ARTICLE

Prolonged survival in the absence of disease-recurrence in advanced-stage follicular lymphoma following chemo-immunotherapy: 13-year update of the prospective, multicenter randomized GITMO-IIL trial

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ABSTRACT

A prospective trial conducted in the period 2000-2005 showed no survival advantage for high-dose chemotherapy with rituximab and autograft (R-HDS) *versus* conventional chemotherapy with rituximab (CHOP-R) as first-line therapy in 134 high-risk follicular lymphoma patients aged <60 years. The study has been updated at the 13-year median follow up. As of February 2017, 88 (66%) patients were alive, with overall survival of 66.4% at 13 years, without a significant difference between R-HDS (64.5%) and CHOP-R (68.5%). To date, 46 patients have died, mainly because of disease progression (47.8% of all deaths), secondary malignancies (3 solid tumor, 9 myelodysplasia/acute leukemia; 26.1% of all deaths), and other toxicities (21.7% of all deaths). Complete remission was documented in 98 (73.1%) patients and associated with overall survival, with 13-year estimates of 77.0% and 36.8% for complete remission *versus* no-complete remission, respectively. Molecular remission was documented in 39 (65%) out of 60 evaluable patients and associated with improved survival. In multivariate analysis, complete remission achievement had the strongest effect on survival (P<0.001), along with younger age (P=0.002) and female sex (P=0.013). Overall, 50 patients (37.3%) survived with no disease recurrence (18 CHOP-R, 32 R-HDS). This follow up is the longest reported on follicular lymphoma treated upfront with rituximab-chemotherapy and demonstrates an unprecedented improvement in survival compared to the pre-rituximab era, regardless of the use of intensified or conventional treatment. Complete remission was the most important factor for prolonged survival and a high proportion of patients had prolonged survival in their first remission, raising the issue of curability in follicular lymphoma. (Registered at clinicaltrials.gov identifier: 00435955)

Introduction

The current first-line treatment strategy for symptomatic and advanced follicular lymphoma (FL) is chemo-immunotherapy, with rituximab in combination with various chemotherapy regimens.[1-2] For a long time now, the upfront use of intensified chemotherapy with autograft has been proposed as an effective treatment option for patients presenting with high-risk disease.[3-8] We previously conducted a prospective randomized trial of these regimens in Italy, including patients <60 years of age who were affected by high-risk FL. The results showed no survival advantage from high-dose sequential chemotherapy with rituximab and autograft (R-HDS) compared to conventional cyclophosphamide, doxorubicin, vincristine, and prednisone supplemented with rituximab (CHOP-R).[9] Despite the limited median follow up of four years, this observation has discouraged the upfront use of intensive chemo-immunotherapy with autograft in FL, including in patients with high-risk disease presentation.

Follicular lymphoma patients now have prolonged life expectancy, with a median survival of ten years. This survival rate is possible because of the availability of rituximab along with improvements in the supportive care instruments.[10-13] The increase in patient survival warrants a long-term update of clinical trials to evaluate the real benefit of any treatment. For this purpose, our previous results of the randomized R-HDS *versus* CHOP-R have been updated by extending the period of analysis to 2017 with a median follow up of 13 years. The prolonged observation of this prospective cohort of patients offers the opportunity to define the following in advanced-stage, high-risk FL patients: (i) the long-term survival following conventional *versus* intensified chemotherapy with autograft, both delivered with rituximab; (ii) the main causes of death; (iii) the main factors affecting long-term outcome; and (iv) the rate of patients with prolonged survival in the absence of disease recurrence.

Methods

Patients' characteristics

Between March 2000 and May 2005, a total of 136 patients were enrolled in the multicenter randomized study, launched in Italy among centers affiliated with Gruppo Italiano Trapianto Midollo Osseo (GITMO) and/or to the Italian Lymphoma Intergroup (IIL).[9] The institutional review boards of all the participating centers approved the study. The study was designed for the first-line treatment of patients aged 16-60 years with a histologically proven diagnosis of FL.[14] Patients were eligible if they had Ann Arbor stage III or IV and a high-risk prognostic presentation, according to the prognostic risk scores in use at the time the protocol was designed, i.e. the age-adjusted International Prognostic Index (IPI) score >2 and the IIL score >3 for FL.[15,16] The CONSORT Diagram in the *Online Supplementary Appendix* gives details about treatment outcome of the 136 enrolled patients. Table 1 describes the main features of the 134 evaluable patients and the main clinical features of patients who are presently alive *versus* those who have died since protocol entry.

Study design, treatment schedule and end points

The aim of the study was to assess the superiority of an intensive chemo-immunotherapy strategy including autologous hematopoietic stem cell transplantation (auto-HSCT) compared to conventional chemo-immunotherapy. A centralized computer generated a simple randomization sequence and patients were randomly assigned either to the intensified or conventional arm.

Both conventional CHOP-R and intensified R-HDS treatments have already been described.[9,17-20] Details of the treatment schedules along with study end points and molecular analysis performed are reported in the Online *Supplementary Appendix*.[9,19,21]

Long-term follow up and statistical analysis

The update was made by taking information from 28 out of 29 participating centers regarding the clinical status of each patient entered in the prospective trial: (i) status alive or dead or lost to follow up, with the date of death or last follow up alive; (ii) cause of death, i.e. lymphoma progression, secondary neoplasm, non-neoplastic late fatal complications, or other causes; (iii) occurrence of secondary hematopoietic or non-hematopoietic neoplasm; or (iv) disease status at last follow up alive, i.e. continuous first, second or more complete remission (CR).

In the present update, alive patients were censored at the date of last contact (February 2nd, 2017), providing a median event-free survival (EFS) and overall survival (OS) follow-up time of 13.01 years [range: 0.5-16.6, interquartile range (IQR); 11.8-14.7]. All analyses were carried out on an intention-to-treat basis.

Survival curves were estimated by the Kaplan-Meier method according to the revised response criteria published in 2007, and compared using the log-rank test.[22-24] EFS, OS, progression-free survival (PFS), and disease-free survival (DFS) were analyzed by the Cox proportional hazards model, comparing the two treatment arms (R-CHOP *vs.* R-HDS) by the Wald test and calculating 95% Confidence Intervals (CI).[25]

The CI of secondary myeloid dysplastic syndrome (sMDS) / acute myeloid leukemia (AML) and solid malignancies in the whole cohort and stratified by the treatment arm were estimated at 5, 10, and 13 years from diagnosis and were assessed by the Gray test.[26] All reported *P*-values were two-sided, at the conventional 5% significance level. Data were analyzed as of January 2018 using R 3.4.3.[27]

Results

Overall survival and causes of death

As of February 2017, 88 (66%) patients were alive at their last follow up. Overall, median survival had not yet been reached at the 13-year median follow up, with a 13-year OS estimate of 66.4% for the whole patient cohort. Similar OS values were observed in the two treatment arms, with 13-year OS estimates of 68.5% and 64.5% for patients in the CHOP-R and R-HDS arms, respectively (Figure 1).

At the latest follow up, 46 patients had died. The main causes of deaths were disease progression for 22 patients (16.4% of the whole series, 47.8% of all deaths), secondary malignancies (3 solid tumor, 9 sMDS/AML) for 12 patients (8.9% of the whole series, 26.1% of all deaths), 12 patients died of various causes, including six fatal cardiovascular events, three documented infections, one graft failure following autograft, one anaphylactic shock following intravenous immunoglobulin (Ig i.v.) infusion, and one late sudden death. Among patients in the CHOP-R arm, 13 of 20 (65%) died from disease-related causes, whereas lymphoma progression was the cause of death for 9 of 26 (35%) patients in the R-HDS arm. Main causes of death per each treatment arm are summarized in Figure 2.

Table 1. Main patient features at presentation according to last survival status

	All patients	Patients alive[1]	Patients dead[1]	*P*
All	134	88	46	
M/F	78/56	45/43	33/13	0.022
Age (y), median (range)	51 (22-59)	50 (22-59)	53 (35-59)	0.297
Histologic grade I-II, n. (%)	98 (73)	65 (73)	33 (71)	0.792
age-adjusted IPI 2 or more, n. (%)	120 (89)	75 (85)	45 (98)	0.024
FLIPI 3 or more, n. (%)	78 (58)	52 (59)	26 (56)	0.775
Ann Arbor stage IV, n (%)	118 (88)	77 (86)	41 (89)	0.648
B symptoms, n. (%)	63 (47)	40 (46)	23 (50)	0.617
ECOG PS 2 or more, n. (%)	80 (60)	49 (56)	31 (67)	0.189
Bulky disease, n. (%)	75 (56)	51 (58)	24 (52)	0.522
Spleen involvement, n. (%)	50 (37)	28 (32)	22 (48)	0.061
Bone marrow involvement, n (%)	113 (84)	72 (82)	41 (89)	0.269
Extranodal involvement, n. (%)	42 (31)	29 (33)	13 (28)	0.578
Abnormal LDH, n . (%)	65 (59)	38 (43)	22 (48)	0.608
Treatment arm (CHOP-R/R-HDS), n.	66/68	46/42	20/26	0.371

IPI: International Prognostic Index; FLIPI: follicular lymphoma IPI; n: number; M: male; F: female; ECOG: Eastern Cooperative Oncology Group; LDH: lactate dehydrogenase. [1]Status after 13 years of median follow up.

Complete remission and molecular response: achievement and durability

Complete remission was documented in 98 (73.1%) patients: 39 (59.1%) of 66 undergoing CHOP-R treatment and 59 (86.7%) of 68 R-HDS-treated patients. CR achievement had a significantly favorable impact on survival, with 13-year OS estimates of 77.0% and 36.8%, for CR *versus* no-CR achievement, respectively (Figure 3A). Moreover, a durable CR was associated with prolonged survival. Overall, of 79 patients in CR at two years since treatment initiation, 65 (82.3%) were alive at 13 years compared to 21 (58.3%) among 36 patients with early relapse (P=0.003).

Molecular response was documented in 39 (65%) out of 60 evaluable patients: 11 (44%) of 25 undergoing CHOP-R treatment and 28 (80%) out of 35 R-HDS-treated patients (P<0.001).[9] Again, MR achievement was associated with a superior OS compared to patients not in MR following treatment (13-year OS estimates of 82.1% and 51.9%, for MR *vs.* no-MR achievement, respectively) (Figure 3B).

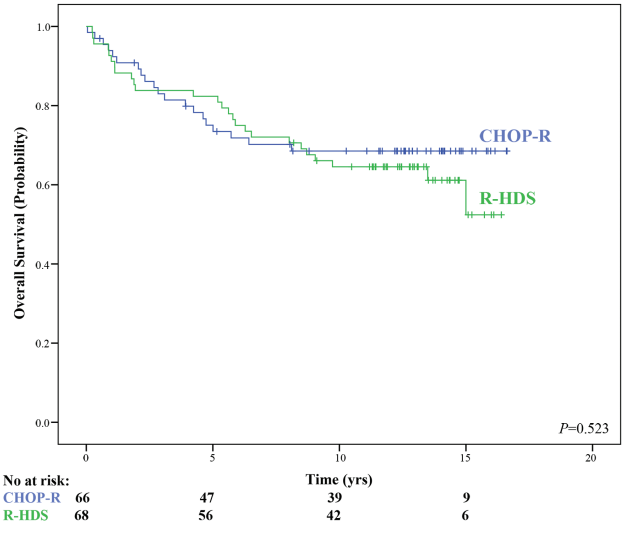

Figure 1. Updated overall survival (OS) according to treatment arms. Intensive chemo-immunotherapy with autograft (R-HDS) *versus* conventional chemoimmunotherapy (CHOP-R). Median follow-up: 13 years. No: number; yrs: years.

Overall, 50 patients (37.3% of the whole series) were alive at this follow up without any disease recurrence (18 in the CHOP-R and 32 in the R-HDS arms) since their first CR achievement. Among 98 patients obtaining CR, 39 had disease recurrence (39.8%). In the CHOP-R and R-HDS arms, the last disease recurrence respectively was recorded at ten years and at seven years from CR achievement. In addition, there were nine late toxic events (1 in CHOP-R and 9 in R-HDS) in patients in their first continuous CR. For patients reaching CR, the DFS estimate was 57.9% at 13 years. The 13-year DFS estimate was 47.1% for the 39 patients in CR following CHOP-R and 65.3% for the 59 patients in CR following R-HDS (Figure 4).

A subgroup of patients was further monitored for their molecular disease at long-term. After a median of four years of molecular monitoring since treatment completion, of the 24 patients alive in their first CR and evaluable for molecular disease, 20 (83%) patients were still in their first MR.

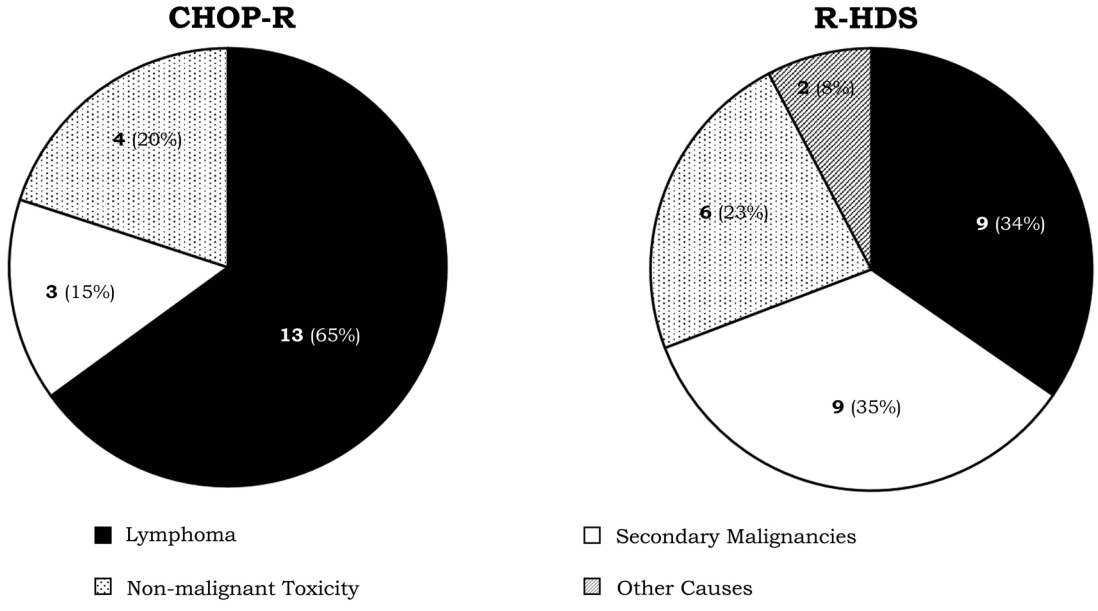

Figure 2. Main causes of death in the two treatment arms. Main causes of death include deaths due to: lymphoma, secondary malignancies (3 solid tumor, 9 secondary myeloid dysplastic syndrome (sMDS) / acute myeloid leukemia (AML)], non-malignant fatal events (6 fatal cardiovascular complications, 3 documented infections, 1 graft failure following autograft) and other causes (not clearly related to treatment).

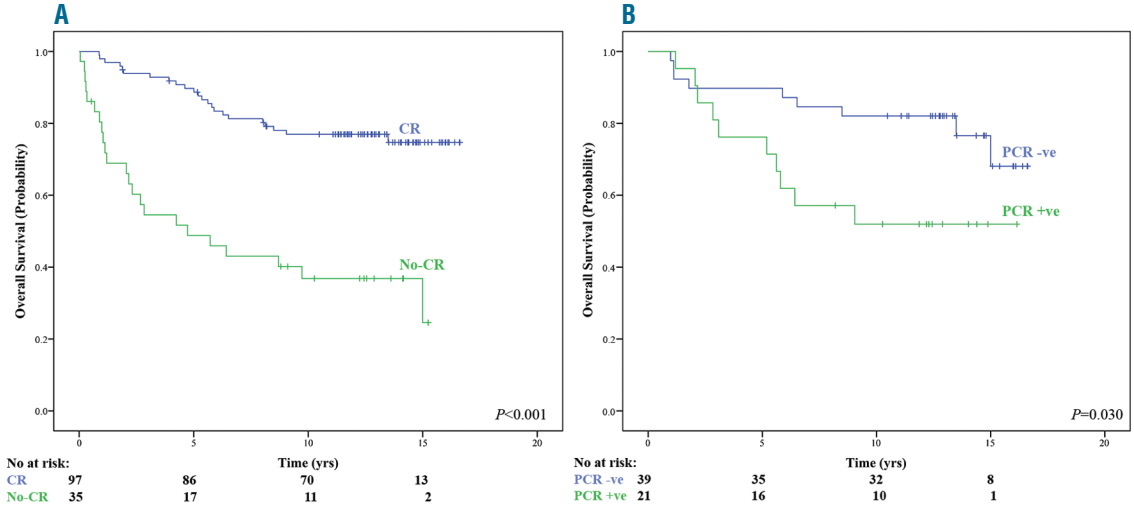

Figure 3. Updated overall survival according to end of treatment clinical status. (A) Complete remission (CR) achievement. (B) Molecular remission [polymerase chain reaction negative (PCR)] achievement. No: number; yrs: years.

The 13-year estimates for EFS and PFS were 37.3% and 46.3% among all patients, respectively. Both EFS and PFS curves remained significantly superior in the R-HDS compared to CHOP-R arm. For CHOP-R and R-HDS, 13-year EFS estimates were respectively 26.6% (median EFS: 1.6 years) and 48.5% (median EFS: 7.4 years) (Figure 5A). The 13-year PFS estimates were 28.8% (median PFS: 1.9%) and 59.1% (median PFS: not reached), for the CHOP-R and R-HDS arms, respectively (Figure 5B).

Rescue of patients with refractory and relapsed disease

Overall, 72 patients (53.7%) had disease progression (45 CHOP-R and 27 R-HDS), following partial response (PR) or refractory disease after induction (33 patients) or recurrence after CR achievement (39 patients). Five patients had progression with documented histological transformation and four with central nervous system involvement. As of the last follow up, 38 (52.8%) out of 72 progressing patients were long-term survivors following salvage therapies after disease recurrence. Among rescued patients, 28 patients were in the CHOP-R and ten in the R-HDS arms. At the last follow up, besides the 50 patients alive in their first CR, 20 patients were long-term survivors in their second CR (14 CHOP-R and 6 R-HDS) and 18 were surviving beyond a second CR (14 CHOP-R and 4 R-HDS).

High-dose therapy and autograft were employed as salvage therapy in 28 patients with disease progression following initial CHOP-R. Nineteen of them at this follow up were long-term survivors, with a median PFS-2 of 6.2 years. Nine patients eventually died because of lymphoma (7 patients) or secondary malignancy (2 patients). Allogeneic stem cell transplant was employed as the ultimate rescue approach in five patients; two of them were long-term survivors at this follow up, while three died (one from graft-*versus*-host disease, one from lymphoma progression, and one from a secondary tumor).

Factors affecting long-term survival

In univariate analysis, the main features at disease presentation and treatment end that significantly favored long-term survival were female sex, age <50 years, treatment completion, MR and CR achievement (see Table 2). When these factors were evaluated in multivariate analysis, CR still showed a strong impact along with a borderline value for female sex (Table 2). When PCR status (assay performed on 60 patients only) was excluded from the multivariate analysis, CR was still the strongest factor favorably affecting survival. In addition, younger age had a strong significant impact along with female sex (Table 2).

Secondary tumor occurrence

The respective cumulative incidences of sMDS/AL at 5, 10, and 13 years were 5.9%, 8.9% and 10.5% for the R-HDS arm and 0.0%, 10.7%, and 10.7%, respectively, for the CHOP-R arm (P=0.832). The respective cumulative incidences of secondary non-MDS/AL neoplasms at 5, 10, and 13 years were 5.9%, 10.4%, and 11.9% for the R-HDS arm and 0%, 4.9%, and 8.8% for the CHOP-R arm (P=0.792). Secondary neoplasms in the R-CHOP arm were carcinomas (five total: two laryngeal, two urothelial, one pancreatic), Hodgkin's lymphomas (two), MDS (two total, one of which evolved in AML), AML (one), and ALL Ph$^+$ (one). In the R- HDS arm, we observed five carcinoma cases (three head-and-neck, one mammary, one gastric), one non-melanoma skin cancer, one plasma cell dyscrasia, four MDS cases, and four AMLs.

Table 2. Univariate and multivariate proportional hazard models for overall survival.

	Univariate		Multivariate (with PCR)		Multivariate (without PCR)[1]	
	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*
Sex (F *vs.* M)	0.46 (0.24-0.88)	0.019	0.38 (0.14-1.04)	0.06	0.43 (0.22-0.84)	0.013
Age (> 50 y *vs.* < 50 y)	2.21 (1.18-4.15)	0.013	2.11 (0.79-5.66)	0.137	2.76 (1.45-5.23)	0.002
Spleen involvement (Yes *vs.* No)	1.62 (0.9-2.9)	0.109	NA	–	NA	–
MRD (Pos *vs.* neg)	2.26 (1.07-6.65)	0.036	0.94 (0.28-3.2)	0.919	–	–
Treatment completed (Yes *vs.* No)	0.39 (0.22-0.70)	0.002	0.49 (0.15-1.64)	0.248	0.56 (0.26-1.22)	0.139
Response (no CR *vs.* CR)	6.61 (2.53-17.25)	<0.001	6.79 (2.66-17.32)	<0.001	3.82 (2.12-6.89)	<0.001
Arm (R-HDS *vs.* CHOP-R)	1.21 (0.68-2.17)	0.524	NA	–	NA	–

HR: Hazard Ratio; CI: Confidence Interval; MRD: minimal residual disease; F: female; M: male; y: years; Pos.: positive; neg.: negative; CR: complete remission; R-HDS: high-dose chemotherapy with rituximab and autograft; CHOP-R: conventional chemotherapy with rituximab. [1]Polymerase chain reaction (PCR) data are available for a subgroups of 60 patients. NA: not included in the analysis.

Discussion

The present study reports outcomes after a median 13 years of follow up of a multicenter prospective trial comparing high-dose chemotherapy and autograft *versus* CHOP chemotherapy, both delivered with rituximab (R-HDS *vs.* CHOP-R), as upfront therapy in high-risk FL patients. To our knowledge, this follow up is the longest ever reported for first-line treatment of FL with rituximab-supplemented chemotherapy. The prolonged observation shows an extraordinary improvement in OS compared to the pre-rituximab era.[15,16] The survival was similar in both treatment arms, confirming over the long-term our preliminary observation that R-HDS does not add survival advantages compared to CHOP-R in the upfront therapy of high-risk FL.[9] CR achievement was the most important factor for prolonged survival. The importance of disease response is further emphasized by the first-time observation that MR achievement is associated with survival duration and a high proportion of patients had prolonged survival in the absence of disease recurrence.

The GITMO-IIL trial was designed for patients with high-risk FL, histologically diagnosed according to the Revised European-American Classification of Lymphoid Neoplasms (REAL)/World Health Organization (WHO) lymphoma classification.[14] The FL diagnosis was confirmed by the high rate of *BCL-2* gene translocation detected in patients with molecular assessment. The high-risk presentation was proved using the clinical prognostic scores available when the protocol was designed.[15-16] The subsequently developed FLIPI score employs other clinical parameters, and a proportion of our patients were not true "high risk" according to FLIPI.[28] Nevertheless, all study patients clearly belonged to a severely ill population, with a 5-year survival expectancies of 43.6% (age-adjusted IPI score) and 38% (Italian Lymphoma Intergroup score), according to treatment available at the time the trial was conceived.[15,16] The 13-year survival of 66.4% recorded in our series represents a marked improvement in life expectancy compared to survival reported in the pre-rituximab era for similar high-risk FL patients. This result is especially notable because only four rituximab doses were applied to the majority of patients, and the treatment schedule was not that most frequently delivered in present times.

Recently, two other prospective trials performed in advanced-stage FL with rituximab-based upfront regimens have been updated: the Italian FOLL05 study comparing R-CVP, R-CHOP, and R-FM and the SWOG study comparing R-CHOP *versus* CHOP followed by radioimmunotherapy.[29,30] Both the FOLL05 study, with 8-year OS of 83%, and the SWOG study, with 10-year OS of 78%, showed extended life expectancies in the absence of rituximab maintenance. These values are in line with our 13-year OS of 66% obtained in a selected group of high-risk FL. The results strengthen the observations from several retrospective studies showing prolonged survival in FL following immunochemotherapy.[10-13] Moreover, results from all of these studies indicate that the CHOP schedule delivered

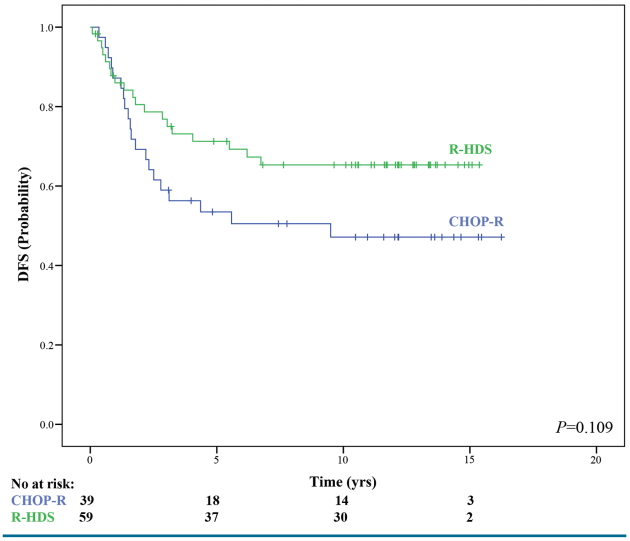

Figure 4. Updated disease-free survival (DFS) according to treatment arms. Intensive chemo-immunotherapy with autograft (R-HDS) *vs.* conventional chemoimmunotherapy (CHOP-R). No: number; yrs: years.

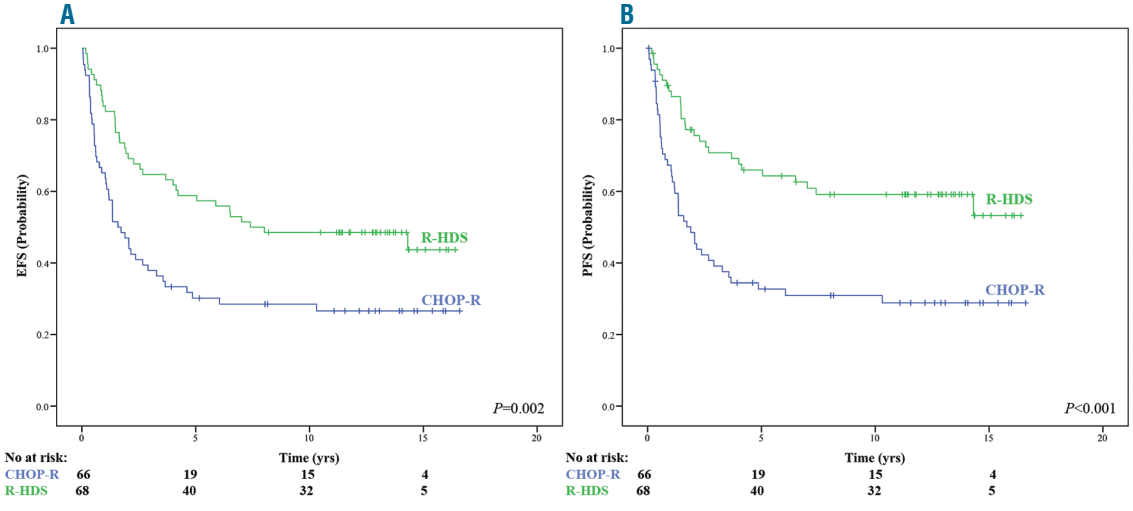

Figure 5. Updated event-free survival (EFS) and progression-free survival (PFS) according to treatment arms. Intensive chemoimmunotherapy with autograft (R-HDS) *versus* conventional chemoimmunotherapy (CHOP-R). (A) EFS. (B) PFS. No: number; yrs: years.

with rituximab is currently the first choice for the upfront treatment of advanced stage FL, ensuring prolonged survival, with adequate information about possible late side effects.

In our whole series, lymphoma progression remained the most frequent cause of failure, accounting for 47.8% of all causes of death. This is in line with several previous observations, including a recent report on a large series of FL.[31] Indeed, lymphoma progression was much more often responsible for fatal outcome among patients allocated to the CHOP-R arm, with 65% of all deaths, compared to the R-HDS arm with only 35% of all deaths. On the other hand, early and late toxicities were the most frequent cause of failure for patients in the R-HDS arm, which counterbalanced the increased anti-lymphoma activity of R-HDS compared to CHOP-R, resulting in analogous overall survival for the two treatment arms. Rituximab maintenance is now used with the aim of reducing disease recurrence risk.[32] In addition, both bendamustine and the novel anti-CD20 obinutuzumab antibody have been proposed as more effective first-line treatments compared to R-CHOP.[33,34] In particular, bendamustine is now frequently used as first-line treatment in place of the CHOP schedule. However, no evidence is currently available to suggest that these novel treatment strategies will substantially reduce the risk for disease-related deaths without affecting the treatment safety profile in the long term. Indeed, our update reinforces the need for prolonged observation to define the true survival advantage of any novel treatment for FL. Novel treatments for FL should combine potent anti-lymphoma activity along with low risk of both early and late toxicities.

Most late toxicities were secondary malignancies associated with the use of high-dose therapy with autograft delivered either upfront in the R-HDS arm or as salvage therapy in a good proportion of patients failing after upfront CHOP-R. This finding is in line with previous reports, including a retrospective study from the Gruppo Italiano Terapie Innovative nei Linfomi (GITIL) group indicating increased risk for secondary MDS/AL in lymphoma patients receiving high-dose therapy and autograft.[35] A recent surveillance study by the Spanish Lymphoma Group (GELTAMO) group has further stressed the risk of secondary MDS/AL in FL patients undergoing autograft.[36] Moreover, both the GITIL and GELTAMO studies indicated a trend for increased risk for secondary solid tumors when autograft is delivered along with rituximab.[35,36] Thus, the risk for late occurrence of secondary malignancy is a main issue in the long-term management of FL patients. This concern must be kept in mind in the long-term assessment of the efficacy of novel drugs and drug combinations.[33,34,37-39]

The present study allows identification of the factors favoring the long-term survival of high-risk FL patients treated with rituximab-containing chemotherapy. Somewhat unexpectedly, CR achievement proved to be the strongest prerequisite for long-term survival. Several recent observations indicate that response to initial treatment along with the achievement of a strong and durable response may favorably affect long-term outcome.[31,40-44] The present update clearly demonstrates in a prospective study that CR achievement shows the strongest association with prolonged survival. The importance of the response depth for long-term survival is confirmed by our molecular monitoring of measurable residual disease (MRD) performed in a subset of patients. Most studies have shown a remarkable prognostic value of MRD assessment in terms of PFS and response duration.[9,17,20,45,46] Nevertheless, the impact on OS could not be fully addressed in most studies, usually because of inadequate follow up.[47,48] Here, it was possible to demonstrate for the first time that MRD assessment is predictive for both PFS and OS, and that MR was associated with a prolonged survival.

The association of response depth with long-term survival in our FL series is further substantiated by the observation that a good proportion of patients (approx. 37% of the whole series) could survive in their first CR at long term. The DFS curves were definitely promising, with a 13-year estimate as high as 65% in R-HDS-treated patients. Moreover, most patients achieving MR following induction treatment maintained their MR during long-term molecular monitoring. Taken together, these results indicate that an extensive disease response in FL may translate into both prolonged survival and in the long-term persistence of CR; a state that has been described as functional cure in other clinical settings. This in turn raises the issue of the curability of FL, at least in patients with a high-risk clinical presentation such as those selected in the present study.

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