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ORIGINAL REPORT

Combination of Rituximab, Bendamustine, and Cytarabine for Patients With Mantle-Cell Non-Hodgkin Lymphoma Ineligible for Intensive Regimens or Autologous Transplantation

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ABSTRACT

Purpose
The combination of bendamustine (B) and rituximab (R) is efficacious, with favorable toxicity in mantle-cell lymphoma (MCL). In this phase II study, we combined cytarabine with R and B (R-BAC) in patients with MCL age ≥ 65 years who were previously untreated or relapsed or refractory (R/R) after one prior immunochemotherapy treatment.

Patients and Methods
In stage one, we established the maximum-tolerated dose (MTD) of cytarabine in R-BAC. In stage two, patients received R (375 mg/m^2 intravenously [IV] on day 1), B (70 mg/m^2 IV on days 2 and 3), and cytarabine (MTD IV on days 2 to 4) every 28 days for four to six cycles. The primary end point (overall response rate [ORR]) was evaluated by positron emission tomography. Secondary end points included safety, progression-free survival (PFS), response duration, and overall survival.

Results
Forty patients (median age, 70 years; 20 previously untreated patients) were enrolled; 93% had Ann Arbor stage III/IV disease; 49% had high Mantle Cell International Prognostic Index scores, with 15% blastoid histology. All R/R patients (35% refractory) had previously received R-containing regimens. The cytarabine MTD used in stage two was 800 mg/m^2, and R-BAC was well tolerated, with an 85% treatment completion rate. The major toxicity was transient grades 3 to 4 thrombocytopenia (87% of patients); febrile neutropenia occurred in 12%. The ORR was 100% (95% complete response [CR]) for previously untreated and 80% (70% CR) for R/R patients. The 2-year PFS rate (± standard deviation) was 95% ± 5% for untreated and 70% ± 10% for R/R patients.

Conclusion
R-BAC is well tolerated and active against MCL.

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INTRODUCTION

Mantle-cell lymphoma (MCL) is one of the more aggressive forms of non-Hodgkin lymphoma, with a median survival of 3 to 5 years.[1] Intensive regimens adopted for younger patients with MCL (age < 65 years) have provided encouraging short-term results,[2-4] with the incorporation of high-dose cytarabine being widely recognized as highly beneficial.[2-7] However, two thirds of patients diagnosed with MCL are older than age 60 years, and effective and well-tolerated low-toxic first-line therapeutic options are urgently needed for this large group of elderly or unfit patients.[5]

Combination chemoimmunotherapy regimens, such as R-CHOP (rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone), are accepted by many groups as standard treatment for elderly patients, and their effectiveness has been recently shown to be improved by rituximab maintenance.[5-8] Bendamustine is also an active monotherapy that is well tolerated by older or frail patients.[9,10] Improved efficacy was demonstrated when bendamustine was combined with rituximab in comparison with R-CHOP in a randomized trial including patients with MCL.[11]

Rituximab, bendamustine, and cytarabine have demonstrated distinct and synergistic mechanisms of action in preclinical studies. Our group recently reported that bendamustine significantly increased cytarabine cytotoxicity in MCL cell lines, especially when administered sequentially.[12,13]

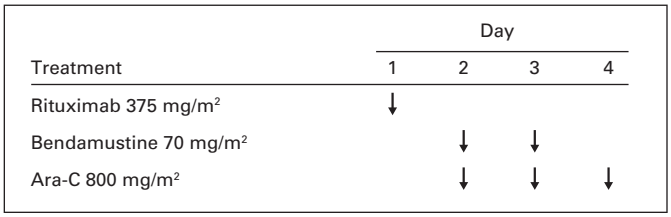

Fig 1. Rituximab, bendamustine, and cytarabine (Ara-C) scheme. Rituximab was administered on day 1 of the first cycle and on day 2 from cycle two onward. Bendamustine was administered intravenously during a 30- to 60-minute infusion on days 2 and 3 of each cycle, and cytarabine was administered during a 2-hour infusion, 2 hours after bendamustine administration, on days 2 to 4. Each treatment cycle lasted 28 days.

Rituximab also potentiated the cytotoxicity of bendamustine against NHL cell lines in a previous study.[14] Therefore, we investigated the efficacy and safety of rituximab, bendamustine, and a relatively low dose of cytarabine (R-BAC) in older or relapsed or refractory (R/R) patients with MCL who were not eligible for intensive regimens.

PATIENTS AND METHODS

Study Design

This open-label, single-arm, phase II clinical trial was conducted in two stages. The dose-finding stage determined dose-limiting toxicity (DLT) and the maximum-tolerated dose (MTD) of intravenous (IV) cytarabine combined with fixed rituximab (375 mg/m^2) and bendamustine (70 mg/m^2) IV doses repeated at 4-week intervals. Stage two evaluated the safety and efficacy of the R-BAC regimen, incorporating the MTD of cytarabine with these fixed doses of rituximab and bendamustine (Fig 1) in a larger group of patients.

The study was conducted in accordance with the principles of the Declaration of Helsinki, Good Clinical Practice, and current national rules. The study, approved by the ethics committee of San Bortolo Hospital (Vicenza, Italy), was registered with the European Medicines Agency (EUDRA-CT 2009-009912-34).

Patients and Eligibility

Eligible patients had confirmed bidimensionally measurable MCL, WHO performance status of 0 to 2, and adequate renal and hepatic functions and were either previously untreated (age $\geq$ 65 years) or R/R after one previous immunochemotherapy treatment ($\pm$ autologous marrow transplantation; age $\geq$ 18 years). Patients were recruited from four major hematology units in northeast Italy and were referred to San Bortolo Hospital for screening, treatment, and follow-up. Additional eligibility details are provided in the Appendix (online only).

A diagnosis of MCL was confirmed by WHO classification criteria, including lymphoma-cell positivity for cyclin D1, SOX11 positivity in cyclin D1–negative or t(11;14)-negative cells, and expression of CD20 and CD5. All specimens were reviewed by two expert hematopathologists (A.M, E.S.G.D.).

Stage One: Dose-Finding Treatment Plan and DLTs

To our knowledge, this is the first clinical study exploring the association of bendamustine and cytarabine in patients with lymphoma. An initial cytarabine dose of 800 mg/m^2 was adopted because of its good toxicity profile in older patients.[15] Stage one of the study was designed according to the modified Fibonacci increment rule, starting with the lowest dose of cytarabine (800 mg/m^2) and adopting the traditional escalation rule, as specified in the Appendix (online only).

Stage Two: Baseline Evaluation, Treatment, Response Assessment, and Supportive Care

Baseline evaluation included bone marrow biopsy and flow cytometry as well as tumor staging using contrast-enhanced computed tomography (CT) scan and positron emission tomography (PET). All patients were meant to receive four cycles of R-BAC, and each treatment cycle lasted 4 weeks (Fig 1). Previously untreated patients could receive up to six cycles if they were age $<$ 80 years, exhibited good treatment tolerance, or developed disease regression from treatment cycles two to four. Patients not responding to the initial two cycles were discontinued.

At the end of treatment, patients underwent CT, PET, and bone marrow biopsy with flow cytometry. CT scan was repeated 3 months later and then every 6 months. Details on dose reductions, supportive care, premedication, blood count checks, definition of complete response (CR), PET evaluation and review, and follow-up are reported in the Appendix (online only).

Assessment of Stem-Cell Mobilization

Eight patients (four untreated, four R/R) were monitored for stem-cell collection on neutrophil recovery after cycle three to assess the potential mobilizing activity of R-BAC (Table 1).

Study End Points

The primary end points of stages one and two were to determine the MTD of cytarabine and overall response rate (ORR), respectively. Secondary end points included safety, CR, progression-free survival (PFS), and duration of response (DOR). Response, overall survival (OS), PFS, and DOR were defined according to revised Cheson criteria.[16]

Statistical Analysis and Study Power

The Kaplan-Meier method was used to estimate median PFS, OS, and DOR, and survival rates were expressed as percentages ($\pm$ 95% CI). We hypothesized that R-BAC would produce a minimum ORR $\geq$ 70%, with an optimum level of activity of 90%. This assumption was based on prior studies indicating an ORR of 71% to 94% in previously untreated patients of similar age distribution receiving alternative regimens[8,17,18] and an ORR of 58% to 75% in R/R patients treated with chemoimmunotherapy combinations.[9,19] It was determined that a planned sample size of at least 36 patients would yield $>$ 90% power (using an overall, two-sided, 5% significance level) when detecting an increase of 20% in ORR after treatment with R-BAC. According to the optimal two-stage design,[20] an ORR would be considered unacceptable if $<$ 29 of 36 patients responded to R-BAC.

RESULTS

Patient Characteristics

The study enrolled 40 patients from June 2009 to October 2011 of median age 70 years. None presented with non-nodal leukemic picture. All R/R patients had been treated with rituximab-containing regimens (Table 1). Two patients had undergone first-line autologous transplantation, and two others had undergone therapeutic splenectomy with chemotherapy.

Stage One: Dose Finding

Six patients (three previously untreated who received six cycles and three R/R receiving four cycles) were independently evaluated after completing 30 cycles of R-BAC at the cytarabine 800 mg/m^2 IV starting dose. This dose was considered to be the MTD because one patient in each cohort experienced a DLT (grade 4 thrombocytopenia). Following criteria specified in the Appendix (online only), no dose modifications were planned, and stage two evaluated the R-BAC treatment scheme shown in Figure 1.

Stage Two: Safety

Thirty-four patients (85%) completed the planned $\geq$ four treatment cycles. Six patients (one untreated, five R/R) discontinued after $<$ four R-BAC cycles because of adverse events (n = 3), progressive disease (PD)/no response (n = 2), or patient decision (n = 1). Of the 182 treatment cycles administered, 15 (8%) were delayed. However, each delay lasted $<$ 14 days. Nine previously untreated patients (45%)

Table 1. Patient Demographics and Clinical Characteristics

Characteristic	All Patients (N = 40)		Previously Untreated Patients (n = 20)		R/R Patients (n = 20)	
	No.	%	No.	%	No.	%
Age, years						
Median	70		72		70	
Range	54-82		65-82		54-82	
Sex						
Male	24	60	9	45	15	75
Female	16	40	11	55	5	25
AAS						
I to II	3	7	3	15	0	0
III to IV	37	93	17	85	20	100
Bulky mass						
Yes	18	45	7	35	11	55
No	22	55	13	65	9	45
Performance status						
0 to 1	24	60	13	65	11	55
2	16	40	7	35	9	45
Previous chemotherapy						
R-CHOP			NA		8	40
R-HyperCVAD*			NA		7	35
R-CVP			NA		2	10
R-FCM			NA		1	5
RB			NA		2	10
Refractory			NA		6	36
Relapsed			NA		14	64
Time to relapse, months						
Median					20	
Range					2-46	
Histology						
Classic MCL	34	85	20	100	14	70
Blastoid variant	6	15	0	0	6	30
SOX11 positive	35	88	17	85	18	90
Ki-67, %						
Median	20		20		25	
Range	5-80		10-40		5-80	
IPI risk category						
Low/intermediate	17	43	9	45	8	40
Intermediate/high	23	57	11	55	12	60
MIPI risk category						
Low	11	28	4	20	7	35
Intermediate	10	25	4	20	6	30
High	19	47	12	60	7	35
Response rates						
OR	36	90	20	100	16	80
CR	33	83	19	95	14	70
PR	3	7	1	5	2	10
NR	3	7	0	0	3	15
PD	1	3	0	0	1	5
Stem-cell harvest						
Mobilization attempt	9	23	4	20	5	25
Successful (CD34+ $> 3 \times 10^6$/kg),†	6	67	4	100	2	40

Abbreviations: AAS, Ann Arbor stage; CR, complete response; IPI, International Prognostic Index; MCL, mantle-cell lymphoma; MIPI, Mantle-Cell Lymphoma International Prognostic Index; NA, not applicable; NR, no response; OR, overall response; PD, progressive disease; PR, partial response; RB, rituximab combined with bendamustine; R-CHOP, rituximab combined with cyclophosphamide, doxorubicin, vincristine, and prednisone; R-CVP, rituximab combined with cyclophosphamide, vincristine, and prednisone; R-FCM, rituximab combined with fludarabine, cyclophosphamide, and mitoxantrone; R-HyperCVAD, rituximab combined with hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone alternating with methotrexate and cytarabine; R/R, relapsed/refractory.

*Followed by autologous transplantation in two patients.

†Median No. of harvested CD34+, 11.2 and 12.7 $\times 10^6$/kg after first and second lines, respectively.

received six cycles because of good tolerance (n = 7) or a continued response between cycles two and four (n = 2). Median numbers of administered cycles were 4.6 and 4.0 for untreated and R/R patients, respectively (range, two to six).

Overall, R-BAC was well tolerated (Tables 2 and 3). The primary toxicity was reversible myelosuppression. Thrombocytopenia required transfusions in 65% of cycles, and 44% of patients received erythropoietin. Thrombocytopenia and leukopenia were significantly

Table 2. Hematologic Toxicity According to Patient Status

	Overall				Previously Untreated Patients		R/R Patients		
	Cycles (N = 182)		Patients (N = 40)		Cycles (n = 100)		Cycles (n = 82)		
Grade 3 or 4 Event	No.	%	No.	%	No.	%	No.	%	*P**
Leukopenia	87	48	23	57	32	32	55	67	< .001
Neutropenia	56	31	16	40	17	17	39	49	< .001
Febrile neutropenia	7	4	5	12	4	4	3	4	NS
Thrombocytopenia	138	76	35	87	70	70	68	83	.02
Anemia	48	26	18	45	22	22	26	32	NS

NOTE. Data refer to cycles with at least 1 day of a grade 3 or 4 event.
Abbreviations: R/R, relapsed or refractory to one prior rituximab-containing immunochemotherapy regimen; NS, not statistically significant.
**P* value refers to the comparison between No. of cycles with grade 3 or 4 event in previously untreated versus R/R patients.

more common in R/R than untreated patients (Table 2). Severe neutropenia (median duration, 2 days; range, 0 to 5 days) was also more frequent in R/R than untreated patients (49% *v* 17%; $P < .001$). Febrile neutropenia was quite uncommon (4% of cycles; 12% of patients). Only one patient discontinued treatment after three cycles because of prolonged grade 3 cytopenia, which slowly resolved 4 months after the last R-BAC dose. Two patients had grade 2 leukopenia and thrombocytopenia for 6 months after stopping R-BAC, which then resolved spontaneously. There was no clear trend toward an increase in cytopenia severity or transfusion requirements with subsequent cycles.

Most nonhematologic adverse events were grades 1 to 2, and common events attributed to R-BAC included fatigue (35%), cutaneous rash/desquamation (15%), and isolated gamma-glutamyl transferase elevation (40%; Table 3). Five patients reported grade 3 or 4 infections (respiratory tract infection, n = 1; *Herpes zoster*, n = 1; *Escherichia coli* sepsis, n = 1; febrile neutropenia of unknown origin, n = 2). Other grades 3 to 4 nonhematologic toxicities included one grade 4 myocardial infarction after one cycle and one grade 3 severe fluid retention with pulmonary edema after two cycles. Although the myocardial infarction was considered unrelated to study treatment, and the patient completed six cycles without additional events, the patient with pulmonary edema was withdrawn. Four patients (10%) had glutamic-pyruvic transaminase/glutamic-oxaloacetic transaminase increases, and one patient discontinued after three R-BAC cycles because of a grade 3 flare. All gamma-glutamyl transferase and glutamic-pyruvic transaminase/glutamic-oxaloacetic transaminase increases returned to pretreatment levels within 2 months of completing treatment. Skin rash, sometimes accompanied by localized itchy areas of cutaneous desquamation, did not progress to epidermal complications and spontaneously regressed. Skin rash was considered possibly related to R-BAC, although other medications could have contributed. There was no evidence of renal toxicity or significant alopecia.

Of the eight deaths reported during the study, seven were attributed to PD (all in R/R group), and one was attributed to cerebral stroke. One patient developed a squamous cell carcinoma of the lung 18 months after completing R-BAC.

Table 3. Nonhematologic Toxicities Occurring in ≥ One Patient

	All Grades		Grade 3		Grade 4	
Event	No. of Patients	%	No. of Patients	%	No. of Patients	%
Nausea/vomiting	3	7	0	0	0	0
Infusion-related reactions	2	5	0	0	0	0
Stomatitis	2	5	0	0	0	0
Fatigue	14	35	2	5	NA	NA
Infection	6	15	3*	7	2†	5
Gamma-GT elevation	16	40	9	23	0	0
GOT-GPT elevation	4	10	1	2	0	0
Alopecia	2	5	0	0	0	0
Rash/desquamation	6	15	0	0	0	0
Cardiac	3	7	1	2	1‡	2

Abbreviations: Gamma-GT, gamma-glutamyl transferase; GOT/GPT glutamic-oxaloacetic transaminase/glutamic-pyruvic transaminase; NA, not applicable.
**Herpes zoster* virus reactivation (n = 1); febrile neutropenia (n = 2).
†Pneumonitis (n = 1) and *Escherichia coli* sepsis (n = 1).
‡Myocardial infarction.

Stage Two: Efficacy and Stem-Cell Mobilization

ORRs were 90% (83% CR; 7% partial response [PR]) for all patients, 100% (95% CR; 5% PR) for untreated patients, and 80% (70% CR; 10% PR) for R/R patients. Three R/R patients had no response (7%), and another had PD (3%; Table 1). This patient was an 81-year-old man with blastoid MCL who previously experienced PD after transiently responding to rituximab and bendamustine. The ORR for seven patients who received first-line R-HyperCVAD (rituximab combined with hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone alternating with methotrexate and cytarabine; two had undergone autologous transplantation) was 86% (all CR). ORRs were 67% (50% CR) for six patients with blastoid MCL (all R/R) and 84% (67% CR) for six patients who were refractory to prior therapy.

After a median follow-up of 26 months (range, 11 to 38 months), 31 patients (78%) were alive and disease free, and median PFS/DOR had not been reached. The 2-year PFS and DOR rates were 95% (± 95% CI, 5%) and 100% for untreated patients and 70% (± 95% CI, 10%) and 87% (± 95% CI, 8%) for R/R patients, respectively (Fig 2). These rates were similar in patients receiving four or six R-BAC cycles and between SOX11-positive and SOX11-negative patients. PET positivity at the end of treatment ($P < .001$), high Mantle-Cell International Prognostic Index (MIPI) score ($P = .02$), and Ki-67 > 20%

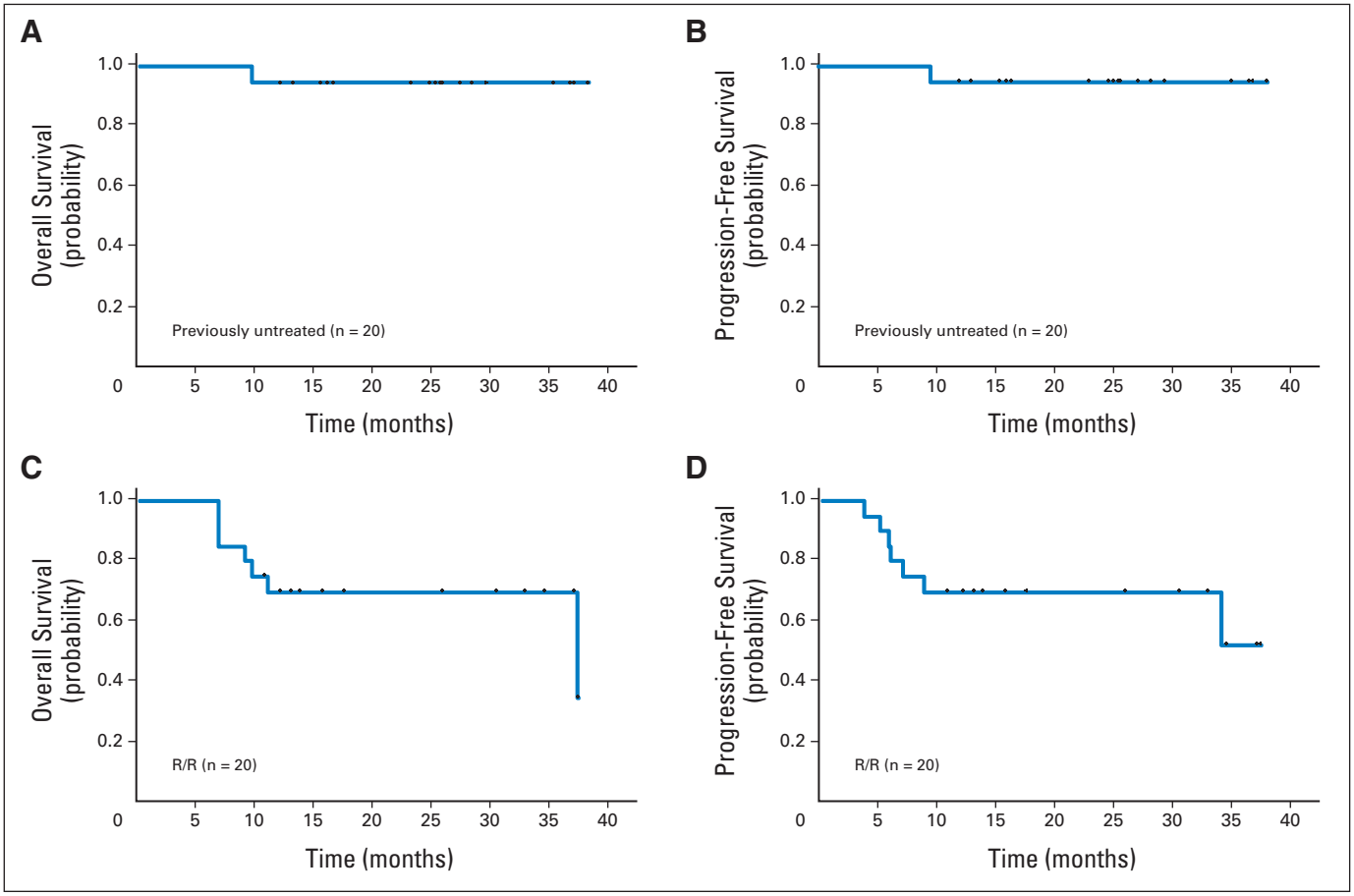

Fig 2. In (A, B) previously untreated and (C, D) relapsed or refractory (R/R) patients with mantle-cell lymphoma, Kaplan-Meier survival curves for (A, C) overall survival and (B, D) progression-free survival.

($P = .03$) were significantly associated with inferior survival. Survival curves of the patient subgroups are shown in Figure 3. First-line R-BAC was particularly effective in terms of stem-cell harvest, with 100% CD34+ cell mobilizing success (Table 1).

DISCUSSION

The sequential R-BAC regimen was active in this series of elderly patients with MCL, inducing high ORR (100% and 80%) and CR (95% and 75%) rates in treatment-naive and R/R patients, respectively. Treatment was well tolerated, with 19 of 20 previously untreated patients (median age, 72 years) completing at least four cycles; the most common toxicity was reversible and manageable grades 3 to 4 thrombocytopenia. Strikingly, none of the treatment-naive patients relapsed or experienced PD during the median 27 months of follow-up, and only one adverse event was reported (fatal cerebral stroke 6 months after completing therapy in a patient with sustained CR) in this group. Patients with relapsed (n = 14) or refractory (n = 6) MCL, all previously treated with rituximab-containing regimens, had promising 2-year PFS (70%) and DOR (87%) rates.

Response rates from the present study compare favorably with those reported for established first-line treatments in elderly patients with MCL. Similar ORRs but relatively low CR rates have been demonstrated with first-line R-CHOP in younger cohorts of patients of median age 61 years[8] or age < 65 years.[21] In these cohorts, ORR, CR rate, and median time-to-treatment failure (TTF) with R-CHOP were 94%, 34%, and 21 months[8] and 96%, 48%, and 16 months, respectively.[21] Our reported 95% CR rate with first-line R-BAC is markedly higher than those reported with R-CHOP and was achieved in older patients with higher MIPI scores. However, this discrepancy might have resulted in part from the differences in criteria used to measure CR between our study[16] and previous studies.[22] Unlike in previous studies, a post-treatment residual mass of any size was permitted as long as it was PET negative in our study. Indeed, two patients achieving PR according to CT scan alone were converted to CR in our study because of PET negativity; both are alive and free of disease after 18 and 26 months. Post-treatment PET has never been systematically evaluated in prospective cohorts of patients with MCL, and our results substantiate its use in clinical practice (Fig 3), confirming what has been suggested in retrospective studies.[23,24] These data, together with the apparently shorter TTF in the two R-CHOP studies, suggest that R-BAC induces responses of higher quality and longer duration than R-CHOP in previously untreated elderly patients with MCL.

A randomized European MCL Network trial compared induction with R-FC (rituximab combined with fludarabine plus cyclophosphamide) with R-CHOP in elderly patients with MCL before evaluating the role of rituximab maintenance.[5,7] Similar to our study, median patient age was 70 years, and 50% of patients had high MIPI

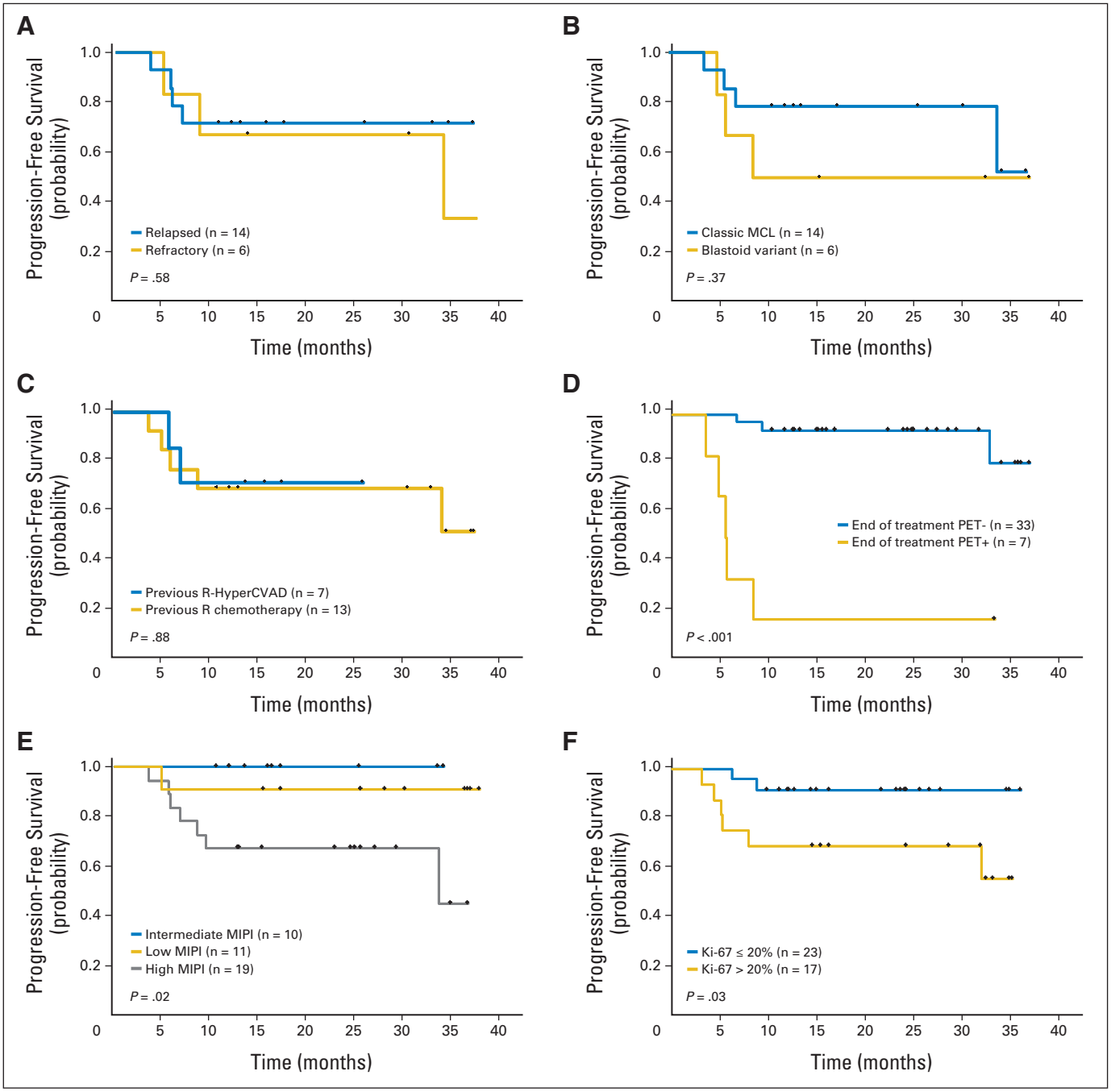

Fig 3. Kaplan-Meier survival curves for progression-free survival (PFS) and PFS stratification based on (A) relapsed or refractory patients, (B) cytologic subtype of mantle-cell lymphoma (MCL), (C) type of previous immunochemotherapy, (D) positron emission tomography (PET) scan evaluation after the end of treatment, (E) Mantle Cell International Prognostic Index (MIPI) score (*P* value refers to difference between low or intermediate *v* high), and (F) Ki-67 expression level. The six refractory patients had previously been treated with R-CVP (rituximab plus cyclophosphamide, vincristine, and prednisone; n = 1), R-CHOP (rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone; n = 3), rituximab plus bendamustine (n = 1), and R-HyperCVAD (rituximab combined with hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone alternating with methotrexate and cytarabine; n = 1). R chemotherapy, rituximab-containing chemotherapy.

scores. Reported CR/unconfirmed CR rates were similar for R-FC (52%) and R-CHOP (50%), and patients responding to R-CHOP or R-FC who did not receive maintenance therapy had a median DOR of 18 months, similar to the median TTF duration previously reported for R-CHOP.[19,21]

A prospective, randomized, phase III study compared RB (rituximab plus bendamustine) with R-CHOP as first-line therapy in patients with MCL.[11] For patients treated with RB, the reported CR was 42%, and median PFS (34 months) was significantly better than that for those treated with R-CHOP. Although our PFS curve (95% 2-year PFS rate) compares favorably with the RB study (at least for the first 2 years), a longer follow-up is needed to confirm this observation. More recently, the addition of bortezomib to R-CHOP (36 untreated patients with MCL; median age, 66 years; 28% with high-risk MIPI

scores)[25] or RiPAD+C (rituximab plus doxorubicin, dexamethasone, and chlorambucil; 39 patients; median age, 72 years; 54% with high-risk MIPI scores)[26] improved response rates but did not significantly prolong PFS (2-year PFS, 44% and median PFS, 26 months, respectively), with responses seemingly less durable than those after treatment with R-BAC.

Efficacy outcomes associated with R-BAC in patients with R/R disease are good for this relatively poorly responsive population after initial relapse. Two studies have investigated the role of RB in the treatment of small series of patients with R/R MCL.[9,10] Compared with these studies, R-BAC elicited a higher CR rate (70% *v* 50% and 59%) and longer PFS (2-year PFS, 70% *v* median PFS, approximately 18 months for RB). However, it is important to note that the patients with MCL in these studies were more heavily pretreated than those in our study (30% to 40% patients had ≥ one prior treatment [maximum, three]) and that the CR rate might have been underestimated because it was assessed by CT scan only.[9,10] On the other hand, one of the studies, conducted by Rummel et al,[9] did not include rituximab-pretreated patients. Overall, with the limits of the different inclusion criteria in the R/R setting and of the shorter follow-up of our first-line patients, R-BAC seems to produce more frequent and durable CRs compared with RB and has a good stem-cell mobilizing capacity. However, remarkably higher myelosuppression was observed. Several other regimens, including investigational drugs administered alone or in combination, in the relapsed setting have reported median PFS durations ranging from 5 to 12 months.[27-34]

The R-BAC regimen was well tolerated in first-line and relapsed settings. Nonhematologic toxicity was considered acceptable, with febrile neutropenia occurring in 12% of patients (4% of administered cycles), whereas hematologic toxicity was frequent. Grades 3 to 4 thrombocytopenia was observed in 87% of patients but was transient (median duration, 3 days) and mainly asymptomatic, with no significant bleeding signs or symptoms (Table 2). The rate of leukocytopenia with R-BAC was similar to that reported for other rituximab-containing chemotherapy regimens. Regimens such as R-FCM (rituximab plus fludarabine, cyclophosphamide, and mitoxantrone)[19] and R-CHOP[8] have demonstrated 54% and 69% grade 3 or 4 leukocytopenia rates and 12% and 5% severe thrombocytopenia rates, respectively. In contrast, RB has demonstrated grade 3 or 4 cytopenia rates in the range of 15% to 25%.[9,10] Overall, myelosupression was significant in the study despite prophylactic growth factor use in all patients (87% and 57% of patients with grades 3 and 4 thrombocytopenia/leukopenia, respectively), requiring transfusion support in the majority of cycles, and was considerably higher than with RB or R-CHOP. Because we also used a particularly low dose of bendamustine (< 70 mg/m^2) in our R-BAC regimen, it is reasonable to assume that the hematologic toxicity (myelosuppression) mainly resulted from cytarabine. Finally, it is worth considering that alopecia was reported for only two patients in our study (grades 1 to 2), whereas most patients receiving R-CHOP experience grade 3 or 4 alopecia.[8]

On the basis of these encouraging results with R-BAC, we have initiated a multicenter trial (FIL-RBAC500) promoted by the Fondazione Italiana Linfomi, with a reduced cytarabine dose of 500 mg/m^2. The FIL trial will include minimal residual disease evaluations in parallel with PET scans. The absence of minimal residual disease, which is a useful tool in MCL, was a flaw in our present study.[35]

In conclusion, these study results support the use of R-BAC in elderly patients with MCL who are not candidates for intensive treatment regimens. This combination elicited durable responses with a low incidence of severe or life-threatening adverse events but with significant transient myelosuppression. On the basis of its remarkable activity as well as stem-cell mobilizing potential in the first-line setting, R-BAC could be a useful option in the preintensification phase for younger patients with MCL, in whom achieving CR before transplantation can elicit long-lasting remissions. Additional studies are awaited to confirm our findings.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

AUTHOR CONTRIBUTIONS

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