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Letter to the Editor

Achieving the Cure of Follicular Lymphoma: is it Time to Finalize Treatment Strategies to Reach This Goal in a Subset of Patients?

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To the editor.

Although exhibiting high response rates and prolonged survival, follicular lymphoma (FL) is still considered an incurable disease.[1] Therefore, the conventional approach currently relies on delaying therapy until necessary, avoiding side effects and long-term toxicities.[2-4] Indeed, treatment is limited to symptomatic patients fulfilling the GELF criteria.[5] Furthermore, conventional chemo-immunotherapy does not allow disease eradication.[1] Therefore, new targeted therapies have attempted to change the disease course in the current era.

Several large cohort studies report a minority (from 20% to 40%) of long-term surviving FL patients who maintain clinical response for 10 or 15 years and may be considered "cured".[2-3,7]

We conducted a retrospective single-institution analysis on FL patients with progression-free survival (PFS) longer than ten years from the last treatment (very long responders - VLR), describing the clinical and histological characteristics at onset, front-line treatment, and treatment response. We included in the study also a subgroup of FL patients who achieved a prolonged PFS even after one or more relapses, analyzing the treatment strategies which allowed such an outcome.

Our purpose was to identify possible distinctive clinical features or treatment approaches of FL patients who turned out to be cured, defining a subset of patients who could be candidates for disease eradication.

Across twenty years (1992-2012), we identified 99 patients affected by FL that achieved a PFS of at least ten years after the first (n= 71) or subsequent treatment lines (n= 28), representing about 12% of the newly diagnosed patients, estimated about 800 in the same time frame.

Data were collected from the retrospective revision of clinical files.

The median follow-up was 169 months (range 120-303). The median age at diagnosis was 53 years (range 25-75). Patients' baseline characteristics are reported in **table 1**. The distribution of clinical features in this cohort of VLRs was not different from large cohorts reported in the literature.[2,7,9]

Among VLRs after front-line treatment (n=71), 31 patients (43.6%) received immune-chemotherapy (mostly R-CHOP), 22 (31%) chemotherapy alone, 2 (2.8%) rituximab alone, and 16 (22.5%) received radiotherapy alone.

Twenty-eight patients became VLRs after the second or subsequent lines of treatment: 19 achieved a long-lasting response after the second line of therapy, 4 after the third line, 3 after the fourth line, including allogeneic stem cell transplantation, and 2 after the fifth line.

Overall, consolidation/maintenance was administered to a minority of patients, given the time frame of data collection. Treatment characteristics are reported in **table 2**.

Considering the type of response achieved after the first line or subsequent lines of treatment that lasted at least 10 years, a CR was documented in 79.7% of patients (79/99) and a PR in 20.2% (20/99). Interestingly, 13.1% (13 out of 99) considered in PR after first-line were found to be VLRs without further treatment. Given the extended follow-up of this cohort, the metabolic response was assessed only in 13 patients (9 CR and 4 PR).

At the time of writing, all patients are disease-free after more than ten years from the last treatment. Seventy-three percent of patients (71/99) still maintain a response after the first line.

As expected, a higher proportion of FL achieved the "cure" after chemo-immunotherapy received in the first line (82% vs. 57%, p 0.036); similarly, patients obtaining CR exhibit a higher probability of being VLR (77% vs. 65% p 0.001).

In our cohort, the VLR outcome was not strictly treatment-dependent and was achievable within any

Table 1. Clinical features of Very Long Responders (VLR) patients with Follicular lymphoma at diagnosis.

Patients Characteristics		Absolute Number or median value	% or Range
Age at diagnosis (years)		53.50	25-75
Ki-67%		30.00	15-70
Sex	Male	51	51.5%
	Female	48	48.5%
Grading	1	31	31.3%
	2	54	54.6%
	3A	14	14.1%
Ann Arbor Stage	I	17	17.1%
	II	11	11.1%
	III	19	19.2%
	IV	52	52.5%
B Symptoms	Yes	2	2.1%
BULKY Disease	Yes	8	8.4%%
Lymphocytosis	Yes	3	3.1%
BM involvement	Yes	44	45.8%
β 2 Microglobulin	Above range	15	27.8%
LDH	Above range	22	21.8%
FLIPI	Low Risk	49	49.5%
	Intermediate Risk	35	35.4%
	High Risk	15	15.1%
FLIPI 2	Low Risk	52	52.5%
	Intermediate Risk	37	37.4%
	High Risk	10	10.1%

BM, Bone Marrow; LDH, Lactate dehydrogenase.

stage, histology subtype, and FLIPI risk category. Unfortunately, it was impossible to determine the clinical characteristics of a control cohort, including all other patients treated in the same time frame.

Long-term follow-up of large trials confirmed the favorable outcome of patients with advanced-stage FL treated with chemo-immunotherapy[3-4] and have shown the possibility of achieving PFS>10 years up to 40% of FL patients.[2] Moreover, in the post-rituximab era, several new therapeutic agents have been developed to further improve the prognosis of FL patients, leading to better overall response (ORR) and CR rates and longer PFS. Therefore, the philosophical approach of physicians towards FL might be changed, as addressed by Jonathan Friedberg with the biggest question: can we cure this disease?[10]

The recently published 13-year update of the multicenter randomized GITMO-IIL trial compared the outcome of 134 high-risk FL patients aged <60 years after first-line therapy with high-dose chemotherapy with rituximab and autograft (R-HDS) versus conventional chemotherapy with rituximab (CHOP-R). The study showed significant superiority of PFS in the R-HDS arm (59.1% and 28.8%, respectively), while no statistical differences in OS were found (64.5% vs. 68.5%, respectively).[2] Nevertheless, the higher eradicative potential of R-HDS + ASCT could be considered aiming at disease eradication. A portion of our VLR patients after the second or subsequent treatment line achieved this result after ASCT (7/28).

Allogeneic SCT is rarely employed in FL; nevertheless, in our experience, it allowed disease eradication in 3 patients after three treatment lines.

Long-term follow-ups of trials, including novel agents, are awaited.

Surely, the landscape of disease monitoring has changed; we have potential new tools to monitor the quality of response, predict patients' outcomes and possibly support the clinician in identifying candidates to be long-term survival. Recent studies demonstrated a high prognostic value of the end-induction PET scan, a predictor of better survival and superior PFS.[6-9,11,14] Unfortunately, in this series, only a few patients underwent the metabolic assessment of disease response. The proportion of false-positive PR observed by CT in our series would probably have been reduced.

Basal biological and clinical features can predict a favorable outcome: many studies showed the prognostic

Table 2. Treatment features of Very Long Responders (VLR) patients with Follicular lymphoma. Treatment characteristics of patients achieving a very long response either a First Line treatment or after second or subsequent line of therapy.

Patients achieving 10-year PFS after the first line of treatment (n=71)	Response after I line	CR	57	80%
		PR	13	18.3%
		SD	2	2.8%
	Maintenance/ consolidation	Radiotherapy	3	4.2%
		Rituximab	8	8%
		Ibritumomab tiuxetan	3	3.08%
	I Line Therapy	R-Bendamustine	1	1.4%
		R-CVP	3	4.2%
		CHOP	16	22.5%
		R-CHOP	20	28.2%
		Purine Analog	6	8.5%
		R-Purine analog	7	9.9%
		Radiotherapy	16	22.5%
		Rituximab alone	2	2.8%
Patients achieving 10-year PFS after at least two lines of treatment (n=28)	Response after the last treatment line	CR	21	75%
		PR	7	25%
		SD/PD	0	0.0%
	II-further line therapy	Radiotherapy	3	10%
		HD+ASCT	7	26%
		Chemo-Immunotherapy	15	54%
		Allo-SCT	3	10
	Maintenance/ Consolidation (After I Line)	Rituximab	2	7%
		Other agents	2	7%
		Ibritumomab tiuxetan	1	3.5%
		Radiotherapy	2	7%
	I Line Therapy	R-CVP	2	7%
		CHOP	7	25%
		R-CHOP	8	28%
		Purine Analog	3	11%
		R-Purine analog	3	11%
		Radiotherapy	4	13.5%
		Rituximab alone	1	3.5%

CR, Complete Response; PR, Partial Response; SD, Stable Disease; R, Rituximab; CVP, Vincristine, Cyclophosphamide, Prednisone; CHOP, Vincristine, Adriblastine, Cyclophosphamide, Prednisone; HD+ASCT, High-dose chemotherapy regimen followed by autologous stem cell transplantation; allo-SCT, allogeneic stem cell transplantation.

role of total metabolic tumor volume (TMTV) and total-lesion-glycolysis in patients with FL as strong predictors of PFS and OS.[13,14] Even the role of baseline SUVmax as an independent PFS predictor is debated (7,10). In the experience of Rossi et al., the rate of POD24 events was related to different SUVmax and mutational burden.[6-7]

Minimal residual disease (MRD)-driven treatment approaches are currently under investigation in FL. In the MIRO phase II trial for early-stage FL, the first results showed that the addition of immunotherapy (with anti-CD20 MoAb) to RT induced a negative MRD in more than 90% of the patients with BCL2/IGH rearrangement at baseline who remain MRD+ after RT.[13] In the FOLL12 study, for advanced FL, MRD positivity after induction treatment and over the follow-up was associated with a higher risk of relapse, suggesting the importance of a combined PET/MRD-based approach.[12]

Long-term follow-up of trials combining PET assessment, reliable MRD monitoring, and lymphoma-associated mutations could allow defining a better risk stratification for outcome prediction, which could also identify candidates to be "cured." Moreover, we must mention the new agents, such as bispecific monoclonal

antibodies and chimeric antigen receptor T-cells (CAR-T), which could furtherly be included in treatment plans aiming at disease eradication.[15-16]

The suggestion in 2023 is that in a subset of young and fit patients with FL, the treatment strategy could move from disease control and treatment of symptomatic disease to a curative approach. To achieve this goal, some suggestions could be:

- To treat patients with low tumor burden disease, giving preference to new agents as an alternative to chemotherapy for specific subgroups.[12-16]
- To monitor treatment response with metabolic and MRD assessment.[12-14,17]
- To evaluate an MRD-driven consolidation, including new agents, in patients considered eligible for disease eradication.[13-16]

We think it is time to design a prospective clinical trial with long-term follow-up, which could consider these points.

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