A retrospective study of R-DHAP/Ox for early progressing follicular lymphoma.

Retrospective analysis of R-DHAP/Ox and ASCT as salvage treatment for relapsed/refractory high risk follicular lymphoma.

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Abstract

The outcome of patients with follicular lymphoma (FL) experiencing disease progression within the first two years from first-line chemo-immunotherapy is poor and optimal subsequent management is uncertain. The combination of rituximab, dexamethasone, high-dose cytarabine, and cisplatin/oxaliplatin (R-DHAP/Ox) is active in germinal center-derived diffuse large B-cell lymphoma and is commonly used in FL prior to autologous stem cell transplantation (ASCT) in some Italian institutions. We identified all patients with FL that underwent R-DHAP/Ox at 3 institutions and retrospectively collected relevant clinical data. A total of 62 patients were identified, 46 of whom had relapsed

within the first two years from the start of frontline chemo-immunotherapy, and 34 of whom underwent ASCT. The overall survival (OS) of patients relapsing in the first 2 years after chemo-immunotherapy was of 74.3% at 5 years (95% C.I. 61-87%), the median time to next treatment (TTNT) after R-DHAP/Ox was 30.9 months (95% C.I. 18-74). Among patients that received ASCT the 5-year OS was 83.8% and the median TTNT was 38.5 months. Multivariate analysis of FLIPI at diagnosis, number of therapies prior to R-DHAP/Ox, response after first line and progression within 2 years from first line, did not demonstrate an association with OS for the considered variables. Prospective trials with R-DHAP/Ox +/- ASCT in patients with FL relapsing within 2 years of frontline therapy are warranted.

Introduction

Data from the LymphoCare study[1] demonstrated that patients with indolent follicular lymphoma that progresses within two years from the start of first-line chemo-immunotherapy with R-CHOP have a median overall survival (OS) of 5 years from the time of progression. These patients represent around 20% of all FL treated with first-line with chemo-immunotherapy, and for them optimal subsequent treatment remains uncertain.

Second-line chemo-immunotherapy followed by consolidation with autologous stem cell transplantation (ASCT) has demonstrated significant activity in patients with previously treated FL[2-4]. While selection of second-line therapy is frequently based on institutional standards, the combination of rituximab, dexamethasone, high-dose cytarabine, and

cisplatin/oxaliplatin (R-DHAP/Ox)[5] is an attractive option because it demonstrated superior outcomes to ifosfamide-based therapy in previously treated diffuse large B cell lymphoma with germinal center subtype[6], which shares the same cell of origin as FL. We hypothesized that the R-DHAP/Ox would be active therapy in patients with FL relapsing within the first two years following frontline chemoimmunotherapy and performed a retrospective study to evaluate the hypothesis.

Methods

The study was performed in accordance with IRB-approved protocols at each site (Universita' di Torino, San Bortolo Hospital, Citta' della Salute e della Scienza di Torino). All subjects had provided informed consent for the use of the clinical data. Patients were considered eligible if they had FL, if they had received at least one line of prior chemo-immunotherapy, and had received R-DHAP/Ox following disease progression. Subjects with histological transformation or grade 3B FL prior to receiving R-DHAP/Ox were excluded. Investigators recorded clinical data from electronic and paper medical records, including number and type of therapies before and after R-DHAP/Ox, response to R-DHAP/Ox and ASCT, main adverse events (infections requiring admission, inadequate stem cell collection, secondary malignancies, transformation to DLBCL), and survival outcomes. Response was estimated by investigators at each site based on standard International Working Group Criteria[7].

Data of the patients were analyzed anonymously. OS was calculated from risk-defining events, as reported in the LymphoCare study[1], that is survival from the time of

progression of disease (POD) for patients progressing in the first 2 years from first-line chemo-immunotherapy and from 2 years after diagnosis for the other group.

Time to next therapy (TTNT) was calculated from the end of one line of therapy to start of the subsequent one. Survival probability was estimated with the Kaplan-Meyer method and difference between groups was tested by log-rank test. Cox proportional hazard regression was used to calculate hazard ratio and test the statistical significance. Median follow-up time was estimated by reverse Kaplan-Meier method. All analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC).

The primary objective was to describe the OS of patients that had experienced progressive disease within two years after first-line chemo-immunotherapy undergoing R-DHAP/Ox +/- ASCT as salvage treatment. Secondary objectives were TTNT after R-DHAP/Ox +/- ASCT, and the association between fundamental clinical variables and OS.

Results

Patients

A total of 67 patients, 42 men and 25 women, were identified; 62 met the eligibility criteria. Five patients were excluded: 2 progressed to DLBCL before starting R-DHAP/Ox, 1 had grade 3b FL, 1 had a previous high grade lymphoma, 1 underwent chemotherapy in first line without anti-CD20 immunotherapy. Characteristics of the population at diagnosis are summarized in table 1.

First line therapy

First-line therapy was rituximab-cyclophosphamide-doxorubicin-vincristin-prednisone (R-CHOP) in 46 (74.2%), R-fludarabine-mitoxantrone in 5 (8%), rituximab-cyclophosphamide-vincristine-prednisone (R-CVP) in 4 (6.4%), R-bendamustine in 2 (3.2%), rituximab-fludarabine-mitoxantrone-dexamethasone (R-FND) in 2 (3.2%), and 1 of each of R-chlorambucil, R-bendamustine-mitoxantrone and R-HDS (HD sequential of etoposide, cyclophosphamide, mitoxantrone, melphalan + ASCT). Rituximab maintenance after first-line was given to 13 patients (21%). Prior to R-DHAP/Ox, 45 (72.6%) underwent only 1 line of therapy, 14 (22.4%) underwent 2 lines of therapy, and 3 (5%) had 3 or more lines.

Response to first-line chemo-immunotherapy was achieved in 92% (58% complete response [CR]); 5 patients (8%) reached only a stable disease (SD). The median TTNT from first-line was 22.1 months (95% C.I. 13.5 – 24.7), 48 patients progressed within the first two years (median TTNT 14.3 months [95% C.I. 10.6 – 19.4]). The characteristics of these early progressors relative to the population from the LymphoCare study are provided in Table 2. Overall response to last therapy prior to R-DHAP/Ox was 87.1% (CR 58%), 6.4% had a stable disease, and 4.8% were in progression of disease. For one patient (1.6%), assessment of response was not reported.

R-DHAP/Ox +/- ASCT

Response to R-DHAP/Ox and ASCT for the whole population and for the early progressors is reported in table 3. Of the patients with early POD after first line, 34 (74%) underwent consolidation with ASCT, 12 patients did not. In 5 cases (42%) this was due to progression of disease, in 3 cases (25%) patients had stem cell collection problems, in 2 cases (16.5%) infectious complications during R-DHAP/Ox precluded further high dose treatment. The remaining 2 patients consolidated R-DHAP/Ox with radio-immunotherapy.

Radio-immunotherapy with ibritumomab tiuxetan (zevalin) was used in 22 total patients (35.5%) pre- or post R-DHAP/Ox and ASCT, and 10 patients (16%) underwent rituximab maintenance after ASCT.

Toxicity

Febrile neutropenia was reported in 10 cases (16%), delay of chemotherapy in 5 cases (8%). In 3 cases, a dose reduction of the therapy by 80% from the beginning was reported, due to age or comorbidities. One patient needed a dose reduction for renal toxicity. Stem cell collection failure was noticed in 6/52 cases (11.5%). Four patients (6.4%) experienced transformation to DLBCL, and 4 secondary malignancies, including 3 myeloid disorders (2 acute leukemia, 1 myelodysplastic syndrome), 1 bladder carcinoma were reported.

Survival

At the time of the analysis, 41 patients were still alive (66%). The causes of death were progression of lymphoma in 11 subjects (52%), secondary myeloid disorders in 3 patients (14%), and other toxicity in 4 patients (19%: 1 related to autologous and 1 to allogeneic transplant, 1 renal toxicity plus unspecified neurological syndrome, 1 to pneumonia). In 1 case (4.7%) the death was unrelated to lymphoma or toxicity, and in 2 cases (9.5%) the cause of death was not reported.

After a median follow-up of 66 months, median OS, OS at 5 years and TTNT after R-DHAP/OX +/- ASCT for the population resulted as reported in table 4. (figure 1)

A multivariate analysis on OS with 4 covariates (FLIPI, progression within 2 years, number of therapies before R-DHAP/Ox, response after first line), showed that after R-DHAP/Ox +/- ASCT, none of these variables had impact on survival.

Overall, 35 patients (56.4%) relapsed after R-DHAP/Ox +/- ASCT, and 34 (54.8%) required further treatment, this representing in most of the cases a third line. Subsequent therapies are being summarized in table 5.

Discussion

To our knowledge, this is the first study to evaluate R-DHAP/Ox and ASCT in patients with FL and early progression following first-line immunochemotherapy. Our data suggest that treatment of these high-risk patients with R-DHAP/Ox and ASCT is active and reasonable.

Compared to the LymphoCare population, our series of Italian patients with early POD had similar characteristics with the sole exception being that the average age in our series was slightly less than the LymphoCare patients, perhaps because these patients were selected to receive intensive therapy (table 2). The OS in this series appears superior to the LymphoCare study (OS at 5 years 74.3% vs 50%), and this is particularly evident for the group undergoing ASCT (OS at 5 years 83.8%). In the LymphoCare study, of people experiencing early POD, only in 7.3% were treated with ASCT, making a direct comparison not possible[1].

This advantage in overall survival could be attributed to effectiveness of this radical program, but some bias might be contributing to that. First of all, this is a selected population, fit enough to undergo an intensive treatment, and probably does not represent all the FL with early POD at our institutions. Also, in the LymphoCare study, patients undergoing observation before first-line chemoimmunotherapy were excluded from the analysis, while in our cohort 8.6% of the patients underwent watchful waiting. To avoid this bias, we calculated the 2-year POD starting from the date of the first cycle of first-line chemotherapy, and not from diagnosis.

One other series has evaluated treatment with single agent PI3K inhibitor idelalisib in FL with early POD[8] and found that ORR was 56.8% (CR 13.5%), median duration of response was 11.8 months, and OS at 5 years from relapse after first-line chemotherapy 79%. Our series demonstrated better response rates and duration of response, but similar OS. Patients undergoing ASCT in our cohort did better overall. As

noted previously, comparing patient populations across studies is challenging. Patients in the idelalisib study were treated in the context of a prospective protocol and received a median of three prior lines of therapy while our cohort consists of retrospectively identified patients treated in a standard clinical setting, and patients mostly received only one prior line of therapy.

TTNT following R-DHAP/Ox in our series was nearly three times TTNT after first-line therapy. Although most patients required additional therapy within 3 years, most cases were well controlled with less aggressive treatment (for example localized radiotherapy), or with a milder chemotherapy, like BR. This might indicate that the disease has probably a less aggressive behavior than before, and R-DHAP/Ox + ASCT might have eliminated some dangerous sub-clones that were responsible for this.

Both short-term and late toxicities in this series were consistent with previously reported series. In particular, despite a significant burden of therapy including radioimmunotherapy in 35.5%, myelodysplasia and myeloid leukemia appear to be comparable to other series with less intensive treatments[9-12].

The multivariate analysis on the whole population, showed that early POD did not predict poor outcome. This could derive from two factors: Our early POD population has a better outcome than the LymphoCare early POD population while our later-progressing patient population was very small and had a worse prognosis than the one of the LymphoCare study. Probably these patients were selected for intensive therapy

due to some other high risk features not identified in our collected data. All the other variables, such as response to first line, number of therapy lines before R-DHAP/Ox and FLIPI score, failed to predict outcome. Again, the small number of patients and events might have biased results.

Although these data are encouraging, the ideal approach to early POD FL is still far from standardized. Our data confirm that patients with FL and early POD have a poor prognosis, but also suggest that R-DHAP/Ox +/- ASCT may be effective therapy in this challenging population. Prospective studies of R-DHAP/Ox +/- ASCT are warranted in high-risk FL.

References

1. Casulo C, Byrtek M, Dawson KL, et al. 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. 2015 Aug 10;33(23):2516-22. doi: 10.1200/JCO.2014.59.7534.

2. Pettengell R, Schmitz N, Gisselbrecht C, et al. Rituximab purging and/or maintenance in patients undergoing autologous transplantation for relapsed follicular lymphoma: A prospective randomized trial from the lymphoma working

party of the European Group for Blood and Marrow Transplantation. J Clin Oncol 31:1624-1630, 2013

3. Robinson SP, Canals C, Luang JJ, et al: The outcome of reduced intensity allogeneic stem cell transplantation and autologous stem cell transplantation when performed as a first transplant strategy in relapsed follicular lymphoma: An analysis from the Lymphoma Working Party of the EBMT. Bone Marrow Transplant 48:1409-1414, 2013

4. Sabloff M, Atkins HL, Bence-Bruckler I, et al. A 15-year analysis of early and late autologous hematopoietic stem cell transplant in relapsed, aggressive, transformed, and nontransformed follicular lymphoma. Biol Blood Marrow Transplant 13: 956-964, 2007

5. Lignon J, Sibon D, Madelaine I, et al. Rituximab, Dexamethasone, Cytarabine, and Oxaliplatin (R-DHAX) is an Effective and Safe Salvage Regimen in Relapsed/Refractory B-Cell Non-Hodgkin Lymphoma. Clin Lymphoma Myeloma and Leukemia 2010, 10(4): 262-269.

6. Thieblemont C, Briere J, Mounier N, et al. The germinal center/activated B-cell subclassification has a prognostic impact for response to salvage therapy in relapsed/refractory diffuse large B-cell lymphoma: a bio-CORAL study. J Clin Oncol. 2011 Nov 1;29(31):4079-87.

7. Cheson BD, Fisher RI, Barrington SF, et al. Recommendations for initial evaluation, staging and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. Journal of clinical oncology: official journal of the American Society of Clinical Oncology. Sep 20 2014;32(27):3059-3068.

8. Gopal AK, Kahl BS, Flowers CR, et al. Idelalisib is effective in patients with high-risk follicular lymphoma and early relapse after initial chemoimmunotherapy. Blood 2017, mar 21.pii blood-2016-12-757740.

9. McLaughlin P, Estey E, Glassman A et al. Myelodysplasia and acute myeloid leukemia following therapy for indolent lymphoma with fludarabine, mitoxantrone, and dexamethasone (FND) plus rituximab and interferon alpha. Blood 2005, 105:4573–4575.

10. Pirani M, Marcheselli R, Marcheselli L et al. Risk for second malignancies in non-Hodgkin's lymphoma survivors: a meta-analysis. Ann Oncol 2011, 22:1845–1858

11. Xu Y, Wang H, Zhou S et al. Risk of second malignant neoplasms after cyclophosphamide-based chemotherapy with or without radiotherapy for non-Hodgkin lymphoma. Leuk Lymphoma 2013, 54:1396–1404

12. Andrade-Campos MM, Liévano P, Espinosa-Lara N, et al. Long-term complication in follicular lymphoma: assessing the risk of secondary neoplasm in 242 patients treated or not with 90-yttrium-ibritumomab-tiuxetan. Eur J Haematol 2016 Dec; 97(6): 576-582.

Tables and figures

Table 1. Patient characteristics at diagnosis

Characteristic		**Number N=62**	**Range, %**
Age at diagnosis	Median	52 y	24-75
Sex	M:F	39/23	1.7
FLIPI	Low (0-1)	9	14.5%
	Intermediate (2)	22	35.5%
	High (≥3)	30	48.8%
	Unknown	1	1.6%
Grade	Grade 1-2	51	82.2%
	Grade 3a	11	17.8%
Type of first line therapy	R-CHOP	46	74.2%
	R-fludarabine-mitoxantrone	5	8%
	R-CVP	4	6.4%
	R-bendamustine	2	3.2%
	R-FND	2	3.2%
	R-HDS	1	1.6%

	R-chlorambucil, R-bendamustine-mitoxantrone	1 1	1.6% 1.6%
Therapies prior to DHAP/Ox	1 2 ≥3	45 14 3	72.6% 22.4% 5%

FLIPI: Follicular Lymphoma International Prognostic Index; NA: not available; R: rituximab; CHOP: cyclophosphamide-doxorubicin-vincristin-prednisone; CVP: cyclophosphamide-vincristine-prednisone; FND: fludarabine-mitoxantrone-dexamethasone; HDS: sequential high-dose of etoposide-cyclophosphamide-mitoxantrone-melphalan + autologous stem cell transplantation.

Table 2. Characteristics of 46 patients progressing within 2 years

Characteristic	**LymphoCare patients** Early POD (n=110)		**Italian patients** Early POD (n=46)		**Patients treated with idelalisib** Early POD (n=37)	
	No.	%	No.	%	No.	%
Age, years						
Median	58		52		NA	
Range	31-88		29-72		NA	
Sex						
Female	38	35	15	34	19	51

Male	72	65	31	66	18	49
Histologic Grade						
1 or 2	63	66	36	78	33	89
3a	33	34	10	22	4	11
Missing	14		0		0	
FLIPI score						
Low, 0 to 1	10	12	7	15	NA	
Intermediate, 2	29	34	13	30	NA	
High, 3 to 5	47	54	25	55	21	56.8
Missing	24		1		NA	

Table 2: Characteristics of the Italian population compared to the cohort of the LymphoCare study that relapsed within 2 years from R-CHOP.

POD: progression of disease; FLIPI: Follicular Lymphoma International Prognostic Index, NA: not available.

Table 3. Response to R-DHAP/Ox and ASCT

	Whole population (n=62)	**Early POD (n=46)**
Median time from last therapy to R-DHAP/Ox	9.2 months (range 0.2-118.8 months)	8.7 months (range 0.2- 27,3 months)
Response to R-DHAP/Ox	ORR: 87.2% (CR 56%) SD: 6.4%	ORR: 86.9% (CR 54%) SD: 6.6%

	PD: 3.2% NA: 3.2%	PD: 4.4% NA: 2.1%
Consolidation with ASCT	44 patients: 71%	34 patients: 74%
Response to R-DHAP/Ox and ASCT	ORR: 91% (CR 81.8%) SD: 2.3% PD: 2.3% NA: 4.4%	ORR: 91.3% (CR 79.4%) SD: 0 PD: 2.9% NA: 5.8%

POD: progression of disease; ORR: overall response rate; CR: complete response; SD: stable disease; PD: progression of disease; NA: not available.

Table 4. Survival analysis

	Whole population undergoing R-DHAP/Ox +/- ASCT (n=62)	**Early POD undergoing R-DHAP/Ox +/- ASCT (n=46)**	**Early POD undergoing ASCT (n=34)**
Median OS	152.9 months (95% C.I. 86.5 - .)	100.1 months (95% C.I. 82.1 - .)	Not reached (95% C.I. 83.0 - NR)
5y OS	79.6% +/- 5.3 (95% C.I. 69.2% – 89.9%)	74.3% +/- 6.7 (95% C.I. 61.2% - 87.4%)	83.8% +/- 6.7 (95% C.I. 70.6% - 96.9%)
TTNT	38.5 months (95% C.I. 18.9 - .)	30.9 months (95% C.I. 18.4 – 74.0)	38.5 months (95% C.I. 19.0 - .)

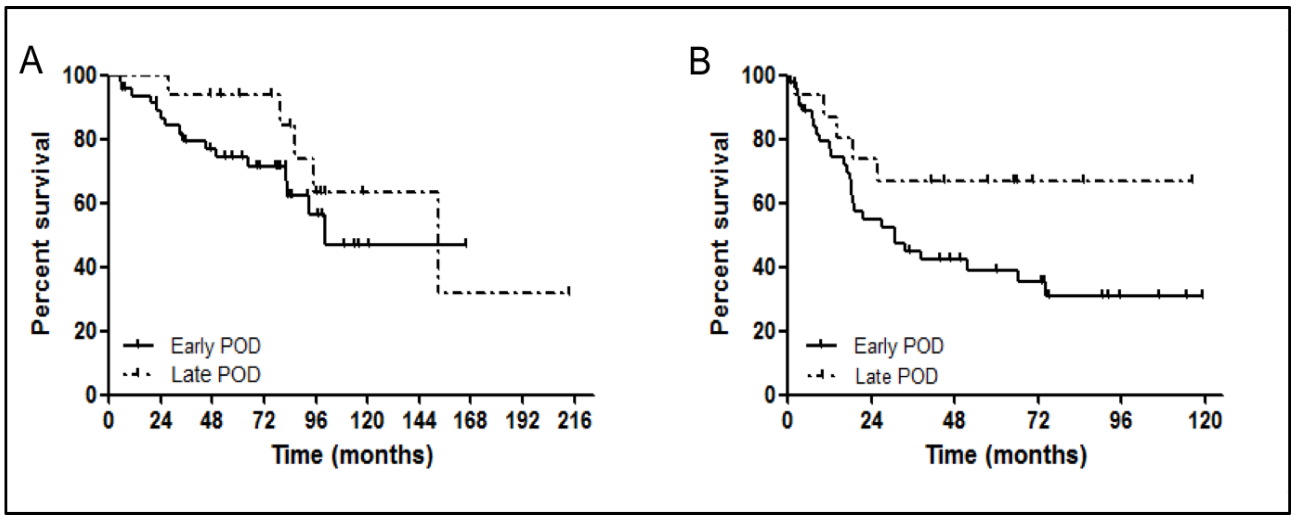
OS: overall survival; TTNT: time to next treatment; POD: progression of disease; C.I.: confidence interval.

Table 5. Subsequent treatments.

Retreated patients (n=34), 54.8%

Chemotherapy (n=27), 79%	**Moderate (n=17), 50%** Bendamustine (n=17), 50%	**Aggressive (n=10), 29%** alkylators (n=10), 29% anthracyclines (n=4), 11%, purine analogs (n=6), 17% consolidation with Allo SCT (n=8), 28%
Non-chemotherapy alone (n=6), 18%	Localized radiotherapy alone (n=2), 6% Pi3K inhibitors (n=2), 6% Lenalidomide + localized radiotherapy (n=1), 3% BCL-2 inhibitor (n=1), 3%	
Overall subsequent non-chemotherapy rituximab (n=26), 76.5%, lenalidomide (n=9), 26.5%, PI3K inhibitor (n=6), 17.6%, BCL2 inhibitor (n=3), 8.8%.		
Missing (n=1), 3%		

Figure 1



OS from risk-defining events (from relapse for early POD and from 2 years after diagnosis for patients relapsing later than 2 yars) of early vs late POD after first line, p=0.29 (A); TTNT after R-DHAP/Ox +/- ASCT for early POD vs late POD after first line, p=0.08 (B).