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ORIGINAL ARTICLE – CLINICAL ONCOLOGY

Comparative analysis of rituximab or obinutuzumab combined with CHOP in first-line treatment of follicular lymphoma

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Abstract

Purpose Rituximab (R) or obinutuzumab (G) combined with CHOP chemotherapy are used in previously untreated follicular lymphoma (FL). The aim is to compare in real life setting the efficacy and safety of these therapeutic strategies and assess the economic impact of introducing G.

Methods This retrospective study, performed in 3 centers, included data from all patients who received R-CHOP or G-CHOP for previous untreated FL from June 1st, 2016 to December 31st, 2020. Progression-Free Survival (PFS) were estimated according to the Kaplan–Meier method. A budgetary impact model was performed from the French health care system's perspective.

Results $N = 124$ patients were included (58 G-CHOP; 66 R-CHOP). Fifty-one and 57 patients achieved a complete response at the end of induction in the G-CHOP and R-CHOP group, respectively. PFS was not significantly longer in the G-CHOP group (HR 0.28; 95% CI 0.08–0.97; p value = 0.14). Hematological toxicity occurred more frequently with G-CHOP than R-CHOP during induction treatment ($n = 58$; 100% vs. $n = 61$; 92%), including higher severe neutropenia (grade ≥ 3) ($n = 26$; 45% vs. $n = 23$; 35%). Infusion-related reactions during the first infusion occurred more frequently with G-CHOP ($n = 19$; 33% vs. $n = 16$; 24%). The introduction of a completed G treatment (induction and maintenance) results in an additional cumulative cost per patient estimated at more than €30,000.

Conclusion Similar results were found in the GALLIUM subgroup analysis study, suggesting that at this time there is no absolute benefit to administer G-CHOP instead of R-CHOP in all patients with previously untreated FL and may encourage clinical and economic trials including quality of life data.

Keywords Follicular lymphoma · Obinutuzumab · Rituximab · Drug therapy

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Introduction

Follicular lymphoma (FL) is the most common indolent B-cell non-Hodgkin lymphoma in the western world (Teras et al. 2016). The median age at diagnostic is about 65 years (Le Guyader-Peyrou et al. 2019; Junlén et al. 2015). FL is a lymphoproliferative disorder of transformed follicular center B cells.

The criteria from the French *Groupe d'Etude des Lymphomes Folliculaires* (GELF) are used to decide to initiate the treatment (Brice et al. 1997).

When required, the standard first-line treatment of FL is based on the combination of intravenous (IV) rituximab (R) 375 mg/m^2 or subcutaneous (SC) R 1400 mg, a recombinant human-murine chimeric type 1 immunoglobulin G1 Monoclonal Antibody (mAb), targeting cell surface CD20 protein, and a chemotherapy regimen during induction (6–8 cycles), followed by a 2 years R maintenance (Bachy et al. 2019). The chemotherapy regimen generally consists of a CHOP association (Cyclophosphamide (C) 750 mg/m^2 Day (D) 1, Doxorubicin (H) 50 mg/m^2 D1, Vincristine (O or V) 1.4 mg/m^2 D1 and Prednisone (P) 40–60 mg/m^2 D1-D5), or a CVP association (without anthracycline) or bendamustine (70–90 mg/m^2 D1-D2) (Hiddemann et al. 2005; Marcus et al. 2008; Flinn et al. 2014; Rummel et al. 2013). While the historical treatment was restricted to chemotherapy, the addition of R for twenty-years has significantly improved the Overall Survival (OS) of patients with FL. A recent analysis of US and French cohorts reported improved OS in the rituximab era, with a 10-year OS above 80% (Junlén et al. 2015). The use of R maintenance therapy every 2 months after induction treatment also contributed to improve progression free survival (PFS) (Salles et al. 2011). Especially because of histologic transformation to aggressive lymphoma, tumor progression remains the first cause of death with disease specific mortality of 10% at 10 years (Sarkozy et al. 2019).

Obinutuzumab (GA101, GAZYVARO) (G) 1000 mg IV, a recombinant humanized type 2 immunoglobulin G1 mAb targeting-CD20 in combination with chemotherapy regimen also demonstrated benefits in term of efficacy and safety in FL patients. As a type 2 immunoglobulin G1, G has lower complement-dependent cytotoxicity than R, but greater antibody-dependent cellular cytotoxicity and phagocytosis, and greater direct B-cell killing effects (Herter et al. 2013; Mössner et al. 2010). The recent GALLIUM randomized trial reports the results of the comparison of G plus chemotherapy (G-CHOP, G-CVP or G-bendamustine) with R plus chemotherapy (R-CHOP, R-CVP or R-bendamustine) followed by G or R maintenance, respectively (Marcus et al. 2017). The study included 1202 previously untreated patients with advanced FL and showed that G-chemotherapy combinations resulted in significantly prolonged PFS in comparison with R-chemotherapy combinations [Hazard Ratio (HR) 0.66; 95% Confidence Interval (CI) 0.51–0.85; p value $=0.001$], although no OS benefit was observed. A chemotherapy subgroup analysis showed no statistically significant difference in PFS between G-CHOP and R-CHOP (HR 0.72; 95% CI 0.48–1.10; p value $=0.13$). However, high grade (3–5) Adverse Events (AEs) were more common in patients receiving G-CHOP (89%) versus (vs.) R-CHOP (74%), with higher hematological toxicity, especially neutropenia (71% vs. 55%) in the G-CHOP group (Hiddemann et al. 2018).

The currently first-line treatment approved in previously untreated patients with FL combines CHOP-chemotherapy with an anti-CD20 mAb (G or R). The aim of this study is to compare in real life setting the efficacy and safety of these both therapeutic strategies (G-CHOP or R-CHOP, followed by mAb maintenance) in patients with newly diagnosed FL. The secondary objective is to assess the economic impact of introducing G through a Budget Impact Model (BIM).

Methods

Study design

We conducted a retrospective multicenter study in three hospitals: Reims University Hospital, Strasbourg University Hospital and Sainte-Anne nonprofit Clinic. Eligible patients were 18 years old or older, with histologically documented, previously untreated grades 1 to 3A FL who received their first-line anticancer therapy (R-CHOP or G-CHOP) from June 1st, 2016 to December 31st, 2020. The follow-up was performed until July 1st, 2021.

All eligible patients have completed induction therapy and started maintenance treatment, except for relapse during induction. Anticancer therapies details for each center are listed in the supplements (Fig. S1).

Patient's records were anonymized prior to analysis. Database was constituted in accordance with the reference methodology MR004 of the *Commission Nationale de l'Informatique et des Libertés (CNIL)*. A non-opposition form was sent to each living patient included in the study. As per the French regulations, no additional ethical review was required.

Data collection

Demographic, clinical and biological data were extracted from patient's Electronic Health Records (EHR) and Computerized Provider Order Entry (CPOE) for anticancer chemotherapy and collected using a structured, standardized

data collection table (Excel®). EHR were EASILY®, *Hospices Civils de Lyon*, Lyon, France, DXCARE®, Dedalus, Le Plessis-Robinson, France, or Base 4D® v16.6, *Strasbourg Oncologie Libérale*, Strasbourg, France, while all centers used the CPOE CHIMIO® v5.7, Computer Engineering, Paris, France. All data were first collected by one pharmacist specially trained in oncology pharmacy. Then, all medical data were double-checked by medical team (one hematologist). The following demographic and administrative variables were recorded for all patients: age, sex, height, weight and center. The clinical and medical data were collected as follow: comorbidities, diagnosis date, anticancer chemotherapy regimen, FL grade, Follicular Lymphoma International Prognostic Index (FLIPI) risk group, bone marrow involvement, extranodal localization, bulky disease (> 7 cm), proliferation index (Ki-67), Ann Arbor stage, Eastern Cooperative Oncology Group Performance Status (ECOG PS), number of cycles for induction and maintenance treatments, postponement or definitive anticancer chemotherapy discontinuation, treatment response (Positron Emission Tomography PETscan), proportion of progression rate, route of administration of the rituximab (IV/SC), type of hospitalization (oncology day or conventional hospitalization) and AEs. All biologic AEs, especially hematological toxicity, were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), v5.0. During the data collection, if an AE appeared several times during the same treatment period with different grades we only listed it once with its highest grade. Severe grades refer to AEs grades ≥ 3.

Statistical analysis

Quantitative variables were described as mean ± standard deviation [minimum and maximum] and qualitative variables as number and percentage. For univariate analysis, logistic regressions were performed to identify factors associated with a statistically significant difference between both groups (G-CHOP and R-CHOP). The variables included were: demographic and clinical treatment data. The results are presented as *p* value. PFS were estimated using Kaplan–Meier method (Prism GraphPad 8, San Diego, USA) and were compared using log-rank test. Regarding safety data, no statistical analyses were performed to compare the results.

Economic analysis

A BIM was developed using Excel® software to evaluate the economic impact of introducing G in the first-line treatment in patients with FL. The analysis was performed from the payer's perspective, which is the French health care system. This analysis was based on real life data from 3 cohorts of patients treated at 3 centers using different immunochemotherapy protocols: Reims University Hospital, Strasbourg University Hospital and Sainte-Anne nonprofit Clinic. The time horizon chosen is 28 months to include the total time of the treatment (6 cycles of mAb-CHOP every 21 days in induction and 12 cycles of SC R or IV G every 2 months in maintenance) for a patient.

This model included the cost of treatments billed in addition to Diagnosis Related Groups (DRGs) tariff (G, SC and IV R), the cost of day and conventional hospitalizations for the treatment administration and the cost of AE-related hospitalizations or emergency visits. Although it is covered by the French health care system, the cost of patient transport was not included in the model because of missing data. The cost of CHOP chemotherapy (associated with R or G) was not integrated because drugs in CHOP protocols were not billed in addition to DRGs tariff and all centers use the same CHOP protocol. This model was based on the most frequently immunochemotherapy protocols used in our study. A total of 3 scenarios were compared:

- Scenario 1: induction therapy with IV infusions of G 1,000 mg (D1, 8, and 15 of cycle 1 and D1 of cycles 2–6) followed by maintenance with IV infusions of G 1,000 mg every 2 months for 2 years (12 cycles),
- Scenario 2: induction therapy with IV infusion of R 375 mg/m^2 (D1 of cycle 1) and SC administrations of R 1,400 mg (D1 of cycles 2–6) followed by maintenance with SC administrations of R 1,400 mg every 2 months for 2 years (12 cycles),
- Scenario 3: induction therapy with IV infusions of R 375 mg/m^2 (D1 of cycles 1–6) followed by maintenance with SC administrations of R 1,400 mg every 2 months for 2 years (12 cycles).

The first administrations of the mAb in scenarios 1 and 2 were performed in conventional hospitalizations (due to a risk of hypersensitivity), and subsequent administrations in day hospitalizations. In the last scenario, all administrations were performed in day hospitalizations. We chose only one scenario for G protocol because the three centers had almost the same practices. Scenario 2 reflects Reims and Strasbourg University Hospitals R protocols and scenario 3 is based on Sainte-Anne nonprofit Clinic R administrations practices.

The cost of G and SC R were based on the responsibility tariff per common dispensing unit in effect since January 1st, 2019 (published in Official Journal of the French Republic (OJFR) n°0233 of October 9th, 2018 and in OJFR n°0298 of December 26th, 2018, respectively) (Légifrance 2018a, b). The cost of IV R biosimilar (used by the 3 centers) is based on the responsibility tariff per common dispensing unit in effect since January 1st, 2020 (published in OJFR n°0270 of November 21st, 2019) (Légifrance 2019). The mean number of R and G administrations was estimated based

on GALLIUM study (Marcus et al. 2017). Dose of IV R is based on mean Body Surface Area (BSA) reported in our study (1.83 m^2). Dose adjustment was not integrated in the analysis because mAb dose adjustment is not recommended in the summary of product characteristics of both drugs, and no mAb dose adjustment was performed in real life in our study. The loss of drug leftover during the preparation was not included in the analysis. Indeed, the vials of G and SC R are fully used at each administration and the preparation of IV R in a centralized unit resulted in negligible loss of product (conservation of drug leftover, long stability). Prices of drug acquisition are described in the supplements (Table S1).

The number of patients was taken from our multicenter study results. The size of the target population was assumed not to change between 2 scenarios compared for a same center. Rates reimbursed by the French health care system for day or conventional hospitalizations and AE-related hospitalizations or emergency visits were obtained via the medical information department and were equivalent for the 3 centers. These prices are represented in the supplements (Table S2).

The output model was the budget impact during the time horizon chosen, defined as the difference in costs between both scenarios (G-CHOP and R-CHOP) for each center and per patient.

Results

Patient characteristics and treatments

A total of 133 patients were eligible for data inclusion. Among these, 7 patients were excluded because of missing histologic grades, one patient because of concomitant radiochemotherapy for a colon adenocarcinoma and one patient because of receiving 8 R-CHOP cycles due to a transformation doubt, without histological evidence.

Baseline patient characteristics are described in Table 1. Finally, 124 patients were included in the study, 58 (47%) in the G-CHOP group and 66 (53%) in the R-CHOP group. The median age of the patients was 59 (± 11 years) at diagnosis and 60 (± 11 years) at treatment initiation. Fifty-two percent ($n = 65$) of patients were male and 92% ($n = 114$) of the patients had 0–1 ECOG PS. Most patients had grade 1–2 ($n = 109$; 88%) and stage III-IV FL ($n = 112$; 90%) with a high FLIPI 1 score ($n = 54$; 44%). Approximately one third of patients (30%) had bone marrow involvement.

In univariate analysis, there were no statistical differences for baseline characteristics between both treatment groups for age, sex, BSA, Body Mass Index (BMI), ECOG PS, FLIPI 1, Ann Arbor stage, histologic grading, extranodal involvement, bone marrow involvement, Ki-67 and bulky disease. All the p value s were higher than 0.05 and because only age showed p value < 0.2, multivariate analysis was not performed.

Due to its neurotoxicity, vincristine was replaced by etoposide for 5 patients in the G-CHOP group and one in the R-CHOP group during induction treatment. Two patients treated with R-CHOP received one cycle with vindesine instead of vincristine due to a worldwide out of stock. Three patients also received high-dose methotrexate during the induction therapy.

Efficacy

All patients in the G-CHOP group and 65 patients (98%) in the R-CHOP group completed induction therapy (6–8 cycles depending on center protocols). Six patients (10%) in the G-CHOP group and 46 patients (70%) in the R-CHOP group completed maintenance therapy, with 48 and 8 still receiving maintenance therapy at the cut-off date in the G-CHOP and R-CHOP group, respectively. The average number of cycles during the maintenance was 6 ± 3 and 10 ± 3 for G group and R group, respectively. A total of 21 patients (12 patients in G-CHOP group and 9 patients in R-CHOP group) cancelled or postponed a cycle of treatment during induction, mainly owing to hematological toxicity (5 patients in G-CHOP group and 4 in R-CHOP group). Cancelled or postponed cycles during maintenance therapy (13 patients in the G group and 21 patients in the R group) were mainly due to hematological toxicity ($n = 5$; 9%) and infections ($n = 7$; 12%) in the G group and to progression ($n = 7$; 11%), infections ($n = 6$; 9%) and Covid19 health crisis ($n = 6$; 9%) in the R group.

Most of the patients achieved a complete response at the end of induction, 51 (88%) and 57 (86%) for G-CHOP and R-CHOP group, respectively. More patients stopped treatment in the R-CHOP group ($n = 11$; 17%) than in the G-CHOP group ($n = 3$; 5%). It should be noted that median patient follow-up was shorter in the G-CHOP group than R-CHOP group. One patient stopped the treatment in the G-CHOP group because of progression and one patient due to toxicity (severe infectious complication in a context of lymphopenia and hypogammaglobulinemia, after 10 cycles of maintenance). Eight patients stopped treatment in the R-CHOP group because of progression and one patient due to toxicity (cardiogenic shock after 2 cycles of maintenance). Only one patient (R-CHOP group) died during treatment period. All treatment results are reported in Table 2.

The number of progressions or relapses assessed in the analysis of PFS was lower in the G-CHOP group than in the R-CHOP group ($n = 1$; 2% vs. $n = 16$; 26%), still with a shorter median follow-up in the G-CHOP group. However,

Table 1 Baseline patient characteristics and comparison according to G- or R- treatment group

	G and R-CHOP No. of patients (%)	G-CHOP No. of patients (%)	R-CHOP No. of patients (%)	*p* value
Total patients	124 (100)	58 (47)	66 (53)	
Centers				
Private nonprofit, Strasbourg	34 (27)	18 (31)	16 (24)	
University hospital, Strasbourg	30 (24)	13 (22)	17 (26)	
University hospital, Reims	60 (48)	27 (47)	33 (50)	
Age (years)				
At diagnosis	59 ± 11 [23–82]	58 ± 11 [23–77]	61 ± 11 [32–82]	0.12
At treatment initiation	60 ± 11 [23–82]	58 ± 11 [23–77]	62 ± 11 [33–82]	0.07
Age > 60	68 (55)	32 (55)	36 (55)	
Patients with different age at diagnosis and treatment initiation	33 (27)	11 (19)	22 (33)	
Sex				1.00
Male	65 (52)	30 (52)	35 (53)	
Female	59 (48)	28 (48)	31 (47)	
Body surface area (BSA, m^2)	1.83 ± 0.19 [1.27–2.20]	1.84 ± 0.19 [1.32–2.20]	1.83 ± 0.18 [1.27–2.20]	0.91
Body mass index (BMI, kg/m^2)	26.2 ± 4.85 [17.0–42.0]	26.2 ± 4.38 [17.0–42.0]	26.3 ± 5.27 [16.0–48.6]	0.88
ECOG PS				0.51
0	52 (42)	22 (38)	30 (45)	
1	62 (50)	32 (55)	30 (45)	
2	9 (7)	4 (7)	5 (8)	
4	1 (1)	0 (0)	1 (2)	
Histologic grading				0.79
1–2	109 (88)	50 (86)	59 (89)	
3A	15 (12)	8 (14)	7 (11)	
Ann Arbor stage (at treatment initiation)				0.91
I	3 (2)	2 (3)	1 (2)	
II	9 (7)	3 (5)	6 (9)	
III	37 (30)	17 (29)	20 (30)	
IV	75 (60)	36 (62)	39 (59)	
Patients with different stage at diagnosis and treatment initiation	12 (10)	7 (12)	5 (8)	
FLIPI 1				0.71
Low (0–1)	25 (20)	10 (17)	15 (23)	
Intermediate (2)	45 (36)	21 (36)	24 (36)	
High (3–5)	54 (44)	27 (47)	27 (41)	
Bone marrow involvement, *patients with data*	24 of 81 (30)	11 of 38 (29)	13 of 43 (30)	1.00
Extranodal involvement	75 (60)	36 (62)	39 (59)	0.88
Bulky disease (> 7 cm), *according to criteria of GELF*	72 (58)	32 (55)	40 (61)	0.67
Ki-67 (%), *patients with data (47 for G-CHOP; 53 for R-CHOP)*	29 ± 15 [5.0—70]	30 ± 15 [5.0–70]	27 ± 15 [5.0–70]	0.34

G-CHOP Obinutuzumab Cyclophosphamide Doxorubicin Vincristine and Prednisone, *R-CHOP* Rituximab Cyclophosphamide Doxorubicin Vincristine and Prednisone, *ECOG PS* eastern cooperative oncology group performance status, *FLIPI* follicular lymphoma international prognostic index, *GELF groupe d'étude des lymphomes folliculaires*

PFS was not significantly longer in the G-CHOP group (HR 0.28; 95% CI 0.08–0.97; *p* value = 0.14) (Fig. 1). Two patients were lost to follow-up during the maintenance (one in each group).

Table 2 Summary of anticancer treatment by treatment group

	G-CHOP No. of patients (%)		R-CHOP No. of patients (%)	
	Induction	Maintenance	Induction	Maintenance
Number of cycles	7 ± 1 [6–8]	6 ± 3 [1–12]	7 ± 1 [3–8]	10 ± 3 [0–14]
Completed regimen	58 (100)	6 (10)	65 (98)	46 (70)
6 cycles *(R-CHOP or G-CHOP)*	41 (71)	–	31 (47)	–
8 cycles *(6 R–CHOP + 2R or 6 G-CHOP + 2G)*	17 (29)	–	34 (52)	–
Patients still receiving maintenance treatment at the cut–off date	–	48 (83)	–	8 (12)
Patients with cancelled/postponed treatment	12 (21)	13 (22)	9 (14)	21 (32)
Causes of cancelled/postponed treatment				
Hematological toxicity	5 (9)	5 (9)	4 (6)	1 (2)
Infections	3 (5)	7 (12)	1 (2)	6 (9)
Covid19 infections	0 (0)	3 (5)	0 (0)	1 (2)
Progression	0 (0)	1 (2)	1 (2)	7 (11)
Covid19 health crisis*, *excluding infections*	0 (0)	2 (3)	0 (0)	6 (9)
Others**	6 (10)	1 (2)	3 (5)	4 (7)
Treatment discontinuation	3 (5)		11 (17)	
Causes of treatment discontinuation				
Progression	1 (2)		8 (12)	
Toxicity	1 (2)		1 (2)	
Others***	1 (2)		2 (3)	
Treatment response (PET scan) at end of induction				
Complete response	51 (88)		57 (86)	
Partial response	6 (10)		8 (12)	
Progression	1 (2)		1 (2)	
Relapse	1 (2)		16 (26)	
Death	0 (0)		1 (2)	
Lost to follow-up	1 (2)		1 (2)	

*COVID-19 health crisis included all logistics parameters due to the crisis (prioritizing care, difficulty in accessing the hospital, patient's will)

**The others causes of cancelled or postponed treatment included mostly programming errors

***The others causes of treatment discontinuation included reactivation of the hepatitis B virus and reasons related to the COVID-19 health crisis

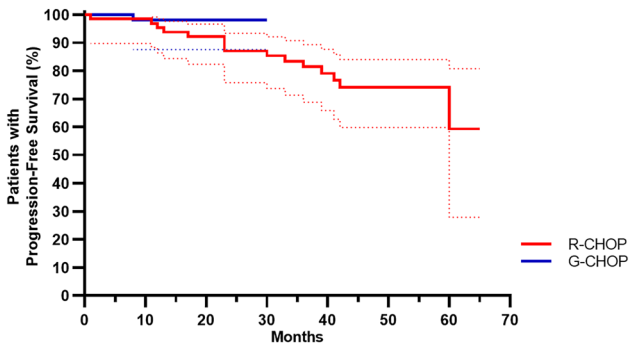

Fig. 1 Kaplan-Meier PFS estimation

Safety

Hematological toxicity occurred more frequently with G-CHOP than R-CHOP during induction treatment ($n = 58$; 100% and $n = 61$; 92%, respectively), but not during maintenance treatment ($n = 26$; 45% and $n = 35$; 53%, respectively). Anemia and leucopenia were the most frequent hematological toxicities in both groups during induction therapy. The frequency of severe leucopenia during the induction was higher in patients treated with G-CHOP ($n = 20$; 34% vs. $n = 15$; 23%). This was also observed for grade 1 anemia ($n = 41$; 71% vs. $n = 39$; 59%) and severe neutropenia ($n = 26$; 45% vs. $n = 23$; 35%). When occurring during induction, neutropenia was more frequently associated to high grades of severity in both groups. Occurrence of thrombocytopenia (all grades) during induction was higher in patients treated with G-CHOP ($n = 42$; 72%) than R-CHOP ($n = 31$; 47%).

Contrary to induction, all grades hematological toxicities were more frequent in R-CHOP group during maintenance except for grade 1 leucopenia and thrombocytopenia. Leucopenia was the most frequent hematological toxicity in both groups during maintenance therapy ($n=21$; 36% in the G group and $n=22$; 33% in the R group). All hematological toxicities reported are described in the supplements (Table S3).

Infusion-related reactions (IRRs) during the first infusion occurred most frequently in the G-CHOP group ($n=19$; 33%) than in the R-CHOP group ($n=16$; 24%). The main symptom of IRRs was cutaneous reaction (7 patients for G-CHOP and 8 patients for R-CHOP). IRRs are summarized in Table 3.

During induction, 24% ($n=14$) and 20% ($n=13$) of the patients were hospitalized for an AE in the G-CHOP and R-CHOP group, respectively (corresponding to 18 AE-related hospitalizations in total in the G-CHOP group and 17 in the R-CHOP group). Hematological toxicity was the main cause of hospitalization during induction treatment in the G-CHOP group ($n=5$) whereas it was digestive toxicity in the R-CHOP group ($n=6$). Among the digestive toxicities, febrile or watery diarrhea (leading to hypokalemia), severe abdominal pain, and other disorders (such as occlusive syndrome or sigmoid stenosis) were found. The most common hematological toxicity was febrile neutropenia, without documented infection. During maintenance treatment, 7 (12%) and 8 (12%) patients were hospitalized for an AE in the G and R group respectively, mainly due to infections. All AE-related hospitalizations (including emergency visits) details are reported in Table 3.

Economic analysis

Costs per patient for each scenario are represented in Table 4. We also represented the budget impact analysis, i.e. the differences between scenario 1 (G) and scenarios using R in each center, per patient and per center. For example, in Reims University Hospital, the total price to complete the treatment (induction and maintenance) with R for one patient is €38,569 whereas with G it is €69,521, resulted in a budget impact of + €30,952 with the introduction of G.

In the other centers, the introduction of a complete G treatment (induction and maintenance) in the first-line treatment of FL results in an additional cumulative cost per patient estimated at €35,303 and €39,721 for Strasbourg University Hospital and Sainte-Anne nonprofit Clinic, respectively. This increase in expenditure is mainly due to the G acquisition cost. The differences in treatment acquisition costs between G and R are estimated at €32,242 for scenario 2 and €34,895 for scenario 3 during a time horizon of 28 months. Considering the number of patients eligible for treatment, the total budgetary impact for each center during the time horizon studied is €897,607, €458,945 and €775,261 for Reims University Hospital, Strasbourg University Hospital and Sainte-Anne nonprofit Clinic, respectively.

Table 3 IRRs and AE-related hospitalizations by treatment group

	G-CHOP No. of patients (%)		R-CHOP No. of patients (%)	
	Induction	Maintenance	Induction	Maintenance
IRRs during the first infusion	19 (33)	–	16 (24)	–
Cutaneous reaction	7	–	8	–
Cytokine release syndrome	5	–	3	–
Otorhinolaryngologic symptoms	4	–	3	–
Others*	12	–	10	–
Patients hospitalized for AEs	14 (24)	7 (12)	13 (20)	8 (12)
AE-related hospitalizations	18	7	17	8
Infections	2	4	4	4
Fever	3	1	4	1
Hematological toxicity	5	0	3	1
Digestive toxicity	2	0	6	0
Cardiotoxicity	1	0	2	2
Others**	12	1	9	2

AEs adverse events, *IRRs* infusion-related reactions

*Others IRRs were cardiac toxicity, headaches, lysis syndrome, gastro-intestinal toxicity, desaturation, low back pain, muscular pains, feeling of hunger, cold in the extremities, malaise and fever/chills

**Others AE-related hospitalizations were pains, hemoptysis, infusion reactions, malaise, escarre, undernutrition, urinary disorder for G-CHOP and infusion reactions, hypokalemia, altered general condition, pulmonary toxicity, vascular disorder, glycemic disorder, cutaneous toxicity for R-CHOP

Table 4 Costs per patient and per scenario for a complete G or R treatment and budget impact analysis (difference in cost between a complete G and R treatment) per patient and per center

Costs per patient for a complete treatment (€)						
	G			R		
	Scenario 1 Reims University Hospital	Scenario 1 Strasbourg University Hospital	Scenario 1 Sainte-Anne nonprofit Clinic	Scenario 2 Reims University Hospital	Scenario 2 Strasbourg University Hospital	Scenario 3 Sainte-Anne nonprofit Clinic
Of treatment acquisition	59,068	59,068	59,068	26,826	26,826	24,174
Related to day or conventional hospitalizations for administrations	9,591	9,591	9,591	8,761	8,761	7,471
For AE-related hospitalizations or emergency visits	862	3,661	3,631	2,982	1,430	924
Total	69,521	72,320	72,290	38,569	37,017	32,569
Differences in cost (€) between a completed G and R treatment = Budgetary impact						
	Per patient			Total per center		
	Reims University Hospital Scenario 1—Scenario 2	Strasbourg University Hospital Scenario 1—Scenario 2	Sainte-Anne nonprofit Clinic Scenario 1—Scenario 3	Reims University Hospital	Strasbourg University Hospital	Sainte-Anne nonprofit Clinic
Of treatment acquisition	32,242	32,242	34,895	935,016	419,145	593,206
Related to day or conventional hospitalizations for administrations	830	830	2,120	24,074	10,792	36,033
For AE-related hospitalizations or emergency visits	− 2,120	2,231	2,707	− 61,483	29,008	46,021
Total Budgetary impact	30,952	35,303	39,721	897,607	458,945	775,261

Discussion

Regarding effectiveness data, the majority of patients completed induction and maintenance treatment in the R-CHOP group and most of the patients are still receiving maintenance treatment in the G-CHOP group at the cut-off date. In our study, the complete response rate at the end of the induction is higher in both groups than in the GALLIUM study (88% G-CHOP and 86% R-CHOP vs. 74% G-CHOP and 69% R-CHOP) (Hiddemann et al. 2018). However, our study did not show PFS significant difference between both groups. Our study results might be due to inadequate statistical power to detect PFS significant difference between both therapies, and also to a short follow-up. Indeed, the follow-up time was different in both groups and most patients in the G-CHOP group did not complete maintenance therapy as opposed to the R-CHOP patients. With only one death during treatment period in our study, and with a short follow up compared to other studies, we were not able to report OS. In the future, it will be interesting to continue the work on a longer follow-up time to reassess PFS and to study OS.

In our study, eight patients (12%) progressed in the 24 months after treatment initiation in the R-CHOP group (vs. only one patient in the G-CHOP group). The evaluation of early progression in the GALLIUM study showed that treatment with G-chemotherapy was associated with a marked reduction in the rate of progression disease in the 24 months after randomization comparatively to R-chemotherapy (Seymour et al. 2019). Other studies demonstrated a particularly poor outcome for patients with FL who suffer progression disease in the 24 months of starting immunochemotherapy (Casulo et al. 2015, 2017).

Neutropenia is one of the most common hematological AEs in patients treated with G (Radford et al. 2013; Salles et al. 2012; Cheson et al.2016; Marcus et al. 2016; Grigg et al. 2017; Sehn et al. 2012). In our study, the most common hematological AE in the G-CHOP group was leucopenia but neutropenia was the most severe hematological toxicity. In the GALLIUM trial, one of the most common AE was also neutropenia (all grades), which occurred in half of the patients (50.6%) treated with G-chemotherapy (vs 45.1% in R-chemotherapy) (Marcus et al. 2017).

Moreover, a higher incidence of severe neutropenia was reported during induction treatment in the G-CHOP group (64.2%) compared to R-CHOP (50.7%) in this study (Marcus et al. 2017).

In our study, although anemia appeared in more than 80% of the patients in both groups during induction treatment, severe anemia is almost inexistent. In the literature, severe anemia is also uncommon, occurring in 7.2% of patients with G-CHOP (vs. 7.5% in the R-CHOP group) and in 8% of patients with G-CHOP (vs. 4% in the R-CHOP group) in GOYA and GALLIUM study respectively (Marcus et al. 2017; Vitolo et al. 2017).

Although the rate of all grades thrombocytopenia during induction treatment is higher in our study (72% for G-CHOP vs. 47% for R-CHOP) than in the literature (10.6% for G group vs. 7.2% for R group in GALLIUM study), severe thrombocytopenia was relatively uncommon (Marcus et al. 2017). The higher frequency of thrombocytopenia all grades can be explained by the higher frequency of grade 1 thrombocytopenia (between 75,000/mm^3 and the lower normal limit according to the CTCAE), which most often have no clinical impact in practice. The GALLIUM study demonstrated also a low rate of severe thrombocytopenia in both G and R groups (6.1% vs 2.7%, respectively). A recent meta-analysis compiled all randomized controlled trials comparing G-chemotherapy regimens with R-chemotherapy regimens, and confirmed a significantly increased rate of severe AEs with G, as well as thrombocytopenia and IRRs (Amitai et al. 2021).

Our study showed lower rates of clinically relevant IRRs during the first infusion (on third of patients receiving G-CHOP and 24% of patients receiving R-CHOP) than in others studies with patients treated for indolent non-Hodgkin lymphoma. The GALLIUM trial also showed a higher frequency of IRRs all grades, usually occurring in the first infusion, in patients treated with G-chemotherapy (68.2% vs. 58.5% in R-chemotherapy group) (Marcus et al. 2017). In this study, specific antibody related events rates were recorded separately and were also higher in the G group than in the R group (59.3% vs. 48.9%, respectively). Similarly to our study, in the phase III GOYA study of 1 418 patients with untreated Diffuse Large B-cell Lymphoma (DLBCL), IRRs any grade occurred in 36.1% of patients receiving G-CHOP (vs. 23.5% in R-CHOP group) (Vitolo et al. 2017). It must be noted that these studies can include IRRs not appeared at first infusion, contrary to our study. Because of retrospective collection data in our study, it was difficult to evaluate specific antibody related events (not found in others studies as well). The retrospective collection data in our study may influence this result, with a majority of AE grades not reported in the medical health records. The increase of IRRs with G can be explained by cytokine release, especially during the first infusion, with peak levels of IL-6, IL-8, IL-10, TNF-α, and interferon-gamma significantly higher with G compared with R (Sarraf and Cheson 2017).

Although hematological toxicity was the main cause of hospitalization during the induction in the G-CHOP group in our study, this therapy was not associated with higher rates of infections leading to hospitalization compared to the R-CHOP group. It could be interesting to study infections all grades in both groups during the induction and maintenance periods. No fatal AEs were noticed.

After efficacy and toxicity analysis, we added some economic considerations. In our study, the budgetary impact was consequent in using G compared to R, mainly explained by the price of a G administration which is almost twice as expensive as a SC R administration and almost three times as expensive as an IV R biosimilar administration. Moreover, the G protocol contains two more administrations during the first cycle (D8 and D15) than the R protocol, increasing the cost of a complete treatment per patient.

Several limitations must be considered in our BIM. Our economic model considers a total replacement of the R treatment by G therapy, probably overestimating the global budget impact because the R protocol is still sometimes used in centers (for example in elderly patients in Reims University Hospital). Then, the economic impact was calculated considering that all patients received all planned cycles, but in reality some patients stopped the treatment (due to progression or toxicity for example).

The difference in cost between Reims and Strasbourg University Hospital is due to the large difference in the average number of hospitalization days for AEs, that can mainly be explained by the retrospective data collection and the few number of patients in the cohort. Sainte-Anne nonprofit Clinic has the highest budget impact per patient because of the less expensive price of IV R than SC R used in others centers during induction treatment. However, the full costs were not integrated because of the health care system's perspective and some missing data. G-CHOP and R-CHOP are administrated during two days in this nonprofit Clinic whereas during only one day in the others centers, thus increasing the cost per patient and probably impacting the quality of life of patients. Despite these limitations, the use of G in first-line treatment in patients with FL seems to increase considerably the cost of therapeutic management.

Conclusion

In conclusion, our study shows similar complete response rates at the end of induction in both groups and a significantly longer PFS is not demonstrated with G-CHOP therapy. Some limitations can be noted in our multicentric study such as a shorter median follow up in the G-CHOP group, the retrospective design and a few number of patients in

the cohort. However, in the literature, G-chemotherapy significantly prolonged PFS compared to R-chemotherapy (including CHOP, bendamustine and CVP) but in the subgroup analysis, the benefit of G-CHOP over R-CHOP therapy remains in discussion. Moreover, safety profiles differ between both groups. IRRs and hematological toxicity appear more common with G-CHOP than R-CHOP treatment. In the literature, the frequency of severe AEs is also higher with G therapy. The budgetary impact of introducing G in the first-line treatment in patients with FL is considerable, mainly due to the G acquisition cost.

Therefore, the choice of the mAb in association with chemotherapy must take the benefit-risk balance into consideration, depending on each patient and should not be considered as closed. Even if the study reports early survival outcomes, the budget impact analysis gives concrete and relevant results about the additional costs related to obinutuzumab introduction that our survival outcome results as well as those from GALLIUM or other studies will probably not counterbalance. Finally, this study raises some questions in patient care with previous untreated FL and these observations may encourage to perform future clinical and economic trials in real life setting including quality of life data, to demonstrate if the benefice of the G-CHOP compared to R-CHOP therapy is real, and should probably encourage the search for predictive factors for the use of one or the other therapy.

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Declarations

Conflict of interest The authors declare that they have no conflict of interest.

References

Amitai I, Gafter-Gvili A, Shargian-Alon L, Raanani P, Gurion R (2021) Obinutuzumab-related adverse events: a systematic review and meta-analysis. Hematol Oncol 39(2):215–221. https://doi.org/10.1002/hon.2828

Bachy E, Seymour JF, Feugier P, Offner F, López-Guillermo A, Belada D et al (2019) Sustained progression-free survival benefit of rituximab maintenance in patients with follicular lymphoma: long-term results of the PRIMA study. J Clin Oncol 37(31):2815–2824. https://doi.org/10.1200/JCO.19.01073

Brice P, Bastion Y, Lepage E, Brousse N, Haïoun C, Moreau P et al (1997) Comparison in low-tumor-burden follicular lymphomas between an initial no-treatment policy, prednimustine, or interferon alfa: a randomized study from the. Groupe d'Etude des Lymphomes Folliculaires Groupe d'Etude des Lymphomes de l'Adulte. J Clin Oncol 15(3):1110–1117. https://doi.org/10.1200/JCO.1997.15.3.1110

Casulo C, Byrtek M, Dawson KL, Zhou X, Farber CM, Flowers CR et al (2015) Early relapse of follicular lymphoma after rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone defines patients at high risk for death: an analysis from the national lymphocare study. J Clin Oncol 33(23):2516–2522. https://doi.org/10.1200/JCO.2014.59.7534

Casulo C, Leademacher J, Dixon J, Salles G, Hoster E, Herold M et al (2017) Validation of POD24 as a robust early clinical endpoint of poor survival in follicular lymphoma: results from the follicular lymphoma analysis of surrogacy hypothesis (FLASH) investigation using individual data from 5,453 patients on 13 clinical trials. Blood 130(1, Suppl 1):412–412

Cheson BD, Trněný M, Bouabdallah K, Dueck G, Gribben J, Lugtenburg PJ et al (2016) Obinutuzumab plus bendamustine followed by obinutuzumab maintenance prolongs overall survival compared with bendamustine alone in patients with rituximab-refractory indolent non-hodgkin lymphoma: updated results of the GADOLIN study. Blood 128(22):615. https://doi.org/10.1182/blood.V128.22.615.615

Flinn IW, Van Der Jagt R, Kahl BS, Wood P, Hawkins TE, Macdonald D et al (2014) Randomized trial of bendamustine-rituximab or R-CHOP/R-CVP in first-line treatment of indolent NHL or MCL: the BRIGHT study. Blood 123(19):2944–2952. https://doi.org/10.1182/blood-2013-11-531327

Grigg A, Dyer MJS, Díaz MG, Dreyling M, Rule S, Lei G et al (2017) Safety and efficacy of obinutuzumab with CHOP or bendamustine in previously untreated follicular lymphoma. Haematologica 102(4):765–772. https://doi.org/10.3324/haematol.2016.152272

Le Guyader-Peyrou S, Defossez G, Dantony E, Mounier M, Cornet E, Uhry Z, et al (2019) Volume 2—Hémopathies malignes. In: Le Guyader-Peyrou S, Defossez G, Dantony E, Mounier M, Cornet E, Uhry Z, et al. Estimations nationales de l'incidence et de la mortalité par cancer en France métropolitaine entre 1990 et 2018. Étude à partir des registres des cancers du réseau Francim. Santé publique France, Saint-Maurice.

Herter S, Herting F, Mundigl O, Waldhauer I, Weinzierl T, Fauti T et al (2013) Preclinical activity of the type II CD20 antibody GA101 (obinutuzumab) compared with rituximab and ofatumumab in vitro and in xenograft models. Mol Cancer Ther 12(10):2031–2042. https://doi.org/10.1158/1535-7163.MCT-12-1182

Hiddemann W, Kneba M, Dreyling M, Schmitz N, Lengfelder E, Schmits R et al (2005) Frontline therapy with rituximab added to the combination of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) significantly improves the outcome for patients with advanced-stage follicular lymphoma compared with therapy with CHOP alone: results of a prospective randomized study of the German Low-Grade Lymphoma Study Group. Blood 106(12):3725–3732. https://doi.org/10.1182/blood-2005-01-0016

Hiddemann W, Barbui AM, Canales MA, Cannell PK, Collins GP, Dürig J et al (2018) Immunochemotherapy with obinutuzumab or rituximab for previously untreated follicular lymphoma in the GALLIUM Study: influence of chemotherapy on efficacy and safety. J Clin Oncol 36(23):2395–2404. https://doi.org/10.1200/JCO.2017.76.8960

Junlén HR, Peterson S, Kimby E, Lockmer S, Lindén O, Nilsson-Ehle H et al (2015) Follicular lymphoma in Sweden: nationwide improved survival in the rituximab era, particularly in elderly women: a Swedish Lymphoma Registry Study. Leukemia 29(3):668–676. https://doi.org/10.1038/leu.2014.251

Légifrance (2018a) Journal Officiel de la République Française n° 0233 du 9 octobre 2018a. https://www.legifrance.gouv.fr/jorf/jo/2018a/10/09/0233. Accessed 28 Sept 2021

Légifrance (2018b) Journal Officiel de la République Française n° 0298 du 26 décembre 2018b. https://www.legifrance.gouv.fr/jorf/jo/2018b/12/26/0298. Accessed 28 Sept 2021

Légifrance (2019) Journal Officiel de la République Française n° 0270 du 21 novembre 2019. https://www.legifrance.gouv.fr/jorf/jo/2019/11/21/0270. Accessed 28 Sept 2021

Marcus R, Imrie K, Solal-Celigny P, Catalano JV, Dmoszynska A, Raposo JC et al (2008) Phase III study of R-CVP compared with cyclophosphamide, vincristine, and prednisone alone in patients with previously untreated advanced follicular lymphoma. J Clin Oncol 26(28):4579–4586. https://doi.org/10.1200/JCO.2007.13.5376

Marcus RE, Davies AJ, Ando K, Klapper W, Opat S, Owen CJ et al (2016) Obinutuzumab-based induction and maintenance prolongs progression-free survival (PFS) in patients with previously untreated follicular lymphoma: primary results of the Randomized Phase 3 GALLIUM Study. Blood 128(22):6. https://doi.org/10.1182/blood.V128.22.6.6

Marcus R, Davies A, Ando K, Klapper W, Opat S, Owen C et al (2017) Obinutuzumab for the first-line treatment of follicular lymphoma. N Engl J Med 377(14):1331–1344. https://doi.org/10.1056/NEJMoa1614598

Mössner E, Brünker P, Moser S, Püntener U, Schmidt C, Herter S et al (2010) Increasing the efficacy of CD20 antibody therapy through the engineering of a new type II anti-CD20 antibody with enhanced direct and immune effector cell-mediated B-cell cytotoxicity. Blood 115(22):4393–4402. https://doi.org/10.1182/blood-2009-06-225979

Radford J, Davies A, Cartron G, Morschhauser F, Salles G, Marcus R et al (2013) Obinutuzumab (GA101) plus CHOP or FC in relapsed/refractory follicular lymphoma: results of the GAUDI study (BO21000). Blood 122(7):1137–1143. https://doi.org/10.1182/blood-2013-01-481341

Rummel MJ, Niederle N, Maschmeyer G, Banat GA, von Grünhagen U, Losem C et al (2013) Bendamustine plus rituximab versus CHOP plus rituximab as first-line treatment for patients with indolent and mantle-cell lymphomas: an open-label, multicentre, randomised, phase 3 non-inferiority trial. Lancet 381(9873):1203–1210. https://doi.org/10.1016/S0140-6736(12)61763-2

Salles G, Seymour JF, Offner F, López-Guillermo A, Belada D, Xerri L et al (2011) Rituximab maintenance for 2 years in patients with high tumour burden follicular lymphoma responding to rituximab plus chemotherapy (PRIMA): a phase 3, randomised controlled trial. Lancet 377(9759):42–51. https://doi.org/10.1016/S0140-6736(10)62175-7

Salles G, Morschhauser F, Lamy T, Milpied N, Thieblemont C, Tilly H et al (2012) Phase 1 study results of the type II glycoengineered humanized anti-CD20 monoclonal antibody obinutuzumab (GA101) in B-cell lymphoma patients. Blood 119(22):5126–5132. https://doi.org/10.1182/blood-2012-01-404368

Sarkozy C, Maurer MJ, Link BK, Ghesquieres H, Nicolas E, Thompson CA et al (2019) Cause of death in follicular lymphoma in the first decade of the rituximab era: a pooled analysis of French and US Cohorts. J Clin Oncol 37(2):144–152. https://doi.org/10.1200/JCO.18.00400

Sarraf Yazdy M, Cheson BD (2017) Impact of obinutuzumab alone and in combination for follicular lymphoma. Blood Lymphat Cancer 7:73–83. https://doi.org/10.2147/BLCTT.S114173

Sehn LH, Assouline SE, Stewart DA, Mangel J, Gascoyne RD, Fine G et al (2012) A phase 1 study of obinutuzumab induction followed by 2 years of maintenance in patients with relapsed CD20-positive B-cell malignancies. Blood 119(22):5118–5125. https://doi.org/10.1182/blood-2012-02-408773

Seymour JF, Marcus R, Davies A, Gallop-Evans E, Grigg A, Haynes A et al (2019) Association of early disease progression and very poor survival in the GALLIUM study in follicular lymphoma: benefit of obinutuzumab in reducing the rate of early progression. Haematologica 104(6):1202–1208. https://doi.org/10.3324/haematol.2018.209015

Teras LR, DeSantis CE, Cerhan JR, Morton LM, Jemal A, Flowers CR (2016) 2016 US lymphoid malignancy statistics by World Health Organization subtypes. CA Cancer J Clin 66(6):443–459. https://doi.org/10.3322/caac.21357

Vitolo U, Trněný M, Belada D, Burke JM, Carella AM, Chua N et al (2017) Obinutuzumab or rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone in previously untreated diffuse large B-cell lymphoma. J Clin Oncol 35(31):3529–3537. https://doi.org/10.1200/JCO.2017.73.3402