

## Research Article

# Are Fludarabine Based Regimens Still Adequate for Relapsed/Refractory Follicular Lymphoma? An 18-Year Single-Center Experience

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## Abstract

There are no standard treatment recommendations in relapsed/refractory Follicular Lymphoma (R/R FL). Fludarabine, an effective but toxic agent, has been commonly used, but trials focusing on the risk-benefit balance in this setting are lacking and novel agents are available.

We conducted a single-center cohort study to evaluate the toxicity profile and supportive care needs of fludarabine-based regimens (FBR) administered in the first or second relapse. We retrospectively evaluated 116 R/R FL patients. Of these, 78 (67%) received FBR and 38 (33%), who were analyzed as an internal reference, received alkylating-based regimens (non-FBR). Similar disease control was obtained with both treatments. Treatment-related toxicities were high in FBR (74%) and non-FBR patients (68%). Growth factor use, transfusion requirements, short-term admissions to emergency room and prolonged hospitalization for toxicity were similar in FBR and non-FBR patients, but the latter were older and had different co-morbidities.

FBR patients over 60 years had higher incidences of grade  $\geq 2$  infections (46% vs. 18%;  $p=0.008$ ). These regimens lead to prolonged hematological recovery, compromising subsequent treatments. With a median follow up of approximately 5 years, secondary malignancies were reported in 14% of patients.

High FBR toxicity and the availability of effective novel agents raise concerns about its adequacy in R/R FL setting. Therapeutic choices require a careful balance between efficacy, toxicity, cost and feasibility of subsequent therapies.

**Keywords:** Follicular lymphoma; Relapse; Therapy; Fludarabine; Toxicity

## Abbreviations

R/R FL: Relapsed/refractory Follicular Lymphoma; FBR: Fludarabine-Based Regimens; non-FBR: Alkylating-Based Regimens; FL: Follicular Lymphoma; CLL: Chronic Lymphocytic Leukemia; R-FM: Rituximab, Fludarabine and Mitoxantrone; R-CHOP: Rituximab, Cyclophosphamide, Doxorubicin, Vincristine and Prednisolone; R-FC: Rituximab, Fludarabine and Cyclophosphamide; TRT: Treatment-Related Toxicities; TTNT: Time to Next Treatment; PFS: Progression-Free Survival; OS: Overall Survival; HSCT: Hematopoietic Stem Cell Transplant; ORR: Overall Response Rate; CR: Complete Remission

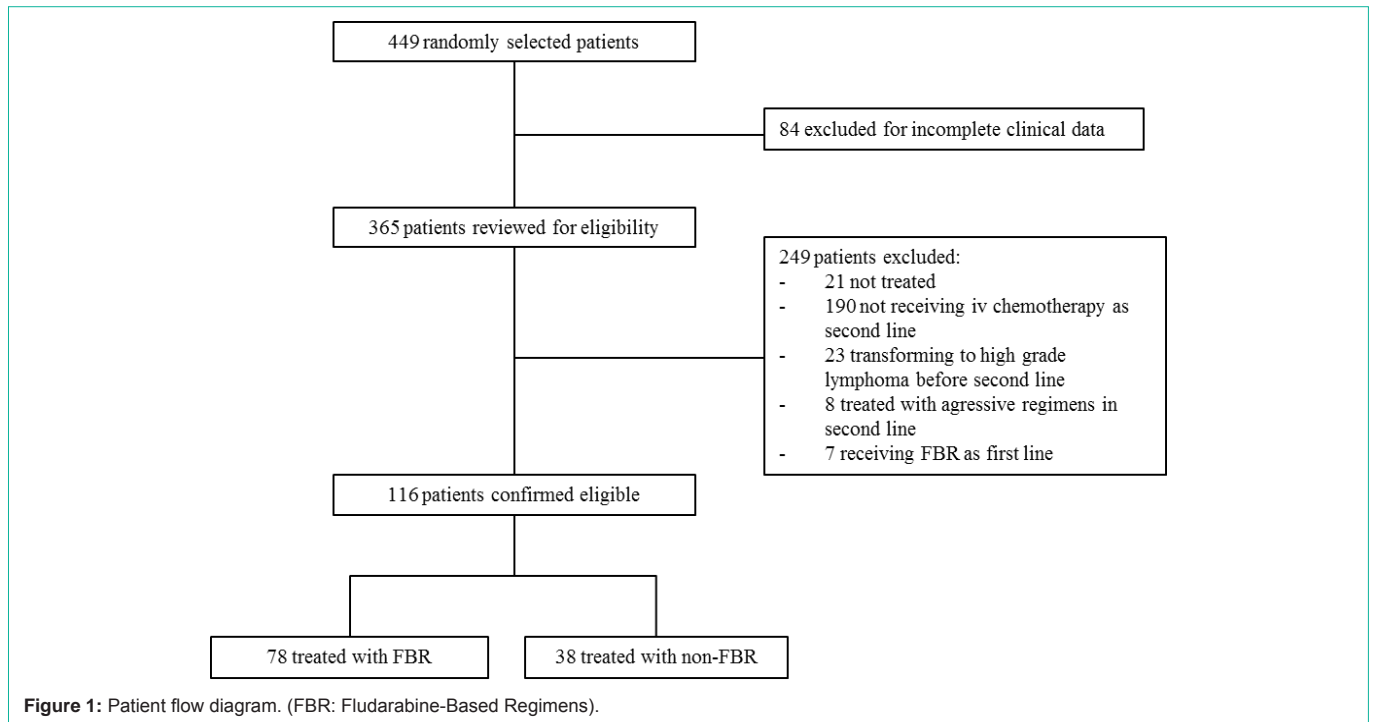
## Background

Follicular lymphoma (FL), a common indolent non-Hodgkin lymphoma subtype [1], is characterized by high response rates to first line treatment, but almost universal relapses and progressively shorter subsequent remissions. Immunochemotherapy is standard for the treatment of advanced, high tumor burden cases [2]. While survival improved with the addition of the anti-CD20 monoclonal antibody rituximab to the clinical armamentarium [3-5], no chemotherapy regimen proved to be significantly superior to others in prospective, randomized studies [6,7].

FBR have been used for the past three decades in the treatment of indolent lymphomas. Their efficacy is well documented but their use has been hampered by frequent adverse events. The toxicity profile is mainly due to myelosuppression and lymphodepletion, with frequent, severe and unusual infections that can limit therapeutic benefits in elderly and fragile patients. A high incidence of second neoplasms was also reported [6,8,9].

In chronic lymphocytic leukemia (CLL) [10,11] and mantle cell lymphoma [5,12] the results of prospective clinical trials lead to precise recommendations on the use of fludarabine. In contrast, in relapsed FL, where this drug has been commonly used, there are no standard treatment recommendations. Trials focusing on the risk-benefit balance of FBR in this setting are lacking but a high incidence of hematological toxicity has been documented [13,14].

In frontline, a randomized trial showed that rituximab, fludarabine and Mitoxantrone (R-FM) was as effective as rituximab, cyclophosphamide, doxorubicin, vincristine and prednisolone (R-CHOP). However, fludarabine use was compromised by excessive toxicity [6]. Similar results were documented in a phase 2 trial where rituximab, fludarabine and cyclophosphamide (R-FC) lead to high response rates but also excessive deaths and premature study termination [15].



Among treatment options for R/R FL, bendamustine, an alkylating agent sharing similarities with the purine-analog structure, has recently been widely adopted [2]. Its toxicity profile compares favorably with anthracycline-and fludarabine-based regimens [16] but long term results have not been published. Restricted availability in some European countries, including Portugal, limited its use as an alternative to fludarabine. Novel agents that may prove beneficial in terms of efficacy and toxicity are becoming available, although cost issues are of concern. We believe it is still relevant to characterize the risks and benefits of FBR in this setting.

Our aim was to evaluate the toxicity profile and associated supportive care of FBR regimens in the real life setting of relapsed FL, profiting from the 18-year experience of a single center where other alternatives were limited.

## Methods

We conducted a single-center cohort study. Fifty percent of all patients with grade 1, 2 or 3a FL referred to our tertiary cancer center in Portugal between 1994 and 2011 were randomly selected for retrospective review. Patients undergoing second or third line treatment until 2014 were included in the analysis. Patients receiving first line FBR, and relapsed patients receiving oral cyclophosphamide, chlorambucil, rituximab alone, Y90 ibritumomab tiuxetan or intensive regimens (ESHAP) were excluded.

FBR were recommended during this period for relapsed disease and included mainly FC (fludarabine 25-30 mg/m<sup>2</sup>/day, x3 days; cyclophosphamide 200-300 mg/m<sup>2</sup>/day x3 days every 28 days, 6 cycles), FMC (fludarabine 20-25 mg/m<sup>2</sup>/day x3 days; Mitoxantrone 8-10 mg/m<sup>2</sup>/day x1 day; cyclophosphamide 200-300 mg/m<sup>2</sup>/day x3 days every 28 days, 4 cycles). Rituximab 375 mg/m<sup>2</sup> was added on day 1 after 2003. Maintenance with rituximab 375 mg/m<sup>2</sup> every 8 weeks started in 2012.

According to local practice, patients not receiving FBR were treated with 6 to 8 CHOP or CVP cycles ±Rituximab [6].

Growth factors were allowed at the physician's discretion. Chemotherapy cycles were delayed or suspended according to toxicities.

The cut-off date for analysis was May 2015. Demographic and clinical variables were recorded. For internal reference, patients receiving non-FBR were also analyzed.

Relevant treatment-related toxicities (TRT) included grade 3-4 hematological events, grade ≥2 infections and allergies, and second neoplasms. The frequency and severity of side effects were recorded according to the NCI-CTCAE v4.0 [17]. Response to therapy, time to next treatment (TTNT), progression-free survival (PFS) and overall survival (OS) (calculated from the start of second or third line treatment) [18] was also evaluated. Patients undergoing consolidation with autologous or allogeneic hematopoietic stem cell transplant (HSCT) were censored for PFS at the time of transplant.

Time-to-event endpoints were analyzed by Kaplan-Meier method. Group comparisons were performed with Pearson's Chi-squared test or Fisher's exact test for categorical variables; t-test or Wilcoxon rank sum test were used for quantitative variables. All tests were two-sided with a 5% significance level. All analyses were done using R software [19].

## Results

### Patient population, treatment and effectiveness

Of 449 randomly selected patients, 116 fulfilled the inclusion criteria (Figure 1). Seventy-eight (67%) patients received FBR as second or third line while 38 (33%) received other regimens. Most patients were treated at first relapse (76% in the FBR and 87% in the

**Table 1:** Patient characteristics and first line treatment.

	FBR (n=78)	Non-FBR (n=38)	p-value
<b>Age at diagnosis, years</b>			
Median [min-max]	56 [26-76]	61 [24-78]	0.087
Age >60 years, n (%)	30 (39%)	20 (53%)	0.213
<b>Age at start of 2<sup>nd</sup>/3<sup>rd</sup> line treatment</b>			
Median [min-max]	60.5 [29-77]	66 [31-83]	0.022
Age >60 years, n (%)	39 (50%)	26 (68%)	0.094
<b>Gender, n (%)</b>			
Female	40 (51%)	21 (55%)	
Male	38 (49%)	17 (45%)	0.838
<b>Comorbidities at start of 2<sup>nd</sup>/3<sup>rd</sup> line treatment, n (%)</b>			
No comorbidities	47 (60%)	25 (66%)	0.709
Diabetes mellitus	13 (17%)	4 (11%)	0.550
Cardiac	7 (9%)	4 (11%)	0.748
Peripheral neuropathy	2 (3%)	2 (5%)	0.596
Renal failure	0 (0%)	4 (11%)	0.010
High infectious risk <sup>1</sup>	6 (8%)	6 (16%)	0.203
Unknown	1 (1%)	0 (0%)	
<b>Year of diagnosis</b>			
Median [min-max]	2002 [1994-2011]	2004 [1995-2010]	0.524
<b>Year of start of 2<sup>nd</sup>/3<sup>rd</sup> line treatment</b>			
Median [min-max]	2005 [1996-2014]	2009 [1998-2014]	0.003
<b>Ann Arbor stage at diagnosis, n (%)</b>			
I/II	6 (8%)	9 (24%)	
III/IV	71 (91%)	29 (76%)	0.036
Unknown	1 (1%)	0 (0%)	
<b>Extranodal involvement at diagnosis, n (%)</b>			
Yes	50 (64%)	20 (53%)	0.326
Number of sites Median [min-max]	1 [1-3]	1 [1-2]	0.779
Bone marrow involvement, n (%)	39 (50%)	16 (42%)	1.000
<b>FLIPI, n (%)</b>			
Low risk (FLIPI 0-1)	5 (6%)	3 (8%)	
Intermediate risk (FLIPI 2)	19 (24%)	13 (34%)	0.765
High risk (FLIPI 3-5)	42 (54%)	20 (53%)	
Unknown	12 (15%)	2 (5%)	
<b>First line treatment regimen, n(%)</b>			
RCHOP/RCVP	32 (41%)	17 (45%)	
CHOP/CNOP	31 (40%)	6 (16%)	0.023
CVP	10 (13%)	12 (32%)	
Other	5 (6%)	3 (8%)	
Alkylating agents + corticosteroids	4 (5%)	3 (8%)	
Rituximab	1 (1%)	0 (0%)	
<b>Number of cycles administered in 1<sup>st</sup> line</b>			
Median [min-max]	8 [3-10]	6.5 [3-11]	0.812
<b>Best response to first line treatment, n (%)</b>			
Complete response	20 (26%)	15 (40%)	
Partial response <sup>2</sup>	45 (58%)	18 (47%)	0.191 <sup>3</sup>
Stable disease / progression	13 (17%)	5 (13%)	
<b>Time to first relapse/progression, years</b>			
Median [min-max]	1.3 (0.2-11.4)	2.3 (0.2-10.3)	0.001

<sup>1</sup>Prior grade 3/4 infections, repeated infections, or clinical conditions leading to increased infectious risk.

<sup>2</sup>Includes response without bone marrow reevaluation.

<sup>3</sup>Comparison of complete response vs. non-complete response.

non-FBR group). First line treatment was mostly CHOP or CVP (93%) with or without rituximab.

Patient characteristics are summarized in Table 1. Non-FBR

patients were older at the start of second/third line treatment (p=0.022) and had a higher incidence of chronic kidney disease (p=0.010). This group additionally had longer response duration to first line therapy (median 2.3 versus 1.3 years, p=0.001). Groups were balanced for gender, other co-morbidities, FLIPI risk and response to first treatment.

Sixty-seven FBR patients (86%) received a backbone of FC. Rituximab was added in 35 patients (45%) and Mitoxantrone in 37 (47%). Five patients received further maintenance treatment with rituximab and four proceeded to high dose chemotherapy with autologous HSCT (n=2) or allogeneic HSCT (n=2). Non-FBR patients were treated with CVP (71%, n=27) or CHOP (29%, n=11), associated with rituximab in 30 cases (79%). Fourteen received rituximab maintenance. Only one patient proceeded to autologous HSCT. Median number of cycles was 4.5 in FBR and 7 in non-FBR patients, as expected per intent-to-treat.

Response rates were high (overall response rate (ORR)/complete remission (CR) 87%/38% in FBR and 81%/42% in non-FBR). With a median follow-up of 56.6 months for FBR and 25.2 months for non-FBR, 2-year PFS was 50% and 60%, respectively. 2-year OS were also identical, 75% in both groups; median TTNT was 30.5 months for FBR and 33.3 months for non-FBR.

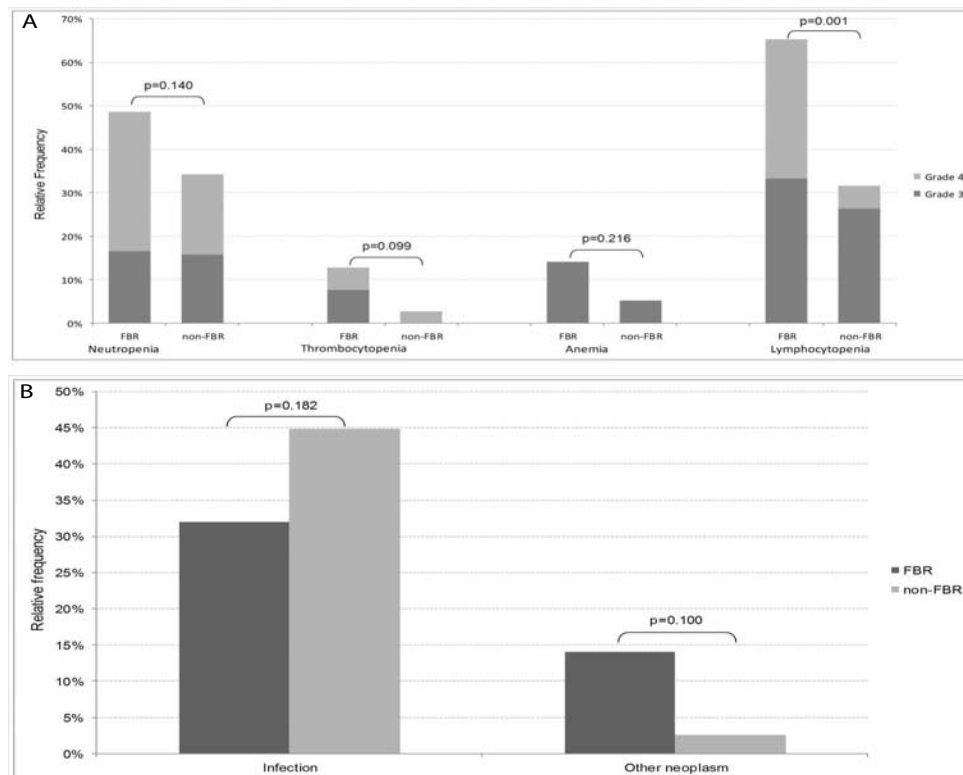
### Toxicity and supportive care

Chemotherapy delay rates (26% for FBR; 24% for non-FBR) and premature treatment discontinuation (28% for FBR; 26% for non-FBR) were similar between the two groups and mainly due to TRT. These were documented in 74% of FBR and 68% of non-FBR patients. No grade 5 toxicities occurred.

Hematological toxicity predominated, with grade 3/4 events similarly reported in the two groups (69% in FBR and 50% in non-FBR patients). The most common toxicity in the FBR group was lymphopenia (Figure 2A). Neutropenia occurred in 49% FBR and 34% non-FBR. There were 4 cases of hemolytic anemia associated to fludarabine. The hematological recovery to grade <3 occurred within 1 month for all non-FBR patients and no persistent cytopenias were seen in this group. In contrast, FBR patients experiencing hematological toxicity had a median time to neutrophil, platelet and hemoglobin recovery of 0.5, 3 and 1.5 months, respectively. Three patients never recovered 1000 neutrophils/ $\mu$ L (follow-up 3-42 months) and one had persistent grade 3/4 thrombocytopenia (follow-up 7 months). The association of rituximab to FBR resulted in higher rates of grade  $\geq$ 3 neutropenia (60% vs. 40% without rituximab, p=0.07). In contrast, advanced age did not increase grade 3-4 hematological toxicity in this group (p=0.326, Figure 3).

Grade  $\geq$ 2 infections were reported in 32% of FBR-receiving patients and 45% in the non-FBR group (p=0.182, Figure 2B). Age over 60 was associated with a significantly higher incidence of grade  $\geq$ 2 infections in the FBR group (46% versus 18% if age <60, p=0.008, Figure 3).

Growth factor use, transfusion requirements, short-term emergency room admissions during chemotherapy and prolonged hospitalization for toxicity were similar in FBR and non-FBR patients (Table 2). 74% of FBR patients received anti-infective prophylaxis as per local recommendations, with oral acyclovir (74%) and oral co-



**Figure 2:** Treatment related toxicities in fludarabine based regimens (FBR) and non-FBR (A) Grade 3 and 4 hematological toxicity (B) Grade  $\geq 2$  infections and second neoplasm.

trimoxazole (56%). Antifungals and other antibiotics were rarely administered. Only 21% non-FBR patients received anti-infective prophylaxis. Oral or intravenous antibiotherapy was required at least once during treatment in 54% of FBR and 47% in non-FBR patients.

Subsequent lymphoma treatment was needed in half of the patients (51% in FBR; 47% in non-FBR). At the start of treatment, 11/40 FBR patients had grade  $\geq 2$  cytopenias (9 thrombocytopenia, 1 neutropenia, 1 both) that were attributed to delayed hematological toxicity in 4 and bone marrow (BM) infiltration in 3; 4 patients had no BM evaluation. In contrast, all non-FBR patients had normal hematological counts at the start of next chemotherapy. Also, grade  $\geq 3$  hematological toxicity and toxicity-related treatment discontinuation were more frequent during subsequent treatment in FBR than non-FBR patients (40% vs. 17%,  $p=0.079$  and 13% vs. 6%,  $p=0.655$ ).

Secondary malignancies were almost exclusively seen in FBR patients. Four had myelodysplasia and 7 other secondary neoplasms (2 breasts, 2 skins, 1 lung and 1 head and neck carcinoma and 1 GIST). Only one non-FBR patient developed a high-grade sarcoma.

## Discussion

In this series comprising R/R FL patients treated with FBR between 1996 and 2014, we confirmed the efficacy of these regimens and the high incidence of hematological and other toxicities (including secondary malignancies), with detrimental impact on subsequent therapies. Short-term toxicities and supportive care requirements in non-FBR patients were also high but these results need to be interpreted with caution given the important differences

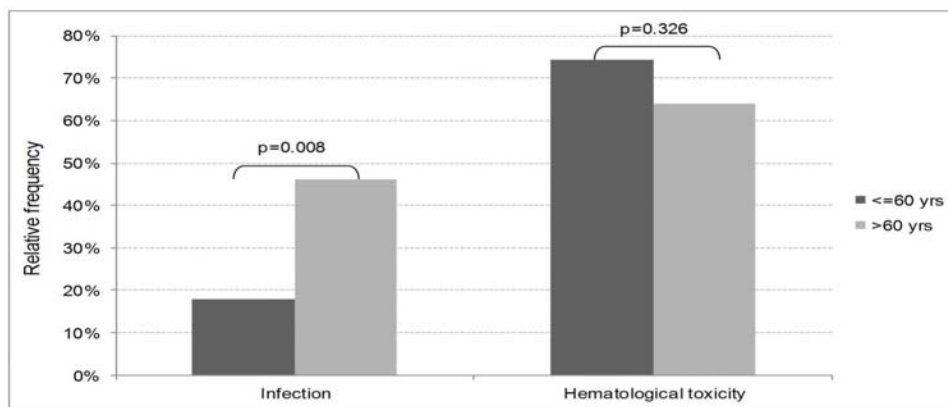
between the two groups. In fact, non-FBR patients were older and had a higher incidence of kidney disease. Non-FBR patients also had longer responses to first line. This agrees with our policy of repeating alkylating-containing regimens for patients with long responses or for those considered unfit for FBR due to age and specific co-morbidities.

We found that patients older than 60 years-old receiving FBR had a significantly higher incidence of grade  $\geq 2$  infections. Increasing age has been previously associated with excessive fludarabine toxicity in lymphomas [20,21], including CLL, where toxicity over 65 years results in the loss of survival benefit seen in younger groups [10,11].

Although acute myelosuppression was similar between groups, FBR resulted in prolonged recovery times and in some cases persistent cytopenias, as previously described [12]. The tolerability to subsequent chemotherapy was also compromised with high incidence of grade  $\geq 3$  hematological toxicity and premature discontinuation.

In contrast to what has been reported after first line CLL treatment [10], in our series the combination of rituximab with FBR was only marginally associated with an increased incidence of grade 3/4 neutropenia. This is in agreement with results from a randomized trial comparing FCM to R-FCM [5], where the incidence of grade 3/4 hematological toxicity was not influenced by rituximab.

Late toxicity of FBR should also be taken into account when deciding treatment, given the expected long-term survival of FL. With a median follow up of approximately 5 years, we confirmed a high incidence (14%) of secondary malignancies. There was only one secondary tumor reported in the non-FBR group, but caution should



**Figure 3:** Infection (grade  $\geq 2$ ) and hematological toxicity (grade  $\geq 3$ ) in fludarabine based regimens (FBR) according to age.

**Table 2:** Supportive care associated with treatment related toxicity.

	FBR (n=78)	Non-FBR (n=38)
<b>Admissions for toxicity</b>		
Patients with $\geq 1$ admission, n (%)	19 (24%)	10 (26%)
Duration, days		
Median [min-max]	10 [3-47]	14 [2-28]
Mean (SD)	13.5 (9.9)	12.9 (11.4)
<b>Emergency room</b>		
Patients with $\geq 1$ occurrence, n (%)	37 (47%)	15 (40%)
Number of episodes		
Median [min-max]	1 [1-5]	1 [1-4]
Mean (SD)	1.7 (1.2)	1.8 (1.1)
<b>Antibiotic treatment, n (%)</b>		
Yes	42 (54%)	18 (47%)
Oral	26 (33%)	11 (29%)
Parenteral	16 (21%)	7 (18%)
<b>Transfusions, n (%)</b>		
Yes	16 (21%)	4 (11%)
Number of cycles with transfusion		
Median [min-max]	1 [1-3]	1 [1-1]
Mean (SD)	1.3 (0.7)	1 (0)
<b>Growth factors, n (%)</b>		
Yes	32 (41%)	15 (40%)
Number of cycles with growth factors		
Median [min-max]	2 [1-8]	5 [1-8]
Mean (SD)	2.5 (1.8)	4.5 (2.3)

be taken in comparing these results, as the duration of follow-up was much shorter in this group.

This association was previously reported by Sacchi et al. [9], where indolent lymphoma patients treated with FBR had a higher incidence of secondary tumors compared to other treatments. Carney et al. [8] also reported a 10.8% incidence of secondary myelodysplasia/acute myeloid leukemia following FBR. Recently, in the FOLL05 trial [6], the incidence of secondary malignancies in patients receiving R-FM was superior to R-CHOP/R-CVP (8% versus 3% and 2.4%, respectively), and secondary acute myeloid leukemia was only seen after fludarabine.

The retrospective, single-center design and low patient numbers are limitations of this analysis. Nevertheless these results reflect the real life setting of R/R FL treatment. Given the lack of randomized trials comparing different regimens, the choice of treatment is often guided by data derived from phase 2 trials combined with the individual clinical experience and availability of different drugs. Attempts have

been made to identify subpopulations at high risk for fludarabine toxicity and a predictive model for infectious complications has been proposed [20] but not widely validated. As there are no established predictors for toxicity, the subjective evaluation of individual patients often remains the determining factor in selecting fludarabine for the treatment of relapsed FL.

In conclusion, although FBR were associated with adequate disease control in relapsed FL, toxicity was frequent and impacted on further therapies. These results are consistent with previous reports in other lymphoma types and should be taken into account for decision-making. With the advent of effective novel agents targeting recently identified biological mechanisms of disease [22-25], the therapeutic choices in tumors as indolent as FL requires a careful balance between efficacy, toxicity, cost and feasibility of subsequent therapies.

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