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FIRST-LINE IMMUNOCHEMOTHERAPY FOR FOLLICULAR LYMPHOMA PATIENTS- SINGLE CENTER EXPERIENCE

Sanja Trajkova **[1],** Svetlana Krstevska Balkanov[1],Aleksandra Pivkova Veljanovska [1], Nevenka Ridova[1], Simona Stojanovska Jakimovska[1], Milce Cvetanovski[1], Dusko Dukovski[1], Lazar Cadievski[1], Bozidar Kocoski [1], Zlate Stojanovski [1], Andrej Nikolovski [2],Bojan Labacevski[3], Irina Panovska Stavridis[1]

[1]University Clinic for Hematology,Medical faculty, Ss. Cyril and Methodius University, Republic of North Macedonia

[2] University Clinic of Surgical Diseases St. Naum Ohridski, Medical faculty, Ss. Cyril and Methodius University, Republic of North Macedonia

[3] Institute of preclinical and clinical pharmacology with toxicology, Medical faculty, Ss. Cyril and Methodius University, Republic of North Macedonia

Introduction: First line therapy of follicular lymphoma [FL] patients is based on anti CD20 immmunotherapy combined with chemotherapy with or without anthracycline. Data from studies presented a superior progression-free survival advantage in favor of Obinutuzumab [O] vs. Rituximab [R]-based immunochemotherapies as first-line therapy in FL patients. Nevertheless the studies presented more adverse events at the same treatment group.

Aim of the study**:** Evaluation of response from first line therapy and adverse events of first-line rituximab vs. obinutuzumab-based immunochemotherapies.

Materials and methods: This is a single center retrospective study presented with 143 adult FL patients diagnosed ad treted at University clinic for hematology, Skopje, N.Macedonia in a period of five years [2018-2022]. The response from first line therapy and adverse events profile of first-line rituximab vs. obinutuzumab-based immunochemotherapies were compared.

Results: A total of 143 patients were included in the analysis, 44% were treated with rituximab and 54,5% with obinutuzumab-based immunochemotherapy.Most of the patients 41,9% have advanced disease [Stage 4], FLIPI 3 [38,4%] and FLIPI 2 and 4 [21,6%]. Most of the patiens had ECOG 1 [41%]. Overall 33.5% of patients experienced infections and 39,1% had COVID infection. Patients treated with O v.s R have high rate of infection [44,8% and 13,3%] [p=0,005], febrile neutropenia was found at 46,1% [O] and 34% [R] treated with G-CSF. At the end of the study complete response was achieved at 69,2%, partal response at 4,1%, 20% of patients died and 11% died from COVID infection [25% of patients previously treated with R and 75% with O [p=0,001].

Conclusion**:** In this retrospective study of first-line treated FL patients comparing R- to O-based therapy, we did observe difference in adverese events profile in two treatment groups in favor of O treatment group.

Keywords: FL, Obinutuzumab; Rituximab, adverese events, infection.

Introduction

Follicular lymphoma [FL] is the most common indolent non-Hodgkin lymphoma in the Western part of the world. The biology of FL cells performs to have been satisfactorily impacted by the introduction of first generation of anti CD20 monoclonal antibody rituximab [R].

Randomized clinical trials have demonstrated that the addition of rituximab to standard chemotherapy induction has improved the overall survival [1]. Maintenance rituximab approaches can improve progression-free survival [PFS] [1].

But introduction of second generation of anti CD20 monoclonal antibody Obinutuzumab [O] was superior to rituximab for PFS in the GALLIUM study [2].

The landmark GALLIUM trial compared obinutuzumab, a glycoengineered type II anti-CD20 monoclonal antibody against rituximab in the frontline management of high-tumor burden FL. Data from studies presented a superior progression-free survival advantage in favor of obinutuzumab vs. Rituximab -based immunochemotherapy as first-line therapy in FL patients. At the landmark of 3 years, 80% of the obinutuzumab + chemotherapy patients were in remission versus 73% of the rituximab + chemotherapy patients. No OS differences were observed. The obinutuzumab-treated patients had

slightly more infusion reactions, episodes of cytopenia, and infections than the rituximab-treated patients.

An interesting question arises whether obinutuzumab is a superior anti-CD20 monoclonal antibody, the answer to the question may be in our next task, selection of an appropriate monoclonal antibody according to the profile of the lymphoma cell in accordance with the general condition of the patient in terms of possible adverse events associated with the therapy.

Aim of the study

Evaluation of response from first line therapy and adverse events of first-line rituximab vs. obinutuzumab-based immunochemotherapy.

Materials and methods

This is a single center retrospective study presented with 143 adult FL patients diagnosed ad treted at University clinic for hematology, Skopje, N.Macedonia in a period of five years [2018-2022]. Clinical data, including treatment received, are extracted from patients' medical records. The survival and adverse events profile of first-line rituximab vs. obinutuzumab-based immunochemotherapies were compared.

Study Design, Patients, and Treatments

Patients eligible for induction therapy were older than 18 years with untreated FL [histologic grade 1, 2, or 3a], diagnosed by a lymph node biopsy performed within 2 months of study registration.

Response was assessed 4 weeks after last induction treatment. Patients achieving a complete response [CR], an unconfirmed complete response [CRu], or a partial response [PR] were eligible for the next study phase. Eligible patients must have received at least four cycles of rituximab plus CHOP , six cycles of rituximab plus CVP, or four cycles of rituximab plus Bendamustine. At least six infusions of rituximab were required for each treatment regimen, without a delay of more than 2 weeks between each cycle.

Assessments

Responding patients were assigned to receive rituximab maintenance [375 mg/m2, once every 8 weeks], starting 8 weeks after last induction treatment. All randomly assigned patients received rituximab maintenance or underwent observation for 2 years or until disease progression, whichever occurred first.

Our study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. Patients provided written informed consent before reciving therapy.

Response was evaluated according to the 2017 International Working Group response criteria for non-Hodgkin lymphoma [3].

During the 2-year rituximab maintenance or observation phase, patients were assessed by clinical examination every 8 weeks and had a computed tomography scan every 6 months. If bone marrow involvement was initially documented, a biopsy was required at the end-of-treatment assessment to confirm CR. Patients completing the rituximab maintenance or observation phase underwent a final restaging assessment within 28 days of the last rituximab dose [or within a corresponding timeframe for those randomly assigned to observation]. For patients with no disease progression, follow-up assessments were scheduled every 3 months for the first 2 years, then every 6 months for an additional 3 years, and then annually in patients consenting to the extended follow-up. Patients with disease progression were followed annually for the initiation of new treatment or until data cutoff in patients consenting to the extended follow-up.

Efficacy and Safety Analyses

The primary end point was investigator-assessed response from first line therapy. Safety outcome measures included adverse events [AEs], serious AEs, grade 3 or higher AEs, and deaths.

Grading of AEs was according to National Cancer Institute Common Terminology Criteria for Adverse Events, version 6.0.

Statistical Analysis

Statistical analysis was performed using the SPSS software package, version 21.0. The value of $p<0.05$ was considered significant for all analyses.

Results

We analyzed data of 143 patients diagnosed and treated at University Clinic for Hematology. According to gender distribution there was male predilection, presented on Figure 1. The average age was 62,3 at male patients and 62 years at female patients.

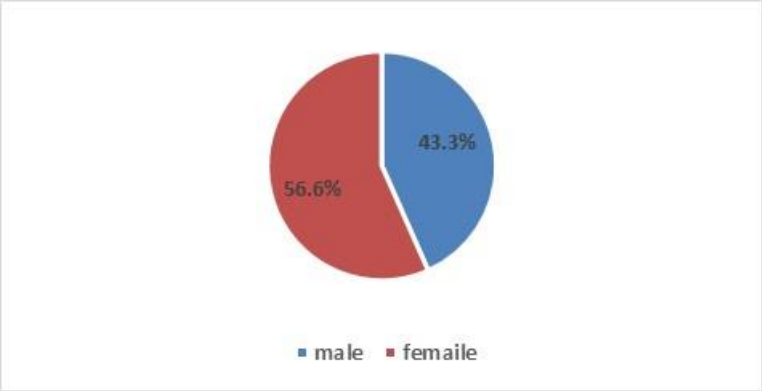


Figure 1. Gender distribution of Follicular lymphoma patients.

Most of the patients treated with immunochemotherapy have advanced stage according to Ann Arbor staging system, presented on Figure 2.

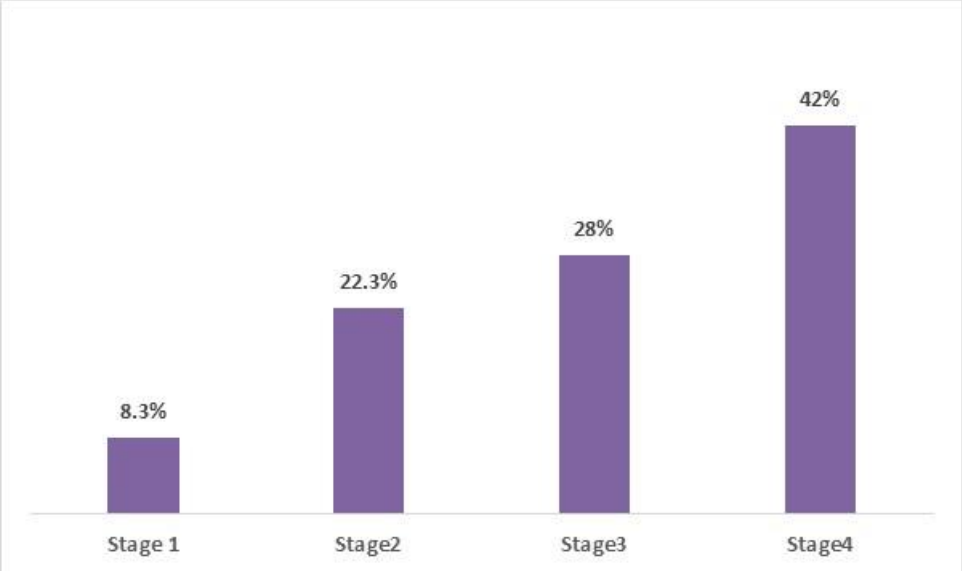


Figure 2. Ann Arbor stage distribution of Follicular lymphoma patients.

Most of the patients treated with immunochemotherapy have FLIPI 3 stage, presented on Figure 3.

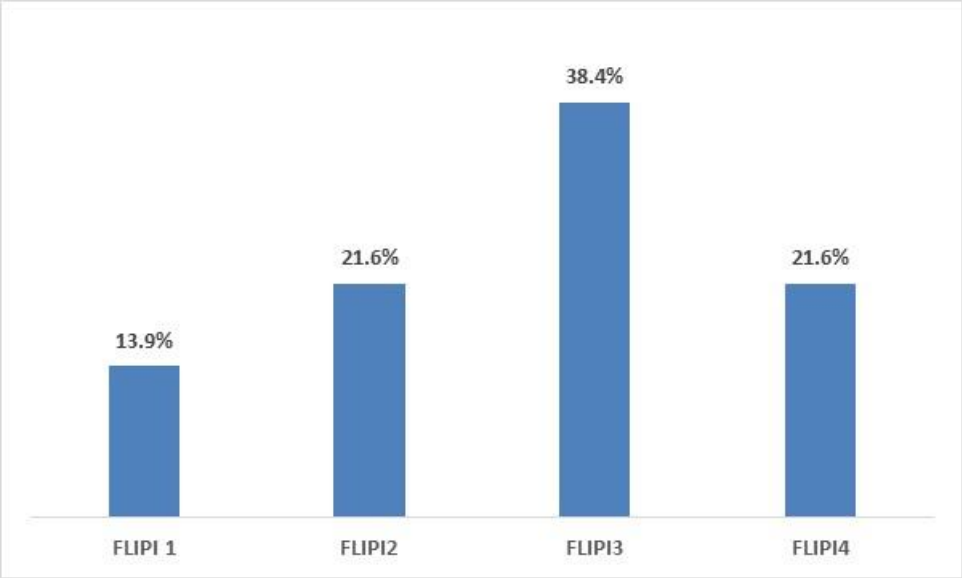


Figure 3. Distribution of Follicular lymphoma patients according to FLIPI.
Most of the patients with Follicular lymphoma treated with immunochemotherapy have ECOG 1, presented on Figure 4.

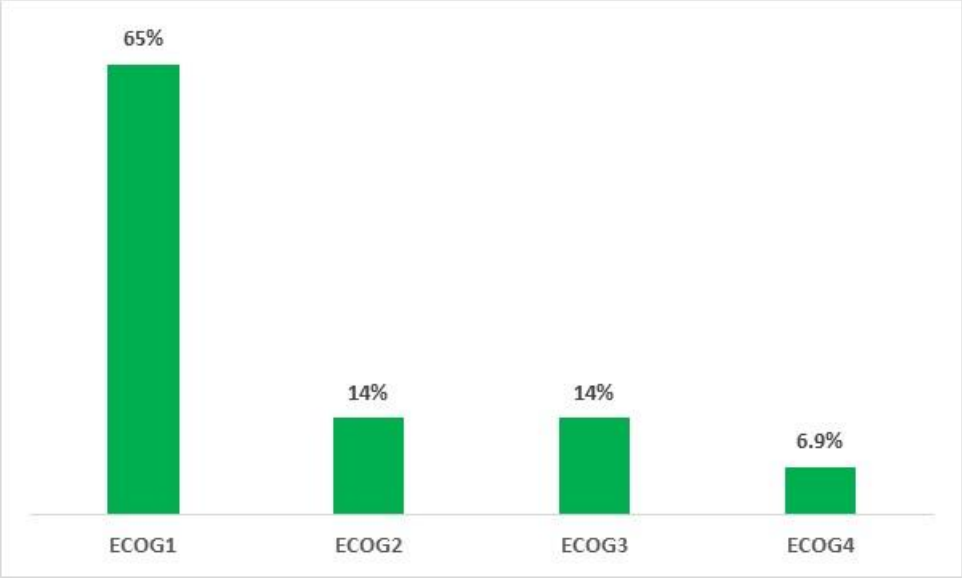
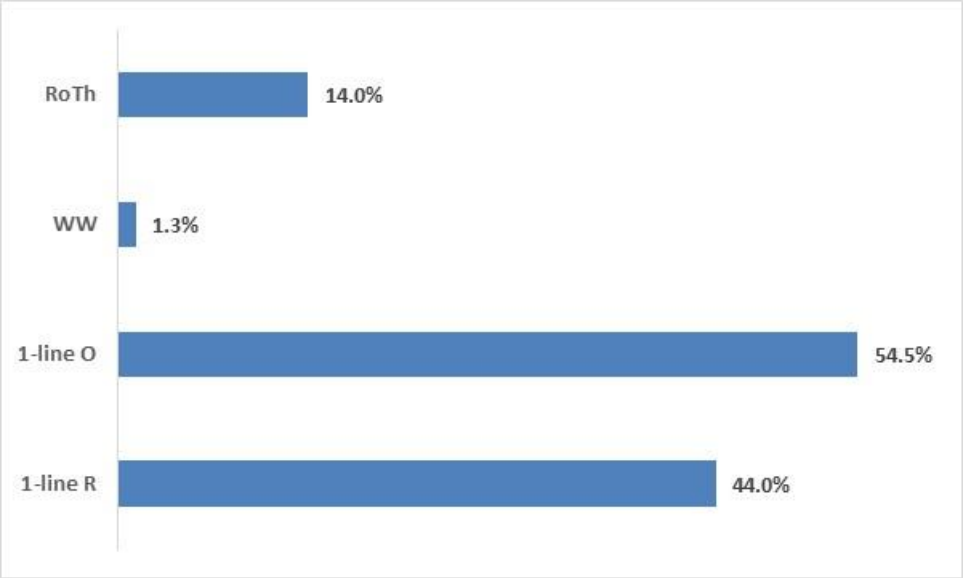


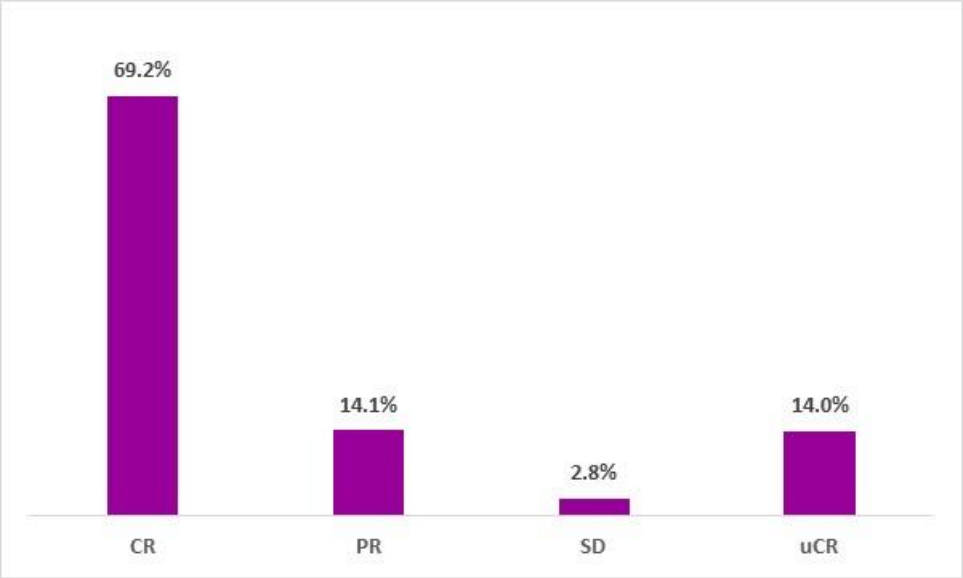
Figure 4. Distribution of Follicular lymphoma patients according to ECOG.

According to first line immunochemotherapy distribution, 44% were treated with rituximab and 54,5% with obinutuzumab-based immunochemotherapy, presented on Figure 5.



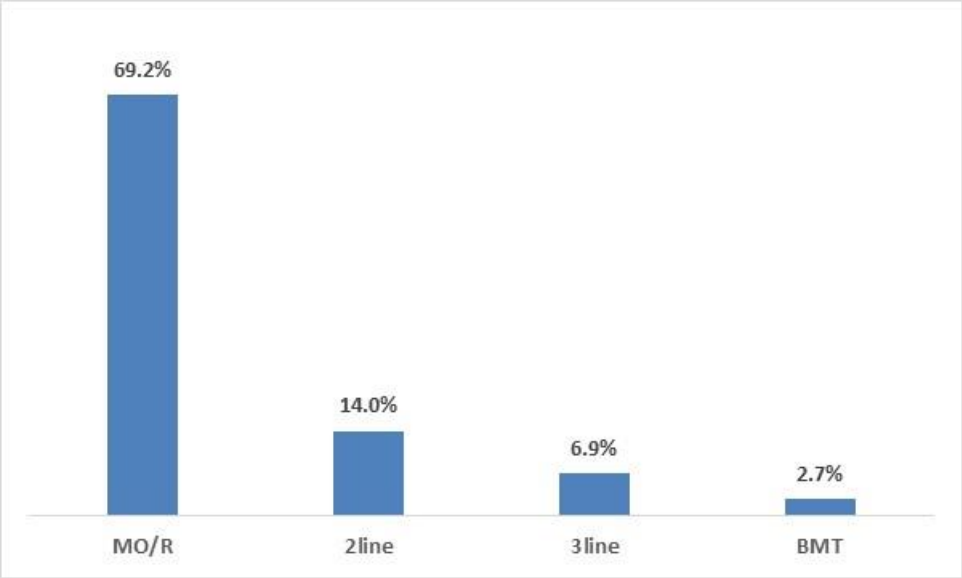
Abbreviations: Ro Th-radio therapy, WW-watch and wait, 1-line O-1-line Obinutuzumab, 1-line R-1-line Rituximab

Figure 5. Immunochemotherapy distribution of Follicular lymphoma patients.
After first line therapy most of the patients 69,2% of them achieved CR, presented on Figure 6.



Abbreviations: CR-Complete response, PR-partial response, SD-Stable Disease, uCR- uncertain complete response

Figure 6. Distribution of Follicular lymphoma patients treated with immunochemotherapy according to response of therapy.
After achievement of CR,Follicular lymphoma patients received maintenance therapy with rituximab or obinutuzumab, only 14% after relapse received second line therapy, and only 2,7% underwent on bone marrow transplantation [BMT] presented on Figure 7.



Abbreviations: MO/R (Maintenance Obinutuzumab/Rituximab), BMT-Bone marrow transplantation

Figure 7. Distribution of Follicular lymphoma patients treated with maintenance therapy and other line of therapy.

Most of the patients were alive at the end of the study, presented on Figure 8.

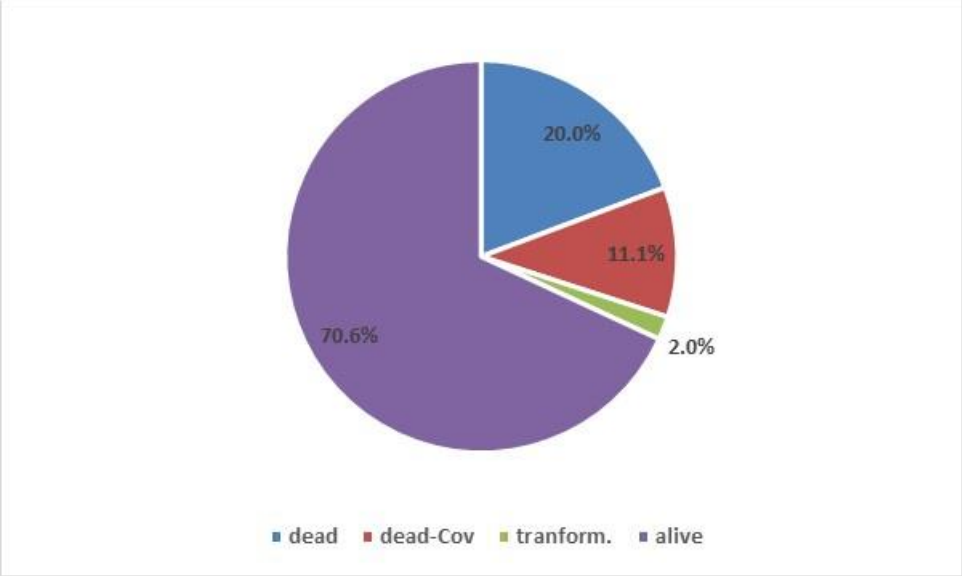
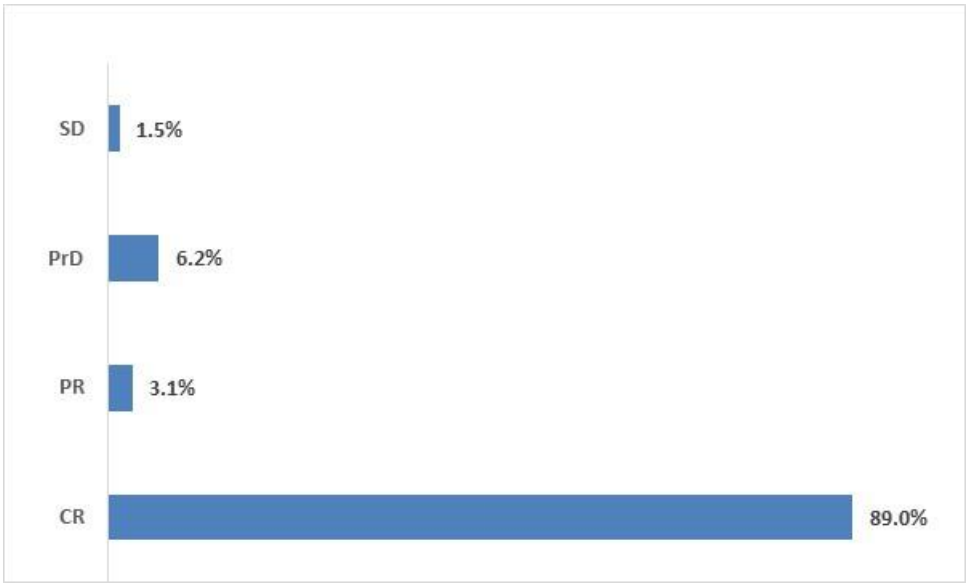


Figure 8. Outcome at the end of the study.

Follicular lymphoma patients treated with rituximab, in 89% achieved CR, presented on Figure 9.



Abbreviations: SD-stable disease, PrD- Progressive disease, PR-Partial response, CR-Complete response

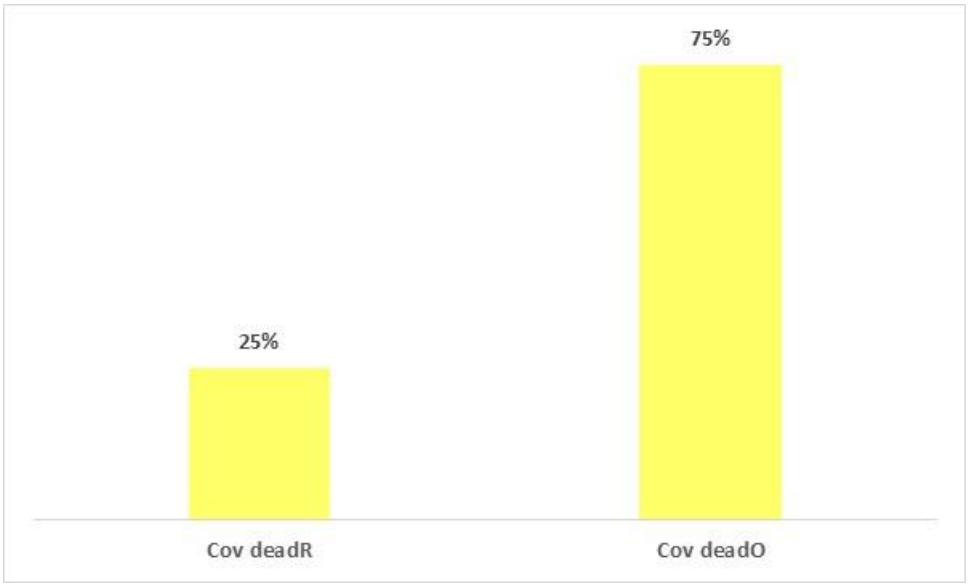
Figure 9. Distribution of Follicular lymphoma patients treated with rituximab based immunochemotherapy.

Similar percentage of Follicular lymphoma patients treated with obinutuzumab achieved CR, presented on Figure 10.

Abbreviations: PrD- Progressive disease, PR-Partial response, CR-Complete response

Figure 10. Distribution of Follicular lymphoma patients treated with obinutuzumab based immunochemotherapy.

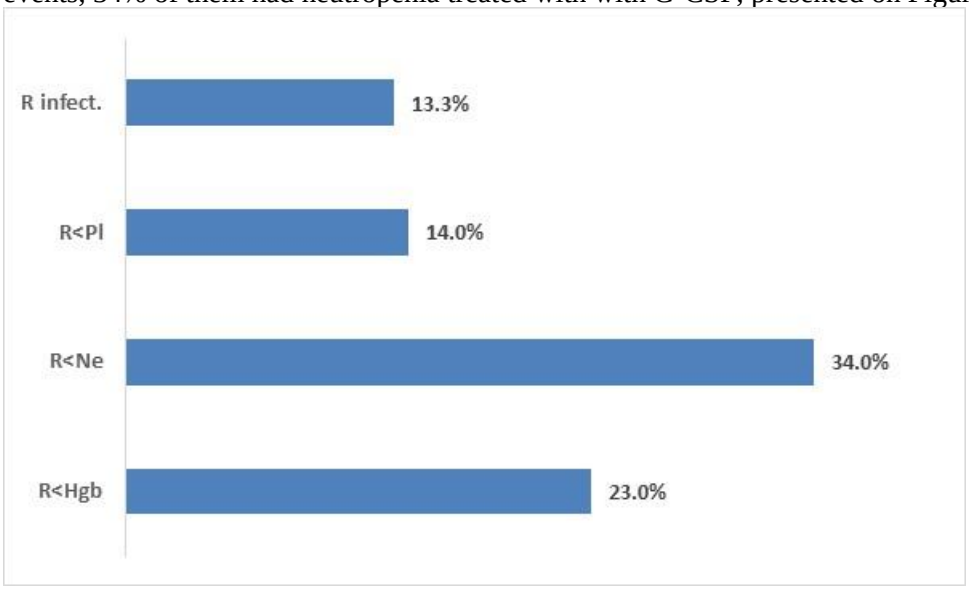
At the time of the study there was pandemia with COVID 19 which affected Follicular lymphoma patients treated with immunochemotherapy. Most of the patients treated with obinutuzumab based immunochemotherapy 75% died from Covid infection, statistical significant with [p=0,001] presented on Figure 11.



Abbreviations: Cov deadR- Patients treated with rituximab and dead prom Covid 19,Cov deadO- Patients treated with obinutuzumab and dead prom Covid 19

Figure 11. Distribution of Follicular lymphoma patients treated with obinutuzumab based immunochemotherapy and dead outcome from COVID19.

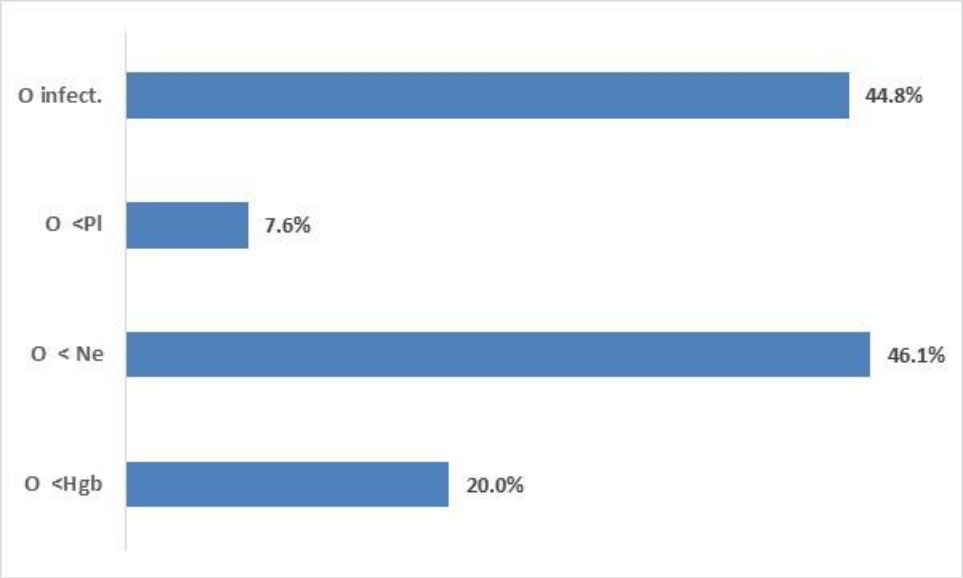
Follicular lymphoma patients treated with immunochemotherapy based on rituximab have adverse events, 34% of them had neutropenia treated with with G-CSF, presented on Figure 12.



Abbreviations: R infect (Patients treated with rituximab with infection,) R<PL (Patients treated with rituximab with low platelets), R<Ne (Patients treated with rituximab with low neutrophils), R<Hgb (l Patients treated with rituximab with low hemoglobin)

Figure 12. Distribution of Follicular lymphoma patients treated with rituximab based immunochemotherapy according to adverse events.

Most of the Follicular lymphoma patients treated with obinutuzumab have infection 44,8%, statistical significant [p=0,005], in correlation with patients treated with rituximab [13,3%] presented on Figure 13.



Abbreviations: O infect (patients treated with obinutuzumab with infection,) O<PL (patients treated with obinutuzumab with low platelets), O<Ne (patients treated with obinutuzumab with low neutrophils), O<Hgb (patients treated with obinutuzumab with low hemoglobin)

Figure 13. Distribution of Follicular lymphoma patients treated with obinutuzumab based immunochemotherapy according to adverse events.

Discussion

The last tvo decades of research into the treatment of advance stage FL has installed immunochemotherapy as the standard approach. However, there is no one universally standard immunochemotherapy regimen. In fact, there is quite a bit of geographic variation in the standards. The most commonly utilized options include either obinutuzumab or rituximab combined with either bendamustine or CHOP, CVP chemotherapy. Given the lack of OS benefit for maintenance therapy with an anti-CD20, it can be considered optional. Maintenance anti-CD20 therapy has a fairly reflective impact on PFS after R-CHOP, and thus is often utilized. On the other hand, maintenance anti-CD20 appears to have much less benefit after BR therapy, and the GALLIUM study suggests it may do more impairment than benefit (2), results from the study are presented on table 1.

Number	**Induction**	**Maintenance**	**3-year PFS (%)**
341	BR	Rituximab	81
345	BO	Obinutuzumab	85
203	R-CHOP	Rituximab	77
196	O-CHOP	Obinutuzumab	82
57	R-CVP	Rituximab	77
60	O-CVP	Obinutuzumab	77

Abbreviations:BR (Bendamustine, Rituximab), BO (Bendamustine, Obinutuzumab), R(Rituximab), O(Obinutuzumab)

Table 1. Efficacy data in frontline therapy from GALLIUM study [2].

In our study the obinutuzumab-treated patients had slightly more episodes of cytopenia, and infections than the rituximab-treated patients. On the other hand, the percentage of achieved CR are similar between the two group of patients, but adverse event is notable in obinutuzumab-treated patients. Covid 19 associated dead is more profound in obinutuzumab-treated patients.

As a result of the design issues with GALLIUM[2], it is impossible to recognise if obinutuzumab is truly a better monoclonal antibody than rituximab in FL or whether the results observed are simply of

function of dosing differences. As a result, obinutuzumab has not been universally accepted as the new standard of care and some investigators continue to administer rituximab.

The selection of an appropriate monoclonal antibody according to the profile of the lymphoma cell in accordance with the general condition of the patient in terms of possible adverse events associated with the therapy.

Nevertheless, numerous requirements remain, including capability to identify high-risk patients at diagnosis with use of new predictive biomarkers for targeted agents, the development of novel treatment combination of standard chemotherapy with B-cell receptor [BCR] signaling inhibitors in combination with angiogenesis inhibitor all in order to reduce the possibility of risk of transformation.

Conclusion

In this retrospective study of first-line treated FL patients comparing R- to O-based therapy, we did observe difference in adverese events profile in two treatment groups in favor of O treatment group. But numerous requirements remain, including capability to identify high-risk patients at diagnosis with use of new predictive biomarkers for targeted agents and development of novel treatment combination. Conflict of interest statement. None declared.

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