CHOP-R arm. Interestingly, B-R outperformed CHOP-R in MCL (35.4 *vs.* 22.1 months), which is important since the addition of rituximab to CHOP regimen never showed advantages in terms of long-term outcomes in these patients[16]. However, overall survival (OS) did not differ between the groups, with median not being reached. One reason may have been short follow-up and small number of events in both arms. Another and more probable reason lies in the cross-over design of the study, i.e. the patients that progressed during or after CHOP-R regimen were salvaged by B-R (N=116). B-R was also characterized by a distinct toxicity profile. Concerning hematologic adverse events, lower rates of leukopenia and neutropenia were observed with consequent lower rates of infectious episodes (37% *vs.* 50%). Concerning non-hematologic events, virtually no alopecia was observed in B-R group with lower rates of paresthesia, which are vincristine-induced in CHOP-R protocol, and stomatitis. On the other hand, skin erythema and skin allergic reaction were more pronounced in B-R group (16% and 15%, respectively).

Another large study in this setting was the BRIGHT non-inferiority study on 447 patients comparing B-R (dose of bendamustine 90 mg/m^2 on days 1 and 2) to CHOP-R or CVP-R (rituximab, cyclophosphamide, vincristine and prednisone) regimens in indolent NHLs or MCL, up to 6 cycles with additional 2 cycles permitted *per* investigator discretion[17]. Primary objective was complete response (CR) as measured by the "revised response criteria for malignant lymphoma"[18]. CR response was achieved in 31%

Table 1. Results of non-inferiority studies comparing B-R regimen and conventional chemotherapy in indolent NHLs or MCL

Author	Phase	B dose (mg/m^2)	Arm	N	Primary outcome	Secondary outcome
Rummel[15]	III	90	B-R *vs*. CHOP-R	549	PFS 69.5 months *vs*. 31.2 months	ORR 93% *vs*.91%*
Flinn[17]	III	90	B-R *vs*. CHOP-R /CVP-R	447	CR 31% *vs*. 25%*	ORR 97% *vs*. 91%*

*nonsignificant; NHL = non-Hodgkin lymphoma; MCL = mantle cell lymphoma; B-R = bendamustine-rituximab; B=bendamustine; PFS = progression-free survival; CR = complete remission; ORR = overall response rate

of B-R group compared to 25% in CHOP-R/CVP-R group, although the difference was not statistically significant. Overall response rate (ORR) was similar between the groups (97% and 91%, respectively). In further analysis, all variables favored B-R regimen with MCL being once again the most prominent one. Concerning safety profile, B-R regimen produced fewer hematologic adverse events, primarily, leukopenia, neutropenia and lymphocytopenia. The rates of infections were similar between the groups. Once again, B-R did not cause alopecia. Drug hypersensitivity was noted in B-R group, mainly in the form of skin reactions, but this toxicity was manageable. At the time of writing this review, no data on PFS and OS in the BRIGHT study were available. Interestingly, B-R regimen was better tolerated than CHOP-R or CVP-R as measured by quality of life (QoL) questionnares[19]. Patients reported improved outcomes on many scales such as cognitive, physical, social and emotional functioning, indicating major QoL improvement in patients receiving B-R.

In conclusion, B-R has demonstrated equal or better effect to the standard of care, improvement in outcomes in terms of PFS, major improvement in MCL histology, distinct but favorable toxicity profile, and better tolerability. This has led some authors to declare the end of the CHOP-R era in indolent lymphomas[20]. The results of these two studies are summarized in Table 1.

However, despite these encouraging results, regulatory agencies did not recognize B-R as a standard of care in indolent NHLs or MCL[21,22]. In the USA, bendamustine is approved for rituximab resistant indolent NHL, whereas in the European Union (EU) only some countries such as Germany or the United Kingdom have approved it for first line treatment of indolent NHLs. In Croatia, bendamustine is approved for rituximab-resistant indolent NHLs[23]. In accordance with the leading guidelines and data from two phase III randomized controlled trials, B-R should become standard of care in the treatment of indolent NHLs, especially for MCL patients who are not fit for high dose chemotherapy[24-26]. Despite this regulatory limitation, B-R is slowly but steadily entering clinical practice all over the world, replacing the CHOP-R regimen in indolent NHLs.

However, none of the pivotal studies had maintenance strategy with rituximab in protocol. Maintenance with rituximab every 2 months in case of CR or partial remission (PR) has become the standard of care in Europe based on PRIMA results showing improved 3-year PFS of 74.9% in maintenance group compared with 57.6% in observation group[27]. To address this question, the MAINTAIN trial was designed[28]. This was a phase III trial with three arms comparing rituximab maintenance for 2 years, 4 years, and observation after B-R induction. This approach showed feasibility and no safety signal was noted in preliminary analysis[29]. However, initial results in subset analysis of 120 MCL patients were disappointing[30]. After median follow-up of 54.2 months, two groups did not differ in PFS (not reached *vs*.54.7 months) or OS. The authors conclude that the follow-up was too short to present definitive results. Until then, maintenance strategy following B-R in indolent NHLs or MCL is purely experimental.

Furthermore, in the era of B cell receptor (BCR) signaling, B-R is attractive backbone regimen for combinations with this inhibitor. Yet, we have learnt a lesson in a hard way with idelalisib, a PI3Kδ inhibitor approved for refractory indolent NHLs[31]. In first line setting, it was combined with B-R in the treatment of indolent NHLs or CLL. Despite excellent response rates, the studies were terminated due to unexpected toxicity affecting survival curve (cytomegalovirus reactivation, *Pneumocystis jirovecii* infections, colitis, trans-

aminitis, and pneumonitis)[32]. This should serve as a warning that combination therapy with BCR inhibitors should not be taken lightly.

Concerning DLBCL, to our knowledge, there is no published study evaluating B-R in first line setting, although a phase II trial is ongoing evaluating feasibility of this approach in elderly patients with previously untreated DLBCL[33].

Bendamustine in Relapsed Setting

Indolent NHLs or MCL

There is only one randomized phase III trial evaluating B-R (dose 90 mg/m^2) *versus* fludarabine based regimen (FR, dose of fludarabine 25 mg/m^2 on day 1-3)[34]. The study included 219 patients with indolent NHLs or MCL, randomized at a 1:1 ratio. The primary objective was PFS, favoring B-R regimen with 34.2 months compared to only 11.7 months in F-R group. The authors demonstrated better OS for B-R group (109.7 months and 49.1 months, respectively). B-R and F-R had a similar toxicity profile, myelosuppression and infections. The importance of this trial is that B-R was highly active in relapsed setting and could be used as a retreatment strategy in relapsed or refractory indolent NHLs and MCL[25]. Other single arm trials evaluating B-R regimen in this setting are summarized in Table 2.

In conclusion, B-R regimen is a viable option in the treatment of patients with relapsed indolent NHLs and MCL not fit for stem cell transplant with high ORR rates, adequate duration of response and manageable toxicity.

There are multiple trials under way exploring addition of other agents such as lenalidomide, bortezomib, duvelisib (dual PI3Kδ and γ inhibitor) or temsirolimus to enhance the activity of B-R regimen itself[39-42].

Table 2. Phase II studies on B-R regimen in relapsed or refractory indolent NHLs and MCL

Author	Phase	B dose (mg/m^2)	N	Primary outcome	Secondary outcome
Rummel[35]	II	90	63	ORR 90%	PFS 24 months
Robinson[36]	II	90	67	ORR 92%	PFS 24 months
Weide[37*]	II	90	57	ORR 89%	PFS 19 months
Visco[38**]	II	70	20	ORR 80%	2-year PFS 70%

*addition of mitoxantrone to B-R regimen; **only MCL patients; NHL = non-Hodgkin lymphoma; MCL = mantle cell lymphoma; B = bendamustine; R = rituximab; ORR = overall response rate; PFS = progression-free survival

Bendamustine in rituximab-refractory indolent NHL

Eventually, a significant proportion of patients will develop refractoriness to rituximab defined as stable disease (SD) or progressive disease (PD) after rituximab therapy or progression during the first 6 months after completion of therapy. Traditionally, these patients had poor outcomes and represented clinical challenge for treatment strategy.

One study explored bendamustine (dose 120 mg/m^2) in 76 patients with rituximab-refractory indolent or transformed NHL[43]. The proportion of patients with transformed NHL was 20%. ORR for the whole group was 77% with 34% CR. ORR for indolent NHLs was 82% with 17 CR and median PFS of 8.25 months. However, duration of response in transformed NHLs was much shorter with PFS being only 4.18 months.

The pivotal study in this area was conducted by Kahl *et al*. including 100 patients with rituximab-resistant NHLs[44]. The median number of previous therapies was 2 with 36% of patients being refractory to previous therapy. Bendamustine was administered as a single agent at a dose of 120 mg/m^2 on days 1 and 2 for up to 8 cycles. ORR for the whole group was 77%. Interestingly, bendamustine produced high-level response in chemorefractory group (ORR=64%) and alkylator-refractory group (ORR=60%) due to its non-cross resistant properties. However, duration of response was rather short being 9.2 months with median PFS of 9.3 months. This study led to approval of bendamustine under current designation in the USA and Croatia[21,23]. Recently, great breakthrough was achieved in this setting with results of the GADOLIN study[45]. This phase III trial explored whether the addition of obinutuzumab, a type II antiCD20 antibody, to bendamustine (90 mg/m^2 on day 1 or 2) followed by maintenance was superior to bendamustine alone. It should be noted that the design of the study was unbalanced since patients in the comparator arm received bendamustine in a dose of 120 mg/m^2 on day 1 or 2. A

total of 396 patients were randomized at the 1:1 ratio. Despite similar ORR between the groups (69.1% *vs.* 63%), PFS was significantly different and not reached in G-B group compared to 14 months in B group after median follow-up of 20 months. This efficacy of G-B regimen to produce lasting responses may be attributed to eradication of minimal residual disease (MRD)[46]. In subanalysis of 93 patients, eradication of t(14;18), a pathognomonic event in FL, was associated with improved outcome, with 82% of patients achieving negativity in G-B group compared to 43% of patients in B group. PFS in patients that achieved MRD negativity in G-B group was not reached as compared with 7.6 months in B group. Outcomes of MRD positive patients were poor regardless of the treatment arm, with PFS of 5.4 months in G-B group and 3 months in B group. The GADOLIN trial subsequently led to approval of obinutuzumab in combination with bendamustine for rituximab-refractory indolent NHLs[47]. It is important to note that this drug has not yet been approved in the EU for this indication[48]. The studies are summarized in Table 3. Owing to excellent outcomes in rituximab-resistant indolent NHLs, the G-B regimen might be included in the standard of care of this hard-to-treat population.

Table 3. Studies on rituximab-refractory indolent NHLs

Author	Phase	B dose (mg/m^2)	N	Primary outcome	Secondary outcome
Friedberg[43]	II	120	76	ORR 82%	PFS 8.25 months
Kahl[44]	II	120	100	ORR 77%	PFS 9.3 months
Sehn [45]	III	120 (G-B) /90 (B)	396	ORR 69.1 *vs.* 63%	PFS not reached *vs.* 14 months

NHL = non-Hodgkin lymphoma; G-B = obinutuzumab-bendamustine; B = bendamustine; ORR = overall response rate; PFS = progression-free survival

Is there a role for bendamustine in relapsed or refractory DLBCL?

In young fit patients with relapsed or refractory DLBCL, high dose chemotherapy combined with rituximab followed by ASCT represents a standard of care[49,50]. However, a significant subset of patients are not candidates for high dose chemotherapy and the standard of care remains elusive in this population[51]. Owing to its properties, mainly as alkylator non-cross resistant and favorable toxicity profile, bendamustine may be the drug of choice in this setting. Several phase II trials evaluated the activity of B-R regimen in relapsed or refractory DLBCL. The largest trial included 69 patients receiving B-R (dose of bendamustine 120 mg/m^2 on day 1 or 2)[52]. The ORR was high (62.7%) with 37.3% of CR, but the response did not translate in PFS, which was only 6.7 months. All published studies on B-R regimen in relapsed or refractory DLBCL are summarized in Table 4.

Table 4. Studies on B-R regimen in relapsed or refractory DLBCL

Author	Phase	B dose (mg/m^2)	N	Primary outcome	Secondary outcome
Ohmach[52]	II	120	69	ORR 62.7%	PFS 6.7 months
Vacirca[53]	II	120	59	ORR 45.8%	PFS 3.6 months
Merchionne[54]	Retrospective	90/120	28	ORR 50%	PFS 8 months

DLBCL = diffuse large B cell lymphoma; ORR = overall response rate; PFS = progression-free survival

In conclusion, there are limited data on B-R activity in relapsed or refractory DLBCL. B-R regimen results in relatively high ORR, but long term outcomes are poor. This regimen should be offered to a limited number of patients in whom more aggressive therapy is not a valid option due to comorbidities. Furthermore, this regimen based on data from phase II trials should not be pursued further in the treatment of DLBCL, especially in the era of BCR inhibitors[55].

Bendamustine in CLL

Bendamustine in the treatment of CLL; first line setting

Due to demonstration of *in vitro* efficacy of bendamustine in CLL cell lines, it has become an attractive agent in the treatment of CLL[56]. The pivotal study in this area is comparison of bendamustine (100 mg/m^2 on days 1 and 2) to chlorambucil (0.8 mg/kg on days 1 and 15) in 319 patients for up to 6 cycles[57]. Primary

objective was ORR achieved in 68% in B arm compared to 31% in Chl arm. Higher rates of CR were noted in patients treated with B (31% and 2%, respectively). This advantage translated in the improvement of PFS with median PFS of 21.6 months in B arm compared to only 8.3 months in Chl arm. Concerning safety profile, B arm was associated with more toxicity, mainly skin allergic reaction, but hematologic toxicities were also more pronounced, resulting in a higher frequency of severe infections (8% *vs*. 3%). Updated results with a median follow-up of 54 months did not show OS benefit when stratifying patients according to age or CLL stage[58]. However, in the analysis according to objective response, median OS was not reached in B group compared to 68.3 months in Chl group. These results led to approval of bendamustine use in CLL in first line setting in patients who are not able to tolerate the FCR (fludarabine, cyclophosphamide, rituximab) regimen[21,23].

Based on *in vitro* studies and activity in indolent NHLs, the question arises if bendamustine could be the backbone chemotherapy in combination with rituximab[14]. The preliminary data come from phase II trial on 117 patients with untreated CLL[59]. B-R (dose 90 mg/m^2 on days 1 and 2) resulted in impressive ORR of 88% with 23.1% of CR. The median event-free survival (EFS) was 33.9 months with the majority of patients being alive at the end of follow-up. However, we must note that ORR (37.5%) was lower in patients harboring ominous del(17p), indicating that B-R is not an appropriate regimen for this subpopulation. There is an ongoing phase III MaBLe study comparing B-R to R-Chl, for which definitive results were not available at the time of writing this review[60].

Yet, due to the fact that bendamustine was compared to chlorambucil, a 'sick young puppy' as the world renowned expert Bruce Cheson would call it, comparison with FCR, the standard of care in young, fit patients without del(17p) was needed[61,62]. To address this question, the CLL 10 study was designed including 561 young fit patients without del(17p) as non-inferiority study comparing B-R (dose 90 mg/m^2 on days 1 and 2) to FCR for up to 6 cycles[63]. Primary endpoint was PFS of 41.7 months in B-R compared to 55.2 months in FCR group, indicating that B-R was inferior in this setting. ORR was similar between the groups (95% *vs*. 96%), with a higher rate of CR in FCR group (31% *vs*. 96%). However, the treatment with FCR comes with multiple adverse events, mainly hematologic toxicities, leading to a greater rate of infections (77% *vs*. 65%). Furthermore, FCR causes prolonged myelosuppression with the possibility of late infections after completion of therapy[64]. Another safety signal in FCR is the occurrence of secondary malignancies with a 2.38 risk to develop therapy-related acute myelogenous leukemia or myelodysplastic syndrome (5.1%) or Richter transformation to DLBCL (9%)[65]. Both entities are associated with dismal outcomes.

In our opinion, despite being inferior to FCR, B-R regimen should be introduced in the real-world clinical setting. The basis of treatment should be made upon specific goals and patient comorbidities, i.e. the choice of B-R regimen should be made individually in first line setting of CLL.

Recently, feasibility of obinutuzumab in combination with FC (fludarabine, cyclophosphamide) or bendamustine in a dose of 90 mg/m^2 (G-B) was explored in the Galton phase IB study[66]. The number of patients in G-B group was 20 with impressive ORR of 90% with 20% CR and 25% CR with incomplete marrow recovery. After median follow-up of 23.5 months, none of the patients progressed or died. The safety profile was manageable with most prominent adverse effect being infusion related reaction in 90% of patients, occurring primarily at first G-B cycle. Based on the efficacy of this regimen, a phase II trial is currently ongoing evaluating G-B in previously untreated CLL[67].

Bendamustine was also investigated in combination with ofatumumab, human antiCD20 antibody leading to cell lysis and antibody-dependent cell-mediated cytotoxicity[68]. This drug was firstly approved in the EU for the treatment of patients refractory to fludarabine and alemtuzumab [69]. In a study on 40 previously untreated patients unsuitable for FCR chemotherapy, the ORR was 95% with 43% CR[70]. Toxicity profile was tolerable with infusion reactions being the most common adverse event. The pivotal study in this area is the OMB11 5991 study on 44 patients not fit enough for FCR regimen[69]. ORR was 95% with 43% CR. It is important to note that more than half of the patients achieved MRD negativity, i.e. B-R can achieve molecular response. This led to approval of this regimen in patients who are not fit enough to tolerate FCR protocol[68]. However, we must note that due to

Table 5. Bendamustine in first line setting of CLL

Author	Phase	B dose (mg/m^2)	Arm	N	Primary outcome	Secondary outcome
Knauf[57]	III	100	B *vs*. Chl	319	ORR 68% *vs*. 31%	Median PFS 21.6 *vs*. 8.3 months
Fischer[59]	II	90	B-R	117	ORR 88%	Median EFS 33.9 months
Eichhorst[63]	III	90	B-R *vs*. FCR	561	Median PFS 41.7 *vs*. 55.2 months	ORR 95% *vs*.96%
Brown[66]	I	90	G-B	20	ORR 90%	NA
Offner[70]	II	90	O-B	40	ORR 95%	NA
OMB11 5991[69]	II	90	O-B	47	ORR 95%	MRD negativity 56%

CLL = chronic lymphocytic leukemia; B = bendamustine; Chl=chlorambucil; B-R = bendamustine-rituximab; FCR = fludarabine, cyclophosphamide, rituximab; G-B = obinutuzumab-bendamustine; O-B = ofatumumab-bendamustine; ORR = overall response rate; PFS = progression-free survival; EFS = event-free survival; NA = not applicable; MRD = minimal residual disease

Table 6. Bendamustine in relapsed or refractory CLL

Author	Phase	B dose (mg/m^2)	Arm	N	Primary outcome	Secondary outcome
Lissitchkov[71]	I	100	B-R	15	ORR 60%	NA
Fischer[72]	II	70	B-R	78	ORR 50%	EFS 14.7 months OS 33.9 months
Cortelezzi[73]	II	70	B-O	47	ORR 72.3%	2-year OS 83.6% 2-year PFS 49.6%
Chanan-Khan[74]	III	70	B-R+ibrutinib B-R	578	Median PFS not reached *vs*. 13.3 months	ORR 83% *vs*. 68%

CLL = chronic lymphocytic leukemia; B = bendamustine; B-R = bendamustine-rituximab; B-O = bendamustine-ofatumumab; ORR = overall response rate; PFS = progression-free survival; OS = overall survival; EFS = event-free survival; NA = not applicable

the clear superiority of rituximab and its worldwide use, ofatumumab is rarely used in clinical practice and the real impact of these regimens in everyday use remains unknown. The results of studies described above are summarized in Table 5.

Bendamustine in the treatment of CLL; relapsed setting

The earliest trial in this setting was a dose finding trial in 15 patients with relapsed or refractory CLL[71]. The maximum tolerated dose was 110 mg/m^2 and the recommended dose was 100 mg/m^2 at four-week interval. The activity was promising with nine patients responding to treatment including 4 CRs. During the 15-month follow-up, only one patient relapsed. The authors concluded that this regimen was active and tolerable in heavily pretreated CLL and should be investigated further on a larger number of patients.

A larger phase II study included 78 patients treated with B-R regimen (dose 70 mg/m^2 on day 1 or 2)[72]. ORR was 50% with 9% CR and 47.4% PR. In subgroup analysis, patients with del(17p) had the worst outcome with ORR being only 7.1%. It is important to note that ORR was high in fludarabine-resistant patients (45.5%). The median EFS was 14.7 months after 24-month follow-up. The median OS was 33.9 months. The regimen was associated with more toxicity than in the first line setting. The adverse events of concern were severe infections that occurred in 12.8% of patients, but this toxicity profile is expected in heavily pretreated patients.

In the Italian phase II trial, 47 patients were enrolled receiving bendamustine (dose 70 mg/m^2 on day 1 or 2) in combination with ofatumumab for up to 6 cycles[73]. B-O regimen resulted in ORR of 72.3% with 17% CR. It also yielded somewhat better ORR of 30%

in del(17p) subgroup. After median follow-up of 24.2 months, 2-year OS and PFS rates were 83.6% and 49.6%, respectively.

However, most interesting is the addition of ibrutinib, an oral Bruton kinase inhibitor to B-R regimen in the phase III Helios study[74]; 578 patients were assigned to receive either placebo or ibrutinib in addition to B-R (dose 70 mg/m^2 on day 1 or 2) for up to 6 cycles. Ibrutinib was administered until disease progression or unacceptable toxicity. The main objective was PFS, which was not reached in ibrutinib group as compared with 13.3 months in placebo group. ORR was higher in ibrutinib group (83% *vs*. 68%). In *post hoc* analysis, all variables favored ibrutinib treatment. The addition of ibrutinib did not result in additional safety signals. One of the possible pitfalls of the study was not including patients with del(17p) for which ibrutinib has become the standard of care[75-77].

In conclusion, B-R regimen seems like a reasonable option in patients failing FCR. Concerning the addition of ibrutinib to B-R, we must wait for reaction of regulatory agencies, i.e. whether ibrutinib will be registered in combination with B-R for the treatment of relapsed or refractory CLL. All the studies are summarized in Table 6.

Conclusion

As shown above, bendamustine alone or in combinations with other agents has shown impressive activity in indolent NHLs, MCL and CLL without del(17p). We must highlight certain combinations which may be a standard of care in various settings of these diseases, as follows:

1. B-R for first line setting in indolent NHLs or MCL,
2. G-B for rituximab-resistant indolent NHLs,
3. B-R for selected patients with CLL without del(17p), and
4. B-R in combination with ibrutinib for relapsed CLL without del(17p).

However, we are in the era of BCR pathway inhibitors, so the question arises whether bendamustine is still relevant while pursuing the 'chemo-free' era. However, these agents have shown unexpected toxicities, especially in first line setting, leading to early termination of multiple trials and causing 'speed bumps' on our way to 'chemo-free' era[78]. Until we learn how to combine these inhibitors with acceptable toxicity profile, bendamustine will remain relevant in every day hematologic practice.

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Sažetak

BENDAMUSTIN: STARI LIJEK U NOVOJ ERI ZA BOLESNIKE S NE-HODGKINOVIM LIMFOMIMA I KRONIČNOM LIMFOCITNOM LEUKEMIJOM

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Cilj ovoga preglednog rada je procijeniti aktivnost bendamustina te njegovih kombinacija u ne-Hodgkinovim limfomima (NHL) i kroničnoj limfocitnoj leukemiji (KLL). Bendamustin je sada indiciran u Republici Hrvatskoj za liječenje rituksimab-rezistentnog NHL-a i u bolesnika s KLL-om koji nisu kandidati za konvencionalnu terapiju. No, kombinacija bendamustina s rituksimabom (B-R) u prvoj liniji terapije indolentnog NHL-a i limfoma plaštene zone pokazala se boljom od konvencionalne kemoterapije pa bi B-R trebao postati zlatni standard u prvoj liniji liječenja ovih limfoma. Protokol B-R također ima aktivnost u relapsnom indolentnom NHL-u te predstavlja opciju za bolesnike koji su progredirali nakon konvencionalne kemoterapije. U rituksimab-rezistentnom NHL-u nedavna studija GADOLIN koja je proučavala dodatak obinutuzumaba bendamustinu pokazala je jasnu superiornost prema bendamustinu i promijenila zlatni standard u ovoj populaciji zahtjevnoj za liječenje. U KLL-u usprkos inferiornosti B-R prema FCR-u u studiji CLL10 B-R je bio obilježen boljim profilom toksičnosti te se može ponuditi pojedinim bolesnicima na temelju individualizirane odluke. U relapsnom okružju KLL-a dodatak ibrutiniba protokolu B-R pokazao je superiornost prema B-R s mogućom promjenom paradigme liječenja ovih bolesnika. Zaključno, bendamustin sam ili u kombinacijama pokazao je visoku aktivnost s povoljnim toksičnim profilom u liječenju indolentnih NHL-a i KLL bez mutacije del(17p).

Ključne riječi: *Bendamustin hidroklorid; Alkilirajuća sredstva; Limfom, ne-Hodgkinov; Rituksimab; Leukemija B-stanica, limfocitna; Obinutuzumab*